UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,
PETITIONER
v.
CONCERT PHARMACEUTICALS, INC.,
PATENT OWNER

PGR2021-00006
PATENT NO. 10,561,659

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. Introduction

The ’659 patent claims the simple substitution of ruxolitinib with its deuterated analog (Compound (I)) in a known method of treating hair loss. The claimed doses reflect the routine optimization of a range taught for both ruxolitinib and Compound (I). While Patent Owner has failed to establish any prior art exception, unchallenged disclosures are more than sufficient to render all claims obvious. Patent Owner’s alleged unexpected results are neither significant nor unexpected, and any need for its unapproved product was previously met by ruxolitinib.

II. No Secondary Considerations

Concert relies on alleged unexpected results and long-felt need (POR, 73–77), but neither support patentability. Concert does not assert any skepticisms, commercial success, or other considerations.

A. Nexus not established

Concert’s purported secondary considerations are not within the scope of any claim and are “not probative of nonobviousness.” *In re Gartside*, 203 F.3d 1305, 1321 (Fed. Cir. 2000).

First, there is no evidence establishing “at least 95%” or “at least 97%” deuterium incorporation, as claimed, for any alleged secondary consideration. EX1001, claims 1, 13; EX1170, 132:12–135:2 (discussing EX2083, EX2118); EX2118 ¶¶4–7 (not addressing deuteration level); EX2014 (same).

Second, Concert's "drug-drug interaction" (DDI) study used a dose not within any claim. *Compare* EX2118 ¶¶4–6 (12 mg Compound (I) "QD" (per day)) *with* EX1001, claim 1 ("16 mg/day or 24 mg/day"); *see also* EX1171, 46:5–20 (DDI affected by drug dose); *see* EX1120 ¶¶17, 40–42; EX1099, 742; EX1136, 9. Rather than a nexus with the *claimed method*, any DDI effect is a "benefit of [the] *Compound (I)*" molecule claimed in *Silverman*. EX2068 ¶29; EX1002, claim 7 (Compound 111).

B. No unexpected results or long-felt need

Concert asserts an "unexpectedly superior efficacy/safety profile" compared to a "Phase 3 study of baricitinib in the treatment of AA." POR, 73–74. Concert's data are unreliable (EX1159 ¶¶10–16) and are at best a "difference in degree" from baricitinib. *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013); EX1161 ¶¶106–11. Moreover, since Concert's protocol is unknown the "comparison is demonstrably inappropriate…." EX1170, 153:19–157:12 (EX2109 was a "misreference"); *see also* EX2059 ¶104.

Concert's clinical comparison (POR, 74–75) does not compare to ruxolitinib, the closest prior art. EX1001, 2:51–3:14, 14:44–47, 18:14–19, 19:55–21:28, 23:31–37; EX1161 ¶¶112–113; *In re Baxter Travenol Labs*., 952 F.2d 388, 392 (Fed. Cir. 1991). Especially where the art taught using ruxolitinib for AA (*e.g.*, EX1003, 9; EX1144, 8), Concert should have compared ruxolitinib and Compound (I) under

equivalent conditions. *Novartis Pharm. Corp. v. W.-Ward Pharms. Int'l. Ltd.*, 287 F.Supp. 3d 505, 532 (D. Del. 2017), *aff'd,* 923 F.3d 1051 (Fed. Cir. 2019) ("Adopting Plaintiffs' assertion that [the prior art] and the [claimed invention] study are not comparable [due to differences in their designs] does not excuse Plaintiffs from identifying the closest prior art to compare with the claimed invention for purposes of the unexpected results analysis.").

Concert's efficacy comparison (POR, 73–75) is based on unreliable, incomplete summary data (EX2083) of unknown source and accuracy. EX1170, 137:8–19, 139:22–143:14; 37 C.F.R. § 42.65. It is meaningless and biased "Open Label Extension" data (EX1163, 1; EX1164, 2; EX1165, 1; EX1166, 1–3; EX1167, 2) unsuitable for comparison with, and not statistically significantly different from, baricitinib's randomized, controlled data. EX1159 ¶¶17–34; EX1168, 21; EX1169, 4; *cf*. EX1158, 1. And Concert's safety results (POR, 74) are exactly as expected, though based only on a conclusory and unreliable press release of unknown relevance. EX1161 ¶¶110–11; EX2026; EX1170, 144:12–145:5 (EX2118 and EX2083 lack side effect data), 145:19–147:16, 153:19–157:12 (EX2019 different Phase II study).

Nor are Concert's AA data commensurate in scope. *In re Grasselli*, 713 F.2d 731, 743 (Fed. Cir. 1983); EX2118 ¶2; EX2059 ¶104. Only claims 2, 15, and 18 recite AA; all other claims are broadly directed to "hair loss disorders." Concert

cites no evidence that its "unexpected" results can be extrapolated to other "hair loss disorders." EX1161 ¶114; EX1170, 19:20–20:22. Concert's study is also not commensurate with claims 2, 15, and 18, which are not limited to humans or any route of administration, especially given that Concert's declarant distinguished prior art AA "animal studies" and asserted that "deuteration… [is] typically irrelevant to topically administered drugs." EX2059 ¶¶64, 73. EX1171, 29:16–32:3.

Concert's alleged reduced DDI evidence also fails. *See* POR, 75–76. There is no "difference in kind" especially where the exhibited DDI for ruxolitinib and Compound (I) are both in a range the FDA categorizes as "weak" inhibition. EX1120 ¶39; EX2095, 22; *Galderma*, 737 F.3d at 739. Concert's data is also unchecked and unreliable. 37 CFR § 42.65; EX1171, 71:16–72:16.

Concert's DDI data further fails to establish a difference in degree. EX1120 ¶¶18, 30–38. Rather than compare with the closest ruxolitinib-ketoconazole prior art in EX1004, Concert used itraconazole (POR, 76), which does not produce "*in vivo* CYP3A inhibition approaching that of ketoconazole" and is "not [a] reasonable alternative[] to ketoconazole." EX1131, 3–4; EX1135, 1; EX1120 ¶¶30–36 (citing *inter alia* EX1134, 3; EX1130, 3–4). That lower, sub-maximal doses (EX2095, 10; EX1171, 46:12–20; 47:16–54:17) of a weaker inhibitor produced less DDI is not unexpected. EX1120 ¶¶37–38.

Regardless, reduced DDI for a deuterated compound is not unexpected. EX1120 ¶¶19–29; EX1171, 35:5–36:5 (DDI proportional to degree of metabolism at inhibited enzyme), 36:15–37:12 (ruxolitinib primarily metabolized by CYP3A4, reduction of metabolism will result in less CYP3A4 DDI). Numerous prior art publications—including from Concert—taught reduced DDI for deuterated drugs. EX1120 ¶¶21–29; EX1122, 4; EX1123, [0090]; EX1124, [0011]; EX1125, [0022]–[0023]; EX1126, 1; EX1128, 15; EX1129, 2:34–44; EX1052, 7

Finally, Concert's recycled long-felt need argument for its unapproved product (POR, 76–77) was already rejected as "premature" in the *Silverman* IPR (EX1176, 36–37). *See also Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d. 1366, 1377 (Fed. Cir. 2019) (no presumption of nexus "[w]here a product embodies claims from [multiple] patents"). More fundamentally, the "need for a treatment for AA" was ***not*** "unmet" (POR, 76) since JAK inhibitors—including ruxolitinib—were already in use to treat AA. EX1003, 9; EX1144, 8; EX1009 ¶¶21–28, 35; EX1161 ¶¶41–46, 48–52; EX1170, 9:8–10:2. And Concert's "Fastrack" and "Breakthrough" designations carry no weight; both have been awarded to multiple other JAK inhibitors for AA. EX1161 ¶¶115–17; EX1154, 1; EX1155, 1; EX1156, 1.

III. *Silverman* and *2015 Uttamsingh* are Prior Art Under §102(a)(1)

Concert bears—but failed to meet—the burden of production to establish a §102(b)(1) exception for *Silverman* (EX1002) and *2015 Uttamsingh* (EX1045, 390–417). *In re Magnum Oil Tools Int'l, Ltd*., 829 F.3d 1364, 1376 (Fed. Cir. 2016).

A. Concert has not established §102(b)(1) prerequisites

Exceptions under §102(b)(1) apply only to disclosures [i] "***made 1 year or less*** before the effective filing date" [ii] from an "***inventor***" (directly or indirectly) "***of a claimed invention***."[1] Application necessitates a claim-by-claim analysis for effective filing date and inventorship. *See Egenera, Inc. v. Cisco Sys., Inc*, 972 F.3d 1367, 1376 (Fed. Cir. 2020) ("like validity, inventorship is a claim-by-claim question"); *Orion IP, LLC v. Hyundai Motor Am*., 605 F.3d 967, 974 (Fed. Cir. 2010) ("Although §102 refers to 'the invention' generally, the anticipation inquiry proceeds on a claim-by-claim basis."). Concert has not proffered—and therefore waived[2]—bases for a §102(b)(1) exception for *Silverman* or *2015 Uttamsingh.*

[1] ***Bold italic*** denotes emphasis added.

[2] Scheduling Order, Paper 21, at 7; PTAB Consolidated Trial Practice Guide (Nov. 2019), at 74; *Finjan, Inc. v. Cisco Sys., Inc.*, 837 F.App'x 799, 812 n.10 (Fed. Cir. 2020) (argument made only in POPR was waived, could not be raised in sur-reply).

1. Concert has not established an earlier effective filing date

Silverman issued by February 2, 2016, and *2015 Uttamsingh* became public August 27, 2015, both ***more than one year*** before the '659 patent's November 1, 2018, actual filing date. For a §102(b)(1) exceptions to potentially apply, Concert must show that each challenged claim is entitled to an earlier filing date.[3]

But Concert has not argued—much less established—that any challenged claim is entitled to an earlier filing date. The effective filing date, therefore, defaults to the November 1, 2018, "actual" filing date, precluding any §102(b)(1) exception. *See* 35 U.S.C. §100(i)(1).

Concert only states that the PCT application "***claims earliest priority*** to a provisional application filed on May 4, 2016." POR, 13. This does not show ***entitlement*** because "[p]atent claims 'are not entitled to an earlier priority date merely because the patentee claims priority.'" *Nat. Alternatives Int'l, Inc. v. Iancu*,

[3] *Droplets, Inc. v. E*TRADE Bank,* 887 F.3d 1309, 1317 (Fed. Cir. 2018) ("burden [is] on the patent owner"); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1380 (Fed. Cir. 2015) (no presumption for provisional filing dates); *Polaris Indus. Inc. v. Arctic Cat Inc.*, IPR2016-01713, Paper 29, at 23 (Feb. 15, 2018) (same); *Apple Inc. v. Qualcomm Inc.*, IPR2018-01251, Paper 44, at 9–10 (Jan. 15, 2020) (same).

904 F.3d 1375, 1380 (Fed. Cir. 2018) (citation omitted). Nor do Concert's declarants provide support, stating only that they "understand" May 4, 2016, "is the earliest filing date to which the '659 patent claims priority." EX2068 ¶2; EX2059 ¶¶2, 12.

Because Concert has not demonstrated—or even argued—that any challenged claim is entitled to an earlier effective filing date, no potential §102(b)(1) exceptions can apply to *Silverman* or *2015 Uttamsingh*, which published ***more than one year*** before the '659 patent's actual filing date.

2. Concert has not shown that Dr. Uttamsingh is an inventor

Concert has not shown Dr. Uttamsingh to be an inventor of ***any*** remaining challenged claim.[4] Indeed, she is not.

Regarding independent claims 1, 9, and 11, Dr. Uttamsingh confirmed that she did not invent or conceive any limitation:

- Compound (I) or pharmaceutically acceptable salts thereof, which are claimed in *Silverman* (EX1172, 13:15–19, 25:7–15);
- using Compound (I) or its salts to treat hair loss disorder in a mammal (*id.*, 19:14–22, 21:3–20, 25:6–15);
- at dosages between 4 and 50 mg (*id.*, 21:22–22:15, 25:6–15);
- using Compound (I) to treat AA (*id.*, 22:21–23:10); or

[4] Concert disclaimed claim 8. Paper 20, D.I., at 6 n.1; EX2020.

- with >95% deuterium incorporation (*id.*, 75:7–11; *see also* EX1002, 4:14–18).

This is unsurprising because Amanda Wagner is the sole inventor of Provisional No. 62/492,758, which contains substantially the same claims except the deuterium incorporation. EX1127, 3, 6; EX1172, 17:4–18:15; *compare* EX1127, 40–41 (claims 1–14), *with* EX1001, 24:31–26:46; EX1172, 18:11–18; 37 C.F.R. §1.41(c) ("The inventorship of a provisional application is the inventor or joint inventors set forth in the cover sheet as prescribed by §1.51(c)(1).").

Dr. Uttamsingh further confirmed that Dr. Wagner conceived all claims in the '758 provisional, which include the limitations of the challenged dependent claims. EX1172, 25:7–15; *compare* EX1001, 24:31–26:45 (claims), *with* EX1127, 40–42 (provisional claims to treating "hair loss disorder in a mammalian subject" by administering 4mg to 50mg of Compound (I) or pharmaceutically acceptable salt thereof; administering at 6mg, 8mg, 12mg, and 24mg; the hair loss disorder being AA; oral administration; tablet formulation; once-a-day and twice-a-day administration; natural isotropic abundance for non-deuterium atoms).

B. Concert has not established an exception for any *Silverman* disclosures

1. *Silverman*'s Compound 111 structure

Concert's argument that Compound 111's structure in *Silverman* is subject to §102(b)(1)(B)[5] because it was re-disclosed in *2015 Uttamsingh* is inconsistent with the narrow scope of the exception. POR, 20–22; *see Helsinn Healthcare S.A. v. Teva Pharms. USA, Inc.*, 855 F.3d 1356, 1360 n.1 (Fed. Cir. 2017) ("one-year grace period in the AIA is less protective than under pre-AIA §102(b)"), *aff'd*, 139 S. Ct. 628 (2019).

Compound 111 was publicly disclosed in December 2013, ***two years before*** *2015 Uttamsingh,* in *Silverman*'s published PCT/US2013/045919. EX1002, 1:6–16; EX1173, 11. Dr. Uttamsingh admits she did not invent Compound 111 and could not identify any part of *2015 Uttamsingh,* such as Compound 111's structure, drafted by her as opposed to counsel. EX1172, 13:15–19, 50:18–52:7.

2. *Silverman*'s Compound 111 uses, doses, and salt forms

Even if Compound 111's structure is excludable (it is not), *2015 Uttamsingh* does not disclose—and cannot remove—*Silverman*'s uses, doses, and salt forms of Compound 111.

[5] Concert does not allege that §102(b)(1)(A) or §102(b)(2) apply to Compound 111's structure.

Section 102(b)(1) exceptions remove only ***the same*** disclosures from the prior art, as Concert acknowledges. 78 Fed. Reg. 11,059, 11,061; POR, 20. For example, when an alleged §102(b)(1) disclosure includes a purported broad statement (e.g., genus), it cannot remove more specific disclosures (e.g., species) from the prior art. *See* 78 Fed. Reg. 11,059, 11,077.

Concert alleges that *2015 Uttamsingh* discloses "*in vitro*" metabolic stability for the free base structure of Compound 111. POR, 23. There is no dispute that *2015 Uttamsingh* ***does not disclose*** the 95% deuterated Compound (I) of claim 1 (Pet., 27–28), or the following *Silverman* disclosures relied upon in the Petition:[6]

- using Compound 111 to treat diseases treated by ruxolitinib, e.g., inhibition of JAK1/JAK2 (*e.g.*, EX1002, 3:28–32);
- "97% deuterium incorporation" (*id.*, 2:7–17, 4:7–17);
- effective doses of Compound 111 (*id.*, 20:9–27);
- co-administering with a "second therapeutic agent" to treat or prevent "alopecia areata" (*id*., 19:34−50);
- salt forms of Compound 111, including phosphate ("phosphoric acid") salt (*id.*, 4:42–5:24);
- compound synthesis (*id.*, 12:23–16:17, Examples 1–3);

[6] *E.g.*, Petition at 13–14, 58 n.17, 66, 69–84.

- tablet form of administration (*id.*, 17:3–9);
- oral administration (*id.*, 17:18–28); and
- once-per-day or twice-per-day administration (*id.*, 20:15–18).

See also EX1120 ¶¶80–96.

These *Silverman* disclosures, not disclosed by *2015 Uttamsingh*, cannot be excluded under §102(b)(1).

3. *Silverman*'s metabolic stability

Concert argues that *Silverman*'s inventors obtained the Example 4 metabolic stability data "from" Dr. Uttamsingh because the data "flowed through" her—though it did not—and is thus excluded under §102(b)(1)(A). POR, 23–27. But §102(b)(1)(A) applies to "subject matter ***disclosed*** directly or indirectly ***from*** the inventor," not information merely requested or supervised by an inventor.

Example 4's data was generated but by Mr. Gallegos—not Dr. Uttamsingh—who had years of experience in conducting hundreds of metabolic assays in hepatosomes. EX1172, 53:20–57:20; POR, 25. Dr. Uttamsingh testified she could not have known the results without testing, did not change Mr. Gallegos's data or calculations, and does not recall making changes to his presentation slide thereof. EX1172, 33:8–34:7, 53:11–54:9, 58:21–59:18, 63:7–14, 64:7–66:17.

Concert and its declarants acknowledge that Mr. Gallegos—not Dr. Uttamsingh—presented the data to some *Silverman* inventors. EX2073, 12;

EX2069 ¶¶9–10; EX2072 ¶9; POR, 25–26. No *Silverman* inventors testify that they learned of the Example 4 data from Dr. Uttamsingh, whether by hypothesized email or otherwise, as opposed to from Mr. Gallegos. *E.g.*, EX2070 ¶8; EX2071 ¶8; EX2072 ¶¶8–9. Nor is there evidence that Dr. Uttamsingh actually sent any email or data. EX1172, 62:6–63:2.

Recognizing this, Concert manufactures an agency theory to attribute Example 4 to Dr. Uttamsingh. POR, 24–27. But §102(b)(1) does not exempt information that was merely requested or "reviewed, analyzed for quality control, and approved" (EX2069 ¶7) by an inventor (which Dr. Uttamsingh is not). Nor does Concert cite any support for broadening §102(b)(1)(A) to cover its agency theory.

Silverman's Example 4 data cannot be excluded based on Dr. Uttamsingh merely requesting, reviewing, and/or approving data obtained and presented by Mr. Gallegos. *See Morgan v. Hirsch*, 728 F.2d 1449, 1452 (Fed. Cir. 1984).

C. The claims are unpatentable even without *2015 Uttamsingh*

Section 102(b)(1) does not apply to *2015 Uttamsingh*. *Supra* §III.A. Nevertheless, the claims are unpatentable even without *2015 Uttamsingh*. *See* Pet., 34, 37, 40, 62.

IV. JAK Inhibitors were Already in Use for AA

Concert argues a POSA would not have been motivated to use or reasonably expected success with JAK inhibitors or ruxolitinib for AA. POR, 9–12, 30–43, 65–

67. There is no need to speculate. By May 2016, JAK inhibitors including ruxolitinib were *already being used* successfully to treat AA as evidenced by clinical reports (EX1003, 9; EX1012, 6; EX1031, 9; EX1088, 13), completed and on-going clinical trials (EX1143, 20; EX1144, 8, 18–19, EX1152, 1), and the prescribing practices of all clinicians in this case (EX2054, 34:15–25 ; EX1170, 9:13–10:9, 43:5–56:20; EX1161 ¶¶87, 105). Not only *would* a POSA have been motivated and had an expectation of success, they *were* motivated and *were* successful. EX1161 ¶¶41–54.

A. *Xing* and its progeny established JAK inhibitors treated AA

Concert's arguments that a POSA wouldn't use ruxolitinib for AA without "precise[ly]" understanding AA's mechanisms and wouldn't have seen "a causal relationship between ruxolitinib administration and improvement in AA" (*e.g.*, POR, 6–9, 30–32, 38) are belied by the facts. Rather than one-off or "anecdotal" reports (POR, 2–3, 36, 39, 66), *Xing* and its progeny were understood to teach AA's relevant mechanism and ruxolitinib's clinical efficacy. EX1161 ¶¶26–38, 57–68; EX2019, 5, 12; EX2037, 1; EX2040, 5, 18; EX2041, 1; EX1012, 7; EX1013, 1; EX1014, 1; EX1015, 12, 15; EX1016, 1, 11; EX1020, 18, 25; EX1021, 1; EX1022, 8, 11; EX1031, 9, 10; EX1050, 2; EX1088, 13; EX1140, 3; EX1144, 7–8; EX2037, 1; EX1139, 1. Ruxolitinib's demonstrated efficacy was lauded as "evidence-based targeting of immune cells and repurposing of existing [FDA] approved drugs [that]

provided rationale to expand clinical trials to include other JAK inhibitors and larger patient cohorts."[7] EX1144, 8.

Concert's spontaneous remission argument (POR, 30, 36) is irreconcilable with the collective force of *Xing* and subsequent clinical trials. EX1161 ¶¶58–60; EX1143, 20; EX1144, 8, 18–19; EX1142. It is also implausible given the observed treatment-effect chronology (EX1067, 1; EX2054, 51:5–14, 88:12–20, 95:25–96:12, 97:12–19) and the severe AA being treated, where remission is rare. EX1145, 3; EX2054, 48:25–50:23. And it is also inconsistent with Concert's reliance on a non-placebo controlled trial for unexpected results. §II.B.

Concert's argument that the art "would not have directed a POSA to treat AA with JAK inhibitors" (POR, 29) is demonstrably false. EX1161 ¶¶69–75. The art had "focus[ed] attention on the Janus kinase/signal transducer and activator of transcription (JAK-STAT) pathway." EX2063, 1. It was "one of the most exciting developments in modern medicine" (EX1020, 21) and demonstrated clinical success "provided rationale to expand clinical trials to include other JAK inhibitors and larger patient cohorts" (EX1144, 8). EX2054, 55:25–57:1; EX1015, 13.

[7] A "complete" (EX2059 ¶17) or "precise" (POR, 9) mechanistic understanding was also unnecessary. EX2054, 119:1–23; EX1170, 9:13–10:9; EX1161 ¶¶39–40; EX1004, 4 ("Initial U.S. Approval:-2011"); EX1141, 5.

"[A]dvocat[ing] for insurance coverage" was already a priority. EX1140, 4; EX1161 ¶73.

B. Side effects do not teach away

Concert's argument that *potential* side effects taught away (POR, 4–5, 10–11, 31–32) fails. JAK inhibitors were *actually* used to treat AA and exhibited limited side effects. EX1144, 8, 18–19; EX1161 ¶¶76–77, 80–81; EX2054, 34:15–24; EX1170, 9:13–10:9; *Teva Pharms. Int'l. GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1358 (Fed. Cir. 2021) (affirming unpatentability where PTAB had found "***potential*** safety concerns" did not outweigh evidence of "***actual*** studies").

Concert improperly relies on side effects from myelofibrosis patients (POR, 4–5, 8–11, 30–32, 74), who are predisposed to blood related toxicities (EX1146, 4; EX1147, 4) and not representative of autoimmune patients.[8] EX1161 ¶¶78–86. Consistent with its safety in more relevant population (EX1148, 3), ruxolitinib in AA patients yielded "only minor adverse effects" (EX1144, 8) and "safety parameters including complete blood count and differential, liver function and lipids

[8] Black Box warnings in 2021 (POR, 10, 32) have no bearing motivation in 2016, and do not prevent use of effective treatments. EX1161 ¶¶84–85.

remained within normal limits" (EX1143, 20). Clinical reports showed no more than mild AEs.[9] EX1012, 6; EX1031, 9; EX1088, 13.

C. Alternatives do not teach away

The possibility of alternatives to oral ruxolitinib for AA (POR, 31) is immaterial. *In re Mouttet*, 686 F.3d 1322, 1333–34 (Fed. Cir. 2012); *Infineum USA L.P. v. Chevron Oronite Co. LLC*, 844 F.App'x. 297, 305 (Fed. Cir. 2021) (unpublished); *Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.*, 713 F.3d 1369, 1376 (Fed. Cir. 2013).

Concert's argument that "more promising" tofacitinib taught away from ruxolitinib (POR, 31–34) is without merit. EX1161 ¶¶48–54. The art viewed the AA efficacy of tofacitinib and ruxolitinib as a class effect driven by JAK1 (EX1161 ¶¶32–35, 51–53, 55–56; EX1014, 1–2; EX1015, 12; EX2068 ¶30), both having similar efficacy in side-by-side preclinical evaluations (EX1004, Fig. 3; EX1016, Fig. 1). EX2054, 46:6–25; EX1144, 8, 24; EX1027, 4.

Rather than "undermine[]" the use of ruxolitinib (POR, 32–34), *Christiano* discloses numerous preclinical ruxolitinib experiments (*e.g.*, EX1005, 113:1–51, 122:30–40, 139:63–140:2), leverages ruxolitinib's success in other indications (*id*.

[9] The neutropenia cited by Concert (POR, 10) was "generally transient and rapidly normalized following the last dose of study medication." EX1059, 6.

96:64–67, 105:43–45), discloses "INCB018424 [ruxolitinib] as a safe intervention predicted to have efficacy in Alopecia Areata" (*id*., 122:21–23), and specifically claims ruxolitinib for treating hair-loss disorders (*id*., claims 1–10). *Cf.* EX1170, 125:18–130:7 (recognizing *Christiano* claims and shows efficacy of "INCB018424," but not recognizing this to be ruxolitinib); *see also* EX1007 ¶25, n. 15.

Concert's argument that a POSA would have "gravitated" towards tofacitinib because ruxolitinib had not been FDA approved for similar immune-mediated diseases (POR, 11–12) is affirmatively misleading. Concert recognized that ***licensing agreements*** "Incyte has with its partners, in particular Lilly, ***prevents the development of ruxolitinib in most inflammatory and autoimmune indications***" EX1174, 6; EX1179, 5. Concert's argument that Dr. Shapiro prescribed tofacitinib over ruxolitinib (POR, 34–35) similarly omits the driving cost consideration. EX2054, 34:22–35:23, 55:3–24. Neither commercial consideration "control[s] the obviousness determination[.]" *Butamax™ Advanced Biofuels LLC, Petitioner*, IPR2013-00214, Paper 46, 24 (Sept. 23, 2014); *Orthopedic Equip. Co.. v. United States*, 702 F.2d 1005, 1013 (Fed. Cir. 1983).

Likewise, interest in topical formulations does not undercut motivation for oral ruxolitinib. POR, 41. *Bayer Schering Pharma AG v. Barr Lab'ys, Inc*., 575 F.3d 1341 (selection among two potential pharmaceutical formulations obvious). The majority of clinical reports used oral JAK formulations (EX1161 ¶86–88) as did

all clinicians in this case. (EX2054, 34:15–24; EX1170, 9:13–10:9; EX1161 ¶¶87). Oral formulations were used over topical because they showed tolerable safety and were expected to—and had demonstrated—significantly greater efficacy. EX1161 ¶¶89–93; EX2054, 37:14–24, 42:13–20, 100:7–101:13; EX1149, 19.

Concert's reliance on out-of-context statements referencing topical (POR, 5–6, 35) are at best "a general preference" for topical that do not teach away from oral. EX1161 ¶¶90–93; EX2037, 1; EX1050, 2; *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.,* 567 F.3d 1314, 1327 (Fed. Cir. 2009); *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1380 (Fed. Cir. 2005). *Christiano*, for example, teaches oral formulations throughout. *E.g.*, EX1005, 96:64–67, 105:1–45. *Cf.* POR, 35.

Concert suggests that an Incyte topical study was driven by side effect concerns for oral. POR, 12. But when asked whether ruxolitinib was being pursued by Incyte as a topical because of "immune suppressive properties" (i.e., side effects) Concert inconsistently stated "[w]e believe that due to the ***licensing agreements*** that ***Incyte*** has with Lilly that they ***would not be able to bring an oral ruxolitinib*** into alopecia areata." EX1175, 8; EX1180, 4–5.

V. Compound (I) was Obvious

Concert's "lead compound" arguments against Compound (I) (POR, 43–47) ignore that "substitut[ing] [of] one equivalent for another" is obvious. *In re Fout*, 675 F.2d 297, 301 (CCPA 1982); Pet., 1–2, 23–24, 62–63. Compound (I) was taught

to be the functional equivalent of ruxolitinib. Pet., 35–36; EX1002, 2:15–20, 20:51–62; EX1120 ¶¶43–53. No more is needed since "a patent claim is invalid where the prior art teaches the functional equivalency between the claimed compound(s) and the prior art compounds." *Coalition for Affordable Drugs IX LLC v. Bristol-Myers Squibb Co.*, IPR2015-01723, Paper 10 at 15 (PTAB Feb. 22, 2016) (explaining *In re Ruff,* 256 F.2d 590 (CCPA 1958)).

Concert is also wrong. A POSA would have selected Compound (I) because its deuteration at ruxolitinib's metabolic hotspots was expected to improve stability[10] (Pet., 34, 37–38, 62; EX1007 ¶¶153–54, 168; EX1120 ¶¶54–61) and "the most promising candidate is the one that has the greatest increase in metabolic stability as compared to the protonated compound" (EX2068 ¶¶58). And *Silverman* specifically taught ruxolitinib's metabolic hotspots were the -2 and -3 positions of the cyclopentyl ring, deuteration of which is Compound (I). EX1002, 3:7–14 (citing EX1055); EX1171, 41:15–45:12; EX1120 ¶¶56–59.

[10] This was taught throughout the art. EX2075 ¶¶74–82; EX1035, 5–6; EX1036, 1; EX1053, 3; EX1034, 4–5.

Although not necessary, *Silverman* Example 4 and *2015 Uttamsingh*[11] each independently reinforce the motivation to select Compound (I). They confirm that, as expected, deuteration at ruxolitinib's hotspots increased metabolic stability. EX1120 ¶¶62–64; EX1007 ¶¶153–54. There would have been no preference for *Silverman* compound 127 (POR, 45–46) as its nineth deuterium at a non-hotspot "would probably not be relevant." EX1171, 40:18–41:5; EX1120 ¶63–64; *see also Novartis*, 923 F.3d at 1059; *In re Mouttet*, 686 F.3d at 1333–34.

VI. Doses of 16 and 24 mg/day were Obvious

A. The claimed doses are within a known range

Concert's arguments that *Silverman* "fails to teach the ***specific*** [16 and 24 mg/day] dose amounts of Compound (I)" (POR, 56–62) and demand that Incyte show that "difference between the claimed doses and the prior-art 30 mg ruxolitinib dose is not meaningful" (POR, 64) are misdirection. Selecting these doses from within *Silverman*'s range would have been a matter of routine optimization (Pet. 31–

[11]Contra to Concert's mischaracterization (POR, 46), Incyte demonstrated in the *Silverman* IPR that *2015 Uttamsingh* artificially inflated Compound (I)'s *in vitro* differences and that no significant clinical differences would be expected (EX2075 ¶¶122–27), as was the case (EX1009 ¶¶52–63; EX1161 ¶¶106–111); §II.B.

32, 68; EX1007 ¶¶172−76). *DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018); *Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737–38 (Fed. Cir. 2013). Nor is there any criticality or unexpected differences in kind. §II.B; EX1161 ¶¶106–114; EX1159 ¶¶31–34; EX1120 ¶¶19–39; EX1009 ¶¶52–63

Concert's attempt to limit *Silverman* to a 1–500 mg range ignores, *inter alia*, that *Silverman* expressly taught a 5–50 mg range covering 11 of the 13 sub-ranges, 7 of 9 specific doses, and the cited "prescribing information for ruxolitinib" doses (EX1004, 4–5). EX1002, 20:9–27. This is an "explicit preference" (POR, 59) for the 5–50 mg range, ripe for routine optimization. EX1007 ¶¶172–176; EX1009 ¶¶32–34. It is also of no moment that *Silverman*'s doses apply to other ruxolitinib analogs (POR, 57); they apply to Compound (I).

Contrary to Concert's arguments (POR, 57–59), *Silverman*'s doses *do* apply to AA as it is a condition "beneficially treated by administration of an inhibitor of… JAK1/JAK2" and "beneficially treated by ruxolitinib" as taught by *Silverman*. EX1002, 3:27–32, 20:52–62; EX1007 ¶¶81, 126–28; EX1003, 5. In fact, the obviousness of optimizing AA dosing within the common *Silverman* and *Ruxolitinib Prescribing Information* range requires no speculation. Titrating ruxolitinib for AA

and other off-label uses[12] within the 5–50 mg/day FDA-approved range was routine. EX1009 ¶¶32–43; EX1161 ¶¶94–100; EX1171, 96:10–19; *cf.* POR, 57, 61. This is evidenced by *Silvestri* (EX1017, 31) which documents titrating ruxolitinib for AA within the FDA approved range beginning in March 2015.[13] EX1009 ¶43; *see also* EX1170, 54:14–55:13 (admitting that "motivation [for the dose] was looking at the data around the use of tofacitinib in other clinical–clinical studies and conditions"); EX1152, 7.

B. Lowering dose provides a separate basis

Concert mischaracterizes the Petition as "arguing that the 30 mg prior-art dose of ruxolitinib is 'close' enough to the claimed doses." POR, 63–64. While they are close, (1) deuteration (EX1120 ¶¶65–79; EX1007 ¶¶198–99), (2) the strong response seen at the prior art doses (EX1009 ¶49; EX1007 ¶¶178–80), and (3) biomarkers (EX1007 ¶¶181–197) collectively provided motivation and an

[12] Rheumatoid arthritis (EX1148, 3) and GVHD (EX1151, 4; EX1157, 1–2; EX1150).

[13] *Silvestri* is relied upon to evidence level of skill in the art, *Yeda Research & Dev. Co. v. Mylan Pharm., Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018), not motivation. *Cf.* POR, 62–63.

expectation of success for the claimed doses. Pet., 46–51; *DuPont*, 904 F.3d at 1006.

1. Deuterium

Notwithstanding Concert's efforts to confuse (POR, 49–73), the expected effects of deuteration motivated using Compound (I) for AA at doses lower than ruxolitinib's known effective 30 and 40 mg doses. Pet. 11, 37–41, 50; EX1007 ¶¶198–99; EX1120 ¶¶66–74.

Deuteration was taught by *Silverman* to "positively impact the ADME properties" (EX1002, 2:12–15) and throughout the art as a means for "***[b]etter tolerability through reduction of overall dose***." EX1034, 3; Pet., 38–40; EX1007 ¶¶48–56; EX1120 ¶67; EX1171, 29:16–31:10. Concert's alleged *general* unpredictability (POR, 69–73) is both wrong (EX1120 ¶¶43–52, 75–79; EX1007 ¶¶51–56) and irrelevant to *ruxolitinib* for which slowing metabolism and enabling lower doses was particularly predictable. EX1007 ¶¶135–150; EX1120 ¶¶67–73. Concert's recycled safety considerations (POR, 70) presuppose deuterium's metabolic stability enhancement and further motivated reduced doses. EX1176, 25 ("the side effect may be managed by a dose adjustment"), 26 ("the dose of a deuterated drug may be lowered to achieve the same concentration as the undeuterated drug").

2. Strong response and linear PK

Concert does not dispute the expectation of Compound (I)'s efficacy at doses of 16 and 24 mg/day based on ruxolitinib's linear pharmacokinetics and strong response at 30 and 40 mg. Pet., 46; EX1161 ¶¶101–04; EX1009 ¶49; EX1007 ¶¶178–80; EX1118 ¶12, n.1 (relying on linear PK and citing EX1059).

While Concert tries to distance Compound (I) from ruxolitinib (POR, 36, 64–67), elsewhere it acknowledged that it "build[s] on the significant existing information regarding the corresponding non-deuterated compound." EX1138, 5; *see also* EX1120 ¶¶49–52; EX1138, 7–11; EX1137, 4; EX1033, 16–17. A POSA would have been guided to use Compound (I) in place of ruxolitinib for AA at reduced doses as a "deuterated drug is… ***virtually indistinguishable in all of its biological properties*"** from its protio analog. EX1033, 8–9; EX1120 ¶¶43–53; EX1011, 5; *Anacor Pharms., Inc. v. Iancu*, 889 F.3d 1372, 1384 (Fed. Cir. 2018).

Novartis Pharms. Corp. v. W.-Ward Pharms. Int'l Ltd., 923 F.3d 1051, 1061–62 (Fed. Cir. 2019), where the claimed and prior art compounds were "pharmacologically different" with "different binding affinities," and *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382–83 (Fed. Cir. 2019), where "[t]he record [did] not contain any clinical (human) data or preclinical (animal) data" and there was "an over 99.5% rate of failure for drugs entering Phase II clinical studies" for the claimed treatment, are inapposite. *Cf.* POR 65–67. Here, by contrast, there are

no "biologically relevant differences" between ruxolitinib and Compound (I) (EX1011, 5; EX1120 ¶¶43–48), Compound (I) was specifically taught as a ruxolitinib replacement (EX1002, 20:52–61), and ruxolitinib had been shown effective in AA via both preclinical and Phase II clinical data (§IV).

3. Dose estimates

Concert's assertion that Dr. Patterson's dose estimates "do not relate to ruxolitinib, JAK inhibitors, or treatment of AA, and are therefore not even 'from the same field of endeavor'" (POR, 50–51) is a strawman. Correlating potency and exposure does not depend on the drug or disease and was used by Concert to predicate ruxolitinib doses for AA. EX1118 ¶¶8–9, 16–18; EX1171, 90:7–93:20; *cf.* POR, 67–69.

Dr. Patterson used Shi's specific pSTAT3 assay (POR, 52–53) "because it is an optimal assay for measuring JAK1 inhibition" (EX1007 ¶185 citing EX1078, 6) and was stimulated with IFN-γ, responsible for AA (EX1161 ¶¶29–30, 34–35; EX1007 ¶¶193). Concert's criticisms are mired in contradictions.

- IL-6: *compare* POR, 52; EX2068 ¶36 *with* EX1171, 121:15–122:5; EX1178, 1; EX1118 ¶10.
- Biomarkers: *compare* EX2068 ¶40 *with* EX1171, 114:15–22, 116:5–17; EX1170, 58:17–61:8.

- Shi (EX1059) and healthy volunteers: *compare* POR, 68 *with* EX1118, 7, n.1 (citing EX1059).

C. Concert does not dispute the '659's express definition of "treat"

Concert's demand for safety and efficacy based on "detailed information" from a "pharmacokinetic-pharmacodynamic relationship" in AA specifically (POR, 68) should be rejected. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013). Concert does not dispute that the claimed "method of treating" requires only "regrowth of hair, prevention of further hair loss, or diminishing the rate of hair loss" (EX1001, 5:66–6:5; EX1007 ¶106; Pet., 23) and does not include any side effect limitation. "A reasonable expectation of success does not mean achieving the best of all possible results." *Trustees of Columbia Univ. in City of New York v. Illumina, Inc.*, 842 Fed. Appx. 619, 625 (Fed. Cir. 2021) (unpublished).

VII. Conclusion

Petitioner respectfully requests the Board hold the claims unpatentable.

Respectfully submitted,

Dated: November 12, 2021 By: /Mark J. Feldstein/

Mark J. Feldstein, Reg. No. 46,693
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

Counsel for Petitioner
Incyte Corporation

CERTIFICATION OF COMPLIANCE

Pursuant 37 C.F.R. § 42.24(c)(1), the undersigned hereby certifies that the foregoing **Petitioner's Reply to Patent Owner's Response** contains 5,596 words, excluding the parts exempted under 37 C.F.R. § 42.24(c) as measured by the word-processing system used to prepare this paper.

Dated: November 12, 2021

By: /Mark J. Feldstein/
Mark J. Feldstein, Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing **Petitioner's Reply to Patent Owner's Response** was served on November 12, 2021 via email directed to counsel of record for the Patent Owner at the following:

Marta E. Delsignore
Daniel P. Margolis
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018-1405
mdelsignore@goodwinprocter.com
dmargolis@goodwinprocter.com

Sarah J. Fischer
Daryl L. Wiesen
Emily L. Rapalino
Gerard J. Cedrone
GOODWIN PROCTER LLP
100 Northern Avenue
Boston, MA 02210
sfischer@goodwinlaw.com
dwiesen@goodwinlaw.com
erapalino@goodwinlaw.com
gcedrone@goodwinlaw.com
DG-ConcertPGR@goodwinlaw.com

Patent Owner has consented to service by email.

Date: November 12, 2021

By: /William Esper/
William Esper
Case Manager and PTAB Coordinator
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP