

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

**SUPPLEMENTAL EXPERT DECLARATION OF
MARK J. RATAIN, MD**

Table of Contents

I.	New Evidence Further Rebuts Patent Owner’s Unexpected Results Arguments.....	1
II.	Ipsen Mischaracterizes My Testimony Regarding Median Relative Doses.....	5
III.	CONCLUSION.....	6

I, Mark J. Ratain, M.D., of Chicago, Illinois, declare as follows:

1. I have been retained by counsel for CSPC Pharmaceutical Group Limited, CSPC Ouyi Pharmaceutical Co., Ltd., and Conjupro Biotherapeutics, Inc. (collectively, “Petitioner”). I understand that Petitioner submitted a petition for inter partes review (“IPR”) of U.S. Patent No. 11,344,552 (“the ‘552 patent”) on January 17, 2025 (“the Petition”). I submitted a declaration in support of that petition. I also understand that on May 23, 2025, the owner of the ‘552 Patent, Ipsen Biopharm Ltd. (“Ipsen”), submitted a Patent Owner’s Discretionary Denial Brief. I submit this declaration in support of Petitioner’s Opposition to Patent Owner’s Discretionary Denial Brief. I also incorporate by reference herein my declaration submitted in support of the Petition, which I understand was submitted as Exhibit 1002. The following statements are based on my personal knowledge and experience and, if called to testify to them, could and would do so.

I. New Evidence Further Rebuts Patent Owner’s Unexpected Results Arguments

2. After the filing of the Petition, Ipsen published a late-breaking abstract with the American Society of Clinical Oncology (“ASCO”), which was available online at least by May 31, 2025 (herein “ASCO Abstract”). Ipsen also presented a poster at the ASCO meeting in Chicago on May 31, 2025 (herein “ASCO Poster”). I attended this meeting in Chicago and viewed the presentation of the poster on May

31, 2025. Both the ASCO Abstract and ASCO Poster describe data related to long-term survivors (those who survived for at least 18 months) that participated in the NAPOLI 3 trial, which tested NALIRIFOX treatment in patients with metastatic pancreatic ductal adenocarcinoma (herein “pancreatic cancer”). NALIRIFOX is the four drug combination of liposomal irinotecan, oxaliplatin, 5-FU, and leucovorin described with specific dosages in the claims of the ‘552 Patent. Long-term survivors constituted 15 of the 120 patients enrolled in the NAPOLI 3 trial, or 12.5% of all participants. A true and correct copy of the ASCO Abstract is being submitted as Exhibit 1201. A true and correct copy of the ASCO poster is being submitted as Exhibit 1202.

3. The ASCO Abstract and ASCO Poster both note that dose reductions of liposomal irinotecan and oxaliplatin were experienced by 66.7% and 80% of long-term survivors, respectively. They both also note that dose delays of liposomal irinotecan and oxaliplatin were experienced by 86.7% and 80% of long-term survivors, respectively. (*See* Ex. 1201 at 1; Ex. 1202.) The ASCO Poster states that “Key Learnings” were that “[j]udicious dose modifications (reductions/delays) enabled prolonged treatment exposure and long-term survival [] in a subgroup of North American patients treated with NALIRIFOX in NAPOLI 3.” (*See* Ex. 1202 (further stating that one of the “Conclusions” is that “[d]ose reductions and/or treatment delays occurred in the majority of long-term survivors, enabling prolonged

exposure, high cumulative doses of both liposomal irinotecan and/or oxaliplatin drugs and an overall mOS of 19.5 months”).) Ipsen also issued a press release on May 31, 2025, related to the NAPOLI 3 trial where it stated that “[d]ose reductions and/or treatment delays for the management of adverse events enabled patients to stay on treatment longer and achieve higher cumulative doses of liposomal irinotecan and oxaliplatin. (See <https://ml-eu.globenewswire.com/Resource/Download/a257a261-01a1-4deb-83ad-5ea349bd295f>.)

4. The data and disclosures presented and promulgated by Ipsen are in direct conflict to their assertions in their Discretionary Denial Brief that there are unexpected results, including the results discussed in Skorupan, and as based on the NAPOLI 3 trial used to gain FDA approval. In fact, this clinical trial does not fully embody the ‘552 claims, since the doses were reduced and/or delayed throughout the trial, the key teaching point of their disclosures related to the recent ASCO meeting. In contrast, the ‘552 claims all describe using the starting dose consistently throughout treatment, administered every two weeks without reduction. Thus, the results of the NAPOLI 3 trial do not reflect the results of practicing the ‘552 claims, and thus cannot support “unexpected results.”

5. Furthermore, a POSA would understand from Ipsen’s disclosures, that the ‘552 claims are not an optimal (or even acceptable) way to treat metastatic

adenocarcinoma of the pancreas. The ASCO Poster notes that dose reductions of liposomal irinotecan and oxaliplatin were experienced by 52.5% and 60% of all participants, respectively, and dose delays were required in 70% and 69.2% of all participants, respectively. (Ex. 1202.)

6. This evidence, that well over half the participants experienced dose reductions (and delays), further confirms that POSAs routinely engage in dosage reductions to optimize treatments and/or achieve a maximally tolerated combination. I testified to this in my prior declaration. (See, e.g., Ex. 1002 at ¶¶ 77-82.)

7. Finally, these data do not suggest better efficacy for long-term survival than prior art treatment regimens. As explained above, only 12.5% of NALIRIFOX patients survived 18 months or longer. (Ex. 1202.) However, a POSA would be aware that the long-term survivors in the “study by Conroy et al. for patients treated with FOLFIRINOX” was 18.6%. (See Ex. 1203 at 4.)

8. Skorupan (Ex. 2033), cited by Ipsen in its Discretionary Denial Brief, acknowledges that NALIRIFOX is “more costly” than FOLFINOX, that the “relative efficacy of NALIRIFOX versus FOLFIRINOX or modified FOLFIRINOX (mFFX) has yet to be explored head-to-head,” and that “differences in study population” is the “most likely” contributor to the outcomes it observed. (Ex. 2033 at 1-3.) It also states “a head-to-head study could address whether there is sufficient improvement in benefit to justify the cost difference” of NALIRIFOX. (*Id.* at 3.)

Therefore, Skorupan does not change my opinion that the evidence does not suggest to a POSA any unexpected results, especially since the NALIRIFOX results cited in Skorupan are primarily due to reduced dosages not claimed in the '552 patent.

II. Ipsen Mischaracterizes My Testimony Regarding Conroy's Median Relative Dose Intensity

9. In its Discretionary Denial Brief, Ipsen quotes part of a single sentence from my declaration to incorrectly suggest that I opined that a POSA's understanding of the median relative dose intensity in Conroy's disclosure would be used to calculate the dose for all patients in a combination substituting liposomal irinotecan for free irinotecan. (Paper 8 at 33.) This is incorrect. As I explained, the relative dose intensity is a way to describe what percentage of the planned dose was administered, but a POSA would understand that half the patients received more and half less than this median. (*See* Ex. 1002 at ¶ 97.) In fact, I further explained that the Conroy Protocol disclosed reducing the dose of oxaliplatin from 85 mg/m² to 60 mg/m² based on known toxicities and that this was "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.)

III. CONCLUSION

10. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

11. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Signature: 
Mark J. Ratain, MD

Date: June 22, 2025