

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

IPSEN BIOPHARM LTD.,
Patent Owner.

Case No. IPR2025-00505¹
U.S. Patent No. 11,344,552

PATENT OWNER'S SUR-REPLY

¹ Apotex Inc., which filed a petition in IPR2025-01531, has been joined as a petitioner in this proceeding.

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I. Introduction

CSPC's reply affirms that its obviousness challenge is without merit. CSPC does not allege obviousness on the basis of one, two, or even three differences between its lead prior-art reference and the '552 patent's claimed invention. CSPC argues that it would have been obvious to make *four simultaneous changes* to FOLFIRINOX, a prior-art chemotherapy regimen that was a prevailing standard of care at the time of invention. Neither in its petition nor its reply does CSPC or its expert explain why a POSA would have been motivated to make *all four of those changes at once*. And such showing is necessary, because all four of those changes are necessary in order to arrive at the '552 patent's claimed invention. CSPC's challenge fails for this reason alone.

CSPC incorrectly suggests that the Board's institution decision "rejected" or otherwise excused CSPC's burden to show requisite motivation. *See* Paper 32 at 4. The Board instituted this proceeding on the record before it, which included declarations² from CSPC's expert Dr. Ratain and no expert testimony from Ipsen's expert, Dr. Oberstein. Critically, the Board's institution decision adopted a construction of "treatment" that Dr. Ratain's declarations do not address. Since institution, CSPC has *not* offered any opinions from Dr. Ratain—either (a) on

² *See* Ex. 1002 (Expert Declaration of Mark J. Ratain, MD), filed in support of CSPC's petition; Ex. 1200 (Supplemental Expert Declaration of Mark J. Ratain, MD), filed in support of CSPC's opposition to Ipsen's discretionary denial brief.

alleged obviousness under the Board’s construction of “treatment” or (b) in rebuttal to opinions offered by Ipsen’s expert Dr. Oberstein. Dr. Oberstein’s opinions of non-obviousness are *unrebutted* by any expert testimony. CSPC’s arguments should be rejected for a failure of proof.

The *unrebutted* expert testimony of Dr. Oberstein establishes—contrary to CSPC’s assertion—there was no “clear roadmap” for a POSA to arrive at the claimed methods, nor would a POSA have been motivated to do so. As Dr. Oberstein opined, a POSA would have been cautious in modifying FOLFIRINOX at all, let alone in the four specific and simultaneous ways CSPC urges, to arrive at the invention. Rather, as Dr. Oberstein opined, a POSA would have been motivated to administer the maximum tolerated dose in treating a patient with metastatic pancreatic cancer, and not—as CSPC argues would have been obvious—undertake multiple dose reductions and replace one drug with a new drug, in a new dose. These opinions directly contradict CSPC’s obviousness theory, and CSPC has offered *no* expert testimony in rebuttal.

Rather than engage with the substance of Dr. Oberstein’s opinions, CSPC instead resorts to baseless accusations of bias through attorney argument. These accusations have no merit. The Board should affirm patentability of the challenged claims.

II. Argument

A. CSPC's Failure to Offer Rebuttal Expert Testimony Exposes Deficiencies in Its Obviousness Challenge

CSPC's Petition relies on the expert declaration of Dr. Ratain (Ex. 1002).

Dr. Ratain's opinions of obviousness assume two alternative constructions of the claim term "treatment": either (1) that "treatment" requires no actual therapeutic efficacy—only administration of the recited regimen with the intent to cause therapeutic improvement—or (2) that, if "treatment" were construed to require clinical efficacy, the '552 patent's claims could not find support in the priority applications. *See* Paper 1 at 26-30, 36-39; Ex. 1002 at ¶¶ 49-50, 216-26. CSPC also filed a supplemental declaration from Dr. Ratain (Ex. 1200), ostensibly in support of its opposition to Patent Owner's request for discretionary denial of institution. *See* Paper 10.

Subsequently, the Board issued its Institution Decision (Paper 13) adopting neither construction advanced by CSPC and Dr. Ratain. Instead, the Board construed "treatment" to require "more than a *de minimis* therapeutic benefit or efficacy for the patient being treated." Paper 13 at 13-14. Ipsen thereafter filed its Patent Owner's Response (Paper 21), supported by the Declaration of Dr. Paul Oberstein (Ex. 2076). Dr. Oberstein expressly adopted the Board's construction of

“treatment” and rendered his opinions on non-obviousness under that construction. *See* Ex. 2076 at ¶¶ 135-36.

CSPC then filed its Reply (Paper 32) *without* any supporting expert declaration. As a result, CSPC has *not* offered any expert testimony on obviousness under the Board’s construction of “treatment.” Dr. Ratain has *not* offered any opinions in rebuttal to Dr. Oberstein’s opinions on non-obviousness. Key among Dr. Oberstein’s *unrebutted* opinions, applying the Board’s claim construction, are: (1) a POSA’s interpretation of CSPC’s asserted references, including the Conroy references, Bayever, Saif, and Ko; (2) a POSA’s understanding of the significance of a starting dose; (3) a POSA’s motivation to use the maximum tolerated dose; (4) a POSA’s motivation to balance efficacy with tolerability; and (5) unexpected results of the claimed treatment methods. For reasons discussed *infra*, the expert testimony of record supports only a conclusion of non-obviousness.

B. CSPC Fails to Establish Motivation to Arrive at the Claimed Invention

1. CSPC’s Motivation-to-Combine Argument Is Legally Deficient

In order to prevail, CSPC must show that a POSA would have been motivated to arrive at *the claimed invention*. *See KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (“[I]t can be important to identify a reason that would

have prompted a [POSA] to combine the elements *in the way the claimed new invention does.*” (emphasis added)); *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 141 F.4th 1367, 1379 (Fed. Cir. 2025) (“It is bedrock law that the inquiry of motivation and reasonable expectation of success *must focus on arriving at the claimed invention.*” (emphasis added)).

Indeed, the CAFC has reversed determinations of obviousness where, as here, the record evidence does not support motivation to arrive at the specifically claimed invention. *See, e.g., In re NuVasive, Inc.*, 842 F.3d 1376, 1382-84 (Fed. Cir. 2016) (vacating an obviousness determination rendered without “an explanation-supported finding that the evidence affirmatively proved” a POSA’s motivation to place—as claimed—“radiopaque markers along the medial plane” of an implant). In *Virtek Vision*, the CAFC similarly found the PTAB’s motivation-to-combine analysis deficient, where it was only asserted that “two coordinate systems were disclosed in a prior art reference and were therefore ‘known.’” *See Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 887-88 (Fed. Cir. 2024) (“It does not suffice to simply be known. A reason for combining must exist.”).

There is no dispute that, in order to arrive at the claimed invention here, a POSA would have had to be motivated to make four specific changes to FOLFIRINOX, all at once. A POSA would have had to be motivated to: (1)

decrease the starting dose of oxaliplatin from 85 mg/m² to 60 mg/m²; (2) remove the 400 mg/m² 5-fluorouracil (5-FU) bolus; (3) substitute free irinotecan with liposomal irinotecan; and (4) administer the liposomal irinotecan at a dose of 60 mg/m². *See* Ex. 2076 at ¶ 230; Paper 32 at 4 (CSPC reciting the same four modifications). All told, these changes entail dose reduction of two drugs (oxaliplatin and 5-FU), removal of one drug (free irinotecan), and the introduction of an entirely new drug (liposomal irinotecan) in a new dose (60 mg/m²).

CSPC does not articulate a POSA's motivation to make all changes necessary to arrive at the '552 patent's claimed invention. Instead, CSPC argues that the Board "recognized that all of these changes were disclosed by making just the *single* prior art combination of Conroy (and its Protocol) with Bayever."³ Paper 32 at 4 (emphasis in original). As an initial matter, the Board's decision did not rest on a "single prior art combination" of Conroy, its Protocol, and Bayever. *See, e.g.*, Paper 13 at 37 (citing Dr. Ratain's declaration), 38 (citing Mahaseth, Saif, and Ko). Regardless, a "single" prior art combination may still fail to establish requisite motivation. *See, e.g., Virtek Vision*, 97 F.4th at 887-88

³ CSPC has offered no librarian declaration to support public accessibility of any of its prior art references. For example, the Conroy Protocol was not available in May 2011 when Conroy was first published according to the Wayback Machine. *See* <https://web.archive.org/web/20110513191548/https://www.nejm.org/doi/full/10.1056/NEJMoa1011923> (last visited Mar. 25, 2026).

(reversing PTAB finding of obviousness based on a combination of two prior art references); *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382-83 (Fed. Cir. 2019) (same).

Even CSPC’s alleged “single” combination of Conroy and Bayever does not motivate the claimed invention, at least because they provide contradictory teachings. Conroy and Bayever provide conflicting guidance on the 5-FU bolus: Conroy teaches a 400 mg/m² 5-FU bolus as a component of FOLFIRINOX, while Bayever—CSPC’s principal reference for liposomal irinotecan—does not include a 5-FU bolus at all. *See* Ex. 1003 at 3; Ex. 1006 at 4-5. CSPC does not reconcile this conflict. Indeed, it is only by using the ’552 patent’s claimed regimen as a guide—and working backwards—that one may arrive at the conclusion that the 5-FU bolus should be removed. *See* Ex. 2073 at 27:6-13 (Dr. Ratain admitting he chose FOLFIRINOX as his starting point of his obviousness analysis because of its “similarity” to the ’552 patent claims). That is precisely the kind of hindsight reasoning the obviousness inquiry is designed to prevent.

CSPC’s invocation of the “flexible” *KSR* standard does not cure its deficient motivation-to-combine argument. While CSPC correctly notes that “[a] POSA can be motivated to do more than one thing,” Paper 32 at 5 (quoting *Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 930 (Fed. Cir. 2024)), a determination of obviousness still depends on evidence of motivation to do all of

the “things” necessary to arrive at the claimed invention. CSPC has not provided—and Dr. Ratain has not offered—any explanation of why a POSA would have been motivated to make all four modifications to FOLFIRINOX at once, as opposed to fewer or different modifications.

2. CSPC’s Cited Cases Are Inapposite

Rather than explain why a POSA would have been motivated to make the allegedly obvious FOLFIRINOX modifications, CSPC attempts to analogize this case to cases involving two-component chemotherapies. *See* Paper 32 at 6-7 (citing *Genome & Co. v. Univ. of Chi.*, PGR2019-00002, Paper 40 at 44 (PTAB Apr. 14, 2020); *Pfizer, Inc. v. Biogen, Inc.*, IPR2017-01168, Paper 59 at 23 (PTAB Oct. 31, 2018); and *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper 60 at 55 (PTAB Oct. 4, 2018)). CSPC’s attempted analogy fails, because its cited cases address circumstances not present here.

In *Genome*, the Board found a two-component treatment obvious based on prior-art teachings that each component exhibited the desired effect (an “anti-tumor effect”) in its own right. *See Genome*, PGR2019-00002, Paper 40 at 42-44. And in *Pfizer*, the Board found a two-component treatment obvious, where each of the claimed components was a known cancer treatment. *See Pfizer*, IPR2017-01168, Paper 59 at 16-23. In each decision, the Board concluded that the combination of two known cancer treatments was “the predictable use of prior art

elements according to their established functions.” *Pfizer*, IPR2017-01168, Paper 59 at 23 (quoting *KSR*, 550 U.S. at 417); *see also Genome*, PGR2019-00002, Paper 40 at 44.

Unlike the petitioners in *Genome* and *Pfizer*, CSPC does not argue that it would have been obvious to combine two known cancer treatments, each of which had demonstrated clinical benefit in its own right. Rather, CSPC argues that it would have been obvious to modify nearly every component of a single four-drug treatment that was considered a standard of care. A POSA would not have considered such modifications to be a “predictable use of prior art elements according to their established functions.” *See KSR*, 550 U.S. at 417. Here, CSPC has not identified any “established function” for the allegedly obvious FOLFIRINOX modifications, much less shown that their combined effect would have been “predictable.”

Celltrion is also inapposite. In *Celltrion*, the Board found that it would have been obvious to add a new drug to a regimen that was already considered a “standard chemotherapy regimen.” *See Celltrion*, IPR2017-01095, Paper 60 at 46-48. Here, CSPC argues that it would have been obvious to substitute 60 mg/m² liposomal irinotecan for FOLFIRINOX’s 180 mg/m² free irinotecan. But unlike in *Celltrion*, liposomal irinotecan was not considered a “standard chemotherapy regimen” in its own right. At the time of the invention in August 2015, liposomal

irinotecan was not an FDA-approved drug and had not been deemed a safe and effective treatment. Since that time, liposomal irinotecan has been approved by the FDA only in combination with other drugs—first, in October 2015, in combination with 5-FU and leucovorin for second-line treatment of metastatic pancreatic cancer, and subsequently, in February 2024, in combination with oxaliplatin, fluorouracil, and leucovorin for first-line treatment. *See* Ex. 2076 at ¶¶ 65, 68; Ex. 2040. Liposomal irinotecan has never been approved—or established—as a stand-alone therapy. *See* Ex. 2076 at ¶¶ 65, 68; Ex. 2073 at 49:7-12 (Dr. Ratain acknowledging that liposomal irinotecan required its own FDA approval to be used for the treatment of metastatic pancreatic cancer). Nor has CSPC argued—let alone established—that a POSA would consider 60 mg/m² liposomal irinotecan interchangeable with 180 mg/m² free irinotecan. To the contrary, both parties’ experts agree that the two are different drugs with different properties. *See* Ex. 2073 at 49:7-12; Ex. 2076 at ¶¶ 270-81. As Dr. Oberstein explained, a POSA would have been cautious in combining liposomal irinotecan with oxaliplatin given the unknown effects of that specific combination, and the prior art as a whole provides no basis for expecting that liposomal irinotecan at 60 mg/m² would be interchangeable with free irinotecan at 180 mg/m² in the claimed four-drug regimen. *See* Ex. 2076 at ¶¶ 270-81. Dr. Ratain has offered **no** testimony to the contrary.

3. The Expert Testimony of Record Does Not Establish Requisite Motivation

The expert testimony of record does not support CSPC's suggestion that toxicity concerns would have motivated a POSA to arrive at the claimed invention. As discussed *supra*, CSPC's allegedly obvious FOLFIRINOX modifications comprise (1) starting dose reduction of two drugs and (2) the substitution of a new drug (liposomal irinotecan), in a new dose. But, as ***unrebutted*** expert testimony establishes, a POSA would have had countervailing efficacy concerns that weighed against multiple dose reductions. And the experts agree that a POSA would not have necessarily been motivated to introduce liposomal irinotecan to the regime.

Dr. Oberstein's ***unrebutted*** expert testimony is that a POSA would not have been motivated to make the extent of modifications that CSPC suggests, due to countervailing efficacy concerns. As Dr. Oberstein explained at his deposition:

I think a person of ordinary skill would have wanted a treatment that was effective and to manage toxicity, but the priority would have been to also make sure it was effective and be able to treat pancreatic cancer.

Ex. 1210 at 133:6-11; *see also* Ex. 2076 at ¶¶ 263-69. As such, Dr. Oberstein opined that a POSA would not have been motivated to undertake multiple dose reductions and introduce a new drug, in a new dose, out of concern for compromising efficacy—especially in a first-line setting. *See, e.g.*, Ex 1210 at 309:18-24 (explaining that most clinicians “would be reluctant to make exchanges

that would dilute” the benefit seen with FOLFIRINOX or otherwise minimize it); *see also* Ex. 2076 at ¶ 263. Rather, a POSA would have been motivated to administer the maximum tolerated dose, rather than undertake multiple dose reductions in addition to substituting a new drug. *See* Ex. 1210 at 277:21-278:8; *see also* Ex. 2076 at ¶¶ 263-69.

This is borne out by Appendix B to Dr. Oberstein’s declaration, which further undermines CSPC’s argument. Appendix B illustrates a number of different and varied approaches to modifying FOLFIRINOX—*none* of which comprises all four of the modifications CSPC alleges would have been obvious to make all at once. *See* Ex. 2076, Appendix B. Critically, every approach reflected in Appendix B entails modifications that were less extensive than the four simultaneous changes CSPC proposes. *See* Ex. 2076 at ¶¶ 265-66. Dr. Oberstein’s *unrebutted* opinion is that the variety of approaches in the prior art (none of which were the claimed method) underscores the absence of any clear direction—much less motivation—toward the four specific modifications CSPC now contends would have been obvious. *See id.* at ¶ 266. If anything, Appendix B demonstrates a lack of clear direction in the prior art—not a “clear roadmap.” *See* Ex. 2076 at ¶¶ 265-66; *see also* Paper 32 at 8-9.

CSPC offers *no* expert testimony in rebuttal. If anything, Dr. Ratain agrees that a POSA would have been motivated to administer treatment at the maximum

tolerated dose. *See* Ex. 1002 at ¶ 77. The expert testimony of record supports only that a POSA would have been motivated to balance efficacy with tolerability and not—as CSPC argues—undertake multiple dose reductions.

CSPC’s reliance on the Memorial Sloan Kettering (“MSK”) retrospective study (Ex. 1216) does not contradict the expert testimony of record. *See* Paper 32 at 7-8. A single-institution retrospective report does not reflect the standard practice that a POSA would follow; to the contrary, Dr. Oberstein’s *unrebutted* testimony is that a POSA would follow the prospective protocol established by Conroy and the NCCN guidelines. *See* Ex. 1210 at 277:21-278:8; Ex. 2076 at ¶¶ 243-52. Moreover, the MSK study reduced all four FOLFIRINOX components proportionally to 80%—a fundamentally different approach from CSPC’s proposed modifications, which involve four specific, non-proportional changes including substitution of an entirely new drug.

Finally, both parties’ experts agree that, to a POSA, liposomal irinotecan was a different drug from the free irinotecan included in FOLFIRINOX, with different properties. *See* Ex. 2073 at 49:7-12; Ex. 1210 at 207:5-15. As Dr. Oberstein opines, a POSA would have been cautious in combining liposomal irinotecan with oxaliplatin, given the unknown effects. *See* Ex. 2076 at ¶¶ 270-81. CSPC has offered *no* expert testimony in rebuttal.

4. The Prior Art Does Not Teach, Suggest, or Motivate 60 mg/m² Oxaliplatin

One of CSPC's allegedly obvious FOLFIRINOX modifications is to reduce the dose of oxaliplatin in FOLFIRINOX (85 mg/m²) to 60 mg/m². Even assuming that CSPC articulated a motivation to make this change in combination with the other three (it does not), the expert testimony of record belies any motivation to make that specific starting dose reduction.

(a) The Conroy References Do Not Teach 60 mg/m² Oxaliplatin

(i) There Is No Dispute That "Treatment" Comprises a Starting Dose

As set forth in Ipsen's Patent Owner's Response, the '552 patent describes embodiments of the claimed treatment by reference to starting doses. Paper 21 at 7 (citing Ex. 1001 at 13:38-46; 30:5-11; Tables 1B-1E). Ipsen's expert Dr. Oberstein has opined further that a POSA would understand the claimed treatments to comprise at least the recited starting dose. Ex. 2076 at ¶ 119 ("The '552 Patent discloses that the doses of the drug components in the claims are directed to the starting, or initial doses of the Onivyde[®] regimen."); *see also id.* at ¶ 102 ("Ipsen's Onivyde[®] product and its use in the NALIRIFOX regimen are embodiments of the '552 Patent's claims.").

As Dr. Oberstein explains, a POSA would have understood the significance of a starting dose in this field of treatment as opposed to subsequent dose modification:

[T]he starting regimen is absolutely essential for when we give medications, and with every regimen we use we identify what we think is the best starting regimen usually based on clinical trial—randomized clinical trial data, as was done with FOLFIRINOX for Conroy and NAPOLI-3, and that is the essential dose that is given. Modifications are based on what a patient experiences subsequent to the initial dose.

Ex. 1210 at 400:20-401:6; *see also* Ex. 2076 at ¶¶ 245-51; Ex. 1210 at 168:2-23 (testifying, *inter alia*, that “a dose reduction is not the starting dose.”). Dr. Ratain did not rebut this opinion.

CSPC does not dispute the import of the ’552 patent’s disclosures regarding a starting dose and offers *no* expert testimony in rebuttal. CSPC’s only response is to mischaracterize Ipsen’s argument. Ipsen does not argue that the claimed treatments are “limited to . . . just a starting dose.” *See* Paper 32 at 12. Rather, Ipsen argues—as CSPC apparently concedes—that the claimed treatments comprise at least the recited starting doses with subsequent dose reductions explicitly contemplated by the specification.

(ii) The Conroy References Do Not Teach a Treatment Comprised of 60 mg/m² Oxaliplatin

As set forth in Ipsen's Patent Owner's Response, a POSA would understand the Conroy references to disclose a treatment comprised of 85 mg/m² oxaliplatin. *See* Paper 21 at 26-32. This is supported by Dr. Oberstein's expert opinions as well as a plain reading of references that explicitly define Conroy's FOLFIRINOX regimen as comprising 85 mg/m²—not 60 mg/m²—oxaliplatin. *See id.*; Ex. 2076 ¶¶ 237-52.

CSPC's reply offers *no* expert testimony in rebuttal. At most, CSPC regurgitates its arguments that are based on potential dose modification over the course of treatment, rather than a starting dose followed by subsequent dose modification. This overlooks, as discussed *supra*, the undisputed intrinsic record and *unrebutted* expert testimony on the significance of a starting dose in the context of the relevant field of treatment.

(b) The Prior Art Is Silent on Any Dose of Oxaliplatin in Combination with Liposomal Irinotecan, 5-FU, and Leucovorin

It is undisputed that Bayever—one of CSPC's two main references—does not disclose any treatment regimen that includes oxaliplatin, much less oxaliplatin at the '552 patent's claimed dose of 60 mg/m². CSPC's reply does not address this or offer any supporting expert testimony. Nowhere does CSPC address the argument, supported by Dr. Oberstein's *unrebutted* expert opinion, that among

approaches for addressing toxicity concerns, oxaliplatin dose reduction was not a preferred option.

None of CSPC's other cited references teaches a treatment comprised of 60 mg/m² oxaliplatin as a starting dose. CSPC purports to address the disclosure of Ychou, which—as Dr. Oberstein opines—would teach, if anything, a dose of 85 mg/m² oxaliplatin. CSPC argues that Ychou “started the trial at 60 mg/m² oxaliplatin” and therefore suggests that dose as a starting point. *See* Paper 32 at 14. But this mischaracterizes Ychou's disclosure. As Dr. Oberstein explains, Ychou's ultimate recommendation—based on the results of the study accounting for both safety and efficacy—is a dose of 85 mg/m² for oxaliplatin. *See* Ex. 2076 at ¶¶ 243-44. A POSA reading Ychou would not have understood that reference to motivate a starting dose of 60 mg/m², which Ychou's own findings do not recommend. CSPC offers *no* expert testimony in support of its characterization of Ychou. Dr. Oberstein's opinion that Ychou, at best, motivates 85 mg/m² oxaliplatin—not 60 mg/m²—stands *uncontested*.

Separately, CSPC's “result-effective variable” argument—that lowering oxaliplatin from 85 mg/m² to 60 mg/m² would have been “routine optimization”—has already been decided in Ipsen's favor. As CSPC itself acknowledges, the Examiner raised the identical argument during prosecution, asserting that oxaliplatin dose was a “result effective variable” rendering the claims obvious. *See*

Paper 1 at 46. Ipsen overcame that argument, and the claims issued. CSPC articulates no basis to revisit an issue already decided in favor of patentability. *See* Paper 21 at 46-47.

C. CSPC Fails to Establish a Reasonable Expectation of Success in the Claimed Treatments

CSPC also fails to establish a POSA's reasonable expectation that all of the four modifications at once would result in the claimed treatment methods.

CSPC improperly relies on the flawed assertion that, because “the prior art showed each component of the claimed invention had known efficacy in treating pancreatic cancer,” a POSA would reasonably expect success in the claimed treatment itself. *See* Paper 32 at 15-16. That assertion rests on an oversimplification of the relevant field and its interrelated teachings. It is undisputed, and supported by Dr. Oberstein's *unrebutted* testimony, that the expectation of success in developing new treatments in this field was particularly low. *See* Ex. 2076 at ¶¶ 303-12. CSPC offers *no* expert testimony in rebuttal. *See* Paper 32 at 16-17. Nor does CSPC address—and Dr. Ratain does *not* rebut—Dr. Oberstein's expert opinion that a POSA would not have expected to maintain efficacy while simultaneously lowering doses of multiple FOLFIRINOX components. *See* Ex. 2076 at ¶¶ 288-93. And CSPC does not dispute that prior-art publications—including those co-authored by its own expert—contradict the

notion that preclinical data provides a reasonable expectation of success in achieving more than a *de minimis* benefit. *See id.* at ¶¶ 294-300.

Rather than address these undisputed issues of fact relating to the expectations of a POSA in the relevant field, CSPC resorts to mischaracterization of Dr. Oberstein’s testimony. *See* Paper 32 at 14-16. Ipsen and Dr. Oberstein do not “misapply the law regarding reasonable expectation of success.” *See* Paper 32 at 14-15. While CSPC correctly states that reasonable expectation of success “does not require absolute predictability of success” or “conclusive proof of efficacy,” *In re Copaxone Consol. Cases*, 906 F.3d 1013, 1026, 1031 (Fed. Cir. 2018), Ipsen does not contend otherwise. The question here is whether any reasonable expectation existed that four simultaneous modifications to a standard-of-care regimen—including the substitution of a new drug at a novel dose—would yield a treatment providing more than a *de minimis* benefit. On that question, the ***unrebutted*** expert record answers in the negative.

As set forth in Ipsen’s Patent Owner’s Response, CSPS must show a POSA’s reasonable expectation of success in achieving the claimed method of “treatment,” which the Board has construed (and CSPC does not dispute) as providing more than a *de minimis* benefit. *See* Paper 13 at 13-14; Paper 21 at 42-46. In rendering his opinions, Dr. Oberstein expressly applied that construction. *See* Ex. 2076 at ¶¶ 126-27, 288-93; Ex. 1210 at 133:6-20. And as he repeatedly

testified at his deposition, he considered whether a POSA would regard it as “more likely than not” that CSPC’s allegedly obvious modifications would result in such treatment. Ex. 1210 at 223:8-15, 225:2-28. CSPC has offered ***no*** expert testimony from Dr. Ratain or otherwise to rebut these opinions.

D. Unrebutted Expert Testimony Supports Unexpected Results

As set forth in Ipsen’s Patent Owner’s Response and supported by the testimony of Dr. Oberstein, a POSA would not have expected multiple modifications, including two dose reductions, to FOLFIRINOX to provide even comparable efficacy. CSPC offers no rebuttal supported by Dr. Ratain.

Further, the evidence of record establishes nexus. There is no dispute that the NALIRIFOX regimen comprises the ’552 patent’s recited components and doses. *See* Paper 21 at 6-8; Ex. 2076 at ¶¶ 65-68. CSPC’s arguments to the contrary appear to rest on claim-construction arguments that are unsupported by the record. *See* Paper 32 at 21-22. CSPC appears to assume a claim construction that would preclude any modification of the recited doses during the course of treatment. *See id.* (arguing that “the claims require specific doses of four drugs two weeks apart.”). For reasons already discussed, this argument ignores the intrinsic record and ***unrebutted*** expert testimony on how a POSA would understand the claimed treatment methods. As explained *supra*, a POSA would

understand the recited treatment methods to comprise at least the recited starting dose, with subsequent dose modifications permitted.

CSPC also appears to assume a claim construction that would require some baseline expectation of patient performance. *See id.* at 22 (“[P]atients who did the best were expected to do better.”). To the extent that CSPC argues that the claimed “treatment” requires benefit, or an expectation of benefit, on a patient-by-patient basis, CSPC fails to identify intrinsic support for such construction or provide any supporting expert testimony. In any event, as Dr. Oberstein explained at his deposition, a POSA would understand the claimed treatments to provide benefit on the basis of the NAPOLI-3 clinical trial. Ex. 1210 at 83:4-25. As Dr. Oberstein explained further, clinical trials allow a clinician to “derive information from a population that would be relevant for any individual.” *Id.* at 335:15-336:15.

The *unrebutted* expert opinions of Dr. Oberstein establish unexpected results that support non-obviousness of the challenged claims. As set forth in his declaration, Dr. Oberstein opined that the claimed methods unexpectedly provided more than a *de minimis* benefit, despite multiple dose reductions and modifications to the FOLFIRINOX regimen. Ex. 2076 at ¶¶ 303-12. Dr. Oberstein cited publications that suggest not only comparable but superior efficacy outcomes to FOLFIRINOX. *Id.* CSPC has offered *no* expert testimony to rebut Dr. Oberstein’s opinions on these publications and the conclusions to be drawn from

them. Ipsen's evidence of unexpected results is supported by *unrebutted* expert testimony.

E. CSPC's Attacks on Dr. Oberstein's Credibility Are Meritless

CSPC has not challenged Dr. Oberstein's expert qualifications and, as discussed *supra*, has not offered expert testimony to rebut his opinions. Instead, CSPC devotes the lead argument in its Reply to meritless attacks on Dr. Oberstein's credibility. Paper 32 at 1-4. These attacks—based on Dr. Oberstein's consulting relationship with Ipsen, a selectively edited video clip, and a laundry list of paragraph citations characterized as “conclusory”—do not withstand scrutiny. CSPC's bias arguments are attorney argument, unsupported by any expert opinion as to how Dr. Oberstein's relationship with Ipsen allegedly infected his medical or scientific judgments. None provides any basis for discounting Dr. Oberstein's testimony, much less reducing it to “little to no weight.”

Dr. Oberstein's unremarkable consulting relationship with pharmaceutical companies such as Ipsen does not evince bias. The consulting relationship between Dr. Oberstein and Ipsen reflects the ordinary course of academic medicine. Such relationships are the norm, not the exception, among physicians of Dr. Oberstein's stature. *See, e.g.*, Ex. 1210 at 116:13-17 (Dr. Oberstein explaining that companies “ask me to commit my time, which is consulting time and effort to give education about a medication because I have expertise in that field”).

CSPC cites no authority that would support discounting Dr. Oberstein’s testimony on the basis of a consulting relationship. CSPC’s reliance on *Varian Med. Sys., Inc. v. William Beaumont Hospital*, IPR2016-00169, Paper 79 at 30 (PTAB May 4, 2017), is inapposite. There, the Board acknowledged that financial interest is “a factor in deciding how much weight to give” testimony, but ultimately credited the expert’s testimony. *See id.* at 30-31. The Board is well-positioned to assess credibility without discounting testimony wholesale based on standard consulting arrangements. *See Athena Automation Ltd. v. Husky Injection Molding Sys. Ltd.*, IPR2013-00290, Paper 45 at 39 (PTAB Oct. 23, 2014) (declining to disqualify or deny weight to testimony of an expert who was an employee of the party offering his opinions).

The fact that Dr. Oberstein has prescribed NALIRIFOX does not evince bias. That an oncologist prescribes a regimen that received FDA approval based on a Phase III clinical trial demonstrating statistically significant improvements in overall survival over the standard of care is unremarkable—it is the practice of evidence-based medicine. *See* Ex. 1210 at 393:23-395:3. And as he testified, Dr. Oberstein’s consulting fees comprise a small fraction of his income. *See* Ex. 1210 at 402:21-403:9 (Dr. Oberstein testifying that the consulting fees he receives from Ipsen “reflect[] around 5 percent or less of [his] income”).

CSPC’s allegations of “conclusory” opinions are meritless and unsupported by expert testimony. CSPC does not identify any opinion that Dr. Oberstein rendered without foundation—it submits only a string cite of paragraph numbers from his declaration, without any expert analysis of what, if any, information is lacking and the significance of that, if any. *See* Paper 32 at 3. Dr. Oberstein is entitled to rely on his experience and professional expertise, none of which CSPC challenges. Regardless, the cited portions are based on Dr. Oberstein’s expertise as well as citation to literature supporting his opinions.

CSPC’s reliance on video clips from a 2025 conference panel—approximately ten years after the time of invention—do not undermine Dr. Oberstein’s credibility. The selected clip is irrelevant to what a POSA would have understood or expected as of August 2015, which CSPC does not dispute is the relevant priority date. *See In re NuVasive*, 842 F.3d at 1384 (in reversing a final written decision of obviousness, finding error in the PTAB’s reliance on expert testimony “made in reference to benefits recognized *after* the priority date” (emphasis in original)). The selected clip is also misleading, as Dr. Oberstein explained at his deposition. *See* Ex. 1210 at 292:13-293:10. The selected clip reflects, at most, that Dr. Oberstein said with hindsight that the dosing *schedules* of NALIRIFOX and FOLFIRINOX are “very similar”—a reference to the shared biweekly administration schedule, which both parties acknowledge. This is not an

admission that the claimed invention is “very similar” to FOLFIRINOX as a whole. To the contrary, Dr. Oberstein testified at his deposition that the regimens differ significantly in drug composition and doses and that nothing in the prior art as of August 2015 would have given a POSA motivation to make all of those changes or a reasonable expectation of success. *See* Ex. 1210 at 292:13-294:25.

III. Conclusion

For the reasons stated herein, the Board should affirm patentability of the '552 patent claims 1-15.

Date: March 25, 2026

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

The undersigned hereby certifies that, according to the word-processing system used to prepare the foregoing document, this document has 5,568 words and thus complies with the applicable word limit.

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

The undersigned hereby certifies that on March 25, 2026 copies of the foregoing document and supporting exhibits were served upon the following parties via electronic mail, with a copy to ipdocket@foxrothschild.com (referencing Attorney Docket No. 340008.00021):

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