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 RESPONSE

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I. INTRODUCTION

U.S. Patent No. 10,561,659 ('659 patent) claims a method of using specific doses of a novel compound to treat alopecia areata (AA), a disease with a complex and only partially-understood etiology for which skilled artisans had repeatedly tried—and failed—to develop a viable therapy. Petitioner Incyte argues that the '659 patent's claims are obvious, but it arrives at that conclusion only by stringing together scattered disclosures from disparate references in a way a skilled artisan never would have done. The Board should reject Incyte's hindsight-driven combinations.

Incyte's arguments fail first because several critical disclosures in Incyte's main reference—Silverman—are not prior art. Incyte relies on Silverman's disclosure of both the structure of Concert's novel compound—variously known as "Compound (I)," "Compound 111," or "CTP-543"—and data demonstrating that the compound is more stable than a prior-art compound, ruxolitinib. But those disclosures are excluded as prior art under both the common-owner and inventor-disclosure exceptions of 35 U.S.C. §102 (AIA). Without those key disclosures, Incyte's arguments cannot stand: Incyte has not pointed to *any* other reference teaching the structure of Compound (I) or its relative metabolic stability.

Even if all of Silverman's disclosures are considered prior art, Incyte's arguments still fail. The prior art would not have directed a skilled artisan to treat

AA with ruxolitinib or another Janus kinase inhibitor; to select Compound (I) specifically; to substitute Compound (I) for ruxolitinib; or to select the claimed doses and frequency. And even if the skilled artisan would have considered Janus kinase inhibitors to treat AA, known safety concerns would have encouraged the use of topical treatments and discouraged oral formulations—and thus would have taught away from deuterated compounds like Compound (I). The scattered references on which Incyte relies also would not have provided a skilled artisan with a reasonable expectation of success. Efforts to develop an AA treatment repeatedly failed, and a handful of anecdotal reports would not have provided any degree of confidence that a skilled artisan could arrive at the claimed methods. Finally, objective indicia support patentability: CTP-543 has demonstrated an unexpectedly superior efficacy/safety profile in the treatment of AA and an unexpected ability to avoid harmful drug-drug interactions, and the claimed methods of treatment satisfy a long-felt need for AA therapies.

For all these reasons, the Board should reject Incyte's hindsight-driven obviousness arguments.

II. STATE OF THE ART

A. AA and Failed Treatment Efforts

AA is one of the most prevalent autoimmune diseases in the United States. Ex. 1005 at 1:47-48; Ex. 2059 ¶17. An AA patient's immune system attacks hair

follicles, resulting in hair loss that is often extensive—or even complete—and sometimes permanent. Ex. 1003 at 5; Ex. 1005 at 1:49-54. The progression of AA is unpredictable; about a third of patients experience spontaneous hair regrowth within the first year of appearance. Ex. 2006 at 1; Ex. 2059 ¶18. While AA is not life-threatening (Ex. 2037 at 1), the disorder has severe—and potentially debilitating—psychosocial consequences. Ex. 1005 at 1:56-59. AA can be a chronic, lifelong condition for which there is no cure. Ex. 1021 at 1.

As of the priority date, skilled artisans had repeatedly tried—and failed—to develop a suitable treatment for AA. The prior art reflected dozens of studies and trials of potential AA therapies. Ex. 2056 at tables 1-2; Ex. 2041 at 1 (referring to 29 trials). Yet many of these studies failed to demonstrate any efficacy, and "most studies had major limitations that hinder the interpretation of these results." Ex. 2056 at 1; *see id.* at table 1. Researchers fell particularly short in showing evidence of an effective AA treatment through randomized clinical trials. *See* Ex. 2008 at 17-18; Ex. 2041 at 1. In short, there was "no universally proven therapy to induce hair re-growth and sustain remission" and it was "unclear if any treatment alters the long-term course of the disease." Ex. 2008 at 6. Despite numerous efforts to develop a treatment, Anzengruber 2016 taught—less than two weeks before the priority date—that that there was "currently no effective evidence-based treatment for AA." Ex. 2058 at 2; Ex. 2059 ¶38.

One confounding factor that made it difficult to study and develop a successful AA treatment was spontaneous remission: As mentioned above, a significant proportion of AA patients experience spontaneous hair regrowth. This phenomenon—well documented in the prior art—makes it impossible to rely on anecdotal reports to demonstrate that hair regrowth is the result of a proffered treatment without a randomized, controlled clinical trial. Ex. 2059 ¶27; *see also* Ex. 2008 at 6 ("It can be difficult to assess the efficacy of interventions in the absence of a control group because spontaneous recovery can occur, particularly in mild forms of the disease."); *id.* at 17 (noting the difficulties arising from "the possibility of spontaneous remission").

Another factor making it difficult to develop a successful AA treatment was the need to avoid serious side effects. Ex. 2059 ¶¶28-30. While AA has a significant impact on an individual's life, the disease is not life-threatening. Thus, serious adverse reactions are far less acceptable in an AA medication than they would be in, say, a medication treating a potentially fatal illness like cancer. *See, e.g.*, Ex. 2037 at 1 (explaining that, because "AA is a benign lifelong genetic predisposition" that often affects young patients, "[s]afety aspects [must] be carefully considered"). Unfortunately, however, a number of potential AA treatments "ha[d] documented side effects, some of which can be unpleasant or potentially serious." Ex. 2008 at 6. This was particularly true for the class of drugs at issue here, Janus kinase (JAK)

inhibitors. Ex. 1027 at 4 (noting "risks for serious adverse events with systemic therapy" using JAK inhibitors); Ex. 1074 at 17 (reporting study of JAK inhibitor for psoriasis where 1.4%, 6.3%, and 8.7% of patients on 4-, 8-, and 10-mg doses developed blood- or lymphatic-related side effects). And public reports documented the FDA's reluctance to approve another JAK inhibitor, tofacitinib, for treatment of psoriasis because of "elevated safety risks." Ex. 2013 at 1. Many patients "may consider the adverse effects of treatment and the unpredictable outcome unacceptable." Ex. 2008 at 6.

In part because of these side effects associated with orally administered, systemic therapies, to the extent the prior art pointed toward any treatment for AA, it was toward a topical treatment. Ex. 2059 ¶¶31, 74-75. Several prior-art references noted that the "risks for serious adverse effects [associated] with systemic therapy . . . may be avoided if topical therapy were an option." Ex. 1027 at 4; *see* Ex. 2041 at 1 (observing that "[m]ost physicians generally prefer topical therapy for AA"); Ex. 2037 at 1 (explaining that while JAK inhibitors "offer advantages for effective oral delivery," they come with "a broad spectrum of side effects," making them "highly interesting candidate molecules for *topical* treatment" of AA (emphasis added)); *see also id.* ("[A] focus of research should be put on ways to increase follicular penetration and reduce systemic absorption."). Incyte's own expert, Dr. Shapiro, agrees. Ex. 2054 at 38:4-5 ("If there is the same efficacy, a topical would

be preferred."); *id.* at 37:9-10 (explaining that a topical therapy is "for sure" preferred from a "safety" perspective); Ex. 2040 at 16 (paper co-authored by Dr. Shapiro concluding that "[t]opical or skin localized treatments are a key focus of interest since AA is a relatively organ-restricted autoimmune condition"); *see also* Ex. 2055 at 144:7-8, 147:6-23, 180:10-13, 181:6-9, 184:10-185:6 (Dr. Patterson agreeing that a number of references would have taught a skilled artisan the preference for topical over systemic treatment).[1]

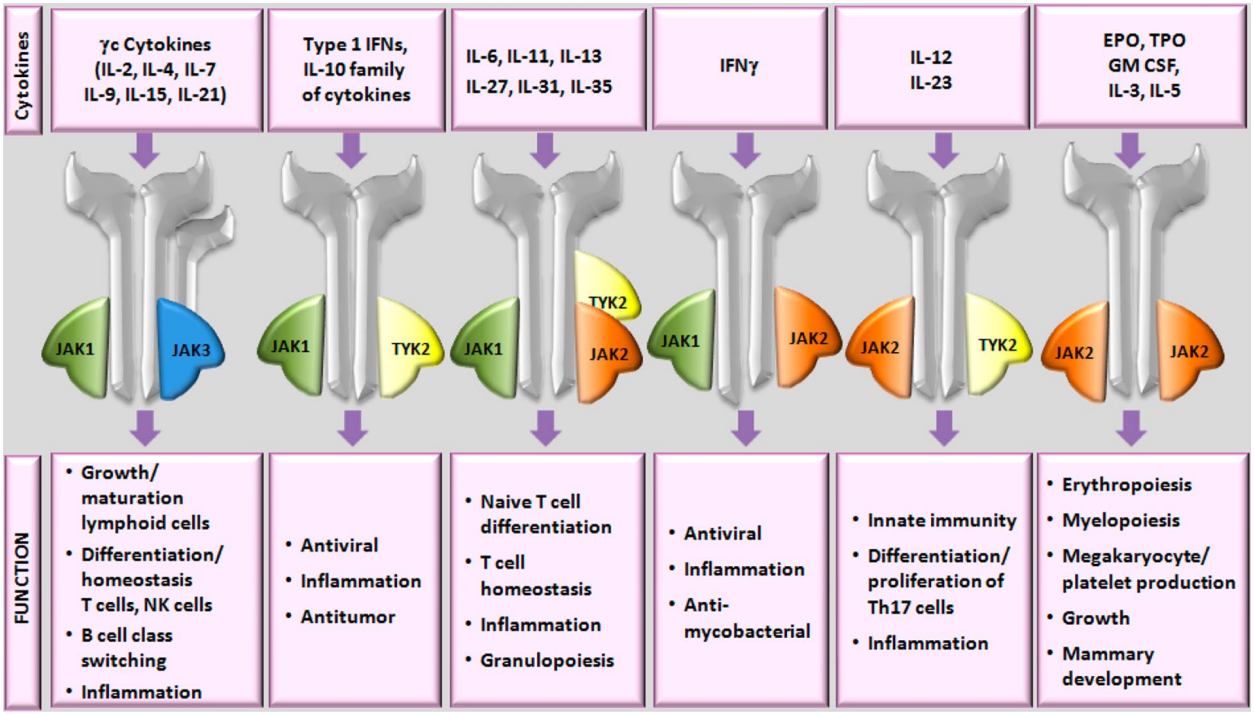
In sum, as of the priority date, persons of ordinary skill in the art had repeatedly and unsuccessfully attempted to develop treatments for AA. Ex. 2059 ¶¶22-26. And to the extent the prior art pointed toward any treatment, it pointed to topical therapies for safety reasons.

B. The Complexity of JAK Signaling Pathways

Among the many treatments that had been studied for AA, Incyte's challenge focuses on a class of compounds known as Janus kinase inhibitors—or JAK inhibitors—including a specific JAK inhibitor called ruxolitinib.

[1] Indeed, a 2020 study funded by Incyte observes that "[a] topical formulation remains the ideal treatment for otherwise healthy AA patients ranging from young children to vulnerable elderly patients." Ex. 2062 at 7.

JAK proteins are part of a cell's complex signaling mechanism, serving as just one link in a complex cascade of processes that relays signals that are important to the body's immune response (among other things). Ex. 1002 at 2:59-65; Ex. 2059 ¶33-34. The cascade begins when one of several different types of signaling molecules binds to one or more receptors on the cell's surface. There are many different types of signaling molecules—including families of cytokines, interleukins, and growth factors—each associated with different cell-surface receptors and different signaling pathways:



Ex. 1071 at 3; Ex. 2059 ¶35. Once a cytokine binds to a receptor, one or more JAK proteins associated with that receptor activate a signaling pathway inside the cell. There are a number of specific JAK proteins—JAK1, JAK2, JAK3, and TYK2—

some combination of which is involved in the signal cascade for each particular signaling molecule and its cognate receptor. *Id.* The JAK proteins, in turn, activate a variety of further signaling molecules, including one or more of seven different types of STAT proteins. Ex. 1020 at 9-11; Ex. 2059 ¶39. A given set of JAK proteins can activate different STAT proteins in different cells. Once activated by a JAK protein, these other signaling molecules move to the cell's nucleus to activate one or more genes to produce further proteins that will then exert downstream effects. Ex. 2059 ¶40. Defects in these signaling pathways are believed to lead to certain autoimmune diseases, including AA. Ex. 2022 at 1, 5.

As of the priority date, however, it was unclear which of the above pathways, and which part of any pathway, would be most relevant to target for treating AA. Ex. 2059 ¶¶19-20. Treatments that had been considered as of May 2016 included drugs intended to target several different parts of these signaling cascades. For example, researchers had studied ustekinumab, an antibody for the cytokines IL-12 and IL-23, as well as AG490, a STAT3 inhibitor. *See* Ex. 1005 at 2:36; Ex. 2085 at 1; Ex. 2106 at 1; Ex. 2055 at 138:18-24; Ex. 2059 ¶21.

C. Treatment of AA with Ruxolitinib and JAK Inhibitors

Despite the multitude of potential targets for treatment of AA, Incyte and its experts use hindsight to focus exclusively on JAK inhibitors as the class of compounds of interest to a skilled artisan. *See* Ex. 2055 at 76:18-25. As their name

suggests, JAK inhibitors block the action of JAK proteins. Ruxolitinib is a JAK inhibitor that mainly inhibits two members of the JAK family: JAK1 and JAK2. *See* Ex. 1001 at 2:51-57; Ex. 1004 at 7; Ex. 2059 ¶36. Other JAK inhibitors, like tofacitinib, inhibit JAK1 and JAK3. Ex. 1068 at 1. Ruxolitinib is FDA-approved to treat various forms of the rare and life-threatening bone marrow/blood cancer known as myelofibrosis. *See* Ex. 1001 at 2:64-3:2; Ex. 1004 at 4; Ex. 2059 ¶37. The precise mechanism of action for ruxolitinib's efficacy in treating myelofibrosis is not known.

As of the priority date, the prior art as a whole would not have indicated to a skilled artisan that JAK inhibitors in general—or ruxolitinib in particular—could be used successfully to treat AA. Ex. 2059 ¶49. That was true for a number of reasons.

First, as discussed above (p. 3), clinical trials of numerous candidates for the treatment of AA consistently failed. Notably, that failure included JAK inhibitors. The JAK inhibitor tofacitinib, for example, failed to produce a durable response in a patient studied with the drug. *See* Ex. 2058 at 1 (noting that there were "initial signs of hair regrowth" but "efficacy quickly waned"). As one reference noted, "[i]n contrast to the therapeutic applications existing for haematology and rheumatology, there [were] no licensed dermatological indications for JAK or STAT inhibitors." Ex. 2063 at 3. It is only with the benefit of hindsight that JAK inhibitors stand out as a potential focus for AA therapy.

Second, it was unclear which JAK inhibitors, if any, could be used successfully to treat AA. As just discussed, the JAK signaling process is complex, with numerous different signaling molecules, four different JAK proteins, and a number of downstream signaling proteins (including at least seven different STAT proteins). The prior art did not teach which mix of JAK proteins should be inhibited to effectively treat AA while avoiding unacceptable off-target effects.

Third, despite their benefits, JAK inhibitors, including ruxolitinib, are associated with a number of serious side effects that occur with significant frequency, including blood-related toxicities such as anemia (low red blood cell count), thrombocytopenia (low platelet count), and neutropenia (low white blood cell count). *See* Ex. 1004 at 6. In one placebo-controlled study, the percentage of individuals who experienced such conditions while taking ruxolitinib was markedly higher than the percentage of patients taking a placebo. *Id.* at 7. Another study reported high levels of neutropenia in healthy volunteers who took ruxolitinib for just ten days. *See* Ex. 1059 at 5-6. Yet another study reported increased rates of neutropenia and serious infection in a tofacitinib study in rheumatoid arthritis. *See* Ex. 2120 at 7, 11; *see also* Ex. 2039 at 3 (describing adverse events from the use of tofacitinib in psoriasis). In light of these side effects, the FDA has thus far required a black-box warning in the prescribing information of all JAK inhibitors approved for treatment of autoimmune conditions. Ex. 2019 at 10; Ex. 2021 at 1, 4-5. While

these significant side effects may be acceptable when treating blood cancers, they are far less acceptable when treating a "benign" condition such as AA. Ex. 2037 at 1.

JAK inhibitors also raise the concern of deleterious drug-drug interactions. The label for ruxolitinib contains a strong warning to avoid administering ruxolitinib with strong CYP inhibitors; strong CYP inhibitors inhibit drug metabolism and risk overexposure to ruxolitinib, increasing the risk of side effects. *See* Ex. 1004 at 5-8. This drug-drug interaction problem limits the ability to administer ruxolitinib concurrently with several classes of CYP inhibitors, including certain antibiotics and antifungals. Each of these safety concerns would have militated against the systemic administration of JAK inhibitors as a treatment for AA. Ex. 2059 ¶41.

Fourth, even if a skilled artisan would have been motivated to study JAK inhibitors in general for AA, ruxolitinib would have been a poor candidate for further development. Although both the JAK1/2 and JAK1/3 pathways were hypothesized to play a role in AA, inhibition of the JAK1/2 pathway was considered riskier from a safety standpoint, because that pathway is implicated in a variety of other important bodily functions. Ex. 2059 ¶46. Thus, a skilled artisan would have hesitated to pursue a JAK1/2 inhibitor like ruxolitinib. Moreover, ruxolitinib is the only FDA-approved JAK inhibitor that had not been approved for immune-mediated skin and joint diseases; ruxolitinib still only has cancer indications, while other JAK

inhibitors are approved for rheumatoid arthritis and psoriasis. Ex. 1004 at 4; Ex. 2059 ¶47. To the extent a skilled artisan would have looked to use JAK inhibitors at all to treat AA, she would have gravitated toward JAK inhibitors approved at the priority date for similar immune-mediated diseases. Ex. 2059 ¶47.

Finally, to the extent JAK inhibitors showed potential in AA, it was as a *topical* treatment. *See, e.g.*, Ex. 2037 at 1; *see also* Ex. 1027 at 4 (identifying "*[t]opical* JAK inhibitors" as an opportunity for development); Ex. 2055 at 144:7-8, 147:6-23, 180:10-13, 181:6-9, 184:10-185:6 (agreeing that a number of references, including those on which Incyte relies, disclosed a preference for topical treatments). As Incyte's expert, Dr. Shapiro, explained, a topical therapy is "for sure" preferred from a "safety" perspective. Ex. 2054 at 37:9-10. Indeed, a skilled artisan would have known that for non-cancer indications, ruxolitinib was being pursued in topical form: Phase 2 clinical trials for topical ruxolitinib to treat AA were underway in January of 2016. *See* Ex. 2130 at 7; Ex. 2059 ¶48.

III. CONCERT'S INVENTION

A. CTP-543

Against this backdrop, Concert developed novel methods of treating hair-loss disorders, including AA, by administering specific doses of a compound known as CTP-543. Ex. 2059 ¶50. Concert invented CTP-543 by modifying the drug ruxolitinib with deuterium atoms at eight key locations. CTP-543 is currently in

clinical trials for the treatment of AA, where it has shown surprisingly promising activity and safety in treating AA at twice-daily doses of only 8 mg and 12 mg. *See* Ex. 2026; Ex. 2059 ¶¶100-103; Ex. 1089 at 19.

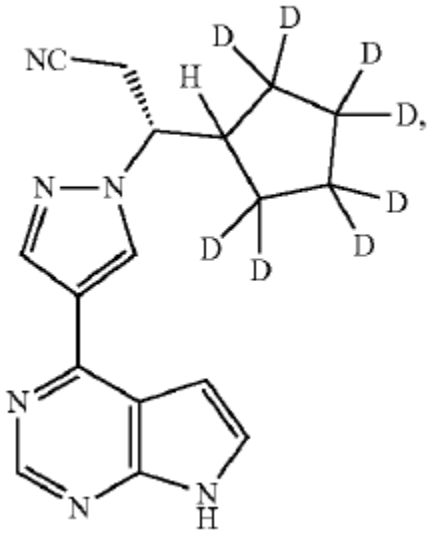
B. The '659 Patent

The '659 patent issued on February 18, 2020, from the U.S. national stage application of a PCT application filed on May 4, 2017. That application claims earliest priority to a provisional application filed on May 4, 2016. The named inventors of the '659 patent are Amanda T. Wagner, James V. Cassella, Philip B. Graham, Virginia Braman, Vinita Uttamsingh, Jana Von Hehn, and Colleen E. Hamilton. Ex. 1001 at 1. The patent is assigned to Concert. *Id.*; *see also* Ex. 2011.

C. The Challenged Claims

Claim 1 covers a method of treating a hair-loss disorder with either 16 mg per day or 24 mg per day of CTP-543—referred to as "Compound (I)"—where each position in the compound designated specifically as deuterium has at least 95% incorporation of deuterium:

Compound (I)



Ex. 2059 ¶51.

Independent claim 9 is similar to claim 1, but specifies that the dose is 8 mg of Compound (I) twice a day. Ex. 2059 ¶52. As in claim 1, each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium. Independent claim 11 specifies 12 mg of Compound (I) given twice a day, but is otherwise the same as claim 9.[2]

The remaining claims are dependent claims. Claims 2-7, 13, 14, and 21 depend from claim 1; claims 10 and 15-17 depend from claim 9; and claims 12 and

[2] Concert disclaimed independent claim 8 to streamline the proceedings. *See* Paper 11 at 74; Ex. 2020.

18-20 depend from claim 11. Ex. 2059 ¶¶53-54. These dependent claims are directed to particular dosing schedules, formulations, and methods of treating AA.

IV. PERSON OF ORDINARY SKILL

Concert proposes that a person of ordinary skill in the art (POSA) would have had:

> a Ph.D. in chemistry, pharmaceutical sciences, molecular biology, or a similar field, or an M.D. with similar background. A person of ordinary skill in the art would also have had at least several years of experience with drug design, drug development, clinical trials, or access to other individuals with that knowledge and experience. Likewise, a person of ordinary skill in the art would have had knowledge and experience in treating hair-loss disorders, or access to a person with that knowledge and experience. A person of ordinary skill in the art would also have had experience in JAK inhibition, deuteration, and AA formulations, or access to a person with that knowledge and experience.

Ex. 2059 ¶14.

This is the same definition as that proposed by Incyte, except Incyte's definition excludes the last sentence. *See* Paper 1 at 19-20. Incyte's proposed definition is incomplete, because it lacks any requirement for experience in JAK inhibition, deuteration, and AA formulations. Ex. 2059 ¶15-16. Concert's proposal is more appropriate because it accounts for the specific facts pertinent to this case—

whereas Incyte's proposal does not attribute the requisite background knowledge to a POSA with respect to the subject matter of the '659 patent as of May 4, 2016.

V. GROUNDS 1 AND 2 SHOULD BE DENIED BECAUSE INCYTE HAS FAILED TO PROVE THAT SILVERMAN'S KEY DISCLOSURES ARE PRIOR ART UNDER §102

Silverman is central to both of the invalidity grounds on which the Board has instituted review. Incyte relies on §102(a)(1) and (a)(2) in its attempt to establish that Silverman is prior art to the '659 patent. Paper 17 at 1. But Silverman is not prior art under §102(a)(2) because it satisfies the common-ownership exception in §102(b)(2)(C), and the central disclosures of Silverman are not prior art under §102(a)(1) because they satisfy the inventor-disclosure exceptions in either §102(b)(1)(A) or (B). Once those disclosures are excluded, the remaining disclosures are insufficient to sustain Incyte's burden of proving obviousness. On that basis alone, the Board should reject Grounds 1 and 2.

A. Standard of Review

"[T]he burden of production" in post-grant review proceedings "is a shifting burden." *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1379 (Fed. Cir. 2015). The petitioner has the initial burden of producing evidence to show that an asserted reference is prior art under §102. *See id.* at 1379-1380. If the petitioner does so, the patent owner must then "argue or produce evidence" that the asserted reference "is not prior art." *Id.* at 1380.

However, while the burden of *production* may shift, the burden of *persuasion* always rests with the petitioner. *Id.* at 1378; *see* Paper 20 at 13. The petitioner has the ultimate burden of "proving a proposition of unpatentability by a preponderance of the evidence," 35 U.S.C. §326(e), including the burden of persuading the Board that each relied-upon reference is, in fact, prior art, *see Dynamic Drinkware*, 800 F.3d 1378-1380.

While the Board concluded that Incyte "satisfied its initial burden of production" to show that Silverman is facially prior art, Paper 20 at 14, for the reasons that follow, Concert has satisfied its burden of producing evidence that essential disclosures in Silverman and its prosecution history are exempted under §102(b). And Incyte is unable to carry its ultimate burden of persuasion.

B. Silverman Is Not Prior Art Under §102(a)(2) Because It Falls Under the Common-Ownership Exception of §102(b)(2)(C)

Incyte argues that Silverman is prior art under §102(a)(2), which provides that a disclosure is prior art if it was "described in a patent" that "names another inventor and was effectively filed before the effective filing date of the claimed invention." *See* Paper 17 at 1. But §102(b)(2)(C) establishes an exception to §102(a)(2) if "the subject matter disclosed [in the asserted reference patent] and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person." Thus, if Silverman and the '659 patent were under common ownership *or* obligatory

assignment by the effective filing date of the '659 patent—May 4, 2016—the entirety of Silverman is not prior art under §102(a)(2).

That exception is satisfied. Concert was the owner of the subject matter disclosed in Silverman as of the effective filing date of the '659 patent. *See* Ex. 2053. Concert was also the owner—or, at the very least, the obligatory assignee—of the invention claimed in the '659 patent as of its effective filing date. Each of the '659 patent's named inventors had an "Employee Confidentiality, Non-Competition, and Proprietary Information Agreement" that read, in relevant part:

> Employee agrees that all Intellectual Property . . . shall be the sole property of the Company and its assigns, and the Company and its assigns shall be the sole owner of all patents and other rights in connection therewith. Employee hereby assigns to the Company any rights Employee may have or acquire in all Intellectual Property and all related patents . . . in the United States and elsewhere.

Exs. 2087-2093, at ¶2 of each agreement; Ex. 2060. As a result of this "hereby assigns" language, Concert owned the invention made by the '659 patent inventors as of the date of the invention. *See Bd. of Trustees v. Roche Molecular Sys., Inc.*, 583 F.3d 832, 842 (Fed. Cir. 2009), *aff'd*, 563 U.S. 776 (2011); *Picture Pats., LLC v. Aeropostale, Inc.*, 788 F. Supp. 2d 127, 135-136 (S.D.N.Y. 2011), *aff'd*, 469 F.

App'x 912 (Fed. Cir. 2012).[3] For the foregoing reasons, *no* disclosure in Silverman qualifies as prior art under §102(a)(2).

C. Key Disclosures in Silverman and Its Prosecution History Are Not Prior Art Under §102(a)(1) Because They Satisfy the Inventor-Disclosure Exceptions in §102(b)(1)(A) and (B)

Incyte also argues that Silverman is prior art under §102(a)(1), which provides that a disclosure is prior art if it was "described in a printed publication . . . before the effective filing date of the claimed invention." *See* Paper 17 at 1. But §102(b)(1)(A) and (B) establish two exceptions to that rule for certain "inventor disclosures." These exceptions apply on a disclosure-by-disclosure basis, and a particular disclosure is not considered prior art if it falls under *either* exception. Here, §102(b)(1)(A) and (B) exclude several disclosures of Silverman and its prosecution history—in particular, the structure of Compound (I) and metabolic stability data for both Compound (I) and the other deuterated compounds disclosed in Silverman. Without those disclosures, Incyte's asserted grounds cannot survive.

[3] Even if the agreements did not effect a present assignment, at the very least they created an obligation of future assignment. Consistent with that obligation, the '659 patent's inventors executed assignments in Concert's favor in October 2017. *See* Ex. 2052.

1. The Inventor-Disclosure Exceptions in §102(b)(1) Apply on a Disclosure-By-Disclosure Basis

Incyte has previously intimated that the §102(b)(1) exceptions do not apply unless *every* disclosure in Silverman is excluded by the inventor-disclosure rule. As the Board has already recognized, however, that is not how the statute works: The inventor-disclosure exception statute can apply to "certain parts of Silverman." Paper 25 at 16.

That is consistent with regulatory guidance, which makes clear that a prior inventor disclosure of *particular elements* disqualifies *those elements* of the intervening disclosure as prior art even if the intervening disclosure contains additional elements. MPEP §717.01(b)(1) ("[I]f the inventor or a joint inventor had publicly disclosed elements A, B, and C, and a subsequent intervening U.S. patent . . . discloses elements A, B, C, and D, then only element D . . . is available as prior art under 35 U.S.C. 102(a)(1)."); 78 Fed. Reg. 11,059, 11,061, 11,067, 11,077 (Feb. 14, 2013). In short, the elements of Silverman and its prosecution history discussed below are not available as prior art, even if there are *other* disclosures in Silverman that qualify as prior art.

2. The Structure of Compound (I) Is Not Available as Prior Art Because One of the Inventors of the '659 Patent Publicly Disclosed It Before Silverman's Publication

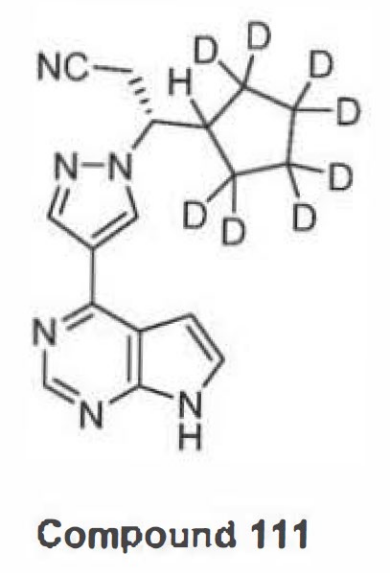
Incyte relies on Silverman for the disclosure of the structure of Compound (I)—indeed, Silverman is its *only* support for the disclosure of the compound's

structure. *See* Paper 1 at 69-84. But that structure was disclosed in a 2015 declaration of Vinita Uttamsingh (2015 Uttamsingh Declaration), an inventor of the '659 patent. Under §102(b)(1)(B), a disclosure is not prior art under §102(a)(1) if (1) the "disclosure [was] made 1 year or less before the effective filing date of [the] claimed invention" and (2) "the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor" of the claimed invention. Both of those conditions are satisfied as to Silverman's disclosure of Compound (I)'s structure.

The first condition is readily satisfied. Silverman issued on February 2, 2016. *See* Ex. 1002 at 1; Paper 1 at 12. That is well within one year of the May 4, 2016, filing of the earliest priority application of the '659 patent. *See supra*, p. 13.

The second condition is also satisfied. Before Silverman was published, a named inventor of the '659 patent, Dr. Uttamsingh, disclosed the structure of Compound (I) in the 2015 Uttamsingh Declaration. Ex. 1045 at 390-417;[4] *see* Ex. 1001 at 1. Specifically, Exhibit B to the 2015 Uttamsingh Declaration disclosed the following structure under the name "Compound 111":

[4] As reproduced in Exhibit 1045 (at 390-413), the declaration's five exhibits precede the declaration itself.



Compound 111

Ex. 1045 at 404. As all parties agree, Compound 111 is the '659 patent's Compound (I) by another name. *See* Paper 1 at 12-13; *cf.* Ex. 1001 at 3:18-31; *see also* Ex. 2068 ¶46.

The 2015 Uttamsingh Declaration became public on August 27, 2015—the date on which the underlying patent application was published. *See* Ex. 1046 at 1. Because that is before the date on which the issued Silverman patent became public, any Silverman disclosures that also appear in the 2015 Uttamsingh Declaration are not considered prior art. This includes the structure of Compound (I).[5]

[5] As explained in the next section, the 2015 Uttamsingh Declaration itself is plainly not prior art.

3. Metabolic Stability Data Concerning Compound (I) Are Not Available as Prior Art Because One of the Inventors of the '659 Patent Publicly Disclosed It Before Silverman's Publication

Incyte also relies on the 2015 Uttamsingh Declaration for its disclosure of the results of two in vitro assays that demonstrated the metabolic stability of Compound (I) (again, under the name "Compound 111"). *See* Paper 1 at 15; Ex. 1007 ¶155. Specifically, paragraphs 4-8 of the 2015 Uttamsingh Declaration described, and Exhibit E of the declaration reported, the results of a CYP3A4 Supersomes assay and a human liver microsomes (HLM) assay comparing the metabolic stability of Compound (I) to that of ruxolitinib. *See* Ex. 1045 at 407, 415-416. Both assays indicated that Compound 111 "ha[s] a longer *in vitro* half-life ($t_{½}$) relative to ruxolitinib"—specifically, a 75-80% longer half-life, *id.* at 407, 416.

But the 2015 Uttamsingh Declaration—including the results of the CYP3A4 and HLM assays—is *not* prior art. Under §102(b)(1)(A), a disclosure is not prior art if it (1) was "made 1 year or less before the effective filing date of [the] claimed invention" and (2) was made by "the inventor or a joint inventor." Both of those conditions are satisfied. The 2015 Uttamsingh Declaration was indisputably a disclosure made by a joint inventor of the '659 patent (Dr. Uttamsingh) within one year of the effective filing date of the '659 patent. *Compare* Ex. 1001 at 1, *with* Ex. 1045 at 414-17; *supra*, p. 13. Thus, metabolic stability data concerning Compound (I) are also unavailable as prior art to the '659 patent.

4. The Silverman Inventors Obtained the Metabolic Data in Silverman's Example 4 Directly or Indirectly from Dr. Uttamsingh, One of the Inventors of the '659 Patent

Finally, the inventor-disclosure exception bars Incyte from relying on metabolic stability data in Silverman's Example 4 and Table 3. Example 4 reports the results of in vitro HLM assays demonstrating the metabolic stability of three deuterated compounds—Compounds 103, 107, and 127—over ruxolitinib. *See* Ex. 1002 at 35:1-20.[6] But the disclosure in Example 4 is not prior art under §102(b)(1)(A); it was "made 1 year or less before the effective filing date of [the] claimed invention" by someone "who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor." As discussed above (p. 21), the first condition is readily satisfied because Silverman was published within the one-year grace period. And the second condition is satisfied because the metabolic data in Silverman that support the disclosure and claims to deuterated compounds were obtained from Dr. Uttamsingh, a named inventor on the '659 patent.

More specifically, in her role as Director of Concert's Drug Metabolism and Pharmacokinetics (DMPK) Group, Dr. Uttamsingh was responsible for the experiment disclosed in Example 4 of Silverman. That example describes an in vitro

[6] These assays—which do not directly involve Compound (I)/111—were conducted earlier in time than those reported in the 2015 Uttamsingh Declaration.

CYP3A4 Supersomes assay conducted on three compounds within the genus of compounds disclosed in Silverman to demonstrate that they had improved metabolic stability. Ex. 1002 at 34:21-35:20. Richard Gallegos, a Senior Scientist in the DMPK Group working under Dr. Uttamsingh's direction and control, performed the assay in duplicate on October 22 and 25, 2013. Ex. 2069 ¶¶6-7. Dr. Uttamsingh subsequently reviewed and confirmed the data; given her role as Director of DMPK, the reporting of such data required her review and approval. *Id.*

Dr. Uttamsingh and those working under her supervision subsequently reported the data to others within the company, including the inventors of the '149 patent. *Id.* ¶¶6-12. The '149 patent inventors therefore learned of the data either directly, or indirectly, from Dr. Uttamsingh. *Id.* ¶¶6, 12; Ex. 2070 ¶¶7, 10; Ex. 2071 ¶¶7, 10; Ex. 2072 ¶¶7, 10. It was common practice for Dr. Uttamsingh or others in the DMPK Group acting under her direction to send emails to parties interested in a given assay providing a preliminary report of the results, or to hold small in-person meetings to share the preliminary results. Ex. 2069 ¶8; Ex. 2070 ¶8; Ex. 2071 ¶8; Ex. 2072 ¶8. In this case, at least some of the '149 patent's inventors likely first learned of the results of the two assays in such communications. *See id.* At the very latest, however, Julie F. Liu, Adam J. Morgan, and Scott L. Harbeson learned the data at a Quarterly Update Meeting on December 3, 2013. Ex. 2069 ¶11; Ex. 2070 ¶9-10; Ex. 2071 ¶9; Ex. 2072 ¶9. Dr. Uttamsingh and Mr. Gallegos prepared a

PowerPoint presentation reporting the data, and Mr. Gallegos presented the PowerPoint at that meeting. Ex. 2069 ¶¶9-10; *see also* Ex. 2073 (excerpts of presentation). The remaining Silverman inventors obtained the information either at that meeting, from those present at the meeting, or from transmission of the PowerPoint to them. Ex. 2069 ¶11-12; Ex. 2070 ¶8-9; Ex. 2071 ¶9; Ex. 2072 ¶9; *see* Ex. 2086 (calendar entry for meeting showing Drs. Liu, Morgan, Harbeson, and Silverman as "Required Attendees").[7] Given that Dr. Uttamsingh's group generated the data, there is no other original source from whom the inventors could have received these data.

Importantly, the only question under the statute is whether the Silverman inventors obtained the information "directly *or indirectly*" from Dr. Uttamsingh. In other words, it does not matter whether Dr. Uttamsingh presented the data to the Silverman inventors face-to-face at the meeting—or whether they received that information indirectly. That standard is necessarily satisfied: No other party within Concert—aside from Dr. Uttamsingh and those working under her direction and control—performed assays of this type. Ex. 2069 ¶12; Ex. 2070 ¶10; Ex. 2071 ¶10; Ex. 2072 ¶10. There was no source for these data *other* than the channel that flowed

[7] The only exception is inventor Bhaumik Pandya, who departed Concert in 2012, Ex. 2060 ¶11, and so would not have obtained assay data before its public disclosure.

through Dr. Uttamsingh. That satisfies the plain terms of §102(b)(1)(A)—again, "direct *or indirect*" communication of the relevant data.

Thus, the data contained in Example 4 and Table 3 of Silverman is not prior art pursuant to §102(b)(1)(A).

5. Without the Excluded Data, Incyte Is Unable to Carry Its Burden

Once the foregoing information is excluded, Incyte has failed to point to *any* prior art teaching the structure of Compound (I) and *any* prior art teaching *anything* about the metabolic stability of Compound (I) or the effect of deuteration at all on ruxolitinib and its metabolic properties. *See* Paper 1 at 12, 26, 33, 38, 69-84. Incyte's challenges cannot survive without those disclosures.

All of the challenged claims require the use of Compound (I). *See* Ex. 1001 at 24:30-26:46. As Incyte's claim chart shows, its only prior-art support for use of Compound (I) in the claimed methods is the disclosure of Compound (I)'s structure in Silverman. Paper 1 at 69-84. Incyte does not argue—and cannot argue—that a POSA would have arrived at the precise, "octo-deuterated" structure of Compound (I) *without* its disclosure in Silverman.[8] Ex. 2068 ¶55.

[8] To be clear, Concert maintains that, even if the Board concludes that *all* of Silverman constitutes prior art, Silverman would not have directed a POSA to Compound (I). *See infra*, pp. 43-47.

Incyte also repeatedly relies on the disclosure of Compound (I) and its metabolic stability data to argue for the obviousness of the use of Compound (I) in the challenged claims. *See* Paper 1 at 26, 62; Ex. 1007 ¶¶117-121, 249-253. But in the absence of any data in Silverman regarding metabolic stability—whether from the Supersomes or HLM assays, and whether for Compound (I) or any other compound—a POSA would have had no reason to believe that Compound (I) would be more stable than ruxolitinib. Ex. 2068 ¶¶43-48, tables 1-2. In fact, the POSA would have had no idea whether deuterating ruxolitinib would have a positive, negative, or neutral impact on ruxolitinib's metabolic stability, nor would the magnitude of any impact have been predictable. Ex. 2068 ¶¶52, 55. Without data providing any hint as to the results of deuteration, Incyte cannot and does not argue that a POSA would have been motivated to, and would have had a reasonable expectation of success in, substituting Compound (I) for ruxolitinib in the treatment of AA.

The Board can end its analysis here. The key disclosures in Silverman are not prior art, and Incyte's asserted grounds cannot survive without them.

VI. GROUNDS 1 AND 2 SHOULD BE DENIED BECAUSE INCYTE HAS FAILED TO PROVE THAT ANY CHALLENGED CLAIM IS OBVIOUS

Even if Incyte could have demonstrated that every portion of Silverman is prior art, Incyte has still failed to meet its burden to show obviousness. Incyte must

demonstrate that a POSA would have had (1) "reason to combine the teaching of the prior art references to achieve the claimed invention," and (2) "a reasonable expectation of success from doing so." *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012).

Incyte cannot make either showing. Incyte's argument that there was a motivation to pursue the claimed methods strings together scattered and irrelevant disclosures in a way a POSA never would have done without the benefit of hindsight. And its argument that a POSA would have had a reasonable expectation of success does not come close to showing that a POSA would have had a fair prospect of successfully using *this* never-before-used compound at *these* doses to treat *this* complex disease, for which skilled artisans had repeatedly failed to develop a viable therapy. The Board should reject Incyte's hindsight-driven analysis.

A. Incyte Has Failed to Show That the Prior Art Taught the Claimed Elements and That There Would Have Been a Motivation to Combine the Asserted References

Incyte posits the existence of a motivation to combine only by using hindsight to cherry-pick disclosures from scattered references. But the prior art would not have directed a POSA to treat AA with JAK inhibitors or ruxolitinib, given the lack of any controlled trial showing their efficacy in AA and the concerns regarding their safety. Nor would the prior art have taught a POSA to select Compound (I) specifically, or to substitute Compound (I) for ruxolitinib at the claimed doses, given

the lack of any data in the prior art showing a benefit of using Compound (I) in AA. And even if a POSA *were* interested in JAK inhibitors at all to treat AA, the prior art expressed a clear preference for topical treatments in light of known safety concerns—thus teaching away from the use of a deuterated compound like Compound (I). Finally, the prior art would not have directed a POSA to select the claimed dosing and regimen for Compound (I), which is nowhere taught in the prior art.

Incyte must show that the prior art would have taught a POSA (1) to treat AA with oral ruxolitinib or another drug in its class *and* (2) to substitute Compound (I) specifically for ruxolitinib *and* (3) to select the claimed dosing and regimen. It has failed to make any one of these showings—let alone all three.

1. The Prior Art Would Not Have Motivated a Skilled Artisan to Treat AA With a JAK Inhibitor

As discussed above, it has proven notoriously difficult to develop safe and effective treatments for AA; as of the priority date, there was "no effective evidence-based treatment" for the disease. Ex. 2058 at 2; Ex. 2059 ¶55. A significant portion of AA patients experience spontaneous hair regrowth, rendering reports of sporadic success in uncontrolled studies unreliable. *See* Ex. 2006 at 1; Ex. 2008 at 6; Ex. 2059 ¶27. And because it is not life-threatening, AA is not amenable to treatments with serious side effects, *see* Ex. 2037 at 1. Unsurprisingly, given these difficulties, the prior art disclosed a persistent failure of trials to treat AA. *See supra*, p. 3.

Moreover, the prior art as a whole did not single out JAK inhibitors as a particular subject of interest any more than the many other treatment options being studied in purely anecdotal contexts. Ex. 2059 ¶56. As discussed above (pp. 7-8), JAKs are just one part of a cell's complex signaling mechanism and just one link in a complicated cascade of processes to relay signals that are important to the body's immune response and several other biological functions. The prior art disclosed that numerous different types of signaling molecules were thought to be involved in the etiology of AA as well as other diseases. *See supra*, pp. 8-11.

Even if a POSA had focused on JAKs from among all the possible choices, he would still not have known whether a JAK1, JAK2, or JAK3 inhibitor would be suitable for treatment of AA with respect to both safety and efficacy. *See supra*, p. 10. And to the extent a POSA would have been interested in a JAK inhibitor as an AA treatment, it would not have been a JAK1/2 inhibitor like ruxolitinib. *See supra*, p. 11. The prior art suggested that the JAK1/3 pathway was involved in mediating AA, and inhibition of the JAK1/2 pathway implicates known safety concerns. *See supra*, p. 11. Thus, a JAK1/3 inhibitor like tofacitinib would have been thought more promising. *See supra*, p. 11; Ex. 2059 ¶58.

A POSA also would have been particularly hesitant to develop JAK inhibitors like ruxolitinib as a treatment for AA because of their significant side effects. *See supra*, pp. 10-11; Ex. 2059 ¶57. Even if they would be acceptable in a treatment for

a potentially fatal illness like cancer, serious adverse reactions are not as acceptable in an AA medication because AA is not life-threatening. Ex. 2037 at 1. Yet ruxolitinib and other JAK inhibitors are known to have a number of serious side effects, including several blood-related toxicities. Ex. 1004 at 6. These side effects are serious enough that the FDA has thus far required a black-box warning on all JAK inhibitors approved for the treatment of autoimmune conditions. *See supra*, p. 10.

To counter these shortcomings in the prior art, Incyte relies on combinations involving Xing and the Ruxolitinib Prescribing Information (Ground 1) and Christiano and Ni (Ground 2). These references would not have meaningfully motivated a POSA to pursue the treatment of AA using ruxolitinib. To the contrary, many of Incyte's references would have undermined the use of ruxolitinib or motivated a POSA to use a different treatment.

a. Christiano

Incyte argues that Christiano taught the use of JAK inhibitors and ruxolitinib to treat AA. *See* Paper 1 at 62-63. But in several respects, Christiano would have *undermined* the motivation to combine with Silverman. Ex. 2059 ¶¶60-62.

First, consistent with the numerous molecules of interest in the art as a whole, Christiano taught a number of other inhibitors aside from ruxolitinib. The proposed categories and specific examples of inhibitors include a JAK1 inhibitor, a JAK2

inhibitor, a JAK3 inhibitor, a STAT1 inhibitor, a STAT2 inhibitor, ruxolitinib, tofacitinib, an antisense RNA that specifically inhibits expression of the gene that encodes the JAK1 or JAK2 protein, a siRNA that specifically targets the gene that encodes the JAK1 or JAK2 protein, an antibody that specifically binds to a JAK3 protein or a fragment thereof, an antisense RNA or antisense DNA that decreases expression of the gene that encodes the JAK3 protein, an antisense RNA or antisense DNA that decreases expression of the JAK3 protein, a siRNA that specifically targets the JAK3 gene, WP-1034, fludarabine, epigallocatechin-3-gallate, Hyperforin, or (in some instances) a combination of some of the foregoing. *See* Ex. 1005 at 2:1-46; Ex. 2055 at 136:15-139:14. Incyte's selection of ruxolitinib from that sprawling list is mere hindsight. Ex. 2059 ¶62.

Second, to the extent Christiano does discuss JAK inhibitors, it places a particular focus on JAK3 inhibition in connection with the treatment of AA. In particular, Example 10 discusses only JAK3 inhibition—not other forms of JAK inhibition—in developing AA therapies. Ex. 1005 at 143:31-39 ("Systemically-administered pharmacological inhibitors of the JAK3 protein tyrosine kinases eliminated the IFN-signature and prevented the development of AA, and topical administration reversed established disease."). As previously discussed, ruxolitinib is a JAK1/2 inhibitor; indeed, Christiano taught that ruxolitinib has 8-20 times less JAK3 inhibition potency than tofacitinib. *See* Ex. 1005 at 141:25-36. A POSA who

was interested in a JAK inhibitor and following Christiano would have selected a JAK3 inhibitor—not ruxolitinib—for further development in AA. Ex. 2059 ¶61.[9]

Christiano's focus on JAK1/3 inhibition is consistent with other references Incyte relies on that similarly would have undermined the use of ruxolitinib to treat AA because they expressed the promise of a competing therapy—tofacitinib, a JAK1/3 inhibitor. For example, Harel 2015 (authored by Dr. Christiano's group) taught the efficacy of tofacitinib in the treatment of AA and called it "surprising" that ruxolitinib showed no effect in an in vitro model system. Ex. 1016 at 8. Along similar lines, Craiglow 2014 reported the use of tofacitinib to treat AA in a patient with plaque psoriasis, calling the results "provocative" but stressing the need for "a clinical trial [to] more fully and systematically address the safety and efficacy of tofacitinib and other JAK inhibitors in the treatment of AA and its variants." Ex. 1050 at 2. Incyte's own expert, Dr. Shapiro, testified that the only JAK inhibitor he

[9] Incyte argues that Christiano claims use of ruxolitinib to treat AA (Paper 1 at 63), but Christiano recites the use of "INCB018424," a compound that Incyte's expert Dr. Patterson conceded was the designation for a racemic mixture of ruxolitinib, not the specific R-enantiomer of ruxolitinib present in the Jakafi product. Ex. 2055 at 150:4-151:25, 152:1-153:2

ever prescribed for his patients as of the priority date was tofacitinib. Ex. 2036 at 33:11-16; 2054 at 35:19-36:18.

Finally, Christiano identifies topical formulations as the formulation of choice. *See* Ex. 1005 174:57-175:7. That, too, is consistent with Incyte's other references: Harel taught that "topical treatment with JAK inhibitors resulted in more robust hair growth than did systemic treatment in AA," Ex. 1016 at 8, and Craiglow reemphasized the serious adverse effects that come with JAK inhibitors and the preference for topical formulations, noting that "[g]iven the potential for serious adverse effects from oral JAK inhibitors, it would be particularly useful to explore the use of topical formulations for these disorders," Ex. 1050 at 2. As explained in greater detail below (pp. 42-43), that preference undermines a POSA's motivation to focus on a deuterated compound like those in Silverman, because, to the extent deuteration is intended to alter metabolism (as Incyte argues), there is no first-pass metabolism for topical formulations. Ex. 2068 ¶¶14-19; Ex. 2074 at 5-6. Indeed, Incyte's own expert Dr. Shapiro acknowledged that he relied on Christiano only for its asserted teaching of *topical* ruxolitinib. Ex. 2054 at 78:9-15. This undermines any motivation to combine Christiano with Silverman's teaching of a deuterated compound.

b. Xing and Other Anecdotal Case Reports

To piece together teachings that are not present in the prior art, Incyte also relies on Xing and a handful of other anecdotal reports of hair regrowth in patients taking ruxolitinib (Higgins, Pieri, and Harris). Paper 1 at 57. But none of these reports involved treatment of AA *with Compound (I)*—a different drug from ruxolitinib. Nor do they involve treatment of AA at the doses claimed in the '659 patent (and supported by a placebo-controlled clinical trial in AA). Rather, the references show anecdotal examples of hair regrowth at doses of ruxolitinib higher than the doses of Compound (I) claimed in the '659 patent. Ex. 2059 ¶63.

With a focus on animal models used in mechanistic studies of AA, Xing discusses, in a single paragraph, a very small AA study using a 20 mg twice-daily dose of ruxolitinib. Ex. 1003 at 10. This study involved only three subjects with no control arm, and it used a different drug (ruxolitinib) and a higher dose (20 mg twice daily) than those claimed in the '659 patent. *See id.* Because of the known spontaneous reversal of AA in approximately one third of patients, *see* Ex. 2006 at 1, reports of hair regrowth in a few isolated patients are not reliable in assessing the efficacy of ruxolitinib in AA, and meaningless with respect to the claimed doses. Xing also refers to topical administration of JAK inhibitors for AA as the "more clinically relevant route of delivery." Ex. 1003 at 10. All of these differences

militate against Incyte's reliance on this study as teaching or suggesting the claimed invention. Ex. 2059 ¶64.

Higgins is a research note about a single patient with AA associated with chronic mucocutaneous candidiasis. Ex. 1088 at 13. The patient received 20 mg of ruxolitinib twice daily (again, higher than the claimed doses in the '659 patent). *Id.* As with Xing, there was no control arm, which is important because the patient in Higgins had a previous history of AA and remission *without* being treated with a JAK inhibitor. *See id.*; Ex. 2059 ¶65.

Pieri discloses the adventitious regrowth of hair in a single patient in a clinical trial for thrombocythemia who happened to have AA. Ex. 1012 at 6-7. Pieri reports that the patient received 15 mg of ruxolitinib twice daily. *Id.* There was no reference to any patients in the control arm of the clinical trial for comparison. *See id.*; Ex. 2059 ¶66.

Harris is a research letter describing observations of hair regrowth in a single patient with both AA and vitiligo who was enrolled in a Phase 2 trial of ruxolitinib. Ex. 1031 at 9. The letter does not report results of that clinical trial, but instead discusses only this single patient, with a focus on the patient's vitiligo. *Id.* As with all these reports, the patient received a higher dose than those claimed by the '659 patent—20 mg twice daily. *Id.*; Ex. 2059 ¶68.

None of these anecdotal case reports would have taught a POSA that there was a causal relationship between ruxolitinib administration and improvement in AA. Ex. 2059 ¶¶64-68; Ex. 2080 at 5. A POSA would have been aware that "[c]ausality cannot be inferred from an uncontrolled observation" and that this "is a limitation shared by all the descriptive studies" or case reports. Ex. 2080 at 4. In particular, in the field of AA treatment, a POSA would have been acutely aware of prior potential treatments that had shown promise in early isolated case reports but ultimately failed to demonstrate efficacy when tested in a controlled clinical trial. Two examples are alefacept and anti-TNF treatments, both of which seemed promising based on the publication of isolated case reports, *see* Ex. 2101, 2103, but proved ineffective when tested in clinical trials, *see* Ex. 2102; Ex. 2104. The failure related to alefacept is particularly telling. Reports of an AA patient exhibiting complete hair growth while being treated with alefacept led researchers to proclaim that it "shows the most promise among biologic therapies as a potential treatment for all types of alopecia areata." Ex. 2101 at 4; Ex. 2059 ¶43. But a subsequent controlled clinical study designed to rigorously evaluate alefacept's utility as an AA treatment failed to establish efficacy, leading researchers to conclude that "AA has a more complex pathophysiologic mechanism" than previously thought, and that "further research into both understanding its pathophysiologic mechanism and the development of effective therapies is needed." Ex. 2012 at 4.

As a result, Incyte cannot establish through these anecdotal reports that the prior art taught that ruxolitinib, let alone Compound (I) at the claimed doses, was an efficacious treatment of AA. *See Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060-1061 (Fed. Cir. 2019) (finding that even randomized clinical trial data in the prior art were insufficient to support reasonable expectation of efficacy); Ex. 2059 ¶¶70-71. In light of the well-known safety concerns described above, the anecdotal reports fail to provide any motivation to combine Xing, an isolated case report in AA, with two references—Silverman and the Ruxolitinib Prescribing Information—neither of which ever mentions using ruxolitinib for treatment of AA.

2. The Asserted References Would Not Have Motivated a Skilled Artisan to Substitute Compound (I) for Ruxolitinib

Even if Incyte could show that a POSA would have been motivated to pursue ruxolitinib, Incyte is still unable to show that a POSA would have been motivated to pursue a deuterated drug or to substitute Compound (I) for ruxolitinib in treating AA.

a. Ni Does Not Supply the Motivation for Use of a Deuterated Drug

Incyte's expert Dr. Patterson relies on Ni for the proposition that "there [was] a need for new and improved formulations of ruxolitinib that not only mitigate adverse side-effects in patients, but still achieve therapeutic efficacy, and also

facilitate administration of the drug such as by reducing the number of doses required to achieve a therapeutic effect," and that deuterated ruxolitinib would have fulfilled such a need. Ex. 1007 ¶133 (quoting Ex. 1006 at [0005]). But all of the efficacy data in Ni relates to myelofibrosis, not to AA. Ex. 1006 at [0133]-[0164]. A POSA would know that achieving the balance of therapeutic efficacy while mitigating side effects is disease-dependent (based on the unique pharmacokinetic-pharmacodynamic relationship of a drug in a particular disease), making it impossible to extrapolate efficacy and safety from one disease to the other. Ex. 2068 ¶¶30, 42, 61-62.

Moreover, to the extent Ni identified a problem with ruxolitinib, it also identified the solution: conventional sustained-release formulations. Ex. 2068 ¶¶49-54. Nothing in Ni would motivate a POSA to choose the unconventional: deuteration. *Id.* Further, Dr. Patterson incorrectly argues that a POSA would assume that a deuterated version of ruxolitinib would behave as the sustained-release formulation did. *Id.* Conventional sustained-release formulations necessarily provide a lower C_{max}, whereas the effect of deuteration on safety-related pharmacokinetic parameters was inherently unpredictable.

b. The Prior Art Taught Away from the Use of Oral Formulations and Therefore Away from the Use Deuterated Compounds

A reference "teach[es] away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference" or "led in a direction divergent from the path that was taken by the applicant." *Allergan, Inc. v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015). That standard is satisfied here.

Even if a POSA would have been motivated to pursue ruxolitinib or another JAK inhibitor as an AA treatment, the prior art discouraged the use of oral or other systemic administration and pushed skilled artisans in the direction of topical formulations. *See supra*, pp. 5-6, 12, 35. That is because, as Incyte's expert Dr. Shapiro explained, a topical therapy is safer. Ex. 2054 at 37:9-10. Craiglow, for example, noted "risks for serious adverse effects [associated] with systemic therapy" and explained that those risks "may be avoided if topical therapy were an option." Ex. 1027 at 4. The literature was clear that "[m]ost physicians" preferred topical therapies for AA, because their more favorable safety profile made them more attractive, particularly for the young and otherwise healthy population of AA patients. Ex. 2041 at 1. That was especially true for JAK inhibitors. Ex. 2037 at 1 (calling for research focus "on ways to increase follicular penetration and reduce systemic absorption"); Ex. 2076 at 6 (discussing positive effects of "topical

administration of ruxolitinib and tofacitinib"); Ex. 2077 at 2 (calling it "particularly useful to explore the use of topical formulations for these disorders"); Ex. 2056 at 8 (extolling the advantages of topical formulations); Ex. 2039 at 4 ("Studies have reported that ruxolitinib is an efficacious topical therapy with limited systemic exposure."). A POSA reviewing these references would have been motivated to pursue the "divergent path" of topical formulations—and would have been "discouraged" from systemically acting oral formulations. *Allergan*, 796 F.3d at 1305; *see* Ex. 2059 ¶73-75.

This divergent path would have been underscored by the fact that topical therapies are more clinically relevant because they deliver the drug directly to the affected organ, *see* Ex. 2040 at 6; Ex. 1016 at 8, as well as by clinical reports of superior efficacy through the topical route as compared to the systemic route, and a lack of predictability in oral therapies, Ex. 1027 at 4; Ex. 1016 at 8; Ex. 2059 ¶72-74, 77. In short, given the riskiness of systemic administration of JAK1/2 inhibitors, especially for a deuterated drug with unpredictable exposure levels, and a lack of solid data showing efficacy, a POSA would have pursued topical formulations instead.

As relevant here, that means a POSA would *not* have pursued a deuterated compound. According to Incyte, the motivation to substitute Compound (I) for ruxolitinib is that deuteration can improve the pharmacokinetics of ruxolitinib by

slowing its metabolism in the liver. *See* Paper 1 at 38-40; Ex. 2059 ¶76. But if a drug is given topically, there is no metabolism in the liver before the drug reaches its site of action in the skin. Ex. 2055 at 244:1-4. Therefore, deuteration is simply irrelevant to topically administered drugs. In other words, the preference for topical administration teaches away from deuteration—and, thus, away from Compound (I).

To the extent Incyte argues that, even if administered topically, deuterated ruxolitinib would have been no worse than ruxolitinib itself, *see* Ex. 1007 ¶¶126-135, that argument ignores the unpredictable effect deuteration can have not only on efficacy but also on safety. Increased exposure as a result of deuteration can lead to unacceptable side effects. Ex. 2068 ¶61. While Dr. Patterson suggests that simply lowering the dose would solve that problem, that oversimplification ignores the fact that whether or not *any* dose of Compound (I) could be both safe and efficacious in AA depends on the particular pharmacokinetic-pharmacodynamic relationship for Compound (I) in AA, a relationship which was simply unknown in the prior art. *Id.* ¶¶30-31, 42, 61-62. Accordingly, there would have been no motivation to substitute Compound (I) for ruxolitinib for AA treatment.

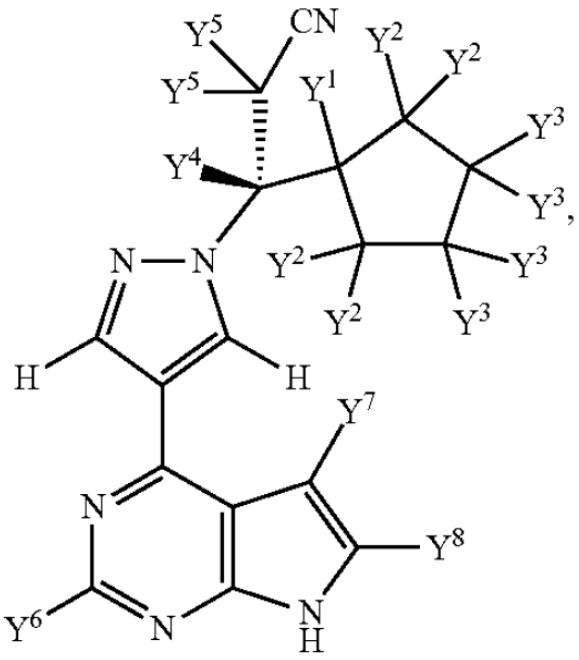
c. The Prior Art Would Not Have Directed a Skilled Artisan to Compound (I) Specifically

Even if a POSA were interested in a JAK inhibitor, or ruxolitinib specifically, for AA, the prior art would not have motivated a POSA to pursue Compound (I). Incyte states that Silverman discloses Compound (I) under the name of "Compound

111." Paper 1 at 87. But Silverman's Compound 111 is just one of a number of compounds within the genus that Silverman discloses. Incyte provides no rationale for why Silverman would have pointed a POSA to Compound 111 in particular.

What Silverman actually discloses is a genus of compounds of Formula I, and salts thereof:

Formula I



Ex. 1002 at 7:7-8:43. The Y^1-Y^8 substituents are each selected from hydrogen and deuterium atoms; Silverman provides tables of possible values for Y^1-Y^8 listing no fewer than 63 different combinations. Ex. 1002 at tables 1-2.

In a footnote in its petition, Incyte argues that claim 7 of Silverman would have focused the POSA on Compound (I) because it "claim[s] Compound (I) 'or a pharmaceutically acceptable salt.'" Paper 1 at 54 n. 14. But Incyte does not explain

why a POSA would have zeroed in on claim 7—as opposed to any other of the 21 claims in the patent.[10] In another footnote, Incyte notes that Compound 111 is "encompassed" within the disclosures of Silverman's Formula I. Paper 1 at 55 n. 15. But, again, Incyte cites nothing in Silverman itself that would impel a POSA to select Compound 111 from among all of the compounds disclosed. *See UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018) (noting that a POSA would not have selected a particular compound "among the many compounds disclosed" because the prior-art reference "contain[ed] no data that would have led" to that compound).

In fact, a POSA would not have selected Compound 111 from Silverman for further study. Silverman provides metabolic stability data for three *other* compounds—Compounds 103, 107, and 127. Ex. 1002 at 35:3-20. Even if there were a motivation to select a compound from Silverman, and even if a POSA were seeking a compound with increased metabolic stability, as Incyte argues, the POSA would have selected one of those three compounds (for which Silverman provides metabolic stability data) rather than Compound 111 (for which Silverman provides no data at all). Ex. 2068 ¶¶56-60.

[10] Even if a POSA were focused on claim 7, it is actually directed to three compounds, not one. Ex. 1002 at 36:66-37:43.

Without any data in Silverman itself on Compound 111, Incyte relies—in both its petition and expert submissions—on the 2015 Uttamsingh Declaration and its disclosure of the results of two assays that demonstrated the metabolic stability of Compound 111. Paper 1 at 15; Ex. 1007 ¶155; *see* Ex. 1045 at 407, 415-416. But even assuming the 2015 Uttamsingh Declaration is prior art (*contra supra*, p. 23), the data in Silverman shows that Compound 127 performed better than Compound 111. *Compare* Ex. 1002 at 35:15-16 (showing a 121% increase in half-life for Compound 127), *with* Ex. 1045 at 407 (showing an 80% increase in half-life for Compound 111); *see also* Ex. 2068 ¶¶59-60.

In any event, Incyte's heavy reliance in this proceeding on the data in the 2015 Uttamsingh Declaration is directly contradicted by the positions Incyte took in the prior IPR challenging Silverman (IPR2017-01256). There, Incyte's expert argued that the data in the 2015 Uttamsingh Declaration would have "provide[d] one of ordinary skill with little value" because (1) the assays in the declaration were "simple" and were not done in the manner "required for publication in peer-reviewed literature"; (2) the "raw *in vitro* half-life data" does not allow a POSA "to reach conclusions on the properties of the compounds"; and (3) "the comparison of *in vitro* half-life ($t_{½}$) is not particularly probative of how the compound might function in vivo." Ex. 2075 ¶¶122-125. The Board should not indulge Incyte's self-serving about-face.

Incyte's reliance on case law is equally misplaced. Incyte points to *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009), to support its argument that "Compound (I) would have been 'a natural choice for further development.'" Paper 1 at 34. But that case only undermines Incyte's argument. There, the court concluded that a compound was a "natural choice" for further development only because there was "evidence that [the compound] was one of the more potent . . . compounds disclosed in [the prior-art reference]." *Altana*, 566 F.3d at 1008. Here, by contrast, there are no data that would have pointed a POSA to Compound 111 in Silverman. The final result in *Altana* also undercuts Incyte's argument. The decision on which Incyte relies arose on a preliminary injunction. After a full trial, the court concluded that the defendants had "failed to produce credible evidence that a person of ordinary skill in the art would have been motivated to select [the compound at issue as] a starting point." *Altana Pharma AG v. Teva Pharm. USA, Inc*., No. 04-cv-2355, 2010 WL 10804665, at *3 (D.N.J. July 15, 2010). Without using hindsight, in other words, there were no data in the prior art to suggest that the compound was a logical starting point for development. The same is true here. Nothing in Silverman points to Compound 111 as a logical choice for further development.

3. The Prior Art Would Not Have Motivated a Skilled Artisan to Select the Claimed Dosing and Regimen

Finally, the claims of the '659 patent disclose specific dose amounts and regimens for use of Compound (I) in the treatment of AA. To arrive at the claimed dosing, Incyte relies on litigation-inspired expert opinions; treatments involving *other* drugs and *other* diseases; broad and overlapping dosing ranges disclosed in Silverman; improper post-art; and anecdotal reports. But its arguments are unavailing.

a. Incyte's Claim That Once-A-Day Dosing Was Obvious Rests on Unreliable and Litigation-Driven Expert Testimony

First, Incyte has not met its burden to show that once-a-day dosing (claim 5 of the '659 patent) would have been obvious. Ex. 2059 ¶97. Notably, Dr. Shapiro has offered contradictory opinions on dosing that shift to suit the moment. In his declaration in the Silverman IPR (IPR2017-01256), Dr. Shapiro offered the opinion that the difference in half-life between ruxolitinib and Compound (I) was "not large enough to have any clinical importance" and that both would need to be dosed twice daily. Ex. 2009 ¶7. Now, Dr. Shapiro's opinion has shifted to support Incyte's position that once-a-day dosing (in claim 5 of the '659 patent) would have been obvious based on the same half-life information. Ex. 1009 ¶51. The Board should not indulge this flip-flopping.

b. Incyte Improperly Relies on So-Called "Related" Drugs for Motivation to Use the Claimed Doses

To assert a motivation for using particular doses of Compound (I) to treat AA, Incyte introduces the concept of "related" drugs, relying on information about different drugs approved for different indications. Paper 1 at 43. But Incyte supports its reasoning with neither law nor science.

Incyte fails to identify a single case finding a motivation for the dosing of one drug based on the behavior of *a different drug* (let alone in *a different disease*). That is unsurprising: courts have long recognized that even small changes in chemical structure can have unpredictable effects. *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1305 (Fed. Cir. 2011) ("[E]ven in cases involving such ostensibly minor chemical differences, *prima facie* obviousness is by no means inevitable."); *In re Mayne*, 104 F.3d 1339, 1343 (Fed. Cir. 1997) (explaining that, in the chemical arts, "minor changes in a product or process may yield substantially different results"); Moreover, the compounds Incyte relies on here—baricitinib and tofacitinib—are markedly different in structure from Compound (I), and Incyte cites to no case supporting its assertion that the behavior of Compound (I) can be predicted by reference to such structurally distinct compounds.

Nor does Incyte provide any credible scientific basis for making such comparisons. A POSA would readily understand that different drugs differ in their

pharmacokinetic behavior and in their pharmacodynamic effects and would appreciate that, for even the *same* drug, the pharmacokinetic-pharmacodynamic relationship will impact different diseases in different ways. Ex. 2068 ¶30; Ex. 2059 ¶¶78-80. The basic textbook Incyte relies upon teaches as much. *See* Ex. 1048 at 153. Incyte's reliance on other drugs to show motivation for the particular dosing of Compound (I) contradicts these basic principles of pharmaceutical science.

Incyte's reliance on baricitinib is representative of its flawed approach. Incyte argues that "in selecting doses for Compound (I), a POSA also would have considered the AA data for baricitinib." Paper 1 at 47. To justify its reliance on baricitinib, Incyte relies on Dr. Patterson's use of a mathematical model for computing the dose of ruxolitinib based on dosing of baricitinib in AA.[11] *See* Paper 1 at 47-48 (citing Ex. 1007 ¶¶182-191). According to Dr. Patterson, in determining a ruxolitinib dose from baricitinib, a POSA would look to references discussing mathematical computations to determine a minimum effective dose. *See* Ex. 1007 ¶¶182-191. But Incyte provides no basis to support the use of these references to calculate an effective dose of ruxolitinib. For one thing, these references do not

[11] Even if the mathematical calculation made sense in this context, Incyte provides no mathematical basis at all to calculate a dose of *Compound (I)* from the ruxolitinib dose.

relate to ruxolitinib, JAK inhibitors, or treatment of AA, and are therefore not even "from the same field of endeavor." *In re Clay*, 966 F.2d 656, 658-660 (Fed. Cir. 1992); *K-TEC, Inc. v. Vita-Mix Corp.*, 696 F.3d 1364, 1375 (Fed. Cir. 2012); *see* Ex. 2068 ¶¶30-42. Nor are these references "reasonably pertinent" to the problem the inventor sought to address—determining an effective dose of Compound (I) in AA. *See Clay*, 966 F.2d at 658-660; *K-TEC*, 969 F.3d at 1375. Incyte cites Reigner (Ex. 1077) for the so-called "similar drug approach," *see* Paper 1 at 47 n. 11, but this reference does not relate to selecting an *effective* dose for a condition or to treat AA. Reigner is about using available human safety data to determine a *safe* starting dosing for novel cytotoxic oncology therapeutics. Ex. 1077 at 1, 5. No one skilled in the art would mistake a safe dose for an effective dose. Ex. 2068 ¶¶30-31, 42, 61-62. Dr. Patterson conceded that the starting dose for human trials is not usually the dose ultimately selected as the optimal dose, and that he did not even use the approach set out in Reigner but chose a different approach. Ex. 2055 at 50:9-15, 228:2-18. Dr. Patterson also relies on Tallarida (Ex. 1075), but that reliance is misplaced. Tallarida relates to combinations of two drugs that act through two different mechanisms, and Dr. Patterson cites no support for using this approach in the context of calculating the safe and effective dose of a new drug. Ex. 2068 ¶33.

Even taken on its own terms, Incyte's and Dr. Patterson's mathematical modeling is flawed. Ex. 2059 ¶81. Dr. Patterson relies on a 7 mg dose as the

"effective dose" of baricitinib in treating AA. But that is based on only a single case report of one patient who took baricitinib and saw improvement in his AA. *See* Ex. 1007 ¶184 (citing Ex. 1021). Even that one patient did not see complete improvement until he took 11 mg/day. Had Dr. Patterson used 11 mg for his calculation, he would have gotten a higher equivalent dose of ruxolitinib. Ex. 2068 ¶34 n. 4.[12] Moreover, Dr. Patterson uses IC_{50} data from two different Shi papers as an integral part of his calculations. But there is no evidence that the assays in those papers were conducted on the same patients at the same time; in fact, they were published three years apart and so are unlikely to be from the same patient population. Ex. 2068 ¶39. Further, the data presented in Shi papers have significant statistical noise, so a POSA would not have a high degree of confidence regarding the accuracy of the IC_{50} values calculated from those data. Ex. 2068 ¶37-38. Dr. Patterson also provides insufficient justification for why a POSA would use the pSTAT3/IL-6 data from the Shi papers, when there is no evidence in the literature that IL-6 is relevant for the treatment of AA. Ex. 2068 ¶39. Finally, the IC_{50} data that Dr. Patterson chose to use show a threefold difference in IC_{50} between

[12] Notably, both 7 mg and 11 mg are higher than the FDA-approved dose of 2 mg for baricitinib; Incyte does not explain why a POSA would selected either a 7 mg or 11 mg dose in light of safety concerns. *See* Ex. 2016.

ruxolitinib and baricitinib, but the IC_{50} data for the same compounds in Clark (Ex. 1071), a reference Dr. Patterson himself cites, show a much larger difference for pSTAT3 (approximately six to ninefold difference in IC_{50}) and significantly more variation when all of the data are analyzed (variances from 0.62-fold to 14.1-fold). Ex. 2068 ¶¶39-40. Dr. Patterson conceded at his deposition that had he used these numbers, the equivalent dose of ruxolitinib would have come out higher than what he calculated. Ex. 2055 at 238:20-25. This further shows Incyte's use of hindsight to cherry-pick preferred data. Dr. Patterson chose to use numbers that would yield the claimed doses, even where those numbers came from separate studies that cannot be compared, rather than using other data in another of his own cited references that would have led to a less favorable result.

A POSA would not have done this sort of calculation, but would instead have undertaken a program of preclinical animal testing and clinical trials to determine whether a safe and effective dose was possible, and if so, what that dose was. Ex. 2068 ¶34.

c. Incyte Improperly Relies on So-Called "Sister Diseases" to Assert a Motivation to Use the Claimed Doses of Compound (I) for AA

In addition to the concept of "related" drugs, Incyte makes the further leap of relying on their use in "sister diseases." *See* Paper 1 at 48. Incyte provides no credible support for its allegations that these so-called "sister diseases" can be used

to determine dosing across different drugs and disease states, instead relying on general statements from a handful of references suggesting that drugs that treat one disease *may* have utility in treating another disease with a common cause. *See* Paper 1 at 48 n. 12. But these references suggest nothing about predicting the *dose* to use for one drug in a given disease based on the use of that drug (or a different drug) in a different disease. At most, they provide a generalized motivation, which is not sufficient to provide motivation to combine particular references to reach the particular claimed method. *See Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1373 (Fed. Cir. 2008).

In fact, a POSA would have known that dosing of a single drug across different autoimmune conditions was quite variable and could not be predicted *a priori*. Ex. 2059 ¶¶82-84. For example, hydroxychloroquine is approved to treat two autoimmune diseases—rheumatoid arthritis and lupus erythematosus—but has markedly different doses for each. Ex. 2017 at 7 (average initial dose for lupus is 400 mg/day, whereas recommended initial dose range for rheumatoid arthritis extends up to 600 mg). Similarly, golimumab is approved at a significantly higher dose for treating ulcerative colitis (200 mg as an initial dose, followed by 100 mg a week later, and then 100 mg every four weeks) than rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis (50 mg once a month). Ex. 2018 at 1.

Even within the class of JAK inhibitors, Incyte has not established that a POSA would look to other diseases to predict dosing regimens. The effectiveness of a particular JAK inhibitor at a particular dose depends on the indication, and thus the dose of one JAK inhibitor in one indication can hardly be used to predict what Compound (I), a different drug, would do in a different indication. Ex. 2059 ¶85. For ruxolitinib, the dose in myelofibrosis varies depending on the condition of the patient, as determined by platelet count, with the starting dose ranging from 5 mg to 20 mg twice a day. *See* Ex. 1004 at 5; Ex. 2059 ¶¶86-87. Tofacitinib requires different dosing depending on the indication: for ulcerative colitis, the recommended dose includes an induction dose of 10 mg twice a day or 22 mg once a day, whereas for psoriatic arthritis, the recommended dose is 5 mg twice a day or 11 mg once a day without any induction dose. Ex. 1066 at 1. Tofacitinib failed to receive approval for treatment of psoriasis, which Incyte calls a "sister disease" (Paper 1 at 48), because of safety concerns at a 10 mg daily dose and lack of efficacy at a 5 mg daily dose. Ex. 2013 at 1. Baricitinib is only FDA-approved for rheumatoid arthritis at 2 mg daily, but for psoriasis baricitinib only showed efficacy at higher doses—those that present safety concerns. *See* Ex. 1074 at 5-7; Ex. 1079 at 1.

In light of these differences, Incyte has not established that a POSA would look to so-called "sister diseases" in selecting a dose for Compound (I) to treat AA.

d. Silverman Does Not Teach the Claimed Doses

Incyte relies on the disclosure in Silverman of a dose range that, it alleges, encompasses the claimed amounts. But this disclosure fails to teach the specific dose amounts of Compound (I) for treatment of AA claimed in the '659 patent.

The range disclosed in Silverman is very broad; it spans "from 1 mg to 500 mg." Ex. 1002 at 20:10; Ex. 2059 ¶¶88-89. Within that broader 1-500 mg range, Silverman also discloses 12 partially overlapping smaller ranges as "[e]xamples"—with no stated preference among them and no guidance on which range might be applicable to Compound (I) or AA. *Id.* at 20:10-15; *see* Ex. 2055 at 192:9-193:11 (acknowledging that there are 13 ranges in Silverman and nine specific doses—none of which are 16 mg/day or 24 mg/day); *id.* at 198:6-14 (acknowledging that Silverman did not include AA in a lengthy list of enumerated diseases). To make its case, Incyte cherry-picks some of these narrower, example ranges—*e.g.*, "10 mg to 20 mg" and "5 mg to 25 mg." *See* Paper 1 at 27 (citing Ex. 1002 at 20:9-15). But there is no explanation, other than pure hindsight, to support Incyte's decision to pluck out these particular examples.

And there is nothing about *either* the narrower ranges *or* the broader 1-500 mg range that suggests the two specifically claimed doses of Compound (I) in the '659 patent, for three independent reasons. First, Silverman does not teach the two doses *specifically* claimed in the '659 patent—16 mg per day and 24 mg per day.

See Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006) (holding that a disclosure of a 100-500 °C temperature range did not anticipate a claimed 330-450 °C range because "disclosure of a genus in the prior art is not necessarily a disclosure of every species that is a member of that genus"). Second, Silverman's disclosure of broad ranges of possible doses is a *general* disclosure that is not specific to Compound (I), and there is no indication that any particular narrower range—much less either of the cherry-picked narrower ranges upon which Incyte relies—is applicable specifically to Compound (I). *See* Ex. 2055 at 193:16-21. As discussed above (p. 44), Silverman disclosed at least 63 different compounds; there is nothing to suggest any particular dosing regimen for Compound (I). Third, and most importantly, none of Silverman's expansive dose ranges is specific to, or even applicable to, the treatment of AA. Silverman does not disclose the use of any compound to treat AA, *see* Ex. 2055 at 192:21-198:14, and therefore its disclosure of a dose range is inapplicable to treatment of that disease.

And even ignoring all of these deficiencies in Incyte's arguments about the ranges disclosed in Silverman, the disclosure of a range in the prior art creates, at best, a presumption of the obviousness of a subset of that range. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). But that presumption can be rebutted where, among other things, (1) the modification provides a new and unexpected result which is different in kind, rather than degree,

or (2) the prior art disclosure is to a broad range that does not invite optimization. *See id.* Both of those conditions are present here.

First, the claims of the '659 patent produce results that are different in kind than the prior art. To the extent that the ranges in Silverman apply to Compound (I) (and, again, there is no evidence that they do), those ranges are not for the treatment of AA. Silverman lists a number of diseases potentially treated by the compounds of the invention, none of which is AA. *See* Ex. 1002 at 2:66-3:6; Ex. 2055 at 198:6-14; Ex. 2059 ¶90. Moreover, Silverman's reference to the prior-art dosing information for ruxolitinib relates to blood cancer, not AA. And Silverman explicitly teaches that dosing will be different for different disease types. *See* Ex. 1002 at 20:19-21; Ex. 2059 ¶91. In contrast, the claims of the '659 patent relate to treatment of hair-loss disorders and specifically AA, an entirely different class of disease from the blood cancers treated by ruxolitinib. In short, the claimed methods provide for a treatment benefit that is different in kind from any disclosure in Silverman.

Second, even if the prior art range in Silverman applied to AA, because Silverman discloses a large range of doses for a genus of compounds and for diverse other uses, the reference does not invite routine optimization of Compound (I) for AA. The ranges in Silverman, both the broadest 1-500 mg range and the 12 narrower examples, express no preference for either of the doses specifically claimed in the

'659 patent—16 mg/day and 24 mg/day—let alone for AA in particular. There is no disclosure in Silverman that suggests any dose of Compound (I) for treatment of AA, and no in vitro or in vivo testing data for Compound (I) at any dose at all.

Incyte's reliance on a handful of cases to support its contention that this disclosure in Silverman provides a motivation to optimize the dose range, *see* Paper 1 at 44, is fundamentally misplaced.

As an initial matter, all of the cases involved prior-art ranges that were taught for the *same purpose* as the value claimed in the patent at issue. *See, e.g., Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 14-cv-882, 2017 WL 1199767, at 33 (D. Del. Mar. 31, 2017) (finding dose obvious where prior art disclosed range for same drug used for the same condition); *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372-1373 (Fed. Cir. 2011) (same). That is not case here: as discussed above (p. 57), the range in Silverman is not for the treatment of AA.

Furthermore, the cases Incyte cites all rely on either an explicit preference in the prior art for a narrow range or the disclosure of a much smaller prior-art range than the broad range in Silverman. For example, the Federal Circuit in *Tyco* found that a claimed range of 6 mg to 8 mg was obvious over prior art that claimed a range of 10 mg to 30 mg, with a lower range for elderly patients (5 mg to 15 mg), and an increasing dose up to 60 mg, for the same condition. *See* 642 F.3d at 1372-1373. Even the broadest prior-art range in *Tyco* of 5 mg to 30 mg is substantially smaller

than the 1 mg to 500 mg range at issue here in Silverman. *See also Acorda*, 2017 WL 1199767, at *32 (finding 10 mg twice daily—*i.e.*, 20 mg total per day—obvious over a prior art disclosed range of 20 mg to 40 mg). Similarly, in *In re Sebela Patent Litigation*, No. 14-cv-6414, 2017 WL 3449054 (D.N.J. Aug. 11, 2017), the prior art disclosed a narrow range that was most preferred. *Id.* at *25. That "most" preferred range in the prior art in *Sebela* was substantially smaller than the broadest range disclosed in Silverman, and in Silverman, there was no indication that any narrower range was more or less preferred. Thus, Incyte's conclusion that the Federal Circuit "has repeatedly found doses obvious where they fell within *similarly narrow* (and even broader) ranges," Paper 1 at 44 (emphasis added), is unsupported. In not a single case cited by Incyte did the prior art have nearly as broad a range as that disclosed in Silverman.

Warner Chilcott is also distinguishable because the prior art range in that case was not for the active therapeutic agent (risedronate), but rather for EDTA, a chelating agent added to prevent the formation of a risedronate-calcium complex that inhibited absorption of risedronate. *See Warner Chilcott Co. v. Teva Pharm. USA, Inc.,* 642 F. App'x 996, 998 (Fed. Cir. 2016). The district court in *Warner Chilcott* found that the amount of EDTA within the range was not critical to efficacy, and on that basis found the claimed amount unpatentable. *Id.* at 1002. Here, to the contrary, the specific dose amount and regimen for JAK inhibitors is critical to its

efficacy; in fact, different doses are required for efficacy depending on the disease being treated and the particular JAK inhibitor at issue. *See supra*, pp. 54-55.

Incyte's attempt to bolster its argument for optimizing dose by citing the portions of Silverman that refer to the Ruxolitinib Prescribing Information regarding dosing does not fill the gap in its argument for motivation. *See* Paper 1 at 43-44. The Ruxolitinib Prescribing Information does not contain any reference to AA, and therefore cannot inform a POSA regarding dosing for patients suffering from AA. *See* Ex. 2055 at 199:2-14. The very same paragraph in Silverman that refers to the Ruxolitinib Prescribing Information explicitly notes that "[e]ffective doses will also vary, as recognized by those skilled in the art, depending on the *diseases treated*, the *severity of the disease*, the route of administration[.]" Ex. 1002 at 20:19-25 (emphasis added). In other words, Silverman teaches that dosing depends on a number of factors, including the disease treated and the severity of the disease. A POSA reading Silverman would understand that the dose of ruxolitinib for a severe form of blood cancer (the only approved indication for ruxolitinib in the Ruxolitinib Prescribing Information) would *not* be instructive regarding the appropriate dose of Compound (I) for an entirely different disease, such as a hair-loss disorder like AA.

Incyte's reliance on its clinical expert, Dr. Shapiro, cannot provide a basis for the dose of Compound (I) in AA; his declaration discusses dosing of a different drug, tofacitinib, with no explanation as to why that is relevant for the dosing of

ruxolitinib, let alone Compound (I). Further, the very references that Dr. Shapiro relies on all state that tofacitinib is a JAK1/3 inhibitor, Ex. 1050 at 1; Ex. 1067 at 1; Ex. 1068 at 1, whereas ruxolitinib is a JAK1/2 inhibitor, Ex. 1004 at 7. Incyte provides no valid basis for applying prior art regarding a JAK inhibitor with a different inhibitory profile compared to ruxolitinib or Compound (I). If anything, the efficacy of a JAK1/3 inhibitor, like tofacitinib, would undermine any expectation of success in using a JAK1/2 inhibitor, like Compound (I), to achieve efficacy at the lower doses claimed in the '659 patent in view of its lack of JAK3 inhibition. Moreover, tofacitinib itself is also known to require different doses for different conditions. *See supra*, p. 55. Incyte has provided no justification for ignoring these differences, and has failed to meet its burden to show that a POSA would look to a different JAK inhibitor approved for a different disease to determine the effective dose of Compound (I) for AA.

e. Incyte Improperly Relies on Post-Art on Ruxolitinib for Motivation to Use Lower Doses

Finding not a single prior art reference that discloses a dose of ruxolitinib lower than 30 mg per day for AA, Incyte tries to fill that gap by relying on Silvestri. While admitting that Silvestri was not published until after the priority date of the '659 patent, Incyte nonetheless relies upon it to argue that a POSA would use 5 mg per day as a starting dose of ruxolitinib for treatment of AA. Paper 1 at 10, 45. But this post-art publication cannot provide the sole motivation to optimize the dosing

regimen. *See Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 287 F. Supp. 3d 505, 524 (D. Del. 2017), *aff'd*, 923 F.3d 1051 (Fed. Cir. 2019). Incyte's reliance on non-prior art to fill an obvious gap in its argument is improper. And, in any event, Silvestri does not teach the claimed daily doses of 16 and 24 mg/day.

Incyte's reliance on *Yeda* is misplaced. In that case, the Court made clear that non-prior-art evidence "cannot be applied, *independently*, as teachings separately combinable with other prior art, but can be relied on for their proper *supporting* roles, e.g., indicating the level of ordinary skill in the art, what certain terms would mean to one with ordinary skill in the art, and how one with ordinary skill in the art would have understood a prior art disclosure." *Yeda Research v. Mylan Pharm. Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018) (emphasis added) (quotation marks omitted). Yet here, Incyte does not confine Silvestri to a supporting role—such as to explain and confirm another, freestanding prior-art reference. Instead, it relies on Silvestri as the *only* reference supporting dosing of ruxolitinib below 30 mg a day. Ex. 2059 ¶96. Under *Yeda*, a non-prior-art reference like Silvestri may not fill that primary role.

f. The Prior-Art Dosing Disclosures on Which Incyte Relies Would Not Lead a Skilled Artisan to the Claimed Doses

The doses claimed in the '659 patent are lower than any of the doses Incyte points to in the prior art. To support its argument that doses of 16 and 24 mg/day are obvious, Incyte relies on a single reference's finding of adventitious hair

regrowth in one patient reportedly taking 30 mg/day of ruxolitinib a day, essentially arguing that the 30 mg prior-art dose of ruxolitinib is "close" enough to the claimed doses. Paper 1 at 46 (quoting *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985)). But as discussed above (p. 37), an anecdotal report of a single patient's hair regrowth when administered ruxolitinib is insufficient to support an expectation of effective treatment using ruxolitinib, much less Compound (I). And the mere arguable proximity of the claimed dose to doses in the prior art does not establish obviousness. *See In re Patel*, 566 F. App'x 1005, 1010 (Fed. Cir. 2014) ("Depending on the technology, even small differences in formulations can be meaningful.")

Incyte has not provided sufficient evidence to show that the difference between the claimed doses and the prior-art 30 mg ruxolitinib dose is not meaningful. Ex. 2059 ¶92. It has not made this showing with respect to the claimed 24 mg dose (in independent claims 1 and 11 and their dependent claims), where the prior-art 30 mg dose was 25% higher. And it has certainly not made this showing with respect to the claimed 16 mg dose (in independent claims 1 and 9 and the claims depending from them), where the prior-art 30 mg dose was 87.5% higher. Nor has Incyte provided any reason that a POSA would disregard the prior-art teaching that the lowest reported dose that showed hair regrowth for an individual with AA was 30 mg, and choose to go to a lower dose. Incyte's reliance on *Titanium Metals* is

misplaced; there, the prior art disclosed two single points, and the claimed amount fell in between the two. 778 F.2d at 782-783. Here, by contrast, the lowest reported dose in the prior art was 30 mg for a different drug. Thus, Incyte has failed to meet its burden to show motivation to arrive at the lower dose of Compound (I) claimed in the '659 patent.

B. A Skilled Artisan Would Not Have Reasonably Expected to Succeed in Combining the Teachings of the Prior Art to Arrive at the Claimed Invention

Even if Incyte could show that all the limitations of the challenged claims were taught in the prior art, and that a POSA would have had a motivation to combine those elements, Incyte cannot demonstrate a reasonable expectation of success.

1. Incyte Has Not Met Its Burden to Show That a Skilled Artisan Would Have Had a Reasonable Expectation of Success Based on the Available Clinical Evidence as of the Priority Date

As numerous cases have recognized, it can be difficult to show a reasonable expectation of success in situations with no or limited clinical trials. In *Novartis Pharmaceuticals v. West-Ward Pharmaceuticals*, 923 F.3d 1051 (Fed. Cir. 2019), for example, the Federal Circuit affirmed a finding that a POSA would not have had a reasonable expectation of success where (1) as of the priority date, "there were no clinical trial data on [the drug in question] as an anti-cancer agent," (2) there were only limited Phase 1 data involving a different drug in the same class; (3) there were

"numerous failed attempts" to develop a treatment for the relevant type of cancer; and (4) "the molecular biology of [the relevant type of cancer was] not completely understood." *Id.* at 1061; *see also id.* at 1055. Similarly, in *OSI Pharmaceuticals v. Apotex*, 939 F.3d 1375 (Fed. Cir. 2019), the Federal Circuit reversed the Board's finding of a reasonable expectation of success where there was a lack of clinical data regarding the claimed method of treating a certain form of lung cancer with the drug erlotinib. *Id.* at 1383. Among other things, the Court noted, "treatment [of the relevant condition] was highly unpredictable with an over 99.5% rate of failure for drugs entering Phase II clinical studies." *See id.*; *see also* Ex. 2055 at 57:12-13.

The scenario in this case is similar. As of the priority date, efforts to develop an AA treatment had consistently failed. *See supra*, p. 3. Despite repeated efforts to develop a treatment, skilled artisans had identified "*no effective evidence-based treatment for AA*." Ex. 2058 at 2 (emphasis added). In light of these teachings, Incyte can hardly claim that a POSA had a reasonable expectation of success at using a novel compound and the specifically claimed dosing regimen to treat a disease with no known therapy.

As discussed above, Incyte highlights a handful of anecdotal reports of hair regrowth in patients taking ruxolitinib. *See supra*, pp. 36-39. But even if these anecdotal accounts would have motivated a POSA to experiment, they would not have provided a *reasonable expectation of success* in using ruxolitinib—let alone

Compound (I)—to treat AA at the claimed doses. As in *Novartis* and *OSI*, there were no randomized clinical trial data on the particular compound of the invention (Compound (I)); there were only anecdotal data on a different drug (ruxolitinib); there had been numerous failed attempts to develop a treatment for the condition in question (AA); and the mechanism of the disease was poorly understood. A POSA would have been wary of anecdotal case reports generally (*see* Ex. 2059 ¶¶42-45; Ex. 2080 at 5); would have considered the known safety issues of JAK inhibitors; and would have been particularly aware of the history of anecdotal case reports with respect to AA treatments, where a number of treatments that looked promising in isolated case reports ultimately failed to show efficacy in randomized clinical trials. Ex. 2059 ¶¶42-45; Ex. 2101 at 4; Ex. 2102 at 4; Ex. 2103 at 3; Ex. 2104 at 3. As a result, a POSA would have had a reasonable expectation of success only if he or she had some evidence-based belief that a treatment method would work in terms of safety and efficacy—rather than merely being motivated to experiment and hoping it would work. Ex. 2059 ¶¶93-95. Incyte's anecdotal reports do not clear that hurdle.

In arguing that there would have been a reasonable expectation of success in substituting Compound (I) for ruxolitinib in the treatment of AA, Incyte relies on the two drugs' similar "potency and selectivity" in inhibiting a particular STAT protein, pSTAT3. Paper 1 at 35. Selectivity and potency are merely pharmacodynamic

properties[13] of the compounds—they describe the compounds' respective affinity for the JAK receptor in the complex JAK-STAT signaling pathway. Ex. 1001 at 2:7-24; Ex. 1011 at 5; Ex. 1051 at 1; Ex. 2068 ¶30. But, even if ruxolitinib and Compound (I) have similar pharmacodynamic properties, whether a drug can be used safely and efficaciously for treatment of a particular disease, and if so, at what dose, depends on the relationship between the drug's pharmacokinetics and pharmacodynamics when tested in the particular disease at issue. In this case, Incyte has not provided any evidence that there was a known relationship between the pharmacokinetics and pharmacodynamics of ruxolitinib in the treatment of AA. The only pharmacokinetic and pharmacodynamic data Incyte relies on for ruxolitinib were separate assays done on healthy volunteers. These assays do not provide any information about the pharmacokinetic-pharmacodynamic relationship for ruxolitinib in AA. *See* Ex. 2068 ¶¶31-32. Without detailed information on that relationship, a POSA would not be able to predict therapeutically safe and effective doses of ruxolitinib for the treatment of AA. And the POSA would certainly not know the pharmacokinetic-pharmacodynamic relationship for Compound (I) in AA. Absent a known relationship between the drug's pharmacokinetics and

[13] Pharmacodynamics is the study of how drugs affect the body, whereas pharmacokinetics is the study of how the body affects drugs. Ex. 1048 at 16.

pharmacodynamics for AA, a POSA would not have been motivated to use ruxolitinib or Compound (I) for the treatment of AA at the doses claimed in the '659 patent nor would the POSA have had an expectation of success in doing so. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (explaining that where "skilled artisans did *not* know the [pharmacokinetic-pharmacodynamic] relationship even for the immediate-release formulation, there was no way to match the dosage for the extended-release formulation to achieve a known therapeutic effect," and so the court "could not find obviousness without finding that the prior art would have taught or suggested a therapeutically effective formulation to one of ordinary skill in the art").

2. Incyte Has Not Met Its Burden to Show That the Deuteration of Ruxolitinib Predictably Allows for the Lower Dosing of Compound (I) in the Treatment of AA

Incyte asserts that a POSA would have substituted Compound (I) for ruxolitinib because deuterating a drug predictably allows for lower dosing compared to the non-deuterated compound. *See* Paper 1 at 38-40; *see also supra*, n. 10. But deuteration is notoriously unpredictable, and Incyte cherry-picks isolated sentences from a series of references and mischaracterizes the teachings of the art as a whole regarding deuteration. Ex. 2059 ¶98.

The effect of deuteration on metabolism is unpredictable. While deuteration can increase metabolic stability in some molecules, the effect, if any, is variable. Ex.

2068 ¶¶42, 52, 55, 57, 62. While deuteration can have a positive effect, it can also have a negative effect (that is, decrease metabolic stability) or have no effect. Ex. 2068 ¶¶52, 55. Further, a POSA would not be able to determine what the magnitude of any effect would be, and therefore could not determine how deuteration would affect dosing. *Id.* A POSA also would not know how deuteration impacts safety. One skilled in the art would appreciate that, by enhancing metabolic stability, increased exposure to a drug related to a class that has an FDA black-box warning for these types of indications might exacerbate already serious side effects. Therefore, a POSA would not have had a reasonable expectation that deuteration would result in a drug with acceptable safety in treating AA.

In fact, Incyte's own references contradict its argument that the deuteration of ruxolitinib would predictably allow for the lower dosing of Compound (I). Several examples from those references reflect the recognition in the art of the *unpredictable* nature of deuteration, Ex. 1044 at 1-2 (deuteration strategies can be confounded by "metabolic switching" and "unpredictable translation of isotope effects from in vitro drug metabolism systems to the in vivo situation is a key challenge; often, little change is observed in terms of in vivo clearance"); Ex. 1053 at 3 (pharmacokinetic data showing that, for two of three deuterated analogs of nintedanib, deuteration actually caused a *decreased* half-life)

A POSA, relying on these statements in Incyte's own references, would not have predicted that Compound (I) and ruxolitinib would be similarly effective at different doses. *Cf.* Ex. 2009 ¶7 (Dr. Shapiro opining that the difference in half-life between ruxolitinib and Compound (I) was "not large enough to have any clinical importance"). In other words, while Incyte attempts to rely on a predictable, positive deuterium effect to close the gap between the lower doses of Compound (I) and higher doses of ruxolitinib in AA, Incyte's own references showcase the unpredictability of deuteration.

Furthermore, a POSA would not have had a reasonable expectation of success because even if a POSA would have believed that deuteration would improve metabolic stability—and therefore positively impact efficacy—the POSA would not know what impact deuteration (and resulting increased exposure) would have on safety. Dr. Patterson's assertion that a POSA would simply lower the dose to overcome safety concerns ignores the fact that achieving just the right balance of efficacy and safety—that is, determining whether or not there is a suitable therapeutic window at *any* dose, and if so, what that dose is—is highly unpredictable. In other words, there is no expectation that "simply lowering the dose" would allow for a safe and effective dose of Compound (I) for treating AA. Ex. 2068 ¶¶61-62.

The foregoing unpredictability is fatal under governing case law. As the Federal Circuit has explained, "predictability is a vital consideration in the

obviousness analysis." *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1298 (Fed. Cir. 2012). "Unpredictability of results equates more with nonobviousness rather than obviousness, whereas that which is predictable is more likely to be obvious. Thus, reasoning that one would no more have expected failure than success is not a valid ground for holding an invention to have been obvious." *Honeywell Int'l Inc. v. Mexichem Amanco Holding S.A. de C.V.*, 865 F.3d 1348, 1356 (Fed. Cir. 2017). Particularly in the chemical arts, where modifications can be unpredictable, a POSA would not have relied on the dosing of ruxolitinib to predict the dosing of a deuterated version of that drug. *See Takeda Pharm. Co. Ltd. v. Torrent Pharm. Ltd.*, No. 17-cv-3176, 2020 WL 549594, at *10 (D.N.J. Feb. 4, 2020) (noting that "in the art of pharmaceutical development, it is difficult to accurately predict the biological effects of the modification of molecules, even when the modification entails a small change").

In sum, Incyte has failed to meet its burden to show that a POSA would have had a reasonable expectation of success in substituting Compound (I) for ruxolitinib in view of the clear teaching in the prior art of the unpredictability resulting from deuteration, and especially in view of Incyte's failure to show what the non-deuterated drug would do at the same doses. And even if the prior art did generally teach that deuteration *may* provide beneficial properties in *some* molecules, that is insufficient to provide a reasonable expectation that substituting Compound (I) for

ruxolitinib at a lower dose to treat AA would be effective. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc*., 566 F.3d 989, 997 (Fed. Cir. 2009) ("Similarly, patents are not barred just because it was obvious 'to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.'" (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988))).

C. The Objective Indicia Support a Finding of Nonobviousness

Two objective indicia—unexpected results and long-felt need—rebut Incyte's obviousness arguments and confirm that the challenged claims were not obvious.

1. CTP-543 Demonstrates Unexpected Results

"Nonobviousness may be established when an invention yielded more than predictable results." *Millennium Pharm., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quotation marks and brackets omitted). "Unexpected results are useful to show the improved properties provided by the claimed compositions are much greater than would have been predicted." *Id.* (quotation marks omitted). The claimed method of treatment demonstrates an unexpected ability to treat AA in two significant ways.

First, CTP-543 demonstrated an unexpectedly superior efficacy/safety profile in a Phase 2 study for the treatment of AA. In particular, CTP-543 produced marked

improvement in patients' "SALT" scores. Researchers use the Severity of Alopecia Tool, or SALT, to measure the degree of a patient's scalp hair loss. Ex. 2059 ¶100. At 24 weeks, 41% of patients on a 12 mg twice-daily dose of CTP-543, had achieved a SALT score of 20 or lower (that is, 20% or less total hair loss). Ex. 2059 ¶101; *see* Ex. 2083. This number increased to 48% of all enrolled patients by week 36 (57% of tested patients). Ex. 2059 ¶101; *see* Ex. 2083. Notably, however, this reduction in SALT scores was not accompanied by the high rate of significant side effects that typically comes with the administration of ruxolitinib. *See* Ex. 2026; Ex. 2059 ¶100-103; *supra*, pp. 4-5, 10-11.

This favorable efficacy/safety profile was unexpected: As Incyte explained in Ni, with respect to sustained-release formulations, "it was not predictable that a sustained-release formulation of ruxolitinib could both maintain therapeutic efficacy and significantly reduce unwanted side effects related to thrombocytopenia or reduced hemoglobin levels." Ex. 1006 at [0066]. It was likewise unexpected that CTP-543 could have great efficacy at low dose with reduced side effects. Ex. 2059 ¶102.

The unexpected nature of CTP-543's ability to improve SALT scores is underscored by its favorable comparison to Lilly's recent Phase 3 study of baricitinib in the treatment of AA. Even at 36 weeks, no more than 35% of patients taking Lilly's baricitinib therapy achieved a SALT score of 20 or lower, regardless of dose.

Ex. 2059 ¶103; Ex. 2081 at 1. As discussed above, CTP-543 tested had surpassed those figures by 24 weeks, and far exceeded them by 36 weeks. *See supra*, p. 74.

Incyte argues that the SALT scores are not unexpected because they are comparable to those found in a ruxolitinib study by Mackay-Wiggan. *See* Paper 1 at 85-86 (citing Ex. 1049). But those studies cannot be compared: the baseline SALT scores for the Concert study were much worse—*i.e.*, recorded much greater hair loss—than those in the Mackay-Wiggin ruxolitinib study. *Compare* Ex. 1049, *with* Ex. 1089 at 6; Ex. 1059 ¶104. As Incyte's expert Dr. Shapiro conceded, individuals with worse baseline SALT scores—*i.e.*, with more hair loss to begin with—are less likely to respond to a given treatment. *See* Ex. 2054 at 159:14-18. Thus, to the extent any comparison can be made at all between the studies, the fact that the patients in the Concert study responded comparably to those in the Mackay Wiggin study demonstrates the superiority of CTP-543 in light of the different patient baseline characteristics.

Second, CTP-543 avoids the risk of drug-drug interactions inherent in ruxolitinib. Ex. 2059 ¶¶105-107. Patients taking ruxolitinib and a CYP3A4 inhibitor face a significant risk of harmful drug-drug interactions. The ruxolitinib label describes a study in which subjects who were administered ruxolinitib and ketoconazole, a strong CYP inhibitor showed a mean 33% increase in C_{max}, a 91% increase in AUC, and mean increase in half-life from 3.7 to 6.0 hours. Ex. 1004 at

5, 7. For this reason, ruxolitinib's label includes a dose-modification warning for patients on CYP inhibitors, and cautions patients to avoid taking ruxolitinib with certain doses of certain CYP inhibitors altogether. *See* Ex. 1004 at 5-8.

Unexpectedly, strong CYP3A4 inhibitors do not have the same effect on Compound (I). Concert conducted a study where healthy volunteers were administered Compound (I) together with itraconazole, a strong CYP inhibitor. The pharmacokinetic data for the Concert study showed an increase in C_{max} of only 13%, an increase in AUC of only 27%, and a change in half-life from 4.18 hours to 4.62 hours. As a result of this avoidance of a large drug-drug interaction effect, the FDA is unlikely to require dose adjustment for CTP-543 when given with CYP inhibitor. Ex. 2068 ¶¶20-29 That is potentially important for AA patients who can have comorbidities that require treatment with strong CYP inhibitors including, *e.g.*, several antibiotics. *Id.*; Ex. 2059 ¶¶106-107.

2. The Claimed Method Satisfies A Long Unmet Need

"Evidence of a long-felt but unresolved need can weigh in favor of the nonobviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016) (en banc). Here, the claimed method of treating AA using particular doses of CTP-543 satisfies a long-felt and unmet need for a treatment for AA.

As of the priority date, no JAK inhibitor had been approved for the treatment of AA, and there were no FDA approved treatments for AA at all. Ex. 2054 at 33:2-6; *see supra*, p. 3. Despite the long-felt need for a proven effective treatment for AA, neither of Incyte's experts—who themselves either treated AA (Dr. Shapiro) or worked on developing a treatment for AA (Dr. Patterson), came up with the idea of using Compound (I). As one prior-art reference put it, "[a] lack of understanding of the molecular basis of [AA] has been an impediment to the development of therapeutic interventions and perpetuates an unmet medical need for patients." Ex. 1013 at 1.

CTP-543 at the claimed doses meets this long-felt need by providing an effective treatment for AA using a JAK inhibitor. Ex. 2059 ¶108. Indeed, in recognition of its ability to satisfy this long-felt need, the FDA has granted Breakthrough Therapy and Fast Track designations to CTP-543 for treatment of AA. Ex. 2014. This objective indication likewise confirms that the claimed method is nonobvious.

VII. DR. PATTERSON'S TESTIMONY SHOULD BE GIVEN LITTLE WEIGHT

The claims of the '659 patent relate to (i) a deuterated (ii) JAK inhibitor (iii) for the treatment of AA. Based on Dr. Patterson's description of his own expertise, he is not qualified to opine on any of those topics. *See Sundance, Inc. v. DeMonte Fabricating, Inc.*, 550 F.3d 1356, 1363-1364 (Fed. Cir. 2008) (Fed. R. Evid. 702 requires that an expert be "qualified in the pertinent art"). Dr. Patterson has never

worked on a deuterated drug. Ex. 2055 at 31:17-19, 31:25-32:3. He has never published on one, either. Ex. 1008 at 2-7. He has no prior experience with JAK inhibitors; he only once tried to make a JAK inhibitor compound, but was unsuccessful. Ex. 2055 at 28:19-23, 29:8-13, 30:1-4, 31:4-7, 79:6-18, 119:9-22. His public faculty profile describes his expertise as "[a]nti-microbial drugs, cancer therapy, antiviral therapy, [and] cyanide antidotes"; it does not include deuterated compounds, JAK inhibitors, or treatment of AA or other autoimmune disorders. Ex. 2015 at 1. At his deposition, Dr. Patterson testified that he has only ever consulted with respect to one AA treatment—which was not a JAK inhibitor—and that he is not a clinician or pharmacokineticist. Ex. 2055 at 26:4-10, 26:15-17, 101:9-103:5, 24:21-24, 53:14-17. He stated repeatedly that he is just a medicinal chemist and that he had to study AA and JAK inhibitors specifically for purposes of this case. Ex. 2055 at 26:4-14, 28:19-23, 29:8-13, 30:1-4, 31:4-7, 79:6-18, 56:25-57:7, 119:9-22. He has never dosed humans or done dosing studies in humans. Ex. 2055 at 56:25-57:7, 45:4-11, 51:5-9.

For all these reasons, Dr. Patterson is not qualified to offer expert testimony on these topics and is not qualified in the pertinent art.[14]

[14] Incyte's only other expert, Dr. Shapiro, never offers the opinion that a POSA would have been motivated to or reasonably expected to successfully use Compound

VIII. CONCLUSION

Incyte has failed to carry its burden of proving that the challenged claims are unpatentable by a preponderance of the evidence. The Board should reject Incyte's challenges to claims 1-7 and 9-21 of the '659 patent and refuse to cancel those claims.

(I) to treat AA; his opinion is limited to a POSA using ruxolitinib. *See* Ex. 1009 ¶2; Ex. 2054 at 45:10-13.

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

I hereby certify that this "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 18,627 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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