UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,

Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,

Patent Owner.

Post-Grant Review No. PGR2021-00006
U.S. Patent No. 10,561,659

PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER RESPONSE TO PETITION

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I. INTRODUCTION

Concert's '659 patent claims using a specific compound at specific doses to treat hair-loss disorders. Incyte has not sustained its burden to establish that these narrow claims are obvious. The key disclosures Incyte relied upon in its petition, including the structure of the claimed compound and data concerning its activity, are not available as prior art under post-AIA §102(b). Even if the disclosures were prior art, Incyte's arguments rely on disclosures using different compounds at different doses to treat various diseases. No study provided sufficient evidence to establish a reasonable expectation of success using even oral ruxolitinib to treat AA, never mind the specific deuterated version developed by Concert, at 16 or 24 mg/day. And objective indicia further support the patentability of the claims. The asserted claims are not obvious, and the petition should be denied.

II. SECTION 102 EXCLUDES KEY DISCLOSURES AS PRIOR ART

Incyte has abandoned its argument that Silverman is prior art under §102(a)(2). As Concert explained (Paper 37 at 17-19), Silverman falls within §102(b)(2)(C)'s "common ownership" exception to §102(a)(2). Incyte has no answer on that point, now arguing only that Silverman and the 2015 Uttamsingh Declaration are prior art under §102(a)(1). Paper 44 at 6-13. But as Concert explained (Paper 37 at 20-28), certain essential disclosures of Silverman are excluded as prior art under the "inventor disclosure" exceptions of §102(b)(1)(A)-

(B), and the entirety of the 2015 Uttamsingh Declaration is excluded under §102(b)(1)(A). In arguing to the contrary, Incyte consistently misstates the law and facts. Incyte relied heavily on these excluded disclosures in its petition; its failure to carry its burden of persuasion here is reason enough for the Board to reject both grounds.

A. Incyte's Challenge to the May 4, 2016, Effective Filing Date Is Untimely and Unavailing

Incyte first argues that Concert waived arguments concerning the §102(b)(1) exceptions. Paper 44 at 6. But Concert's patent owner response spent more than a dozen pages walking through those exceptions and their application to this case. Incyte's suggestion of waiver is meritless.

In fact, it is *Incyte* that has waived a key argument it now advances. Throughout these proceedings, Incyte has never questioned that May 4, 2016, is the effective filing date of the '659 patent. *See* Paper 1 at 3, 5, 6, 9, 15, 18, 19; Paper 17 at 1. Despite this, Incyte's reply protests that Concert has not "established" that the '659 patent's claims are "entitled to an earlier filing date" and thus the effective filing date is "the November 1, 2018, 'actual' filing date." Paper 44 at 7. But that argument turns the standard of review on its head: it was *Incyte*'s burden to challenge the priority date in its petition.

The Board's decisions are clear: even though there is no presumption that a patent is entitled to its earliest claimed priority date, the "petitioner first must raise

the issue" before the burden of production shifts to the patent owner. *Lupin Ltd. v. Pozen Inc.*, IPR2015-01775, Paper 15, at 11 (Mar. 1, 2016); *Huawei Techs. Co. v. Samsung Elecs. Co.*, IPR2017-01980, Paper 9, at 10 (Feb. 27, 2018); *Comcast Cable Commc'ns, LLC v. Rovi Guides, Inc.*, IPR2019-01420, Paper 9, at 12 (Feb. 11, 2020).[1] Even once the petitioner challenges priority, the patent owner's burden is only one of *production—i.e.*, the burden to "argue or produce evidence" that the patent-in-suit is entitled to an earlier priority date. *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015). "[T]he burden of persuasion . . . never shifts"; it always remains with the petitioner. *Id.* at 1378.

Incyte failed to carry its initial burden. Before its reply, Incyte *never* argued that the '659 patent is not entitled to the May 4, 2016, priority date. To the contrary, Incyte's filings have repeatedly assumed that date to be the critical date. Thus, Incyte never shifted the burden of production: Concert had no reason to "establish" the unchallenged priority date in its patent owner response. Incyte's suggestion that

[1] The decision in *MaxLite, Inc. v. Jiaxing Super Lighting Elec. Appliance Co.*, IPR2020-00208, Paper 14 (June 1, 2021), clarified that, once the petitioner properly raises the issue, the burden of production shifts to the patent owner for each claim limitation. *Id.* at 8. Still, *the petitioner* must raise the issue of priority in the first instance. *See id.* at 5 & n.2.

Concert should have anticipated Incyte's new argument is an improper attempt to raise new arguments in reply.

None of Incyte's cases support its belated argument. Citing *Droplets, Inc. v. E*TRADE Bank*, 887 F.3d 1309, 1317 (Fed. Cir. 2018), Incyte argues that the "burden [is] on the patent owner." Paper 44 at 7 n.3. But *Droplets* merely held that "Section 120 places the burden on the patent owner to provide a clear, unbroken chain of priority" in the patent itself. 887 F.3d at 1317. Concert plainly did so. Ex. 1001 at (60). Incyte's citation of *Dynamic Drinkware* is equally misplaced. The question in that case was whether there was a "basis to presume that a reference patent" relied upon *by the petitioner* is "entitled to the filing date of its provisional application." 800 F.3d at 1380. In rejecting such a presumption, the court relied on the fact that "Dynamic, as the petitioner, had the burden of persuasion to prove unpatentability by a preponderance of the evidence, and this burden never shifted." *Id.* at 1379. *Dynamic Drinkware*'s discussion of presumptions thus has no relevance here: as the decisions cited above demonstrate, *even though* the '659 patent "is not presumed to be entitled to the earlier filing dates of ancestral applications that do not share the same disclosure," "*[n]onetheless*, a petitioner"—here, Incyte—"first must raise the issue." *Lupin*, *supra*, at 11. Finally, *Polaris* and *Apple* (Paper 44 at 7 n.3) concerned situations where the petitioner had already shifted the burden to the patent

owner; the decisions did nothing to undermine the principle that the petitioner must first raise the question of priority.

Even if considered, Incyte's belated argument is still not enough to carry its initial burden to challenge priority. To properly raise the issue, a petitioner must "identify[], specifically, the features, claims, and ancestral applications allegedly lacking written description support for the claims based on the identified features." *MaxLite*, *supra*, at 5; *Lupin*, *supra*, at 11. In making its bald assertion about priority for the first time, Incyte has failed to specify even one claim limitation of any claim of the '659 patent that is not supported by the May 4, 2016, provisional application.

In short, Incyte never shifted the burden to Concert on the question of priority. Even if it had, Concert has already satisfied any burden of production. As Concert previously explained (Paper 11 at 8 n.2), the claims of the '659 patent are supported by U.S. Provisional Application No. 62/331,827. *Compare* Ex. 1001 claims 1-21 with Ex. 2004 at [11]-[20], [31]-[34], [48], [54], [75].[2]

[2] Incyte's suggestion that Concert cannot renew this argument from its preliminary response, Paper 44 at 6 n.2, is wrong for two reasons. First, Concert had no burden to address priority until *Incyte* first raised the issue. Second, the language in the scheduling order here is different from that in the case Incyte cites. *Compare Finjan, Inc. v. Cisco Sys., Inc.*, 837 Fed Appx. 799, 809 n.10 (Fed. Cir. 2020)

B. Dr. Uttamsingh Is a Properly Named Inventor of the '659 Patent

Incyte next argues that Concert cannot satisfy any §102(b)(1) exception because "Concert has not shown" that Dr. Uttamsingh is an inventor. Paper 44 at 8. As an initial matter, Incyte has waived any such argument by not challenging inventorship in its petition. In any event, Incyte's argument again misstates the standard of review: under *Dynamic Drinkware*, Concert's burden is—at most—a burden of *production*, not *persuasion*. Concert has satisfied that burden, and Incyte has not disproven Dr. Uttamsingh's inventorship.

Notably, Incyte never bothers to discuss the legal standard of inventorship. "Co-inventors need not physically work together or at the same time, make the same type or amount of contribution, or make a contribution to the subject matter of every claim of the patent." *Trovan, Ltd. v. Sokymat SA, Irori*, 299 F.3d 1292, 1301-1302 (Fed. Cir. 2002) (quotation marks omitted). Instead, "each joint inventor must generally contribute to the conception of the invention." *Id.* That means "each needs to perform only a part of the task which produces the invention." *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1460 (Fed. Cir. 1998).

(arguments not raised "will" be waived), *with* Paper 21 at 7 (issues "may be deemed waived").

Concert satisfied its burden of production under this standard. Dr. Uttamsingh is named as an inventor on the face of the '659 patent. Ex. 1001 at (72). The record reflects her oath, under penalty of perjury, that she is an inventor of the claimed invention. Ex. 1047 at 22. The other evidence is consistent with that oath. For example, Dr. Uttamsingh developed and oversaw the assay demonstrating Compound (I)'s improved metabolic stability vis-à-vis ruxolitinib. *See* Ex. 2069 ¶¶6-12; Ex. 1047 at 635-640; Ex. 1172 at 28:14-29:6, 41:9-14, 42:4-6, 48:17-22, 49:12-17. Concert relied on this type of data in selecting the deuterated compound for development and determining its dose. *See, e.g.*, Ex. 2073 at 6-12. Dr. Uttamsingh plainly performed—at the very least—"*part* of the task" that resulted in the idea of administering Compound (I) to treat hair-loss disorders at the claimed doses.

Incyte argues that Dr. Uttamsingh "confirmed that she did not invent or conceive any limitation." Paper 44 at 8. That is incorrect: Dr. Uttamsingh plainly did not concede a lack of inventorship. Incyte never asked Dr. Uttamsingh about her role on the Concert team, her involvement in the conception of the invention, or her inventorship of the '659 patent's *issued claims*. Instead, during her deposition, Incyte's counsel pointed to various claims in Provisional No. 62/492,758 and asked whether—"based on [that] Exhibit"—it "appear[ed]" that the claims of the provisional application were Dr. Uttamsingh's "original idea" and whether she "originally conceived" of them. Ex. 1172 at 20:11-14, 21:8-19, 22:4-23:3, 25:7-12.

Dr. Uttamsingh responded that, "based on the information in this exhibit," *id.* at 21:13-14—which did not bear her name—it did not so "appear[]," *id.* at 25:7-15. Dr. Uttamsingh was discussing her "understanding" of what "appear[ed]" on the face of a potentially unfamiliar document (*id.* at 22:7-8, 23:5-6, 25:14-15)—not renouncing her contributions to the conception of the claimed invention or recanting her sworn inventorship oath. And *even if* the Board were to read Dr. Uttamsingh's answers as speaking to whether the provisional claims were her "original idea," that vaguely worded phrase is not the legal test: the question is whether she "generally contribute[d] to the conception of the invention" such as by "perform[ing] only a part of the task which produce[d] the invention." *Ethicon*, 135 F.3d at 1460. Incyte has not even attempted to prove that this standard is not satisfied.

The fact that the provisional application erroneously named only Amanda Wagner as an inventor of the claimed material is immaterial. Because "correction of inventorship of a provisional application is normally not necessary," *E.I. du Pont de Nemours & Co. v. MacDermid Printing Solutions*, 525 F.3d 1353, 1360 (Fed. Cir. 2008), there was no need for Concert to amend the provisional application to add Dr. Uttamsingh.

Incyte's argument warps the standard of review to raise an improper collateral attack on Dr. Uttamsingh's inventorship. As Dr. Uttamsingh's declarations and

inventorship oath make clear, she is a joint inventor of the '659 patent. Incyte has not proven otherwise.

C. Incyte's Arguments Regarding the Specific Excluded Disclosures Are Without Merit

As Concert explained (Paper 37 at 20-28), §102(b)(1) requires the exclusion of both the structure and metabolic stability of Compound (I). Without the excluded data, Incyte is unable to carry its burden. Incyte's arguments regarding the specifics of the excluded disclosures (Paper 44 at 10-13) all fail.

First, Incyte argues that Compound (I)'s structure is not excluded because it was previously disclosed in a PCT application. Paper 44 at 10. That argument is a red herring. Incyte's petition pointed only to Silverman—not the PCT application—to substantiate the prior disclosure of Compound (I). Paper 37 at 27. Only Silverman is part of Incyte's alleged combinations. That choice has statutory consequences. Under §102(b)(1)(B), the only question is whether an inventor of the '659 patent disclosed the structure of Compound (I) before it was disclosed in Silverman. Incyte's "re-disclosure" argument attempts to read an exception into §102(b)(1)(B) not found in the statute itself.

Second, Incyte argues that §102(b)(1)(B) does not require the exclusion of Compound (I)'s "uses, doses, and salt forms." Paper 44 at 10. But with the structure of Compound (I) excluded from consideration, there is no compound to have uses, doses, or salt forms. Incyte has no response to that argument.

Third, Incyte argues that the §102(b)(1)(A) exception does not apply to the metabolic stability data in Silverman because the data were not obtained "directly or indirectly from [Dr. Uttamsingh]." Paper 44 at 12-13. Incyte relies on the fact that some tasks related to the assays were physically performed at Dr. Uttamsingh's direction by Richard Gallegos and, according to Incyte (despite the evidence to the contrary, *see* Paper 37 at 25-26), reported by Dr. Gallegos to the Silverman inventors. Paper 44 at 12-13. But it is a familiar principle in patent law that inventors often rely on "the assistance of others." *Trovan*, 299 F.3d at 1302. Applying that principle in this context, §102(b)(1)(A) *does* exclude information that was gathered and communicated at Dr. Uttamsingh's direction and under her control—even if another person carried out some of the physical steps involved.

Incyte's argument also ignores the broad legal standard. The statutory language requires only that Dr. Uttamsingh have "indirectly" provided the data. Moreover, Concert has only a burden of *production—i.e.*, of offering sufficient evidence to conclude that Dr. Uttamsingh indirectly provided the relevant data. The declarations of Dr. Uttamsingh and several Silverman inventors satisfy that burden. The burden of *persuasion* is then on Incyte to demonstrate, by a preponderance, that Dr. Uttamsingh did not provide the relevant data. Incyte has failed to do so.

III. INCYTE HAS NOT DEMONSTRATED THE NECESSARY MOTIVATION OR REASONABLE EXPECTATION OF SUCCESS

A. Neither Ruxolitinib nor CTP-543 Was "In Use" for AA

To support its obviousness contentions, Incyte argues that "[b]y May 2016, JAK inhibitors were already being used successfully to treat AA." Paper 44 at 14. But as Concert explained (Paper 37 at 30-39), Incyte relies on *isolated case reports* showing remission in a *handful of patients* with AA who took *different doses* of ruxolitinib. These case reports lacked placebo-controlled clinical trials—of particular importance for AA, where spontaneous remission is common—and the isolated case reports used doses far from those claimed in the '659 patent. Rather than directly responding to Concert's argument, Incyte simply points back to the same handful of isolated case reports, while adding citations to non-prior art. Paper 44 at 13-16 (discussing "collective force" of Xing and non-prior art "subsequent clinical trials"). Such citations cannot manufacture a reasonable expectation of success.

B. Side-Effects from JAK Inhibitors Would Have Undermined Motivation and Reasonable Expectation of Success

Even without deuteration, JAK inhibitors had well-known safety issues—sometimes even necessitating black-box warnings. Incyte's back-of-the-hand treatment of those issues conflicts with the realities facing a POSA. Incyte criticizes Concert for relying on side-effects reported in myelofibrosis patients (Paper 44 at

16), but the only data in the prior art from randomized controlled ruxolitinib trials were from myelofibrosis studies. The general safety concerns with the JAK class of compounds in other indications were well known. Ex. 2019 at 10. Incyte and its expert instead rely on uncontrolled case reports regarding AA to conclude that side-effects were not an issue. That comparison is improper, even by Incyte's standards. Ex. 1159 ¶12. Incyte also does not dispute that more serious side-effects are tolerated in myelofibrosis, a life-threatening disease, than in AA, where patients are otherwise healthy.

C. A POSA Would Not Have Been Motivated to Focus on Oral Ruxolitinib

Incyte argues that the fact that a POSA would have focused on alternatives to oral ruxolitinib is immaterial (Paper 44 at 17), but the cases it cites stand for the unremarkable proposition that "mere disclosure of alternative designs does not teach away." *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Here, the prior art provided an explicit reason *not* to pursue an oral JAK1/2 inhibitor, like ruxolitinib, because of safety concerns.

Faced with the evidence that tofacitinib was the more promising JAK inhibitor being studied for AA, Incyte argues that this merely demonstrates a focus on JAK inhibitors that inhibit JAK1 as a class. Paper 44 at 17. Incyte's argument ignores the different effect of tofacitinib and ruxolitinib on other JAK pathways as they pertain to efficacy and safety in treating AA. It is undisputed that while tofacitinib

inhibits JAK1/3, ruxolitinib inhibits JAK1/2, and JAK2 inhibition is more likely to impact blood cell growth and development, leading to blood-related side-effects and toxicity. Ex 1071 at 10 & fig. 3. Even Incyte does not really dispute that Christiano's main focus is JAK3 inhibition (a target not impacted by ruxolitinib) to treat AA. Incyte argues only that Christiano also discloses preclinical (*i.e.*, animal) experiments with ruxolitinib and describes ruxolitinib's success in treating *other* diseases. This does not demonstrate that the POSA would have focused on ruxolitinib for AA over tofacitinib.

Indeed, only tofacitinib had been approved for immune-mediated diseases. Incyte suggests its licensing arrangement prevented it from developing ruxolitinib for immune-mediated diseases (Paper 44 at 18), but the existence of this licensing arrangement *corroborates* the lack of focus on ruxolitinib for AA. Incyte was well-positioned to recognize the alleged promise of ruxolitinib for AA, yet there is no evidence that Incyte or any of its licensees are developing the drug for the oral treatment of AA.

Incyte argues that the clear preference for topical treatment over oral treatment for AA does not undercut the motivation for pursuing oral ruxolitinib, pointing to the fact that the majority of clinical reports on JAK inhibitors related to oral formulations. Paper 44 at 18-19. Because oral formulations were more readily

available, however, researchers used oral formulations in some clinical reports despite the preference for topical administration. Ex. 2054 at 47:13-22, 122:3-13.

Incyte argues that a "'general preference' for topical" does not "teach away from oral" (Paper 44 at 19), but that misses the point: the general preference for topical formulations teaches away from *deuteration*. Incyte does not dispute that there is no motivation to deuterate a compound used for topical treatment. *See* Paper 37 at 42-43.

D. The Use of Compound (I) for AA Was Not Obvious

Incyte has failed to establish that a POSA would have been motivated to choose Compound 111 from Silverman or had a reasonable expectation of success in using it to safely and effectively treat AA. Incyte's assertion (Paper 44 at 19-20) that a POSA would expect Compound (I) to be the "functional equivalent of ruxolitinib" is unsupported. And its new argument that the '659 patent's claims would be obvious even without the stability data in Silverman or the Uttamsingh Declaration (Paper 44 at 20) is both waived and incorrect. The effects of deuteration, even at the metabolic hotspots, are notoriously unpredictable. Incyte's own references suggest that any assumption to the contrary is "pernicious," Ex. 1033 at 14; at times, deuteration can even *accelerate* metabolism. Ex. 1122 at 2; Ex. 2068 ¶¶52, 55; Ex. 1044 at 1-2, 6, 8; Ex. 1053 at 3; Ex. 1043 at 69; Ex. 1052 at 11.

E. The Claimed Dosing Regimens Were Not Obvious

1. Incyte Relies on Hindsight

Incyte argues that 16 and 24 mg/day doses of CTP-543 would have been obvious in light of the 30 mg/day dose of ruxolitinib because a POSA would have been motivated to use a lower dose of the deuterated molecule. Paper 44 at 24; Ex. 1120 ¶75. But even if there would have been a motivation to use a lower dose *in the abstract*, Incyte provides no explanation, other than hindsight, for why a POSA would have been motivated to use the *specific claimed doses*. Incyte notes that, in some cases, deuteration can reduce metabolism (Paper 44 at 24), but that falls far short of explaining why one would expect the surprising effectiveness of CTP-543 at 16 or 24 mg/day. It also ignores the fact that decreased metabolism is not necessarily desirable for drugs with safety concerns like JAK inhibitors. Ex. 1027 at 4.

2. A POSA Would Not Have Arrived at the Claimed Regimens Through Routine Optimization

Incyte's "routine optimization" argument fails for several reasons.

First, while Silverman discloses a multitude of exemplary dose ranges, none are identified as useful for treating a hair-loss disorder. Silverman does not even suggest that its compounds *can* be used to treat a hair-loss disorder, much less within the exemplary ranges. To the contrary, Silverman discloses that "[e]ffective doses will also vary, as recognized by those skilled in the art, depending on the diseases

treated." Ex. 1002 at 20:19-27. The prior art does not disclose *any* range of effective doses encompassing the claimed regimen, and therefore the cases cited by Incyte related to "routine optimization" are inapposite. *Teva Pharms. USA, Inc. v. Corcept Therapeutics, Inc.,* No. 2021-1360, 2021 WL 5816289, at *4 (Fed. Cir. Dec. 7, 2021) (prior-art range case law is inapplicable where "the general working conditions disclosed in the prior art [do] not encompass the claimed invention"); *Galderma Labs, LP v. Tolmar, Inc.*, 737 F.3d 731, 737-738 (Fed. Cir. 2013).

Second, Incyte's argument conflates the *dose amounts* disclosed by Silverman with the *dosing regimens* of the claims. Silverman discloses only the "effective amount," not the frequency of administration. Ex. 1002 at 20:9-18. The "effective amount" refers to "an amount which, *when administered in a proper dosing regimen*, is sufficient to treat the target disorder." Ex. 1002 at 19:67-20:2 (emphasis added). Notably, the challenged claims do not merely require a dose of 16 or 24 mg; they require administering the specified dose once or twice per day. Thus, Incyte fails to show how routine optimization would even lead to the claimed invention.

Third, Incyte's focus on one narrower range disclosed by Silverman (5-50 mg) to support its "optimization" theory is misleading. Silverman broadly discloses that "an effective amount of a compound of this invention can range from 1-500 mg." Ex. 1002 at 20:9-10. While Silverman discloses a number of narrower, exemplary ranges, it does not indicate for which compounds, diseases, routes of administration,

sex, age, excipients, etc. (all of which Silverman discloses may affect the dosage amount) these ranges are applicable. Nor does Silverman express a general preference for any particular narrower range. Incyte's unsupported allegation to the contrary (Paper 44 at 22) is a transparent attempt to avoid caselaw that plainly contradicts its position. *See E.I. DuPont de Nemours & Co. v. Synvina, C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("disclosure of very broad ranges may not invite routine optimization").

Fourth, Incyte's allegation that the prior art demonstrates "[t]itrating ruxolitinib for AA and other off-label uses within the 5-50 mg/day FDA-approved range was routine" (Paper 44 at 22-23) is incorrect. As Incyte's expert admits, none of the prior-art references that Incyte cites as purportedly reflecting this practice provide any detail concerning how the doses were selected. Paper 44 at 23 n.12 (citing Ex. 1148, Ex. 1151, Ex. 1157); Ex. 2174 at 149:6-10, 147:16-19. The only other "evidence" Incyte relies upon to support this proposition is an article by Silvestri, which is not even prior art. Paper 44 at 23 n.12.

3. A POSA Would Not Have Arrived at the Claimed Regimens by Lowering the Prior-Art Ruxolitinib Doses

Incyte also argues that a POSA would have arrived at the claimed 16 and 24 mg/day regimens by simply "lowering" the ruxolitinib doses that, according to Incyte, the prior art taught for the treatment of AA—a number that Incyte itself puts as 30 mg. Paper 44 at 23-27.

But a POSA would not know how effective, if at all, ruxolitinib would be at treating AA. Paper 37 at 36-39, 65-69; Ex. 2059 ¶¶24, 38, 42, 63-68, 77. Incyte's references are mere case studies; in the absence of a control group, a POSA would not have reasonably expected administration of ruxolitinib to effectively treat AA, particularly since "[t]he high, but unpredictable, rate of spontaneous remission [in AA] means that it is difficult to objectively assess the efficacy of treatment." Ex. 1145 at 3. Incyte attempts to sidestep this fundamental problem by asserting that spontaneous remission is implausible because in "severe AA," "remission is rare." Paper 44 at 15. But, as Incyte's expert admitted, nothing in the prior art suggests that spontaneous remission is rare in cases of severe AA. Ex. 2174 at 99:21-100:5.

Incyte cherry-picks a number of statements in the prior art to suggest a POSA would have predicted that deuterating ruxolitinib at the eight precise locations of Compound (I) would improve its metabolic stability, and thereby allow it to be dosed in lower amounts. Paper 44 at 24. But the art related to deuteration, as a whole, taught unpredictability. *See supra*, at 14. Incyte extracts a single sentence from one reference to support its claim that deuteration provides "[b]etter tolerability through reduction of overall dose." Paper 44 at 24. However, Incyte excludes from its quotation the qualifier that deuteration provides only "the potential for" better tolerability. Ex. 1034 at 3. "Potential" does not mean a POSA would have expected Compound (I) to exhibit such properties. Rather, the prior art characterized the

supposition that deuteration improves stability as a "naïve view" that is "surprisingly pernicious" because "there are no hard and fast rules for predicting what examples will work." Ex. 1033 at 14.

Incyte wrongly states that "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." Paper 44 at 25. As explained throughout Concert's patent owner response (*e.g.*, at 36-39, 65-69), the prior art did not disclose a "strong response" to treatment of AA with ruxolitinib at these, or any other, doses; a POSA would not have concluded that there was a reasonable expectation of success in treating AA with ruxolitinib (much less CTP-543) at the claimed doses based on such limited reports. And, without a known efficacy threshold, linear pharmacokinetics has no bearing on whether a POSA would have expected the claimed doses to be effective; it only means that administering lower amounts of the drug will lead to proportionately lower concentrations of the drug in the blood. Ex. 2174 at 160:22-163:3.

Incyte argues that the criticism that Dr. Patterson uses methods that bear no relationship to AA or ruxolitinib in making his flawed estimates of ruxolitinib dose is a "strawman," because "correlating potency and exposure" is not drug or disease dependent. Paper 44 at 26. But Incyte continues to confuse a compound's "potency" with its efficacy. *See* Paper 37 at 67-69 (explaining the difference). Potency alone

does not determine efficacy, which depends on other properties of the drug and the disease. Ex. 2059 ¶87. Incyte's other attempted defense of Dr. Patterson's arguments—that Concert's criticism are "mired in contradictions" (Paper 44 at 26-27)—is plainly wrong; Incyte merely lists three bullet points that invite the Board to "compare" references that are, in fact, entirely consistent with one another.

IV. OBJECTIVE INDICIA SUPPORT PATENTABILITY

A. Unexpected Results

Concert showed that CTP-543 (1) has an unexpectedly superior efficacy and safety profile in treating AA, and (2) unexpectedly shows reduced drug-drug interactions. Incyte's counterarguments are unavailing.

Incyte first attempts to dismiss these unexpected benefits by arguing lack of nexus because the claims require "at least 95%" or "at least 97%" deuterium incorporation for Compound (I). Paper 44 at 1-2. But CTP-543 *does* have at least 95% deuterium incorporation. Ex. 1176 at 50. And even if CTP-543 had less than 95% deuterium incorporation, Incyte's expert conceded that if the benefits of deuteration were present for a less deuterated compound, at least those same benefits would be present for a more highly (>95% or >97%) deuterated compound. Ex. 2173 at 104:5-105:6. The nexus requirement does "not require the patentee to prove perfect correspondence," but to "demonstrate that the product is essentially the

claimed invention" *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1361 (Fed. Cir. 2021). Here, Concert has shown the required nexus.

Incyte next argues that for efficacy, ruxolitinib is the closest prior art so a comparison with ruxolitinib "under equivalent conditions" is necessary. Paper 44 at 2-3. But it is undisputed that there *were no* prior-art data from placebo-controlled clinical trials on the efficacy of ruxolitinib in treating AA. Ex. 2174 at 60:5-63:7. That is, there were no "equivalent conditions" for ruxolitinib, a drug that had only been tried for treatment of AA in isolated case reports. Moreover, "[d]irect comparison with the closest prior art is not required in all cases" and courts have "found indirect comparisons persuasive of unobviousness." *In re Merchant*, 575 F.2d 865, 869 n.8 (C.C.P.A. 1978).

In any event, CTP-543 showed unexpected results over ruxolitinib. The average baseline SALT score was much higher in the CTP-543 study than the ruxolitinib study—88 versus 65.63. *Compare* Ex. 1089 at 6, *with* Ex. 1049 at 2. As Incyte's expert Dr. Shapiro conceded, individuals with higher baseline SALT scores are less likely to respond to treatment. *See* Ex. 2054 at 159:8-25. Thus, even if the *reduction* in SALT scores between the CTP-543 and ruxolitinib studies are similar, the *baseline* SALT scores in the CTP-543 study made treatment response less likely. Especially in light of its lower doses, CTP-543's results are thus unexpected.

Incyte next attacks the statistical significance of the data showing CTP-543's superiority over baricitinib. This argument is not from the perspective of a POSA and should be given no weight. Dr. Thisted analyzed only some of the data to reach his conclusion. But Incyte's dermatology expert, Dr. Damsky, admitted that it was hard to say whether a POSA would have independently viewed the data this way. Ex. 2174 at 177:15-19. As Dr. Ko explained, these data show a POSA that the results achieved by CTP-543 by 24 weeks and 36 weeks surpassed the results obtained by baricitinib. Ex. 2059 ¶103.

Incyte's arguments that the superior efficacy data are not "commensurate in scope" with the claims for a variety of reasons do not withstand scrutiny. "Commensurate" does not mean "identical" but rather "reasonably commensurate with the scope of the claims." *In re Huai-Hung Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

Turning to the second unexpected result—reduced drug-drug interaction (*see* Ex. 2059 ¶¶105-107)—Incyte offers several unfounded arguments. Incyte attacks Concert's DDI study for using itraconazole, which Incyte claims is weaker than ketoconazole used in the ruxolitinib study. Paper 44 at 4. But Incyte's own expert conceded that the ruxolitinib label describes both itraconazole and ketoconazole as "strong inhibitor[s]." Ex. 1004 at 5; Ex. 2173 at 99:3-22. Concert's use of itraconazole was also consistent with FDA warnings against ketoconazole use in

DDI studies. Ex. 1131 at 1. Incyte's criticism of the 200 mg dose used in the Concert study ignores that this is the median dose given in reported DDI studies using itraconazole. Ex. 1131 at 2; Ex. 1135 at 2; Ex. 2173 at 63:11-64:3. And Incyte's argument that the sample population used in the DDI study—healthy subjects—is outside the scope of the claims, Ex. 1120 ¶41, is misplaced. The FDA recommends that "[m]ost clinical DDI studies can be conducted using healthy subjects." Ex. 2095 at 10. Indeed, the ruxolitinib DDI study also used healthy subjects, Ex. 1004 at 6-7, and as Incyte's expert admitted, DDI studies are generally run in healthy subjects to determine the proper labeling for dosing in patients. Ex. 2173 at 65:5-22.

Incyte's argument that the DDI effect is merely a difference in degree is inapt. The undisputed evidence shows that while the ruxolitinib label requires a drug-drug interaction warning regarding dose modification in the presence of strong CYP inhibitors (including, specifically, itraconazole), the label for CTP-543 likely will not. Ex. 2068 ¶¶28-29. This is plainly a practical difference in kind.

Incyte's argument that a reduction in drug-drug interactions would be expected is likewise unsupported. Where there is data on reduced DDI, the deuterated agent in the cited prior art is *causing* the DDI (*i.e.*, slowing the metabolism of another drug). Here, the issue is not whether ruxolitinib slows the metabolism of another drug but the opposite—whether its metabolism is slowed. Hence, Incyte's comparisons are inapt. *See, e.g.*, Ex. 1128; Ex. 1052; Ex. 2173 at

31:3-8, 35:2-8. In any event, a few examples do not create an expectation of reduced DDIs generally from deuteration. Ex. 1128 at 6, 16 (noting unpredictability of impact of deuteration on DDIs absent testing).

B. Long-Felt Need

Incyte accuses Concert of "recycl[ing]" a long-felt need argument that was "rejected as 'premature' in the Silverman IPR." Paper 44 at 5. But Concert has introduced additional data now proving CTP-543's dramatic efficacy in treating AA. Ex. 2083; Ex. 2118. That other drugs also received Fast Track and Breakthrough Therapy designations for AA further corroborates the existence of an unmet need (*see* Ex. 1155; Ex. 1156) and refutes Incyte's argument that ruxolitinib had solved any need as of the priority date.

V. CONCLUSION

The Board should reject Incyte's challenges.

December 13, 2021

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. §42.24

I hereby certify that this "PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER RESPONSE" complies with the word count limitation of 37 C.F.R. §42.24(a)(1)(ii) and (b)(2) because the response contains 5,596 words, excluding the cover page, signature block, and the parts of the response exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document captioned "PATENT OWNER'S SUR-REPLY TO PETITIONER'S REPLY TO PATENT OWNER RESPONSE" and Exhibits 2173-2174 were served electronically via e-mail on this December 13, 2021, as follows:

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