

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

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

**PETITIONERS' RESPONSE TO PATENT OWNER'S
REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION**

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EXHIBIT LIST

Exhibit	Description
Ex. 1200	Supplemental Expert Declaration of Mark J. Ratain, MD
Ex. 1201	Chung, <i>et al.</i> , Journal of Clinical Oncology, 43(17 suppl): LBA4175 (2025)
Ex. 1202	Chung, <i>et al.</i> , NAPOLI 3 Phase 3 Trial of NALIRIFOX in Metastatic Pancreatic Ductal Adenocarcinoma: Characteristics of Long-term Survivors. Presented at ASCO Annual Meeting on May 31, 2025
Ex. 1203	Rochefort, <i>et al.</i> , The Oncologist, 24:1543-1548 (2019)
Ex. 1204	Translation Certification of the English Translation of Conroy Protocol (Ex. 1004)
Ex. 1205	U.S. Patent No. 9,492,442
Ex. 1206	NCCN Clinical Practice Guidelines for Pancreatic Adenocarcinoma published on February 3, 2025.
Ex. 1207	Patel, <i>et al.</i> , Journal of Clinical Oncology, 43(4 suppl):716 (2025)

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I. INTRODUCTION

Petitioner CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively “Conjupro” or “Petitioner”) submits this opposition to the Request for Discretionary Denial of the Petition by Patent Owner Ipsen Biopharm Ltd. (“Ipsen”).

As explained in the Petition, the Challenged Claims were pending before the Office for several years after being rejected numerous times for obviousness based on largely the same prior art references. In Remarks prior to allowance, Ipsen made three arguments to overcome the obviousness rejection: (1) that there was no motivation to combine the references; (2) that there was no reasonable expectation of success; and (3) unexpected results. The Examiner allowed the claims without providing any reason for allowance, and therefore it must be presumed that any of these reasons could have formed the basis for allowance.

Ipsen’s transparent attempt to misrepresent the Petition as just repeating the arguments during prosecution fails. While Ipsen argued during prosecution that there was no motivation to combine the references because the Conroy and Bayever references did not disclose the key 60 mg/m² oxaliplatin limitation and that Melis had a number of drawbacks, here, the Petition relies upon the Conroy Appendix, which was never disclosed or considered by the Examiner, and the Conroy Protocol, which was never expressly discussed during prosecution but only identified in IDSs

disclosing over a thousand other references. Therefore, it is reasonable that the Examiner did not appreciate that these references disclosed this key limitation and therefore erred, a fact Ipsen completely ignores in its discretionary denial brief (Paper 8, herein “DDB”). Moreover, the Petition relies upon Cantore instead of Melis for disclosing this oxaliplatin element, which does not suffer from any of the criticisms leveled against Melis by Ipsen during prosecution. Even if the Board were to find that the Conroy Appendix and Protocol and Melis were considered by the Office, it was material error for the Examiner to not rely on these references even though they filled the critical gap that Ipsen alleged was missing from the prosecution. This alone compels denial of Ipsen’s discretionary denial request.

Moreover, when Ipsen argued that there was no motivation to combine the references and that there was no reasonable expectation of success, it mischaracterized the key Bayever reference as being limited to second-line therapy, and thus, Ipsen argued, the POSA would not be motivated to combine it with first-line therapy Conroy or expect any success in doing so. Critically, Ipsen now admits in its DDB that Bayever is ***not*** limited to second-line therapy, and now argues that its misrepresentation of Bayever during prosecution was harmless or should have been recognized by the Examiner. This cannot withstand scrutiny. By being misled by Ipsen into allowing the claims based on these false statements, the Examiner committed material error which also precludes Ipsen’s discretionary denial relief.

In addition, Ipsen's entire argument during prosecution that there was no reasonable expectation of success was based on an erroneous claim construction which required that these methods of treating claims show actual clinical efficacy. As shown in the Petition, both the intrinsic and extrinsic evidence reject this construction since the claimed method of treating is broad enough to cover administering the various chemotherapy drugs just *for the purpose* of providing clinical efficacy. Ipsen largely ignores this key claim construction dispute in its DDB, but because the Challenged Claims were presumably allowed due to this erroneous claim construction, this too constituted material error by the Examiner barring discretionary denial.

Ipsen's efforts to try to rehabilitate its defective unexpected results argument only amplify its problems. In its DDB, Ipsen acknowledges that the main reference it relied upon during prosecution – Wainberg – to show clinical superiority of the claimed regimen over the prior art FOLFIRINOX regimen – was fraught with inherent limitation which Wainberg itself cautioned. Ipsen tries to deflect blame by again arguing that the Examiner must have known of these flaws, but Wainberg's faulty suggestions of clinical superiority were refuted by a number of subsequent scientific references, which are described for the first time in the Petition and below. This proves that the Examiner also materially erred for allowing the claims based on deficient unexpected results data.

Finally, Ipsen’s “settled expectations” argument backfires. The grim prognosis and survivability of patients with metastatic pancreatic cancer would not have dissuaded POSAs from using well known treatment options; it would have especially driven POSAs to try to care for their patients in any way they could to arrive at obvious methods of treatment, such as the Challenged Claims, regardless of Ipsen’s expectation of trying to recoup its financial investments.

II. LEGAL STANDARD

A. Standard for Discretionary Denial.

The Board considers whether the same or substantially the same prior art or arguments were previously before the Office during prosecution. 35 U.S.C. § 325(d); *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 at 7-8 (PTAB Feb. 13, 2020) (precedential). In making this consideration, the Board uses a two-part test: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and, if the first part is met, (2) whether the petitioner has shown that the Office erred in a material way with respect to patentability. *Id.* at 8.

In applying this framework, the Board should consider the following factors:

(a) [T]he 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.

Factors (a), (b), and (d) guide consideration of the first prong of *Advanced Bionics* and factors (c), (e), and (f) guide consideration of the second prong. *Oticon Medical AB v. Cochlear Ltd.*, IPR2019-00975, Paper 15 (Oct. 16, 2019) (precedential).

In the Acting Director's March 26, 2025 Memorandum ("Director's Memo"), the PTAB outlined a non-exhaustive list of relevant considerations for discretionary denial including:

1. Whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims;

2. Whether there have been changes in the law or new judicial precedent issued since issuance of the claims that may affect patentability;
3. The strength of the unpatentability challenge;
4. The extent of the petition's reliance on expert testimony;
5. Settled expectations of the parties, such as the length of time the claims have been in force;
6. Compelling economic, public health, or national security interests; and
7. Any other considerations bearing on the Director's discretion.

III. ARGUMENT

The Board should not exercise its discretion to deny the Petition under Section 325(d) because (1) the Petition presents substantially different prior art and arguments from those previously presented; and (2) even if there is overlap among the art, the Office was misled into material error during prosecution by Applicant's mischaracterization of the prior art and unexpected results.

A. The Office Did Not Consider the Conroy Protocol and the Conroy Appendix.

While Conroy was discussed during prosecution, the Office did not consider Conroy in the context of the Conroy Protocol and the Conroy Appendix.

1. The Conroy Protocol and Appendix Disclose the Critical Limitation of a 60 mg/m² of Oxaliplatin Dose.

The Conroy Protocol and Appendix disclose the critical element of a 60 mg/m² oxaliplatin dose within the FOLFIRINOX regimen for first-line treatment of metastatic pancreatic cancer. Even though this aspect of the Conroy Appendix and Protocol played a significant role in each of the grounds of the Petition (*see* Pet. at 39-41, 58, 60), Ipsen flagrantly ignores this in its Discretionary Denial Brief (“DDB”). Ipsen’s intentional failure to even mention the Conroy Appendix and Protocol, (*see generally* DDB), proves fatal to Ipsen’s request for discretionary denial.

As Ipsen acknowledges, (DDB at 5-6), the claims during prosecution were rejected no less than five times over the course of several years based in part on the Office’s understanding that even though the Conroy article disclosed a 85 mg/m² dose of oxaliplatin within FOLFIRINOX, as opposed to the claimed 60 mg/m² dose of oxaliplatin, the POSA could adjust this dose to the claimed amount because it was known that oxaliplatin in the claimed regimen was a “result effective variable,” especially in view of the prior art, such as the Melis reference, which disclosed a 60 mg/m² dose of oxaliplatin in pancreatic cancer treatments. (*See* Rejection at Ex. 1084 at 190-201, 314- 327; Ex. 1088 at 57-69; Ex. 1097 at 188-203; Ex. 1119 at 9-22.)

In Ipsen’s last Remarks prior to allowance of the claims, Ipsen vigorously challenged this proposition. Ipsen, citing MPEP §§ 2143 and 2144, argued that a “‘result effective variable’ is one that can be varied to have a predictable effect on

the final outcome.” (Ex. 1119 at 147.) Ipsen then criticized the Office’s reliance on Melis, contending that Melis failed to “recognize any predictable outcome that may be achieved by varying the dose of oxaliplatin.” (*Id.* (emphasis in original).)

In anticipation of this very argument by Ipsen during prosecution, the Petition specifically addresses this issue regarding the “result effective variable” of the oxaliplatin dose by emphasizing the explicit teachings of the Conroy Appendix and Protocol. (*See* Pet. at 33 (“the prosecution never recognized that Conroy, the Conroy Protocol, and the Conroy Appendix disclose that FOLFIRINOX patients were administered with 60 mg/m² oxaliplatin.”); 43-44 (“But the Examiner failed to appreciate that Conroy disclosed that the median dose intensity of oxaliplatin was 78%, and that the Conroy Protocol and Appendix disclosed numerous instances of oxaliplatin dose reductions to 60 mg/m² based on various toxicity events, which a POSA would have readily understood.”).)

Petitioner’s expert, Dr. Ratain, specifically explained why the teachings of the Conroy Protocol and Appendix confirm that the 60 mg/m² oxaliplatin dose was indeed a result effective variable actually taught by these references, which is unrebutted on the record. Dr. Ratain explained that both the Conroy Protocol and the Appendix specifically disclose that within the FOLFIRINOX regimen, the dose of oxaliplatin should be reduced from 85 mg/m² to 60 mg/m² based on various known toxicities. (Ex. 1002 at ¶¶ 104-106.) Dr. Ratain concluded that “[t]hese oxaliplatin

dose reductions to 60 mg/m² are also consistent with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m² dose and indicate that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m² based on various toxicity events.” (*Id.* at ¶105; *see also id.* at ¶106.)

Both the Conroy Protocol and Appendix explicitly teach that oxaliplatin should be adjusted to 60 mg/m² based on certain well known side effects in chemotherapy, such as the reduction of a certain type of white blood cell (granulocytes), the reduction of platelets, conditions of low white blood cell count (neutropenia), conditions of low platelet count (thrombocytopenia), and diarrhea. For example, the Conroy Appendix discloses in chart form the following:

		Irinotecan	Oxaliplatin
Granulocytes < 1.5 x 10⁹/L	Hold treatment until granulocytes ≥ 1.5 x 10 ⁹ /L (one or two weeks if necessary).	<u>1st occurrence:</u> reduction of dose to 150 mg/m ²	<u>1st occurrence :</u> no reduction of dose
		<u>2nd occurrence:</u> maintain the dose at 150 mg/m ²	<u>2nd occurrence:</u> reduce the dose to 60 mg/m ²

Platelets < 75 x 10⁹/L	Hold the treatment until recovery (platelets $\geq$ 75 x 10 ⁹ /L).	<u>1st occurrence :</u>	<u>1st occurrence:</u>
		no reduction of dose	reduce the dose to 60 mg/m ²
		<u>2nd occurrence:</u>	<u>2nd occurrence:</u>

Febrile neutropenia Grade 4 neutropenia during more than 7 days	<u>1st occurrence:</u> reduce the dose of irinotecan to 150 mg/m ² and delete the bolus 5FU dose
	<u>2nd occurrence:</u> reduce also the dose of oxaliplatin to 60 mg/m ²

Grade 3-4 thrombocytopenia	<u>1st occurrence:</u> reduce the oxaliplatin dose to 60 mg/m ² and the continuous 5-FU dose to 75 % of the original dose
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Diarrhea grade 3-4 or Diarrhea + fever and/or neutropenia grade 3-4	<u>1st occurrence:</u> reduce the irinotecan dose to 150 mg/m ² and delete the bolus 5FU dose
	<u>2nd occurrence:</u> reduce also the oxaliplatin dose to 60 mg/m ² and reduce the dose of continuous 5FU to 75 % of the original dose

(Ex. 1017 at 4-6 (highlighting added).)

None of these teachings of reducing oxaliplatin to the claimed 60 mg/m² dose were discussed during prosecution even though the “result effective variable” of the

oxaliplatin was a crucial issue for both Ipsen and the Office, and Ipsen blatantly ignored any mention of this in its DDB.

While the Conroy Protocol was technically disclosed in an IDS during prosecution,¹ the Conroy Appendix was not. In addition, the Conroy Protocol that was submitted by Ipsen during prosecution was in French and no translation was

¹ In its POPR, Ipsen argues that Petitioner's reliance on the Conroy Protocol is defective because, while Petitioner provided an English translation of the Protocol from French with the Petition and described it as a certified translation, Petitioner did not include the actual certification as an exhibit. However, Ipsen's objection to the evidence is premature since it should be made within 10 business days of institution, which would then allow Petitioner to submit the translation certification as supplemental evidence within 10 business days of the timely filed objection. *See* 37 C.F.R. § 42.64(b). Regardless, attached hereto as Exhibit 1204 is the translation certification of English translation of the Conroy Protocol. Moreover, while the Conroy Protocol is identified on the IDSs, Ipsen never submitted an English translation of the Protocol (certified or otherwise) as part of its IDSs, which is even more compelling reason why the Office never substantively considered the Conroy Protocol.

provided. (*See, e.g.*, Ex. 1119 at 308-395.) This, in itself, is sufficient basis to deny Ipsen's request for discretionary denial because the first prong of *Advanced Bionics* is not satisfied. *See Thorne Research, Inc. v. Trustees of Dartmouth College*, IPR2021-00491, Paper 18 at 8-9 (PTAB August 12, 2021) (“[T]he fact that one piece of art from the combination was previously presented and/or argued to the Office is insufficient to satisfy the first prong of *Advanced Bionics*...even though Bieganowski was cited, the other two references in the Petition, Rosenbloom and Brenner, were not before the Examiner...[t]herefore, we find that the same or substantially the same art or arguments were not previously presented to the Office during prosecution.”); *Motorola Mobility v. Multifold International Inc.*, IPR2025-00040, Paper 10 at 30-31 (PTAB May 21, 2025) (first prong of *Advanced Bionics* not satisfied where prior art not considered by the Examiner demonstrated a reasonable likelihood of invalidating at least claim 1).

2. Even if the Conroy Protocol Was Considered, Neither the Conroy Protocol or Appendix were Discussed During Examination, Which Demonstrates Material Error by the Office for Failing to Recognize Their Significance.

Even if the Board determines that the Conroy Protocol and Appendix were considered by the Examiner as part of the Conroy article, the Board should still deny Ipsen's request for discretionary denial because the Office erred in a manner material to the patentability of the Challenged Claims. As discussed above, the Conroy

Protocol and Appendix disclose the critical 60 mg/m² oxaliplatin dose within FOLFIRINOX which Ipsen accused the prior art of failing to disclose during prosecution. Both the Protocol and Appendix clearly demonstrate that dose reductions of oxaliplatin from 85 mg/m² to 60 mg/m² was a result effective variable based on certain side effects, and the Conroy article further discloses that the median dose intensity of oxaliplatin administered in the clinical trial was 78%. A POSA, reviewing this information, would understand that a significant portion of the patients who participated in the FOLFIRINOX clinical trial as described in Conroy and the supporting Protocol and Appendix, were administered with the claimed 60 mg/m² oxaliplatin dose, as confirmed by Dr. Ratain. (Ex. 1002 at ¶¶ 97, 105; Ex. 1200 at ¶ 9.)

Under the second prong of *Advanced Bionics*, the Board considers “whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 8. “An example of a material error may include misapprehending or overlooking specific teachings of the relevant prior art where those teachings impact patentability of the challenged claims.” *Id.* The Board evaluates *Becton, Dickinson* factors (c), (e), and (f) in order to determine whether the Office committed material error.

Applied here, factor (c) – “the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection” –

clearly supports a finding of material error, since the 60 mg/m² oxaliplatin dose of the Conroy Protocol and Appendix was never even discussed by Ipsen or the Office during prosecution. Moreover, factor (e) – “whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art” – also weighs in favor of material error by the Office, since as explained above, Petitioner has clearly shown through the Conroy Protocol and Appendix that not only is the oxaliplatin dose a result effective variable within the context of known metastatic pancreatic cancer treatments, but that the Protocol and Appendix each disclose the claimed 60 mg/m² oxaliplatin dose within FOLFIRINOX, which the Examiner erred by failing to recognize. Finally, factor (f) – “the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments” – is not applicable here. As discussed above, because the critical aspects of the Conroy Protocol and Appendix were never evaluated or argued during prosecution, there is no need to rely upon additional facts or evidence to warrant reconsidering something that was never even addressed.

Indeed, as the Board has recognized, “if the record of the Office’s previous consideration of the art is not well developed or *silent*, then a petitioner may show the Office erred by overlooking something persuasive under factors (e) and (f).” *Advanced Bionics*, IPR2019-01469, Paper 6 at 10 (emphasis added). Applied here, the *utter silence* of any discussion during prosecution and in Ipsen’s DDB regarding

the disclosure of the crucial 60 mg/m² oxaliplatin dose in the Conroy Protocol and Appendix is so deafening that it warrants denial of Ipsen's discretionary denial request based on material error. *See Klein Tools, Inc. v. Milwaukee Electric Tool Corp.*, IPR2024-01400, Paper 17 at 25-26 (PTAB April 8, 2025) (finding material error where despite patent owner's argument that the Examiner clearly understood the art, "[g]iven the prosecution history's *silence* on Burchia and Metabowerke, however, we do not view the alleged understanding as in any way 'clear[]'") (emphasis added); *Amazon.com Inc. v. Nokia Tech.*, IPR2024-01140, Paper 9 at 16 (PTAB February 12, 2025) (finding material error where the prosecution was "*silent*" as to the key prior art reference and "there was no discussion or analysis of [this art] apart from its inclusion on the IDS.") (emphasis added).

3. The Office's Failure to Consider Cantore, Which Also Disclosed the Claimed 60 mg/m² Oxaliplatin Dose, Also Constituted Material Error.

As discussed in the Petition, the Office should not exercise its discretion to deny the Petition because among other things, the Petition also relies upon Cantore for the key 60 mg/m² oxaliplatin dose limitation of the claims instead of Melis, which was the reference discussed in prosecution. In its DDB, Ipsen merely states in conclusory fashion that "Cantore does not address the deficiencies of Melis" without providing any support. (DDB at 17.) But this is wrong.

As the Petition points out, “[w]hile Patent Owner apparently distinguished Melis based on the fact that it excluded the claimed treatment of patients with metastatic disease, involved only weekly administration of oxaliplatin instead of the claimed “every two weeks” administration, and did not involve co-administration with irinotecan (Ex. 1119 at 146-48), none of these criticisms of Melis can be leveled against Cantore,” (Pet. at 33). The Petition further distinguishes Cantore from Melis by stating that:

Cantore discloses that 60 mg/m² oxaliplatin with irinotecan “shows evidence of being therapeutically beneficial, in patients with progressive metastatic pancreatic cancer,” and no patients were ever reported in Cantore to have to resort to higher doses of oxaliplatin, like the 85 mg/m² of Melis. (Ex. 1009 at 5.) Other criticisms of Melis—that it excluded patients with metastatic pancreatic disease and only involved weekly and not bi-weekly administrations (Ex. 1119 at 147-48 (emphasis in original))—do not apply to Cantore. Thus. Cantore is substantially different from Melis and Patent Owner’s arguments in trying to overcome Melis cannot be applied to Cantore.

(Pet. at 46.)

Ipsen tries to suggest that Cantore actually “teaches away” from disclosing a 60 mg/m² dose of oxaliplatin because it states that future studies should evaluate “higher doses of irinotecan and oxaliplatin” in patients. (DDB at 17.) But rather than a teaching away, this just confirms the “excellent tolerability of this regimen” which

used 60 mg/m² dose of oxaliplatin in treating patients with metastatic pancreatic cancer. (Ex. 1009 at 4.)

While Cantore was cited in an IDS, it was never discussed during prosecution and never formed the basis of a rejection. Moreover, as just discussed, Cantore does not suffer from the alleged shortcomings leveled by Ipsen during prosecution against the Melis reference, which apparently was the basis for the Examiner to eventually withdraw his rejections based on Melis and allow the claims. Thus, *Becton, Dickinson* factors (c), (e), and (f) weigh in favor of finding material error by the Office in overlooking Cantore.² See *Advanced Bionics*, IPR2019-01469, Paper 6 at

²For much of the same reasons, the Office also committed material error to the extent it overlooked Mahaseth, which disclosed removing the 400 mg/m² bolus dose of 5-FU from FOLFIRINOX. (See Pet. at 17, 41-45.) While Mahaseth was identified on an IDS, the subject of its disclosure of removing the bolus was never discussed during prosecution and was never the basis of a rejection. Moreover, Bayever also taught a non-bolus regimen of administering the claimed 2400 mg/m² 5-FU dose. (See *id.* at 39-43.) Thus, to the extent the Office allowed the claims because it was misled into believing that the prior art did not disclose a 2400 mg/m² 5-FU dose in FOLFIRINOX or in other first-line treatments of metastatic pancreatic cancer, such

10 (silence in the record “may show the Office erred by overlooking something persuasive under factors (e) and (f).”); *Klein Tools*, IPR2024-01400, Paper 17 at 25-26 (finding material error based on “silence” in the record of the prior art reference); *Amazon.com*, IPR2024-01140, Paper 9 at 16.

B. Ipsen Intentionally Misled the Office Into Error By Arguing That Bayever Was Not Relevant to the First Line Treatment of the Claims.

In its DDB, Ipsen concedes that Bayever is not limited to second-line therapy (DDB at 20-21), as it must, since the Petition pointed out, among other things, that all of the published claims of Bayever never once limited the method of treatment to second-line therapy, but broadly covered any method of treating pancreatic cancer with the same doses of liposomal irinotecan, 5-FU, and leucovorin as those of the Challenged Claims, regardless of whether the patient was previously treated for pancreatic cancer. (Pet. at 20-21.)

Instead, Ipsen now argues, incredibly, that it never mischaracterized Bayever as a second-line treatment during prosecution, but merely suggested that Bayever *covers* second-line treatment. (DDB at 20-21.) However, Ipsen’s attempt to downplay its mischaracterization of Bayever fails.

as Bayever, this too was material error. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 10.

After all, as discussed above, Ipsen's pending claims were being continuously rejected for several years based on numerous office action rejections where the Examiner combined the FOLFIRINOX regimen of Conroy with Bayever's liposomal irinotecan method of treating pancreatic cancer. Ipsen needed to change tactics, and it did so when it argued for the first time on February 25, 2025, just prior to allowance, that Bayever was limited to second-line treatment, and therefore, the POSA would allegedly never combine it with the first-line treatment of FOLFIRINOX. (Ex. 1119 at 145-146.)

Under the subheading, "No motivation to combine the references," Ipsen argued that:

Additionally, 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. Bayever covers the liposomal irinotecan, 5-FU, LV regimen currently approved for ONIVYDE® (irinotecan liposome injection), which is indicated for the treatment of patients with metastatic adenocarcinoma of the pancreas *after* disease progression following gemcitabine based therapy - i.e., as a *second-line therapy* for metastatic pancreatic cancer. See www.accessdata.fda.gov/drugsatfda_docs/label/2015/207793lbl.pdf and the present Specification at page 2, lines 19-22; see Response to Final Office Action filed February 25, 2021, at page 9. By contrast, Conroy describes assessing FOLFIRINOX "as compared with gemcitabine as first-line therapy." See Conroy at abstract. As set forth

in more detail below, *a person of ordinary skill in the art would not combine teachings regarding first-line cancer treatments and second-line cancer treatments.*

(*Id.* (emphasis added).) Ipsen's intentions could not have been clearer. It unmistakably argued that Bayever should not be combined with the first-line therapy of Conroy because Bayever was to second-line therapy, which Ipsen now admits in its DDB to be false.³ (See DDB at 21 (stating Bayever is "not limited to [a] second

³ To avoid any doubt that Bayever was not limited to second-line therapy, Bayever (the parent application) issued as Ipsen's U.S. Patent No. 9,492,442 which claims a method of treating pancreatic cancer that is not limited to second-line therapy but also covers first-line therapy. See Ex. 1205, Claim 1 ("[A] method of treating an exocrine pancreatic cancer, the method comprising intravenously administering an antineoplastic therapy once every two weeks to a human patient having the exocrine pancreatic cancer, the antineoplastic therapy consisting of: a. administering a 60-80 mg/m² dose of a liposomal irinotecan composition in a diluted irinotecan injection formulation to the human patient in a single infusion over about 90 minutes, the diluted irinotecan injection formulation comprising irinotecan liposomes in 500 mL of an injectable liquid and a volume of a 5 mg/mL liposomal irinotecan composition effective to deliver the dose of liposomal irinotecan, in combination with b.

line therapy regimen”).) Ipsen further exacerbated its mischaracterization of Bayever as a second-line therapy during prosecution by equating it to FDA approval of Ipsen’s drug ONIVYDE, which was not in the prior art (Ex. 1061), and which at the time had only been approved for second-line therapy, even though, as stated above, none of the published claims of Bayever were limited to second-line therapy.

But Ipsen went even further in misrepresenting Bayever during prosecution. In its next subheading, “No reasonable expectation of success,” Ipsen argued:

Initially, in contrast to the assertions of the Examiner, there would have been no reasonable expectation that including oxaliplatin from a first-line treatment regimen (e.g., as disclosed in Conroy) into a second-line treatment regimen (e.g., as disclosed in Bayever) would yield an effective and tolerable first-line treatment pursuant to the claims. In general, results from second-line treatments cannot establish a reasonable expectation of similar results in treating patients who have not previously received an antineoplastic agent

administering a therapeutically effective amount of leucovorin and 5-fluorouracil, to treat the exocrine pancreatic cancer in the patient, wherein the irinotecan liposome composition comprises phosphatidylcholine, cholesterol, and a polyethyleneglycol-derivatized phosphatidyl-ethanolamine, and the irinotecan liposomes in the liposomal irinotecan composition have a diameter of approximately 80-140 nm.”).

(and vice versa). Expectations of efficacy and safety of treatments are entirely different at these two separate stages: in second-line therapy, the tumor may have become more malignant and difficult to treat; patients receiving second-line therapy are also likely significantly more sick and less able to tolerate therapy than those receiving a first-line therapy.

(Ex. 1119 at 148-149 (emphasis added).)

Thus, Ipsen clearly argued during prosecution that there was no reasonable expectation of success because the POSA would not expect the second-line treatment of Bayever to work with the first-line treatment of Conroy.⁴ There is simply no ambiguity regarding Ipsen's mischaracterization of Bayever as being limited to second-line treatment. In fact, if during prosecution, Ipsen acknowledged that Bayever covered both first-line and second-line treatment of pancreatic cancer, as it does now in its DDB, then its entire arguments of Bayever during prosecution

⁴ Putting aside Ipsen's mischaracterization of Bayever as being limited to second-line therapy, the Petition and its supporting declaration from Dr. Ratain refute Ipsen's argument that a POSA would not be motivated to combine regimens of second-line treatment to treat patients for first-line therapy, which is a further example of material error by the Office which was never addressed during prosecution. (Ex. 1002 at ¶¶ 130-137.)

regarding the motivation to combine references and reasonable expectation of success *collapse* and, because they do, reconsideration of the patentability of the claims is warranted.

Despite perpetuating these misleading statements about Bayever throughout the last office action response prior to allowance, Ipsen now argues in its DDB that the Examiner should have known that Bayever was not limited to second-line treatment despite Ipsen's misleading statements, and cites caselaw for the unremarkable proposition that examiners are presumed to have "fully considered" references that were discussed during prosecution. DDB at 21-22. *See, e.g., Johnson & Johnson Surgical Vision, Inc. v. Alcon Inc.*, IPR2021-00898, Paper 17 (PTAB November 9, 2021). However, all of Ipsen's cases are distinguishable here because they did not deal with applicants whose mischaracterizations of key prior art references resulted in allowance. Applied here, when applicants *mislead* the Office into committing a material error, which is this case, the Board has refused to exercise its discretion to deny the petition. *See Samsung Bioepis Co. Ltd. v. Alexion Pharma. Inc.*, IPR2023-01070, Paper 9 at 66 (PTAB December 19, 2023) (in declining discretionary denial, "We agree with Petition that the Examiner was *misled* by [patent owner] and misapprehended Evans as evidenced by the Reason for Allowance.") (emphasis added); *Danisco US Inc. v. Novozymes A/S*, IPR2019-01010, 2019 WL 57777771, *8 (PTAB November 5, 2019) (in declining

discretionary denial, “Under the circumstances of this case, it appears that the Examiner erred or was *misled* by [patent owner’s] arguments when considering the obviousness of claim 2 over the prior art, or did not actually consider claim 2 at all.”) (emphasis added); *Dr. Falk Pharma v. Ellodi Pharmaceuticals, L.P.*, IPR2025-00056, Paper 10 at 15-17 (PTAB June 3, 2025) (in declining discretionary denial, the Board agreed that [patent owner] “*misled the Examiner*” into incorrectly analyzing the key prior art reference during prosecution) (emphasis added); *Medtronic Corevalve LLC v. Speyside Medical, LLC*, IPR2021-00239, 2021 WL 3621948, *10-12 (PTAB August 16, 2021) (in declining discretionary denial, the Board agreed with petitioner that “*the Examiner was misled* by the applicant’s assertion that ‘Leonhardt does not disclose replacing the leaflet actuation of the native aortic heart valve.’”) (emphasis added).

In a last-ditch effort to try to rationalize its mischaracterization of Bayever during prosecution, Ipsen desperately and falsely argues that its misleading statements were not material *even though affirmatively made* because Ipsen allegedly suggested similar arguments in a prior Office Action response and the claims were still rejected. (DDB at 23.) In the prior February 25, 2021 Remarks, that Ipsen did identify Conroy as a first-line treatment and cited ONIVYDE’s FDA approval as being limited to second-line treatment at the time, which Bayever was broad enough to cover. (See Ex. 1098 at 206; see also Ex. 1119 at 9-22 (Examiner’s

responses to February 25, 2021 remarks not mentioning or traversing such an argument).) However, the discussion of ONIVYDE was in the context of providing **background information** regarding objective indicia of non-obviousness, not a discussion where applicants argued that first line treatments and second line treatments should not be combined or expected to work together. (Ex. 1098 at 206 (“Respectfully, and to provide **additional background** that may help distinguish the claimed methods from the cited disclosures, in 2015, ONIVYDE® (irinotecan liposome injection) was approved by the US FDA...a second-line therapy for metastatic pancreatic cancer.”) (emphasis added).)

But even for the sake of argument that Ipsen previously made similar arguments during prosecution (it did not), if Ipsen really believed that its misrepresentation of Bayever was not material because the claims were still being rejected, then why did it **double-down on further emphasizing these misleading statements** in its last Remarks prior to allowance? Clearly, these mischaracterizations were material such that it misled the Examiner into erroneously allowing the claims.

C. Saif and Ko, Not Considered During Prosecution, Provide Further Motivation to Replace the MM-398 Liposomal Irinotecan in Bayever with the Regimen Disclosed in Conroy and the Conroy Protocol and Appendix.

1. Saif was Never Disclosed During Prosecution and Its Critical Combination with the Prior Art of the Petition Compels Declining Discretionary Denial.

Saif was never expressly considered during prosecution. It was never discussed during prosecution and was not listed in IDSs that dumped well over a thousand references on the Examiner, which Ipsen glaringly fails to address in its DDB. As discussed in the Petition, Saif disclosed the critical motivation of replacing non-liposomal irinotecan with Ipsen's MM-398 liposomal irinotecan in the established gold standard FOLFIRINOX regimen of first-line treatment of metastatic pancreatic cancer to render the Challenged Claims obvious. (*See* Pet. at 21-23, 32, 42-43.) Thus, it closes the critical gap that Ipsen alleged was missing when it argued that the POSA would not combine the liposomal irinotecan formulation of Bayever (reported in Saif) with the FOLFIRINOX regimen disclosed in Conroy and the Conroy Protocol and Appendix.

Ipsen's attempt to try to argue that Saif was cumulative to other references cited in IDSs fails. Saif was reporting on the encouraging results of Ipsen's MM-398 liposomal irinotecan based on the NAPOLI-1 clinical trial results, and IDSs during prosecution did disclose the results of this study. However, it is undisputed that none of the IDS references cited by Ipsen in its DDB specifically suggested replacing the non-liposomal irinotecan of FOLFIRINOX with MM-398 for first-line treatment.

(DDB at 13-14 (citing purportedly cumulative references, none of which suggest using the NAPOLI-1 treatment in combination with FOLFIRINOX, as Saif does).)

Ipsen makes much of the fact that Saif's discussion of NAPOLI-1 used a different combination of drugs than FOLFIRINOX and the Challenged Claims because NAPOLI-1 did not include oxaliplatin. (DDB at 14.) ***But that was the whole point*** of publications like Saif and Ko that reported to the POSA that liposomal irinotecan could be used with oxaliplatin in the standard FOLFIRINOX first-line treatment. Saif and Ko published favorable results regarding the safety and efficacy of Ipsen's MM-398 liposomal irinotecan in the second-line setting, and because of this, they suggested that it should be evaluated in first-line settings by replacing non-liposomal irinotecan in FOLFIRINOX. While Ipsen accuses Petitioner of cropping and manipulating the language of Saif, below is the actual language of Saif highlighted in the Petition:

2. Now that we have combination of 5-fluorouracil, oxaliplatin, irinotecan, leucovorin (FOLFIRINOX) as an option for first-line treatment too, how will this regimen fit in the algorithm of the treatment.

3. It seems logical to test this drug/regimen further: will it be worth replacing irinotecan in FOLFIRINOX with MM-398. However, bone marrow toxicity has to be borne in mind.

(See Pet. at 22 (citing Ex. 1007, 1) (internal footnotes omitted).)

Saif, having discussed the “exciting” results of MM-398 liposomal irinotecan in second-line therapy is asking how “this regimen fit[s] in the algorithm” of “first-line treatment” “FOLFIRINOX.” Saif then answers his question by stating that “it seems logical” to further test this regimen in first-line settings and specifically asks whether it would be worth “replacing irinotecan in FOLFIRINOX with MM-398.” While Saif cautions that “bone marrow toxicity” needs to be “borne in mind,” a POSA would of course have to consider all standard toxicity events when evaluating new treatments. However, this clearly does not take away from the fact that Saif is suggesting that “replacing irinotecan in FOLFIRINOX with MM-398” is worth studying because it is “logical” based on MM-398’s positive safety and efficacy results in second-line treatment.

In its DDB, Ipsen tries to argue that statement 2 is unrelated to statement 3, and that it is “misleading” for Petitioner to argue that statement 3 is addressing the question of statement 2. But this defies Saif’s plain reading. These statements are clearly related because statement 2 is asking how MM-398 fits into first-line FOLFIRINOX and the statement 3 reveals that it is “logical” to test MM-398 as a replacement for irinotecan in FOLFIRINOX. That Saif posits the replacement of irinotecan in FOLFIRINOX with MM-398 in the form of a question does not make it any less of a suggestion to the POSA that such a combination is worth investigating, especially since Saif immediately then states that such a combination

should take into consideration bone marrow toxicities. In fact, Dr. Ratain opined that “[a] POSA would have understood this suggestion for further testing and replacing the non-liposomal irinotecan in FOLFIRINOX with a liposomal irinotecan, e.g., MM-398, to be a suggestion for a new or modified first-line therapy.” (Ex. 1002 at ¶ 141; *see also* ¶ 235 (“As with Saif, Ko also suggested that given the emergence of FOLFIRINOX as a first-line standard in advanced pancreatic cancers, MM-398 should be further explored in the first-line therapy setting.”).) Ipsen fails to rebut Dr. Ratain’s interpretation of these prior art references from the viewpoint of a POSA, but instead relies upon a plain misreading of the references by its IPR attorneys. *See Icon Health & Fitness, Inc. v. Strava, Inc.*, 849 F.3d 1034, 1043 (Fed. Cir. 2017) (“Attorney argument is not evidence” and it would be improper for the Board to adopt such arguments provided without the requisite explanation).

Under these circumstances, Saif was not considered in any way during examination – it was not identified in Ipsen’s IDSs disclosing over a thousand references, and certainly was not included in any argument previously presented to the Examiner. Since Saif is part of a new combination of references that was never considered by the Examiner, the PTAB should decline discretionary denial because it does not satisfy the first prong of *Advanced Bionics*. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9; *Thorne Research*, IPR2021-00491, Paper 18 at 8-9 (“we find that the same or substantially the same art or arguments were not

previously presented to the Office during prosecution” because of new prior art combinations never considered by the Office); *Halliburton Energy Servs., Inc. v. U.S. Well Servs., LLC*, IPR2021-01036, Paper 12 at 20 (PTAB Jan. 19, 2022) (the first part of the *Advanced Bionics* framework was not satisfied where the Petition set forth obviousness grounds based on combinations involving a reference previously considered by the Examiner with other references that had not been considered); *K/S HIMPP v. Bragi GmbH*, IPR2023-01205, Paper 8 at 20 (PTAB Mar. 19, 2024) (“[A]lthough one reference, Shaffer, was previously presented to the Office, in each asserted ground, Petitioner relies on either Hain or Hain in combination with Sørensen. Because neither of those references was before the office, Patent Owner has not satisfied the first prong of the *Advanced Bionics* test.”); *ResMed Inc. v. New York University*, IPR2022-00990, Paper 16 at 15-16 (PTAB Dec. 6, 2022) (first prong of the *Advanced Bionics* framework is not satisfied because “there are no rejections based on the combination of references asserted here.”).

2. It was Material Error for the Examiner to Overlook the Teaching of Ko Since It Also Provided the Key Motivation of Combing Bayever’s Teaching of a Liposomal Irinotecan with the First-Line FOLFIRINOX Regimen of Conroy with the Conroy Protocol and Appendix.

While Ko was listed on IDSs during prosecution, the Examiner materially erred in not considering this critical reference which specifically disclosed replacing

non-liposomal irinotecan in the first line FOLFIRINOX regimen with Ipsen's MM-398 liposomal irinotecan formulation.

The *Becton, Dickinson* factors clearly weigh in favor of finding material error. Ko was never evaluated during prosecution and certainly was never the basis of a rejection, and therefore factor (c) weighs against discretionary denial. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8. While Ipsen tries to obfuscate this issue by arguing that Ko is cumulative because the clinical trial which was the subject of Saif and Ko was before the Office during prosecution, this is of no moment. But as discussed above, there is no dispute on the record that the *specific teachings of Ko* which suggested combining the MM-398 liposomal irinotecan formulation with first-line FOLFIRINOX was *never discussed during prosecution*.

With respect to *Becton, Dickinson* factor (e), the Petition clearly explains the significance of the teaching in Ko and why the Examiner's failure to appreciate this resulted in material error. (*See e.g.*, Pet. at 21-23, 32 (in discussing reasons for declining discretionary denial, describing Ko as "other references raised here in this Petition (which were not discussed during prosecution) clearly suggested that based on promising results of liposomal irinotecan for second-line therapy, '[i]t seems logical to test [liposomal irinotecan]' to determine whether 'it would be worth replacing irinotecan in FOLFIRINOX with MM-398 [liposomal irinotecan].'"); 42-

43 (discussing the significance of Ko and Saif as further motivation to combine Bayever with FOLFIRINOX).)

Ipsen tries to deflect the significance of Ko by accusing Petitioner of selectively cropping quotes. Not so. Below is the full text of the section in Ko which was highlighted in the Petition:

Additional studies may explore this drug’s potential role in the first-line setting and as part of combination regimens for APC. Moreover, given the emergence of FOLFIRINOX as a front-line standard in patients with good performance status, the utility of PEP02 [MM-398] in irinotecan-pretreated patients, alone or in combination with gemcitabine, also merits further investigation.

(Ex. 1008, 5; Pet. at 23). While Ipsen tries to argue that this statement is referring to MM-398’s use as a monotherapy, this makes no sense since Ko is talking about additional studies that may explore MM-398’s “potential role in the *first-line setting and as part of combination regimens* of APC (advanced pancreatic cancer).” (Ex. 1008 at 5 (emphasis added).) The very next line then discusses the gold standard of first-line treatment of APC – FOLFIRINOX, and then states that the utility of MM-398 in this first-line regimen also merits further investigation. *Id.* In fact, it is Ipsen that crops the quote from this passage by removing the first line of this passage to try to hide the fact that this discussion of MM-398 was specifically in reference to combination regimens in first-line settings, including FOLFIRINOX, which Ko

describes as the “front-line standard.” *Id.* Ipsen’s strained interpretation goes against the plain reading of the passage, but it also lacks credibility because it contradicts Dr. Ratain’s understanding of this passage, who was a POSA at the time, and indicated that this was a clear suggestion by Ko that Ipsen’s MM-398 should be studied in the FOLFIRINOX regimen as a replacement of non-liposomal irinotecan. (Ex. 1002 at ¶¶ 143-146, 235 (citing Ex. 1008).) As discussed above, Ipsen provided no scientific rebuttal to Dr. Ratain’s opinion, only spurious attorney argument. *See Icon Health*, 849 F.3d at 1043 (“Attorney argument is not evidence” for PTAB review).

During prosecution, the claims were rejected over and over again based on the Examiner’s understanding that it would have been obvious to replace non-liposomal irinotecan in FOLFIRINOX with the MM-398 liposomal irinotecan of Bayever. Each time, Ipsen adamantly argued that the POSA would never combine the liposomal irinotecan therapy of Bayever with FOLFIRINOX, and Ipsen presumably convinced the Examiner of this when the claims were ultimately allowed. Ko and Saif directly refute Ipsen’s misstatements during prosecution that there was no motivation to combine liposomal irinotecan with FOLFIRINOX. To the extent the Examiner failed to recognize this because these references were never discussed during prosecution and that Ko was listed on IDSs along with over a thousand other references, this too was material error that affected the patentability of the

Challenged Claims and thus compels declining discretionary denial. *See Dr. Reddy's Labs. S.A. v. Eye Therapies, LLC*, IPR2024-00467, Paper 14 at 19-20 (PTAB August 13, 2024) (in declining discretionary denial, “we do not equate an examiner’s initial on an IDS with meaningful evaluation of the prior art...circumstances of this case suggest that the examiner overlooked the [key references]”); *Motorola Mobility*, IPR2025-00040, Paper 10 at 33-34 (in declining discretionary denial, “[w]e also reject Patent Owner’s unsupported interpretation of the MPEP that an Examiner’s ‘obligation to consider the information’ identified in an IDS ‘means the examiner concluded that the reference could not support a rejection in an Office action.’”); *Posco Co. Ltd. v. Arcelormittal*, IPR2024-01376, Paper 11 at 19-20 (PTAB March 18, 2025) (material error still occurred despite the repeated identification of key references in the IDSs, because the Examiner did not substantively consider them); *Klein Tools*, IPR2024-01400, Paper 17 at 25-26 (despite being cited in IDSs, the Office’s “silence” during prosecution of discussing the references showed material error).

D. Ipsen Fails to Meaningfully Address Petitioner’s Claim Construction Issue Regarding the “Method of Treating” Limitation of the Challenged Claims Which Was Never Considered During Prosecution and Therefore Further Compels Rejecting Ipsen’s Discretionary Denial Request.

The Petition also identified Ipsen’s erroneous claim construction of “method of treating” as another decisive reason that the Office was led into material error in

allowing the claims. Petitioner argued that “the method of treatment claims are only directed for the *purpose* of potentially bringing about a clinical benefit but that clinical efficacy is not required” and that “a proper claim construction of ‘method of treatment’ does not require clinical efficacy in a human patient, and thus Ipsen’s lack of reasonable expectation of success and unexpected results arguments during prosecution should be further discounted.” (Pet. at 35.)

In its DDB, Ipsen largely ignores this critical claim construction issue, even though it formed a significant part of the Petition’s reasons why the Board should decline discretionary denial. Ipsen relegates this claim construction issue as part of its unexpected result position during prosecution, and then argues that an unexpected result of clinical efficacy is not necessarily a claim limitation. (DDB at 28.)

However, Ipsen completely ignores the fact that its improper construction of “method of treating” as requiring clinical efficacy formed the entire basis of its “No reasonable expectation of success” arguments in its last Remarks to the Examiner prior to allowance. There, Ipsen argued that the cited references failed to establish a reasonable expectation of success because they failed to take into account numerous factors that “affect tolerability and *efficacy*” of the invention, and that “there would have been no reasonable expectation” that including a first-line treatment into a second-line treatment “would yield an *effective* and tolerable first-line treatment pursuant to the claims.” (Ex. 1119 at 148 (emphasis added), 149 (“Expectation of

efficacy and safety of treatments are entirely different at these two stages...Bayever similarly does not provide any teachings regarding how adding oxaliplatin to its combination regimen may affect *efficacy*, tolerability, or even the PK parameters of the liposomal irinotecan...None of the cited references suggest lowering the dose of oxaliplatin of Conroy with the expectation that reducing the dose would yield a safe and *effective* treatment.”) (emphasis added).)

Thus, Ipsen was able to seemingly convince the Examiner to allow the claims because those claims required clinical efficacy in the form of a safe and effective cancer treatment, and the prior art references of Conroy and Bayever allegedly did not show that because there was no reasonable expectation of clinical success by combining first-line and second-line therapies. As detailed in the Petition and the Ratain declaration, Ipsen’s claim construction which equated “treating” with actual clinical efficacy is legally wrong because it is not supported by intrinsic and extrinsic evidence. (See Pet. at 26-30.) For example, as stated in the Petition:

To the extent that the Office was misguided by Patent Owner *that a reasonable expectation of success of practicing the Challenged Claims* required evidence of clinical efficacy, this also was an error that materially affected the patentability of those claims. By not requiring a clinical efficacy threshold, the bar to proving obviousness of the Challenged Claims is much lower since the POSA would only need to combine the prior art to arrive at a first-line treatment regimen

administered *for the purpose of treating metastatic pancreatic cancer*, and not with the expectation that the regimen would have superior clinical efficacy over the gemcitabine/nab-paclitaxel control arm. As Dr. Ratain explains, methods of treating metastatic pancreatic cancer are always with the hope that the patient will live longer, but that is often not the case. (Ex. 1002, ¶¶49-50.) However, these are still valid methods of treatment because they are administered for the *purpose* of trying to extend and improve life, not a guarantee that they will. (*Id.*) (Pet. at 49-50 (emphasis added).)

Ipsen completely ignored this point in its DDB, and because Ipsen misled the Examiner in allowing the claims based on an erroneous claim construction, this too constituted material error that precludes discretionary denial. *See Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (“material error may include misapprehending or overlooking specific teachings of the relevant prior art”); *Samsung*, IPR2023-01070, Paper 9 at 66 (declining discretionary denial because “Examiner was misled” by patent owner “and misapprehended” the prior art).

In addition, and to the extent Ipsen attempts to improperly read limitations from the specification into the claims (DDB at 28-29), this is improper. While claims must be read in view of the specification, the Federal Circuit has long cautioned against “reading a limitation from the specification into the claim” absent some express disavowal or lexicography. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1323 (Fed. Cir. 2005) (*en banc*). The ’552 Patent claims a “method of treating” pancreatic

cancer consisting of administering particular drugs at claimed doses “to treat” the cancer. (*See* Ex. 1001, Claims 1-15.) The word “efficacy” or any derivative thereof does not appear once in any claim (*see id.*), and Ipsen does not cite any evidence showing it disavowed claim scope or acted as a lexicographer (DDB at 28-29). Thus, the claims cover any treatment, whether efficacious or not.

Accordingly, Ipsen’s arguments during prosecution that the claims were not obvious because there was no showing of an “effective” treatment were misleading. (*See* Pet. at 27-30, 35, 49-50 (citing, among other references, Ex. 1002 at ¶¶ 49-60).)

E. Ipsen Also Misled the Office Regarding the Unexpected Results of the Claimed Invention.

The Petition has properly and reasonably shown how Ipsen’s unexpected results argument misled the Examiner. The Petition addresses why Ipsen’s purported unexpected results arguments related to *both* tolerability and efficacy based on, Wainberg⁵ were misleading and led to Examiner error. (*See* Pet. at 50-52 (further

⁵ Contrary to Ipsen’s arguments, (DDB at 27-28), Petitioner does not contend it was error to consider post-filing evidence. Rather, as explained herein and in the Petition, Wainberg does not suggest to a POSA that the Challenged Claims exhibited unexpected results, at least because the improvements were not substantial and

explaining error is especially true in view of other post-filing references—Nichetti and Nevala-Plegamm—that demonstrate that there was no substantial differences or any alleged improvement between the Challenged Claims and these other well-known treatments).)

As an initial matter, and contrary to Ipsen’s arguments (DDB at 24), Petitioner addressed why Ipsen’s prosecution arguments related to both tolerability and efficacy were defective. (*See, e.g.*, Pet. at 33-34 (arguing the Examiner was likely persuaded by prosecution arguments related to Wainberg that the claimed treatment had “better tolerability” that “resulted in superior efficacy” over FOLFIRINOX).)

For instance, with regard to tolerability, the Petition states:

Patent Owner’s unexpected results argument is defective because rather than being unexpected, the POSA would have *fully expected* that administering a *lower dose* of oxaliplatin with liposomal irinotecan would result in *lower toxicity* because *it was commonly known that lower amounts of chemotherapy drugs correlate to fewer side effects*. (Pet. at 33 (emphasis added) (citing Ex. 1002 at ¶¶254-261); *see also* Pet. at 46-47 (citing Ex. 1002 at ¶¶69-72, 77-82 and explaining that dose reductions were routine practice and that a POSA would have found this to be a matter of routine

because Wainberg notes the inherent limitations in its study design, including issues with efficacy, prevent comparison. (*See, e.g.*, Section III.E.)

optimization and taught by the prior art).) These well-known and routine practices of a POSA are relevant to a finding of obviousness. *See, e.g., Regeneron Pharmaceuticals, Inc. v. Mylan Pharmaceuticals Inc.*, 714 F. Supp.3d 652, 775 (N.D. Va. 2024) (“[T]he Federal Circuit has held that ‘well-known, standard medical practices’ are obvious, especially as it relates to addressing patient responses such as side effects and outcomes.”), *citing Genentech, Inc. v. Sandoz Inc.*, 55 F.4th 1368, 1376-1378 (Fed. Cir. 2022) (in finding dosing claims obvious over the prior art, “varying doses in response to the occurrence of [patient response] would seem to be a well-established, hence obvious, practice. Thus, claiming it as an invention would appear to be at best a long shot.”).

While Ipsen concedes that the Petition argues that the Examiner erred in relying on arguments related to a purported superior efficacy, Ipsen incorrectly argues that its prosecution statements did not lead to Examiner error because the Examiner was “presumably” aware of the inherent limitations acknowledged by Wainberg. (*See* DDB at 25.) This argument fails. As explained *supra* III.B, the Board regularly declines to exercise discretionary denial where, as here, the Examiner was *misled* by Ipsen or otherwise potentially erred in appreciating references’ disclosures. *See Samsung*, IPR2023-01070, Paper 9 at 66 (declining discretionary denial and finding “Examiner was misled by [patent owner] and misapprehended

[the art]”); *Danisco*, 2019 WL 57777771, *8 (same); *Ellodi*, IPR2025-00056, Paper 10 at 15-17 (same); *Medtronic*, 2021 WL 3621948, *10-12 (same).

Here, it is highly likely that the Examiner was misled during prosecution by Ipsen’s arguments that the *prima facie* case of obviousness was rebutted by the purported unexpected results. Specifically, Ipsen argued during prosecution that it was surprising that the “claimed lower dose combination” “achieved unexpected therapeutic effects over that of the standard first-line FOLFIRINOX regimen in Conroy,” i.e., it achieved 12.6 months (NALIRIFOX) vs. 11.1 months (FOLFIRINOX) median overall survival (OS) along with better tolerability. (Ex. 1119 at 151-153 (citing Wainberg to further argue that the “primary efficacy outcomes [of Patent Owner’s regime] are each higher than those reported in Conroy for FOLFIRINOX”).) Ipsen touted Wainberg’s findings as “tangible benefits” of “improved efficacy” over the prior art. (*Id.* at 153.) Other than conclusory statements, Ipsen did not provide any support for its claim that the somewhat greater progression free survival and mean overall survival observed by Wainberg was a “significant efficacy improvement” or was otherwise unexpected. (*See id.*) After Ipsen made this argument, the Examiner, without any further analysis or explanation, issued a Notice of Allowance. (*See* Pet. at 13 (noting argument was made in the February 25, 2022 response and Notice of Allowance issued shortly thereafter).)

For at least the following reasons, Ipsen's arguments relating to unexpected results must fail and the Examiner's acceptance of these arguments was material error.

1. There is Substantial Evidence, Including Additional Post-Filing Evidence, That Demonstrates No Unexpected Superiority Over FOLFIRINOX.

The sole reference Ipsen relied upon to allege unexpected results, Wainberg, cautioned that the studied therapies "cannot be reliably compared" and "direct comparisons...cannot be made" due to "limitations inherent in Wainberg's study design," none of which was raised by Ipsen during prosecution. (Pet. at 34 (noting that Wainberg's noted limitations included issues with efficacy precision and hypothesizing).) After presented with this argument, the Examiner issued a Notice of Allowance that was silent as to Wainberg and thus, contrary to Ipsen's argument in its DDB, this indicates that the Examiner did not appreciate Wainberg's clear inherent limitations. *See Klein Tools*, IPR2024-01400, Paper 17 at 25-26 (finding material error where Examiner was silent as to reference and therefore any alleged understanding was not clear). Therefore, Petitioner has shown that it was material error for the Examiner to accept any unexpected results argument presented by Ipsen based on Wainberg.

In addition, the Petition showed that there is heightened evidence of Examiner error here because other post-filing references—Nichetti and Nevala-Plagemann

(Exs. 1010-1011)—refute any claim that the claim therapy has demonstrated “superior efficacy,” because these references suggest there is no benefit to the Challenged Claims. Specifically, Petitioner demonstrated how these publications suggested to a POSA that the claimed therapy (NALIRIFOX) exhibited “*identical*” or *worse* efficacy than FOLFIRINOX. (*See* Pet. at 34-35, 51-52 (citing Ex. 1002, ¶¶164-170, 258-262; Ex. 1010 at 1-10; Ex. 1011 at 1-2).)

Ipsen asserts that these references suffer from the same defects as Wainberg but fails to explain why any “limitations” or “critiques” in these references demand a different finding or impact the obvious analysis. (DDB at 25-26.) Rather, and as further explained in the Petition, Nichetti found there was “no difference observed” in overall survival between NALIRIFOX and FOLFIRINOX, and actually observed a lower overall survival in NALIRIFOX (11.1 months) vs FOLFIRINOX (11.7 months). (*See* Ex. 1002, ¶258 (citing Ex. 1010 at 1, 5).) Nevala-Plagemann concluded that the difference in treatment outcome between NALIRIFOX and FOLFIRINOX was “not clinically [or] statistically significant” and thus “NALIRIFOX does not seem to raise the bar, but rather exposes patients and health-care systems to financial toxicities.” (*Id.* at ¶259 (citing Ex. 1011 at 1-2 (further noting that the toxicity differences observed were “clinically insignificant”).)

Ipsen attempts in its DDB to undercut the significance of the Petition’s discussion of Nichetti and Nevala-Plagemann by relying on Skorupan (Ex. 2033),

which Ipsen alleges confirms Wainberg’s suggestion that the Challenged Claims (as shown in NALIRIFOX) provided superior efficacy over the FOLFIRINOX prior art. (DDB at 26-27.) However, rather than show alleged clinical superiority of NALIRIFOX over the prior art FOLFIRINOX, Skorupan actually acknowledges that NALIRIFOX is “more costly than FOLFIRINOX and the *relative efficacy* of NALIRIFOX versus FOLFIRINOX or modified FOLFIRINOX (mFFX) has *yet to be explored...*” and that a head-to-head study *could* address whether there is sufficient improvement in benefit to justify the cost difference.” (Ex. 2033 at 1, 3 (emphasis added).) Skorupan further states that “differences in study population contributed to the disparate efficacy results” of the observed outcomes. (*Id.* at 3.) Thus, Ipsen’s reliance of Skorupan only magnifies the inherent limitations of Wainberg and endorses the Petition’s explanation through references like Nichetti and Nevala-Plagemann that Ipsen’s unexpected results arguments during prosecution were defective and resulted in material error that affected the patentability of the Challenged Claims. (*See also* Ex. 1200 at ¶ 8.)

Notably, even more recent publications—published after the filing of the Petition—further demonstrate the lack of unexpected results and the growing consensus that NALIRIFOX offers no advantage over FOLFIRINOX.

For instance, the National Comprehensive Cancer Network (NCCN) released their Clinical Practice Guidelines in Oncology for Pancreatic Adenocarcinoma⁶ on February 3, 2025, which consistently identifies FOLFIRINOX, but not NALIRIFOX as a preferred treatment for various pancreatic cancers. (Ex. 1206 at 45-55 (identifying FOLFIRINOX and Gemcitabine as the preferred treatment for multiple therapies.) In fact, the NCCN identifies NALIRIFOX as an option (and only the third option) for only “Locally Advanced Disease (First-Line Therapy)” and “Metastatic Disease (First-Line Therapy)” but only for certain patients. (*Id.* at 47, 49.) And in both cases, the NCCN notes that “[w]hile NCCN recognizes that there is high-level evidence supporting the use of NALIRIFOX over gemcitabine and albumin-bound

⁶ The NCCN Clinical Practice Guidelines in Oncology are the “recognized standard for clinical direction and policy in cancer care and are the most thorough and frequently updated clinical practice guidelines available in any area of medicine,” which “document evidence-based, consensus-driven management to ensure that all patients receive preventative, diagnostic treatment, and supportive services that are most likely to lead to optimal outcomes.” (See <https://www.nccn.org/guidelines/guidelines-process/about-nccn-clinical-practice-guidelines#:~:text=The%20NCCN%20Clinical%20Practice%20Guidelines,to%20lead%20to%20optimal%20outcomes.>)

paclitaxel, it should be recognized that this regimen ***does not appear to have an advantage over FOLFIRINOX*** and adds considerably more expense compared to FOLFIRINOX.” (*Id.*; *see also id.* at 87 (stating same).)

In addition, Ipsen’s recently released information about the long-term follow-up to their NALIRIFOX study only serves to further show the obviousness of the challenged claims and the lack of unexpected results. Specifically, the study found that to optimize long term survival, the dosages in the Challenged Claims ***needed to be further reduced***, which as explained by Petitioner is a common and familiar practice and taught by the asserted art. (*See* Ex. 1207 at 1 (stating that “[d]ose adjustments (dose reductions and dose delays) occurred in a higher proportion of patients presenting with longer OS [overall survival]”); Ex. 1201 at 1 (stating that “[l]iposomal irinotecan and oxaliplatin dose reductions were experienced by 66.7% and 80.0% of long-term survivors, respectively, and dose delays by 86.7% and 80.0% respectively”); Ex. 1202 (showing same); *see also* Pet. at 16, 41-44, 47-48, 50-51; Ex. 1002 at ¶¶ 69-82 (explaining dose reductions were and are routine practice and would render claims obvious).) This evidence suggests what was already known to a POSA, i.e., that reducing dosages of these chemotherapy drugs would result in increased tolerability. (*See* Ex. 1002 at ¶¶ 69-82; Ex. 1200 at ¶¶ 2-7.) In addition, the data does not suggest NALIRIFOX had better efficacy for long-term survival. (*See* Ex. 1200 ¶ 7 (citing Ex. 1203 and noting a greater percentage of

FOLFIRINOX patients experienced long-term survival).) Therefore, these publications demonstrate that dosages *other than those claimed* are critical for optimizing the use of liposomal irinotecan.

2. The Examiner Erred and Any Unexpected Results Arguments Fails Because There Has Been No Showing of a Difference in Kind.

The Examiner erred by not requiring an unexpected difference in kind as compared to the closest prior art. “When assessing unexpected properties [the Examiner was required to] evaluate the significance and ‘kind’ of expected results along with the unexpected results.” *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014). “While a ‘marked superiority’ in an expected property may be enough in some circumstances to render a compound patentable, a ‘mere difference in degree’ is insufficient.” *Id.* In addition, “‘differences in degree’ of a known and expected property are not as persuasive in rebutting obviousness as differences in ‘kind’—i.e., a new property *dissimilar to the known property*.” *Id.* (emphasis added).

Here, the prior art clearly taught that liposomal irinotecan, oxaliplatin, leucovorin, and 5-FU were all known to and used by POSAs to treat pancreatic cancer. (*See, e.g.*, Pet. at 7-9 (citing, among other references, Ex. 1002, ¶¶ 63-66, 83-91, 95-98, 120-122, 139, 147-156; Exs. 1003, 1005, and 1006 (treatments that used said drugs).) A POSA would have known that these drugs, alone or in combination,

can be used to treat pancreatic cancer. (*See, e.g.*, Pet. at 17-18 (describing use of these drugs “alone or in combination” to treat pancreatic cancer); 21-22 (same).) Thus, and even setting aside the evidence contradicting Ipsen’s claims, there has been no showing that any alleged improvement(s) identified by Ipsen during prosecution are “markedly superior.”

Indeed, as Dr. Ratain stated, a POSA would appreciate that the study differences and cautionary statements made by Wainberg suggest that any differences in results may be due more to chance than any property of the Challenged Claims. (Pet. at 51; Ex. 1002 at ¶ 257.) Even when evidence shows a drug is “more potent,” “stronger,” or has “superior efficacy”, this will, without more, be insufficient to overcome a *prima facie* showing of obviousness unless there is a showing that such an improvement is significant. *See Teva Pharms.*, 752 F.3d at 977 (collecting cases and holding that a claim may still be obvious “even if the level of success may have turned out to be somewhat greater than would have been expected”); *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (holding “[m]ere improvement in properties does not always suffice to show unexpected results” and further stating that unexpected results may be found upon a demonstration of “**substantially** improved results” but only “in the absence of evidence to the contrary”). Because Ipsen did not make a showing of “substantial” improvement and because Petitioner has established that evidence contradicts the alleged

improvements, Petitioner has reasonably established that the Examiner likely erred in granting the Challenged Claims.

Accordingly, not only were Nichetti and Nevala not before the Examiner, Petitioner has also identified multiple examples where either Ipsen misled the Examiner or the Examiner erred, all of which warrants reconsideration of the patentability of the Challenged Claims under prong two of *Advanced Bionics*.

F. Ipsen’s Criticisms of the Obviousness Arguments of Petitioner and Its Expert Dr. Ratain Backfire.

Ipsen’s criticisms that Petitioner and its expert have presented flawed obviousness arguments are without merit. As an initial matter, seminal patent law requires the evaluation of the prior art from the perspective of a POSA. *See, e.g., Phillips*, 415 F.3d at 1318 (stating expert testimony can be useful to ensure technical understandings are viewed consistently with that of a POSA); *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 420, 426 (2007) (confirming obviousness is viewed through the lens of a POSA and that expert analysis that aids in the resolution of questions of fact “can and should” be taken into account.) By contrast, “[a]ttorney argument is not evidence” and it would be improper for the Board to adopt such arguments provided without the requisite explanation. *Icon Health*, 849 F.3d at 1043.

Here, and as also described herein, the Petition identified multiple errors made by the Examiner during prosecution as well as multiple strong challenges to

patentability. (*See* Pet. at 13-14, 32-35, 45-46, 49-52 (identifying errors made during prosecution); *see also* Pet. at 39-57 (providing arguments and support for Ground 1 obviousness challenge), 58-60 (providing arguments and support for Ground 2 obviousness challenge), 60-64 (providing arguments and support for Ground 3 obviousness challenge).) As more fulsomely explained in Petitioner's challenges, Conroy's disclosure of FOLFIRINOX was a well-known treatment for pancreatic cancer that had known toxicity concerns and many modified versions of the regimen were being pursued. The prior art showed that a reduction of FOLFIRINOX's oxaliplatin dose to the claimed 60 mg/m² was already known and practiced, and suggested that it was "logical" to "replac[e] irinotecan in FOLFIRINOX with [liposomal irinotecan]." (*See id.* at 32.) This evidence, along with Petitioner's other arguments, present multiple compelling grounds supporting the obviousness of the Challenged Claims.

In addition, and pursuant to this standard and 37 CFR § 42.65, Dr. Ratain provides the perspective of a POSA with testimony supported by the disclosure of the asserted references and other evidence. (*See generally* Ex. 1002.) There is no suggestion that Petitioner's reliance on expert testimony is overly extensive and, because Ipsen does not provide any expert testimony, there is no reasonable dispute between experts on dispositive issues. (*See* USPTO FAQs for Interim Processes for

PTAB Workload Management⁷.) Instead, Ipsen’s limited critiques are that Petitioner and Ratain (1) ignored “the full scope of the prior art” including irrelevant non-chemotherapy art and (2) misunderstood Conroy’s disclosure. Both critiques are without merit.

1. Ipsen Wrongly Claims a POSA Would Disregard the Closest Prior Art Involving Chemotherapy Drugs in Favor of Non-Chemotherapy Treatments, Like Radiation.

Ipsen alleges impermissible hindsight, (*see* DDB at 29), but does not point to any reliance by Petitioner or Dr. Ratain “upon information that could have been gleaned only from the disclosures of the [’552] Patent.” *See Prollenium Us Inc. v. Allergan Industrie, Sas*, IPR2020-00902, Paper 18 at 63 (PTAB Dec. 9, 2020) (finding allegations of impermissible hindsight insufficient and instituting IPR).

Instead, Ipsen proffers a wholly unsupported and misleading argument that a POSA, aware of the limitations of chemotherapy—including FOLFIRINOX, would have abandoned the pursuit of systemic chemotherapy for “non-chemotherapy options” such as “radiation therapy” and immune mediated genetic therapies. (DDB at 29-30.) Ipsen continues by arguing “the low success rate of new treatments for

⁷USPTO FAQs for Interim Processes for PTAB Workload Management (<https://www.uspto.gov/patents/ptab/faqs/interim-processes-workload-management>)

metastatic pancreatic cancer undermines *any reasonable expectation of success.*”

(*Id.* at 30.) The premise of Ipsen’s argument is inherently flawed.

When the prior art suggests one approach is or may be effective, it is not impermissible hindsight to base an unpatentability argument on this approach. *See, e.g., Mylan Pharmaceuticals Inc. v. Janssen Oncology, Inc.*, IPR2016-01332, Paper 84 at 30-31 (PTAB Jan. 17, 2018) (finding allegations of hindsight bias unpersuasive where at least “some research” was focused on the claimed cancer treatment and thus petitioner’s “reasoning incorporates and relies on the knowledge of a [POSA].”) Indeed, the “‘proper question’ is not ‘whether a [POSA] writing on a blank slate’ would necessarily have chosen [to pursue systemic chemotherapy, let alone FOLFIRINOX] over another medium for further development, but whether he or she ‘would have seen a benefit’ to modifying the teachings of [the asserted art] to achieve the claimed [invention].” *Janssen Biotech Inc. v. Celltrion Healthcare Co.*, No. CV 17-11008-MLW, 2018 WL 10910845, *14 (D. Mass. July 30, 2018) (quoting *KSR*, 550 U.S. at 424). “[I]t is not impermissible use of hindsight to analyze the differences between the claimed composition and a composition in the prior art that was directed to the same problem.” *Id.*

Here, there is no dispute that the asserted prior art is in the same field and reasonable pertinent to the same problem sought to be solved by Ipsen. The evidence also suggests that multiple attempts to modify FOLFIRINOX were being undertaken

at the time. (See Pet. at 46-47; Ex. 1002 at ¶¶ 68-76 (stating modifications to FOLFIRINOX and other chemotherapy drugs were routine practice and identifying other examples pursued around the time of the alleged invention, including FOLFOX and FOLFIRI); see also Pet. at 2-3, 32-33, 42-47, 61 (discussing motivations to combine art).) Thus, it is clear that POSAs saw unmistakable benefits in continuing to modify or optimize these pancreatic cancer treatments. By contrast, Ipsen does not identify any rationale to forego these proven chemotherapy regimens in place of other less established therapies never even discussed during prosecution, such as Ipsen's reliance in its DDB on "radiation" or "personalized treatment options." (See DDB at 29-30.)

Ipsen's reliance on *OSI Pharmaceuticals, LLC v. Apotex, Inc.* is misplaced. There, the challenged claims required the use of erlotinib to treat non-small cell lung cancer ("NSCLC") and the two obvious challenges were based on a primary reference—that disclosed over a hundred example compounds to treat no fewer than a dozen different tumors—and one of two other references; but none of the references disclosed erlotinib's effect on NSCLC. *OSI Pharmaceuticals, LLC v. Apotex, Inc.*, 939 F.3d 1375, 1379, 1384-85 (Fed. Cir. 2019). Petitioner's claim that there was a reasonable expectation of success was called into question because nothing in the prior art suggested that erlotinib would have any efficacy in treating NSCLC, a finding supported by evidence that from 1990 to 2005 less than 0.5% of

new drug compounds being developed passed Phase II trials (with presumably even less passing Phase III). *Id.* at 1384-85. However, the court was quick to note that their decision does not mean efficacy data is always required for a reasonable expectation of success and there is no requirement of absolute predictability. *Id.* at 1385 (noting its finding was limited to the facts of that case). *See also* Pet. at 48-49 (Petition’s discussion distinguishing *OSI* from Patent Owner’s arguments of this case during prosecution).

By contrast here, all of the compounds in the prior art had been used to effectively treat metastatic adenocarcinoma of the pancreas at the claimed dosages. (*See, e.g.*, Ex. 1002 at ¶¶ 65-66, 88, 105, 110, 117-119, 130.)

2. Ipsen Misreads the Median Dose Intensity Data of Conroy to Arrive at Its Faulty Conclusions.

Ipsen takes Dr. Ratain’s opinions out of context to falsely claim that Conroy discloses using 66.3 mg/m² of oxaliplatin instead of the claimed 60 mg/m². (DDB at 32-33.) As Dr. Ratain further explains, “[b]ecause these [median relative] doses represents the doses received by the typical patient, a POSA would understand that some patients received more than, while other patients received less than, the identified median relative dose” and thus would “suggest to a POSA that a typical patient received a dose equivalence of less than the prescribed” amount. (*See* Ex. 1002 at ¶ 97; Ex. 1200 at ¶ 9.) The median relative dose does not suggest that any

one patient actually received the exact percentage of the prescribed dose identified. (Ex. 1200 at ¶ 9.) Indeed, Dr. Ratain explains, that the “Conroy Protocol discloses that the oxaliplatin dose should be reduced from 85 mg/m² to 60 mg/m² based on various known toxicities,” which is “consistent with the disclosure in Conroy that the median dose intensity of oxaliplatin was 78% of the standard 85 mg/m² dose and indicate that a significant portion of the patients undergoing the FOLFIRINOX trial were reduced to 60 mg/m² based on various events.” (*Id.*; Ex. 1002 at ¶¶105-106 (citing Ex. 1004 at 16-18; Ex. 1017 at 3-7).) Said another way, the Conroy Protocol (and Conroy Appendix) show what the oxaliplatin dose was reduced to, i.e., 60 mg/m², and enough patients received this reduced dose to bring the median relative dose down to 78% of 85 mg/m² so that the median dose received by all patients was 66.3 mg/m². (*See* Ex. 1200 at ¶ 9.)

G. Ipsen’s Research and Development Investment Are Not the “Settled Expectation of the Parties” Contemplated by the Director’s Memo.

The “settled expectations of the parties, such as the length of time the claims have been in force,” is a factor to be considered for discretionary denial.⁸ Ipsen does not address the pendency of the Challenged Claims or what Petitioner’s expectations

⁸<https://www.uspto.gov/sites/default/files/documents/InterimProcesses-PTABWorkloadMgmt-20250326.pdf>

were or are. (*See generally* DDB.) Instead, Ipsen speciously asserts that it, alone, “has a settled expectation with regard to its investment and effort” in developing cancer treatment options. (*Id.* at 34-35.) The sole expectation of Ipsen (regardless of what they are) is not the “settled expectation of the *parties*,” i.e., the Director did not state the “settled expectation of patent owner” should be considered. When properly analyzed, this factor weighs in favor of institution.

The '552 Patent issued less than three years prior to the filing of the Petition. (*See* Ex. 1001.) Considering IPRs may not even be brought for the first nine months following issuance (35 U.S.C. § 311(c)(1)), an insignificant amount of time has passed. Petitioner did not delay in filing its Petition but rather challenged the claims while the patent was in its infancy and before any expectations could become “settled.” Further, and contrary to Ipsen’s self-serving expectation, there is no guaranteed right to a patent for performing clinical research. There is no expectation, especially for relatively new patents like the '552 Patent, against a patent challenge. Moreover, even if the Challenged Claims are found unpatentable, Ipsen still has an FDA approved drug that it can still sell such that its expectation regarding its return on investment remains. Thus, Ipsen has not shown that Petitioner’s IPR challenge precludes Ipsen’s ability to recoup its alleged financial expectations.

Finally, Ipsen tries to argue under “settled expectations” that the grim prognosis and low survivability of metastatic pancreatic cancer favors discretionary

denial. No – just the opposite is true. The dire health crisis facing these patients and the medical community would have strongly motivated POSAs to arrive at obvious methods of treatment based on well-known options. As Dr. Ratain explained, based on pancreatic cancer’s “devastating diagnosis,” the prior art was forced to develop several combination therapies, including FOLFIRINOX, which used different combinations of the claimed compounds of the Challenged Claims, including liposomal irinotecan, 5-FU, leucovorin and oxaliplatin. (*See* Ex. 1002 at ¶¶ 62- 82.) The flexible approach to determining obviousness under *KSR* includes considering “any need or problem known in the field of endeavor at the time of invention and addressed by the patent” that “can provide a reason for combining the elements in the manner claimed.” *KSR*, 550 U.S. at 419. Subsequent courts have recognized that, just as with market forces and design incentives, medical needs also can motivate POSAs to combine known elements to arrive at obvious inventions. For example, in *Regeneron Pharmaceuticals*, the Court found that there was market pressure dictated by medical necessity to employ extended dosing regimens which led to the finding of obviousness of the dosing regimen claims. 714 F. Supp.3d at 769; *see also Adapt Pharma Operations Limited v. Teva Pharmaceuticals USA, Inc.*, 25 F.4th 1354, 1366 (Fed. Cir. 2022) (known drawbacks of existing medical kits for administering naloxone based on warnings from FDA provided the requisite motivation to render the method of treatment patent invalid for obviousness); *Skedco, Inc. v. Strategic*

Operations, Inc., 287 F. Supp.3d 1100, 1138 (D. Or. 2018) (“A reasonable juror could determine that at the time of the invention, a POSA would have been motivated to make this combination by a desire to improve similar devices to satisfy the design and market need for more realistic, durable, cost effective trauma training devices which could be used in the field for mass casualty live training simulations.”).

Applied here, rather than dissuade POSAs, the grim prognosis of metastatic pancreatic cancer patients would have provided extra motivation for POSAs to arrive at the Challenged Claims based on well-known methods since they were faced with urgent medical needs.

H. Compelling Economic and Public Health Interests Favor Institution.

Failure to consider the merits of the Petition would run counter to compelling economic and public health interests. As discussed *supra*, the NCCN has noted that “it should be recognized that [the NALIRIFOX] regimen *does not appear to have an advantage* over FOLFIRINOX and adds *considerably more expense compared to FOLFIRINOX.*” (Ex. 1206 at 47, 49) (emphasis added). Allowing Ipsen to maintain its improper patent on this obvious treatment will mean patients will continue to be subjected to “considerably more expense” over other treatments. However, a determination that these claims are invalid would allow would-be competitors to produce similar drugs. The public has a compelling economic and

health interest in reducing the cost of prescription drugs and thus a strong interest in the Board's review of Petitioner's arguments.

I. Other Considerations Bearing on the Director's Discretion Warrant Institution.

“[T]he Board should consider a petitioner's argument based on the volume of references submitted to the Office during examination and any applicant information or assistance regarding the relevance of references.” *Ecto World, LLC et al. v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 6-7 (PTAB May 19, 2025) (designated precedential and holding fact that patent owner submitted “over 1,000 references, which is over 40 times the size of a typical IDS” may demonstrate denial under § 325(d) is not warranted). As explained *supra* and in the Petition, the Examiner of the '552 Patent did not appreciate the relevance of all art cited during prosecution, which is not surprising given that Ipsen inundated the Examiner with an enormous amount of prior art – *over 1400 references* spread throughout multiple IDSs. As this Board has long held, “to inundate the Examiner with a large volume of prior art [] may obscure a single reference that is material and thus may be effectively as improper as withholding a material reference.” *Ex Parte Morning Surf Corp.*, 230 U.S.P.Q. (BNA) ¶ 446 (B.P.A.I. Feb. 28, 1986).

During prosecution, Ipsen submitted twenty (20) Information Disclosure Statements that included well over a thousand references. (*See generally* Exs. 1084-

1123 (the '552 File History).) In fact, the '552 Patent cites on its face 1,341 different references. (*See* Ex. 1001 (citing 88 patents and 1,253 non-patent literature publications).) With the sole exception of Bayever and Conroy, none of the asserted art cited in the Petition was discussed during prosecution even though material to patentability.

The Board's decision declining to exercise its discretion to deny institution under § 325(d) in *Fellowes, Inc. v. Treefrog Devs., Inc.*, is particularly instructive. There, the petitioner's cited art relied on a reference disclosed during prosecution. IPR2020-01435, 2021 WL 707179, at *7-8 (PTAB Feb. 22, 2021). However, the Board found the petitioner "demonstrate[d] that the Examiner erred by overlooking, or failing to appreciate, the materiality" of the prior art because the "Examiner was inundated with" "an enormous amount of prior art" and the asserted art (1) disclosed the purportedly missing element and (2) was not "expressly used by the Examiner as the basis for a rejection." *Id.* The Board held this "suggests [the art] was not sufficiently considered during examination of the claims" and "provides persuasive evidence of Examiner error." *Id.* (declining to review error as to other art as moot).

As explained above, while Ko, an untranslated Conroy Protocol, Mahaseth, and Cantore were disclosed in IDSs as part of the mountain of evidence submitted by Ipsen during prosecution, the Petition shows that the Examiner committed material error for failing to recognize their significance by allowing the Challenged

Claims. (*See supra* n.2 (discussing Mahaseth's suggestion to remove bolus); III.A (discussing disclosures of using 60 mg/m² doses of oxaliplatin in Conroy Protocol and Cantore); III.C (discussing Ko's suggestions/motivations).) In addition, other asserted art, including at least the Conroy Appendix and Saif, were never even disclosed in an IDS or much less considered by the Examiner, thus further compelling rejection of Ipsen's discretionary denial request.

Because the Examiner erred by failing to appreciate the materiality of the disclosures in references actually submitted during prosecution and Petitioner has identified other references never before the Examiner, the Board should decline to exercise its discretion to deny institution.

IV. CONCLUSION

Based on the foregoing, the Board should decline to exercise discretionary denial under § 325(d).

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioners' Response to Patent Owner's Request for Discretionary Denial of Institution contains, as measured by the word-processing system used to prepare this paper, 13,391 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting towards the word limit.

Dated: June 23, 2025

By: /s/ Lukas Toft

Lukas Toft

Reg. No. 75,311

Counsel for Petitioners

CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e), I hereby certify that on June 23, 2025, I caused a true and correct copy of the foregoing Petitioners' Response to Patent Owner's Request for Discretionary Denial of Institution to be served by electronic mail, as authorized by Patent Owner, at the following email addresses:

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