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 PRELIMINARY RESPONSE

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2002	Declaration of Emily L. Rapalino
2003	Declaration of Gerard J. Cedrone
2004	U.S. Priority Application No. 62/331,827 (filing date May 4, 2016)
2005	Declaration of Vinita Uttamsingh (dated February 15, 2021)
2006	J. Mackay-Wiggan et al., *Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata*, J. Clin. Invest. Insight (Sep. 22, 2016)
2007	M.F. McMullin et al., *The use of erythropoiesis-stimulating agents with ruxolitinib in patients with myelofibrosis in COMFORT-II: an open-label, phase 3 study assessing efficacy and safety of ruxolitinib versus best available therapy in the treatment of myelofibrosis*, Exp. Hematol. Oncol. 4:26 (2015)
2008	F.M. Delamere et al., *Interventions for Alopecia Areata (Review)*, 2 Cochrane Database Syst. Rev. (2008)
2009	Declaration of Jerry Shapiro, M.D., IPR2017-01256 (Sept. 9, 2018)
2010	Declaration of Alison H. Fitzgerald (dated February 16, 2021)
2011	U.S. Patent No. 10,561,659—Patent Assignment
2012	U.S. Patent No. 9,249,149—Patent Assignment
2013	C. Helfand, *FDA swats down Pfizer's Xeljanz in plaque psoriasis,* Fierce Pharma (Oct. 15, 2015), available online at: https://www.fiercepharma.com/regulatory/fda-swats-down-pfizer-s-xeljanz-plaque-psoriasis

2014	Concert Pharmaceuticals, Inc., Press Release: *Concert Pharmaceuticals Receives FDA Breakthrough Therapy Designation for CTP-543 for the Treatment of Alopecia Areata* (July 8, 2020), available online at: https://ir.concertpharma.com /news-releases/news-release-details/concert-pharmaceuticals-receives-fda-breakthrough-therapy
2015	Steven E. Patterson, Ph.D. Faculty Biography, University of Minnesota, Center for Drug Design, available online at: https:// drugdesign.umn.edu/bio/cdd-faculty-staff/steven-patterson
2016	*FDA Advisory Committee Recommends the Approval of Baricitinib 2mg, but not 4mg, for the Treatment of Moderately-to-Severely Active Rheumatoid Arthritis* available online at: https://investor .lilly.com/news-releases/news-release-details/fda-advisory-committee-recommends-approval-baricitinib-2mg-not
2017	Plaquenil® (Hydroxychloroquine) Prescribing Information (Rev. Oct. 2006)
2018	Simponi® (Golimumab) Highlights of Prescribing Information (Rev. 01/2016)
2019	W. Damsky et al., *The emerging role of Janus kinase inhibitors in the treatment of autoimmune and inflammatory diseases,* J. Allergy Clin. Immunol. (2020)
2020	Statutory Disclaimer in a Patent Under 37 C.F.R. § 1.321(a), dated February 12, 2021 (Application No. 16/098,338)
2021	Xeljanz® (Tofacitinib) Highlights of Prescribing Information (Rev. 09/2020)
2022	S. Banerjee et al., *JAK-STAT Signaling as a Target for Inflammatory and Autoimmune Diseases: Current and Future Prospects*, Drugs (2017)
2023	Austedo® (Deutetrabenazine) Highlights of Prescribing Information (Rev. 12/2020)

2024	Order, *Concert Pharm., Inc. v. Incyte Corp.*, No. 19-2011 (Fed. Cir. Jan. 24, 2020)
2025	Mandate, *Concert Pharm., Inc. v. Incyte Corp*, No. 19-2011 (Fed. Cir. April 16, 2020)
2026	Concert Pharmaceuticals, Inc., Press Release: *Concert Pharmaceuticals Reports Positive CTP-543 Results from Phase 2 Alopecia Areata Trial* (September 3, 2019), available online at: https://ir.concertpharma.com/node/10986/pdf

I. INTRODUCTION

Alopecia areata (AA) is a hair-loss disease that is often accompanied by intense feelings of grief, anxiety, fear, and embarrassment. AA affects not only individuals, but also families, particularly families of adolescents and young adults. There are currently no FDA-approved treatments for the disorder. Patent Owner Concert Pharmaceuticals has developed novel methods of treating hair-loss disorders, including AA, by administering specific doses of a compound known as CTP-543. Concert invented CTP-543 by modifying the drug ruxolitinib with deuterium atoms at eight key locations. The unexpected properties of CTP-543 make it superior to ruxolitinib for treating AA. CTP-543 is currently in clinical trials for the treatment of AA, where it has shown surprisingly promising activity at twice-daily doses of 8 mg and 12 mg.

The patent challenged here, U.S. Patent No. 10,561,659 ('659 patent), claims Concert's specific dosing regimens for CTP-543, which the patent refers to as "Compound (I)." The '659 patent issued after the patent examiner considered numerous references—including those cited in Petitioner Incyte's petition—and concluded that the relevant claims "are free of the prior art." Ex. 1047 at 1544. Incyte now seeks post-grant review of that determination, but it offers no valid basis to second-guess the examiner's judgment. The Board should deny institution for three independent reasons.

First, Incyte fails to demonstrate that its key reference is prior art. All of Incyte's asserted invalidity grounds rely on U.S. Patent No. 9,249,149 (Silverman) as their primary reference. Paper 1 at 2; *see* Ex. 1002.[1] Remarkably, however, the petition fails to analyze Silverman's prior-art status *at all*—the only "discussion" of the issue is Incyte's bare assertion that Silverman is "prior art." Paper 1 at 1, 12. In fact, Silverman is *not* prior art: it falls within exceptions articulated in AIA § 102(b). And this fact alone is dispositive: because Silverman is "the principal reference in each of the" asserted grounds, there is no basis to institute proceedings without it. *Marvell Semiconductor, Inc. v. Intellectual Ventures I LLC*, IPR2014-00552, Paper 79, at 7 (P.T.A.B. Nov. 30, 2015).

Second, even if Incyte could rely on Silverman as prior art, the Board should exercise its discretion to deny institution under 35 U.S.C. § 325(d). Three of Incyte's references (Silverman, Christiano, and Xing) were directly before the examiner. Two others (the Ruxolitinib Prescribing Information and Ni) were before the examiner in substance, even if not in the same exact form. The examiner was particularly attuned to these references: after the examiner initially allowed the claims, Concert prevented issuance of the patent and specifically brought the

[1] As discussed below (in Section IX), Incyte's third asserted ground is moot because Concert has disclaimed the relevant patent claim.

references to the examiner's attention. The examiner expressly indicated that he reviewed and considered all of them, and Incyte offers no reason—other than its own say-so—to conclude that the examiner erred. In short, each of the *Becton* factors points against institution, and a denial under § 325(d) is therefore appropriate. *See Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8, at 17-18 (P.T.A.B. Dec. 15, 2017) (designated precedential in relevant part, Aug. 2, 2019).

Third, Incyte's asserted grounds for institution fall short on the merits. Incyte has failed to show that the prior art would have motivated a skilled artisan to select Compound (I) of Silverman for further study or to use it to treat AA. And Incyte certainly has not shown that a skilled artisan would have selected the specific doses claimed in the '659 patent based on the prior art. Incyte suggests that the effects of deuterating ruxolitinib would have been predictable, but Incyte's *own references* refute that proposition. And even if a skilled artisan would have relied on the prior art's teachings about ruxolitinib, those disclosures did not render the specific method claims in the '659 patent obvious.

In short, Incyte dodges key issues and distorts the teachings of the relevant references. In light of the serious deficiencies in the petition, Incyte has failed to carry its burden of showing that it is "more likely than not" that one of the challenged claims is unpatentable. 35 U.S.C. § 324(a). The Board should deny institution.

II. STATE OF THE ART

A. Alopecia Areata

AA is one of the most prevalent autoimmune diseases in the United States. Ex. 1005 at 1:47-48. An AA patient's immune system attacks hair follicles, resulting in erratic 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. While the physical symptoms of AA are not life-threatening, patients suffer severe psychosocial consequences as a result of their disease. Ex. 1005 at 1:56-59. AA can be a chronic, lifelong condition; there is no cure for the disorder. Ex. 1021 at 1.

Today, as in 2016, there are no FDA-approved treatments for AA, and off-label treatments have shown only limited efficacy. Ex. 2006 at 1. Broad spectrum steroids have been used to treat the disease, but with limited success. Ex. 1003 at 5. Diphencyprone, dinitrochlorobenzene, intralesional corticosteroids, and dithranol have also been used as treatments, but there are no randomized clinical trials showing that they are actually effective. Ex. 2008 at 4. It is also unclear whether any of these therapies alters the long-term course of the disease. *Id.* In short, as of the priority date, there was a long-felt unmet need in the art for a safe and effective treatment for AA. Ex. 1013 at 1; Ex. 1068 at 1.

B. Ruxolitinib and Janus Kinase Inhibitors

Ruxolitinib is a chemical compound that inhibits the action of certain proteins known as Janus Kinases (JAKs). Ex. 1001 at 2:51-57. JAK proteins relay signals that are important to the body's immune response. When a protein called a cytokine binds to a receptor on the exterior surface of a cell, JAK proteins associated with that receptor activate a sequence of steps inside the cell that eventually produce downstream biological effects. *See id.* at 2:57-63. There are several different types of cytokines—including erythropoietin (EPO) and interferon gamma (IFN-γ)—that can bind to receptors to trigger a JAK signaling pathway, and different JAK proteins—such as JAK1, JAK2, and JAK3—can be involved in the signal cascade. A hyperactive JAK response can lead to certain autoimmune diseases. Ex. 2022 at 1, 5. Ruxolitinib inhibits two members of the JAK family: JAK1 and JAK2. *See* Ex. 1001 at 2:51-57; Ex. 1004 at 7. Other JAK inhibitors, like tofacitinib, inhibit JAK1 and JAK3. Ex. 1068 at 1.

Ruxolitinib is FDA-approved to treat rare and life-threatening bone marrow/blood cancers such as "intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis." *See* Ex. 1001 at 2:64-3:2; Ex. 1004 at 4. The precise mechanism of action for ruxolitinib's efficacy in treating the blood cancers is not known.

Despite its benefits, ruxolitinib and other JAK inhibitors come with a number of serious side-effects, including blood-related toxicities such as anemia (low red blood cell count), thrombocytopenia (low blood platelet count), neutropenia (low white blood cell count), and lowered hemoglobin. *See* Ex. 1004 at 6. These side-effects occur with significant frequency. For example, in one placebo-controlled study, the percentage of individuals who experienced anemia, thrombocytopenia, or neutropenia while taking ruxolitinib was 96.1%, 69.7%, and 18.7%, respectively (compared to 86.8%, 30.5%, and 4.0%, respectively, for patients taking a placebo). *Id.* at 7. The FDA has required a black-box warning in the prescribing information of all JAK inhibitors approved for treatment of autoimmune conditions to highlight their side-effects. Ex. 2019 at 10; *see also* Ex. 2021 at 1, 4-5.

It was not known in the prior art whether it would be possible for a JAK inhibitor to be effective against AA while mitigating these harmful side-effects. In treating myelofibrosis, certain benefits and harmful side-effects of ruxolitinib are thought to arise from ruxolitinib's inhibition of cytokine signaling pathways, including the EPO signaling pathway. Ex. 2007 at 4. Concert discovered that certain JAK inhibitors have unexpectedly high potency against a different cytokine signaling pathway, the IFN-γ pathway, as compared to the EPO signaling pathway; as Concert discovered, that difference is important in providing particular doses that would be both safe and effective for treating AA.

C. Deuteration

One potential—though unpredictable—way to alter a drug's pharmacokinetic properties is through deuterium modification, also known as deuteration. *See* Ex. 1001 at 2:7-12. Deuteration is the process of replacing one or more hydrogen atoms in a molecule with a rare, heavy isotope of hydrogen called deuterium to create a new molecule. To date, only one deuterium-modified drug has been approved by the FDA. *See* Ex. 2023.

Deuteration may, "[i]n select cases," affect a drug's pharmacokinetic properties and rate of metabolism. Ex. 1001 at 2:15-19. A metabolic change caused by deuteration is called a kinetic isotope effect (KIE) or deuterium isotope effect (DIE). As Incyte's own references demonstrate, however, a skilled artisan would have difficulty predicting *ex ante* whether—and to what extent—deuteration will result in a KIE for the metabolism of any *particular* drug compound. *See infra* Section VII.B.3.

III. 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

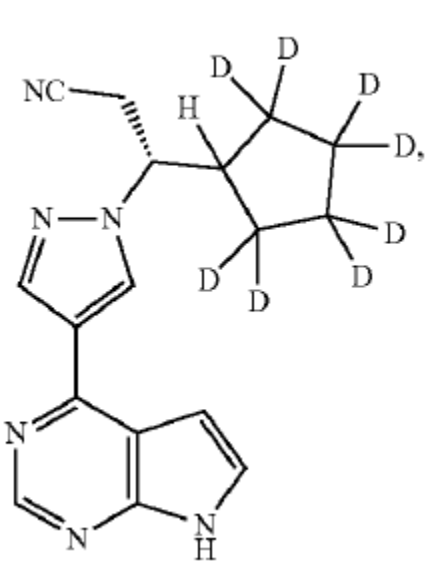
priority to several provisional applications, including to a first provisional application filed on May 4, 2016.[2]

The '659 patent discloses a method of treating, in a subject, hair-loss disorders that are beneficially treated by administering a JAK1 and/or JAK2 inhibitor. The named inventors 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.

[2] Incyte does not challenge this priority date. *See, e.g.*, Paper 1 at 3. And for good reason: the claims of the '659 patent are supported by U.S. Provisional Application No. 62/331,827 (Ex. 2004), the earliest provisional application to which the '659 patent claims priority. *Compare* Ex. 1001 claims 1, 5, 6, *with* Ex. 2004 at [11], [13], [18], [54]; *compare* Ex. 1001 claims 2, 9, 15, 18, *with* Ex. 2004 at [20]; *compare* Ex. 1001 claims 3, 4, 16, 19, *with* Ex. 2004 at [19]; *compare* Ex. 1001 claim 7, *with* Ex. 2004 at [31]; *compare* Ex. 1001 claims 8, 9, 11, 14, *with* Ex. 2004 at [11], [13], [18], [34], [54]; *compare* Ex. 1001 claim 10, *with* Ex. 2004 at [12], [48], [75]; *compare* Ex. 1001 claim 12, *with* Ex. 2004 at [12], [18]; *compare* Ex. 1001 claims 13, 17, 20, *with* Ex. 2004 at [54]; *compare* Ex. 1001 claim 21, *with* Ex. 2004 at [13].

A. 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)

Independent claim 9 is similar to claim 1, but specifies that the dose is 8 mg of Compound (I) twice a day. 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.[3]

[3] Concert has disclaimed independent claim 8. *See infra* Section IX.

Dependent claims 2-7, 13, 14, and 21 depend from claim 1; dependent claims 10 and 15-17 depend from claim 9; and dependent claims 12 and 18-20 depend from claim 11. These dependent claims are directed to particular dosing schedules, formulations, and methods of treating AA.

B. Summary of the Relevant Prosecution History

As discussed below (in Section VI), Incyte's obviousness combinations rely on substantially the same art that was before the examiner, and therefore its petition should be denied under 35 U.S.C. § 325(d). Incyte mischaracterizes the prosecution history of the '659 patent, accuses the examiner of misunderstanding the information disclosed by Concert, and asserts that Concert did nothing to correct this alleged misunderstanding. *See* Paper 1 at 1. None of Incyte's allegations are supported by the prosecution history. To the contrary, the record demonstrates that the examiner reviewed and understood the cited prior art and that Concert not only disclosed the references upon which Incyte now relies, but affirmatively called the examiner's attention to them.

After reviewing the application, the examiner initially allowed the claims on September 6, 2019, stating:

> The examiner performed a chemical structure as well as an inventor and classification search to identify any potential prior art. While the non-deuterated compound may be known in the prior art, there is nothing to suggest the present compound would be an obvious variant of the

> known compound. The Examiner was unable to identify any prior art which contained the limitations seen in the present application.

Ex. 1047 at 170-71.

After the Notice of Allowability, Concert affirmatively prevented issuance of the patent. In an interview with the examiner on October 24, 2019, Concert explained that it intended to file a Request for Continued Examination (RCE) to amend the scope of the claims in light of new Phase 2 clinical data. Ex. 1047 at 187. Concert also informed the examiner that it planned to file an Information Disclosure Statement (IDS). *See id.*

Concert subsequently filed the RCE and IDS on October 29, 2019. Ex. 1047 at 189, 1521-22. As relevant here, the IDS directly identified three of the references upon which Incyte currently relies in Grounds 1 and 2 of the petition: Silverman (Cite AC), Xing (Cite CY), and Christiano (Cite AB). *Id.* at 1521-22. The IDS also identified two references that are materially indistinguishable from references on which Incyte now relies—namely, an earlier version of the Ruxolitinib Prescribing Information (Cite CM), and the publication of WO 2014/078486 A1 (Cite BC), which is essentially identical to Ni. *See id.* The examiner signed the IDS with the notation that "all references [were] considered except where lined through." *Id.* at 1552 (capitalization removed). No references were lined through. *See id.* at 1551-

52. The examiner also annotated the IDS in one place, adding "Filed on May 8, 2015" next to the Silverman prosecution history and initialing that line. *Id.* at 1552.

After considering these additional references and the proposed amendments to the claims, the examiner issued a new Notice of Allowability, stating:

> Claims 1, 2, 5-10, 23-26 and 32-40 are free of the prior art. The examiner performed a chemical structure as well as an inventor and classification search to identify any potential prior art. The Examiner was unable to identify any prior art which contained the limitations seen in the present application.

Ex. 1047 at 1544.

IV. PERSON OF ORDINARY SKILL AND CLAIM CONSTRUCTION

For purposes of this submission only, Concert does not challenge Incyte's definition of a person of ordinary skill in the art or proposed claim constructions. Concert reserves the right to address Incyte's proposals should trial be instituted.

V. GROUNDS 1 AND 2 SHOULD BE DENIED BECAUSE INCYTE HAS FAILED TO SHOW THAT SILVERMAN IS PRIOR ART UNDER AIA § 102

Incyte's key reference is Silverman; that patent is central to all of the invalidity grounds asserted in the petition. Yet despite Silverman's importance, Incyte makes no effort—*none*—to establish that it qualifies as prior art under AIA § 102. Incyte's only "discussion" of the issue is a passing mention of Silverman as

"Concert's prior art U.S. Patent No. 9,249,149" in the introduction to the petition. Paper 1 at 1.

It is not enough for Incyte to simply assert that Silverman is prior art with a bare, conclusory statement. The burden is on *Incyte*, as the petitioner, to show that the conditions for instituting post-grant review have been met—including that all of its asserted references qualify as prior art. Incyte has not even tried to carry that burden. The Board should deny institution for that reason alone. And even if the Board could move past Incyte's failure of proof, Silverman is not prior art under § 102. Silverman falls within multiple exceptions set forth in § 102(b), and for that reason, too, the Board should deny institution.

A. Incyte's Deliberate Failure to Even Discuss Silverman's Prior-Art Status Is Fatal to the Petition

Before the Board can institute post-grant review, Incyte must "demonstrate that it is more likely than not that at least 1 of the claims challenged in the petition is unpatentable." 35 U.S.C. § 324(a). That means demonstrating that the references on which it relies are *actually* prior art under § 102. As the Board has explained, the "[p]etitioner has the burden to persuade [the Board] that [a reference] is invalidating prior art." *Kingsford Prods. Co. v. Creative Spark, LLC*, IPR2016-01831, Paper 7, at 25 (P.T.A.B. Mar. 17, 2017).

Incyte has failed to carry that burden. Incyte's petition contains *no* proof of Silverman's prior-art status; as mentioned, the sum total of Incyte's analysis is a

single allusion to Silverman as "Concert's prior art U.S. Patent No. 9,249,149." Paper 1 at 1. That is not enough. In *Kingsford*, the Board explained that the burden of production shifts to the patent owner only "*after* [p]etitioner comes forward with evidence suggesting that a reference is prior art." IPR2016-01831, Paper 7, at 26 (emphasis added) (citing *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1380 (Fed. Cir. 2015)). Incyte has failed to take that first, critical step. And that failure is fatal to institution, because Silverman is the backbone of all of Incyte's asserted grounds of invalidity. In other words, Incyte's failure to establish that Silverman is prior art forecloses its ability to establish any asserted ground.

Although denial of institution does not depend upon the reason for Incyte's failure of proof, it is worth noting that Incyte's effort to avoid discussing Silverman hardly appears accidental. The "Scope and Content of the Prior Art" section of the petition states the grounds on which Incyte believes *seven* other references qualify as prior art under § 102. Paper 1 at 3-11. With respect to Christiano, for example, the petition describes the issuance date and application chain and asserts that the patent is prior art under AIA §§ 102(a)(1) and (2). *Id.* at 7. Incyte's discussion of Xing, the Ruxolitinib Prescribing Information, Ni, Craiglow, Harris, and Pieri follows suit—in each instance, Incyte cites a provision of § 102 and explains the

grounds on which it believes the reference is prior art. *Id*. at 4-10.[4] Yet a similar analysis of Silverman as prior art is conspicuously absent.

In light of Incyte's extensive discussion of the other references' status as prior art under § 102, Incyte's failure to discuss Silverman—which, again, is central to its asserted grounds—seems to be little more than an effort to avoid questions about its status as prior art. *See infra* Section V.B. But in avoiding these questions, Incyte has failed to carry its burden of proof. The Board should deny institution on this basis alone.

B. Silverman Is Not Prior Art Under AIA § 102

Even if the Board could look past Incyte's fundamental failure of proof, the Board should still deny institution because Silverman is not prior art under the AIA. Section 102 articulates two grounds on which a reference could qualify as prior art: a reference can be a "printed publication" under subsection (a)(1), or it can be a patent that was "effectively filed before the effective filing date of the claimed invention" under subsection (a)(2). Importantly, however, subsection (b) creates various exceptions to the baseline rules of §§ 102(a)(1) and (2). Several of those

[4] Incyte discusses an eighth reference, Silvestri, but concedes that it is not prior art. *See* Paper 1 at 10.

exceptions apply here—thus foreclosing Incyte's ability to rely on Silverman as prior art and defeating its asserted grounds of obviousness.

1. Silverman Is Not Prior Art Under Subsection (a)(1) Because It Satisfies the Inventor-Disclosure Exceptions in § 102(b)(1)(A) and (B)

Section 102(b)(1) contains two exemptions for references that would otherwise qualify as prior-art printed publications under subsection (a)(1). These exceptions establish a one-year grace period for certain disclosures that originate with the inventor of the claimed invention. Both of these "inventor disclosure" exceptions apply here.

Subsection (b)(1)(B). Under § 102(b)(1)(B), "[a] disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if . . . the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor." This somewhat dense language boils down to two straightforward questions: Was Silverman (the "disclosure") published within one year of the effective filing date of the '659 patent (the "claimed invention")? And, if so, was the material contained in Silverman (the "subject matter disclosed") made public before Silverman was published ("before such disclosure") by one of the '659 patent's inventors ("the inventor or a joint inventor")? The answer to both questions is yes—and so Silverman is not prior art.

The first condition is easily 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* Paper 1 at 3; *see also supra* p. 8 n. 2.

The second condition is also satisfied: before Silverman was published, its central disclosure was "publicly disclosed" by one of the '659 patent's inventors.[5] In particular, Vinita Uttamsingh—one of the named inventors of the '659 patent—submitted a declaration to the PTO during the prosecution of Silverman. Ex. 1045 at 390-417 (Uttamsingh Decl.); *see* Ex. 1001 at 1 (listing Dr. Uttamsingh as one of the named inventors of the '659 patent).[6] Dr. Uttamsingh's declaration became public on August 27, 2015—the date on which the underlying patent application was published. *See* Ex. 1046 at 1.

Crucially, the Uttamsingh declaration discloses the key subject matter that underlies Incyte's reliance on Silverman. Incyte repeatedly argues that Silverman

[5] Incyte does not rely on the Silverman *application* as the supposedly invalidating reference—instead it relies on Silverman itself (which differs from the application).

[6] The declaration has five exhibits, A-E. As the materials are reproduced in Ex. 1045, the five exhibits *precede* the declaration itself. *See* Ex. 1045 at 390-413.

taught the structure of Compound (I)—or Compound 111, as it is known in Silverman. *See* Paper 1 at 1, 12-13, 16, 26, 34, 62, 66. The remainder of Incyte's reliance on Silverman, including the dosing ranges on which Incyte's arguments depend, flows from that basic disclosure of the compound. Yet the Uttamsingh declaration had previously disclosed Compound (I)'s structure (again, as "Compound 111"). Ex. 1045 at 404 (Uttamsingh Decl. Ex. B).

That prior disclosure cuts off Incyte's ability to rely on Silverman as prior art under subsection (b)(1)(B). As the Manual of Patent Examining Procedure makes clear, the key question is not whether the Uttamsingh declaration uses the same wording as Silverman, but whether it contains the same essential subject matter as Silverman. *See* M.P.E.P. § 2153.02 (explaining that the question is not whether "the disclosure by the inventor or a joint inventor [is] a verbatim or ipsissimis verbis disclosure of the intervening grace period disclosure," but whether "the subject matter of the disclosure to be excepted as prior art [was] previously publicly disclosed by the inventor or a joint inventor"). Again, the essential subject matter is the same here: The Uttamsingh declaration discloses Compound (I), and each of the disclosures in Silverman on which Incyte relies depends on that patent's disclosure

of the same compound. *See* Paper 1 at 34 (arguing that Compound (I) is "one of only three compounds specifically claimed in Silverman").[7]

Subsection (b)(1)(A). Silverman also falls within the exception found in § 102(b)(1)(A). Under that provision, "[a] disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if . . . the disclosure was made by . . . [one] who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor." Here, as above, the provision boils down to two straightforward questions: Was Silverman (the "disclosure") published within one year of the effective filing date of the '659 patent (the "claimed invention")? And, if so, was the material contained in Silverman (the "subject matter disclosed") obtained by the

[7] In addition to disclosing the structure of Compound (I), the Uttamsingh declaration also detailed the protocol and results of two assays that demonstrated the metabolic stability of the deuterated compound. *See* Ex. 1045 at 407 (Uttamsingh Decl. Ex. E); *id.* at 415-16 (Decl. at 2-3). Incyte attempts to rely on these assay results in the petition and expert declarations. *See* Paper 1 at 15; Ex. 1007 at ¶ 155. But the Uttamsingh declaration is decidedly *not* prior art: it was a disclosure made by a joint inventor within one year of the effective filing date of the '659 patent. *See* AIA § 102(b)(1)(A).

Silverman inventors from one or more of the '659 patent's inventors ("the inventor or a joint inventor")?

Again, the answer to both questions is yes. As discussed above, the first condition is satisfied because Silverman was published within the one-year grace period. *See supra* p. 17. And 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 the Drug Metabolism and Pharmacokinetics Group, Dr. Uttamsingh was responsible for the experiment disclosed in Example 4 of Silverman. That example describes an in vitro assay conducted on three compounds within the genus of compounds disclosed in Silverman to demonstrate that the compounds had improved metabolic stability. The Silverman inventors obtained the data for that example directly or indirectly from Dr. Uttamsingh. Ex. 2005 ¶¶ 5-7. These data reporting the improved metabolic stability of the disclosed genus of compounds were a critical part of the disclosure of Silverman and support Silverman's claims to the genus of deuterated compounds. Incyte's reliance on the disclosure in Silverman of Compound (I) necessarily implicates these data, because a compound and its properties are "inseparable." *See, e.g.*, *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc.*, 655 F.3d 1291, 1307 (Fed. Cir. 2011).

For the foregoing reasons, Silverman satisfies either the subsection (b)(1)(B) carve-out or the subsection (b)(1)(A) carve-out, and so it is not prior art under § 102(a)(1).

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

Silverman is also not prior art under § 102(a)(2) because it falls within the § 102(b)(2)(C) exception. That exception provides that a disclosure is not prior art under subsection (a)(2) where "the subject matter disclosed [in the asserted reference] 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 by the effective filing date of the '659 patent—May 4, 2016—Silverman is not qualifying prior art under § 102(a)(2).

That exception is easily satisfied. As of the effective filing date of the '659 patent, Concert was indisputably the owner of both Silverman and the application for the '659 patent. *See* Ex. 1002; Ex. 1047; Ex. 2010; Ex. 2011; Ex. 2012. Thus, Silverman is not prior art under subsection (a)(2), either.

VI. GROUNDS 1 AND 2 SHOULD BE DENIED PURSUANT TO § 325(d) BECAUSE THE EXAMINER CONSIDERED SUBSTANTIALLY THE SAME PRIOR ART

The decision to institute post-grant review lies within the Board's discretion. In determining whether to institute proceedings, the Board may "reject the petition [where] the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d). That is the case here: Incyte seeks to relitigate references and disclosures that the Patent Examiner already considered during prosecution. Discretionary denial is therefore appropriate.

The Board has articulated several nonexclusive factors that guide its application of § 325(d). Among other things, the Board considers:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
>
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
>
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
>
> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
>
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and

(f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8, at 17-18 (P.T.A.B. Dec. 15, 2017) (designated precedential in relevant part, Aug. 2, 2019). Both individually and collectively, these factors strongly favor a discretionary denial in this case.

A. The Asserted Art Is Either Identical to or Materially Indistinguishable from the Prior Art Before the Examiner

The first, second, and fourth *Becton* factors address whether "the same or substantially the same art or arguments previously were presented to the Office." *Advanced Bionics, LLC v. Med-El Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6, at 10 (P.T.A.B. Feb. 13, 2020) (designated precedential, March 24, 2020). These factors weigh against institution where the petitioner's asserted references are the same as, or are materially indistinguishable from, those previously before the examiner. *See Exa Bio-Rad Labs., Inc. v. 10X Genomics, Inc.*, IPR2019-00566, Paper 21, at 7-8 (P.T.A.B. July 22, 2019) (finding that *Becton* factors (a) and (b) favored discretionary denial where two of the petitioner's asserted references were before the examiner and the third reference had no "material differences" from those before the examiner); *Husky Injection Molding Sys., Ltd. v. Plastipak Packaging, Inc.*, IPR2020-00438, Paper 23, at 12 (P.T.A.B. July 29, 2020) (finding that the "first part of the *Advanced Bionics* framework"—*i.e.*, *Becton* factors (a), (b),

and (d)—was satisfied where the reference in question "previously was presented to the Office during the prosecution").

These three factors counsel against institution here, because there is virtually complete overlap between the art asserted in the petition and the art considered by the examiner. Ground 1 asserts obviousness over Silverman, Xing, and the Ruxolitinib Prescribing Information, and Ground 2 asserts obviousness over Silverman, Christiano, and Ni. *See* Paper 1 at 25. But Silverman, Xing, and Christiano were directly before the examiner. And the Ruxolitinib Prescribing Information and Ni are not materially distinguishable from references that were before the examiner.

1. Silverman, Xing, and Christiano Were Before the Examiner

As discussed above (in Section III.B), after the examiner's initial Notice of Allowance, Concert submitted a Request for Continued Examination, followed by an Information Disclosure Statement. *See* Ex. 1047 at 189, 1521-22. The IDS identified three of Incyte's current references: Silverman (Cite AC), Xing (Cite CY), and Christiano (Cite AB). *Id.* at 1521-22. With respect to these three references, therefore, the art before the examiner and the art at issue in the petition are identical.

2. The Version of the Ruxolitinib Prescribing Information Before the Examiner Is Not Materially Different from the Version Cited in the Petition

The IDS also included a 2011 version of the Ruxolitinib Prescribing Information (Cite CM). *See* Ex. 1047 at 1522; *see also id.* at 619-32. The petition relies on a 2015 version of the Prescribing Information, *see* Ex. 1004, but there is no material difference between the two.

Virtually all of the disclosures from the Ruxolitinib Prescribing Information on which Incyte relies were contained in the 2011 version. The petition cites the Prescribing Information for its disclosure of twice-daily administration of ruxolitinib. Paper 1 at 28 (citing Ex. 1004 at 4-5). That information is found repeatedly throughout the 2011 version. *See, e.g.*, Ex. 1047 at 619-20. The petition cites the Prescribing Information for its disclosures of oral administration of ruxolitinib and administration of ruxolitinib as a tablet. Paper 1 at 30, 51, 56 (citing Ex. 1004 at 4, 6-7). Those disclosures, too, can be found throughout the 2011 version. *See, e.g.*, Ex. 1047 at 619-22. Section 11 of both versions states that "[e]ach tablet contains ruxolitinib phosphate" along with acceptable carriers and diluents. Paper 1 at 29, 31, 55-56 (citing Ex. 1004 at 7); *see* Ex. 1047 at 625. Sections 2.1 and 7.1 of both versions recommend titration "based on safety and efficacy," Paper 1 at 44 (citing Ex. 1004 at 4-6), and teach "increased drug exposure and dose reduction . . . of ruxolitinib where metabolism was inhibited," *id.* at 50 (citing Ex.

1004 at 5-7). *See* Ex. 1047 at 620, 624. And Section 12.3 of both versions teaches that ruxolitinib had a "[m]ean ruxolitinib C_{max} and total exposure (AUC) [that] increased proportionally" with the dose. Paper 1 at 46 (citing Ex. 1004 at 7); *see* Ex. 1047 at 626.

In the end, there are only two minor differences between the two versions. First, the 2015 version recites doses with daily totals ranging from *5 mg* to 50 mg, while the 2011 version recites doses with daily totals ranging from *10 mg* to 50 mg. *Compare* Ex. 1047 at 4-6, *with* Ex. 1004 at 619-22; *see* Paper 1 at 27, 44, 49. But even if the Board accepts Incyte's argument that the ruxolitinib prescribing information is somehow relevant to the claimed treatment of AA (despite no mention of AA in the ruxolitinib label, *see infra* Section VII.A.2), none of the claims of the '659 Patent cover a total daily dose extending to either 5 mg or 10 mg; the lowest total daily dosage contemplated by the claims is 16 mg. *See* Ex. 1001 at 24:29-26:46. And regardless, Incyte alleges that Silverman teaches doses of 5-25 mg per day (*see* Paper 1 at 59), so its reliance on the Ruxolitinib Prescribing Information for this proposition is at best cumulative. Second, the 2015 version includes a once-daily dosing regimen, while the 2011 version does not. *Compare* Ex. 1047 at 5, *with* Ex. 1004 at 619-22. But that difference is also immaterial. The 2011 version includes a 5 mg dose only as a dose modification—not as an initial recommended dose. *See* Ex. 1047 at 5. And here, too, Incyte alleges that Silverman contains the

same teaching (*see* Paper 1 at 30, 56), so its reliance on the Ruxolitinib Prescribing Information is again cumulative.

3. Ni Is Not Materially Different from WO 2014/078486 A1, Which Was Before the Examiner

Ni itself was not before the examiner, but it is materially indistinguishable from WO 2014/078486 A1 ("the '486 publication"). The '486 publication *was* part of the examination. It was included in Concert's IDS and contained in the prosecution history. *See* Ex. 1047 at 1406-53; *see id.* at 1521 (Cite BC). And it was cited on the face of the '659 Patent. Ex. 1001 at 1.

The '486 publication mirrors Ni in every relevant respect. Both claim priority to the same two U.S. provisional applications. *Compare* Ex. 1006 at 1 ¶ 60 (listing application nos. 61/726,893 and 61/769,408), *with* Ex. 1047 at 1407 ¶ 30 (same). Both list the same inventors. *Compare* Ex. 1006 at 1 ¶ 72 (listing Ni, Parikh, Yeleswaram, Eriskcon-Viitanen, and Williams), *with* Ex. 1047 at 1407 ¶ 72 (same). And, apart from minor formatting differences, the specification of the '486 publication is identical to that of Ni. *Compare* Ex. 1006 at 2-19, *with* Ex. 1047 at 1409-43.[8] In short, the '486 publication recites *all* of the disclosures from Ni on which Incyte relies; Ni was effectively before the examiner.

[8] The language of Ni's claims differs slightly from the claim language of the '486 publication. But Incyte does not rely on that claim language in the petition.

4. Incyte's Other Supporting References Were Either Before the Examiner or Do Not Constitute Prior Art

In addition to the references on which it expressly relies in its two asserted grounds of obviousness, Incyte also cites Craiglow, Harris, Pieri, and Silvestri as supporting prior art. *See* Paper 1 at 8-11. But the first three—Craiglow, Harris, and Pieri—were all cited in the IDS and were therefore before the examiner. *See* Ex. 1047 at 1551-52 (Cite Nos. CD, CG, CP). And Silvestri is not prior art by Incyte's own admission, so it is not relevant to the *Becton* analysis. *See* Paper 1 at 10 ("*Silvestri* was published ten days after the earliest priority date[.]"); *Becton*, IPR2017-01586, Paper 8, at 17 (focusing on "the *prior art* evaluated during examination" (emphasis added)).

B. Incyte Has Failed to Identify Any Material Error by the Examiner

The third, fifth, and sixth *Becton* factors "relate to whether the petitioner has demonstrated a material error by the Office." *Advanced Bionics*, IPR2019-01469, Paper 6, at 10. "Factor (c) focuses on the record developed by the Office in previously reviewing the art or arguments. It informs, therefore, the petitioner's showing under factors (e) and (f), which focus on the petitioner's evidence of previous Office error[.]" *Id.* These factors also weigh in favor of denial under § 325(d).

Factor (c). The asserted art was evaluated during the examination. As discussed above, Concert submitted an IDS containing all of the above references—Silverman, Xing, Christiano, Craiglow, Harris, Pieri, the Ruxolitinib Prescribing Information, and the '486 Publication—and the examiner indicated that he considered all of them. Specifically, the examiner signed the IDS with the notation that "all references [were] considered except where lined through." Ex. 1047 at 1552 (capitalization removed). No references were lined through. *See id.* at 1551-52. The examiner also annotated the IDS in one place, adding "Filed on May 8, 2015" and initialing next to the Silverman prosecution history—suggesting that particular attention was given to that reference. *Id.* at 1552. Panels of the Board have previously given weight to such annotations in applying the *Becton* factors. *See Husky Injection Molding Sys.*, IPR2020-00438, Paper 23, at 11-12. The same result is warranted here.

Indeed, this is a particularly strong case for finding that the asserted art was evaluated during the examination because of the manner in which that art was introduced. As discussed, after initially receiving a Notice of Allowance, Concert prevented issuance of the patent. More specifically, Concert initiated an interview with the examiner to explain that it intended to submit an RCE and an IDS. Ex. 1047 at 187. And Concert subsequently followed through with that course of action. This series of events was especially likely to call the asserted art to the examiner's

attention—and to cause him to review those materials thoroughly. *See Prism Pharma Co. v. Choongwae Pharma Corp.*, IPR2014-00315, Paper 14, at 9, 11 (P.T.A.B. July 8, 2014) (designated informative) (finding particular attention paid to references where patent owner prevented issuance, requested an interview, submitted an IDS, and filed an RCE, and the examiner stated the claims were "free from prior art").

Factor (e). Incyte does not identify any error committed by the examiner. In the opening paragraphs of the petition, Incyte argues that the examiner "[e]rroneously believ[ed] that 'Compound (I)' recited in the claims was novel." Paper 1 at 1. But Incyte offers no support for this assertion—it simply declares it to be true. *See id.* And there is no reason to believe that the examiner misunderstood the nature of Compound (I). Incyte repeatedly argues that Silverman taught that compound's structure, *see supra* Section V.B.1, and the examiner explicitly stated that he considered all the cited references, including Silverman, *see supra* Sections III.B, VI.B. Thus, Incyte offers nothing but speculation that the examiner erred.[9]

[9] Elsewhere, Incyte cites the examiner's statement that "there [was] nothing to suggest the present compound would be an obvious variant of the known compound." Paper 1 at 18 (quoting Ex. 1047 at 170-71). Incyte does not tie this statement to the error it alleges at the outset of the petition. And for good reason:

Factor (f). Finally, Incyte does not offer any "additional evidence [or] facts [that] warrant reconsideration of the prior art or arguments." *Becton*, IPR2017-01586, Paper 8, at 18. To be sure, Incyte supplements the references and arguments that were already before the examiner with declarations from two putative experts. *See* Ex. 1008; Ex. 1010. But "the mere introduction of declaration testimony alone does not strongly support reconsideration of the prior art and arguments"—at best, an expert declaration might "slightly weigh[] against denying institution." *Hisense Visual Tech. Co., Ltd. v. LG Elecs. Inc.*, IPR2020-01164, Paper 15, at 20 (P.T.A.B. Jan. 7, 2021). And here, the declarations do not even offer that slight support. For

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the examiner made this statement in his *initial* notice of allowability, before Concert's RCE and the submission of its IDS. The examiner did not repeat that statement in the final notice of allowability. There, the examiner stated only that, after reviewing the IDS (which included the Silverman patent disclosing the structure of Compound (I)) and performing relevant searches, he "was unable to identify any prior art which contained the limitations in the present application." Ex. 1047 at 1544; *see supra* Section III.B. This change in language highlights that, after Concert explicitly brought the reference disclosing the compound to the examiner's attention, he was clearly aware of its existence.

the reasons discussed below (in Section VIII), the declarations are flawed and are entitled to little weight.

In sum, each of the *Becton* factors counsels against institution. The Board should deny the petition pursuant to § 325(d).

VII. GROUNDS 1 AND 2 SHOULD BE DENIED BECAUSE INCYTE HAS FAILED TO MEET ITS BURDEN TO SHOW THAT ANY CLAIM OF THE '659 PATENT IS OBVIOUS

Even if Incyte could demonstrate that Silverman is prior art *and* overcome the § 325(d) factors, it has still failed to meet its burden on the merits to show that the Board should institute review of Ground 1 or Ground 2. Ground 1 asserts obviousness over Silverman in view of Xing and the Ruxolitinib Prescribing Information, while Ground 2 asserts obviousness over Silverman in view of Christiano and Ni. *See* Paper 1 at 25. But Incyte has not shown that all of the claimed elements are present in the asserted references. Nor has it demonstrated that a skilled artisan would have been motivated to combine the prior art to arrive at the claimed invention, or that there would have been a reasonable expectation of success in doing so. And it has failed to adequately rebut secondary considerations of nonobviousness. In short, Incyte has not shown that it is "more likely than not" that it will prevail on Ground 1 or 2. 35 U.S.C. § 324(a).

A. Incyte Has Failed to Meet its Burden to Show that the Prior Art Taught or Suggested All of the Claimed Elements

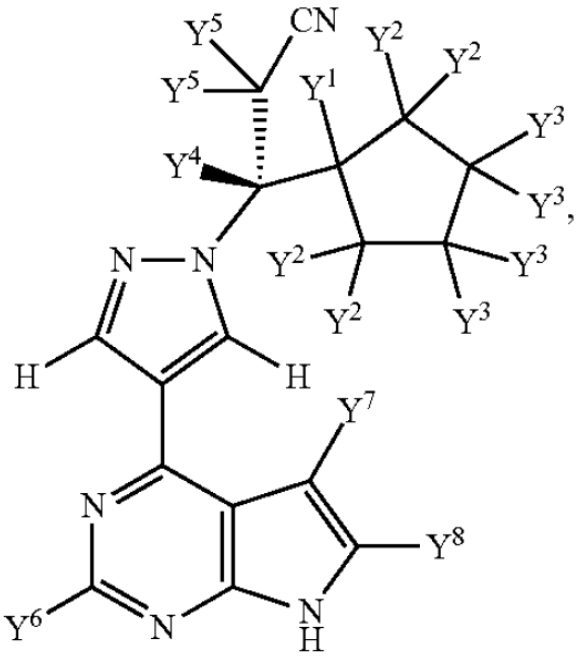
As an initial matter, Incyte has failed to show that the prior art taught or suggested all of the elements of the challenged claims. Specifically, Incyte has failed to show that the prior art taught Compound (I), the use of Compound (I) to treat AA, or the specific dose amounts claimed in the '659 patent.

1. 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 skilled artisan to Compound 111 specifically.

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. Other than in two footnotes in the petition, Incyte does not even suggest that a skilled artisan would have selected Compound 111 specifically. In one of those footnotes, Incyte argues that claim 7 of Silverman "claim[s] Compound (I) 'or a pharmaceutically acceptable salt.'" Paper 1 at 54 n. 14. But that is an incomplete characterization of claim 7, which is actually directed to *three* compounds. Ex. 1002 at 36:66-37:43. Incyte offers no reason why a person of skill in the art would specifically choose Compound 111 from among those three. In the other 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 provides no specific rationale for selecting Compound 111 from among all of the compounds disclosed in Silverman. *See, e.g.*, *UCB, Inc. v. Accord Healthcare, Inc.*, 890 F.3d 1313, 1329 (Fed. Cir. 2018) (noting that skilled artisan would not have selected a particular compound "among the many disclosed" in a prior-art reference because the reference "contain[ed] no data that would have led" a skilled artisan to that compound).

In fact, a person of ordinary skill in the art would affirmatively not have selected Silverman's Compound 111 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, a skilled artisan would have selected one of those three compounds (for which Silverman provides data showing an extension of half-life over ruxolitinib) rather than Compound 111 (for which Silverman provides no data at all).

Without any data in Silverman itself on Compound 111, Incyte relies—in both the petition and its expert submissions—on a declaration submitted by Vinita Uttamsingh during Silverman's prosecution. *See* Paper 1 at 15; Ex. 1007 at ¶ 155. In particular, Incyte relies on the declaration's disclosure of the results of two assays that demonstrated the metabolic stability of Compound 111. *See Ex*. 1045 at 407 (Uttamsingh Decl. Ex. E); *id.* at 415-16 (Decl. at 2-3). But the Uttamsingh declaration is *not* prior art: It was indisputably a disclosure made by a joint inventor

of the '659 patent (Vinita Uttamsingh) within one year of the effective filing date of the '659 patent. *See* AIA § 102(b)(1)(A); *compare* Ex. 1001 at 1, *with* Ex. 1045 at 414-17; *see also supra* Section V.B.1 n. 7.

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 (quoting 566 F.3d at 1008). But that case only undermines Incyte's argument. There, the court concluded that a compound known as "Compound 12" was a "natural choice" for further development only because there was "evidence that Compound 12 was one of the more potent . . . compounds disclosed in [the prior-art reference]." 566 F.3d at 1008. Here, by contrast, there is no data that would have pointed a skilled artisan 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, however, 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 Compound 12 as a starting point." *Altana Pharma AG v. Teva Pharms. USA, Inc*., No. 04-cv-2355, 2010 WL 10804665, at *3 (D.N.J. July 15, 2010). Without using hindsight, the court explained, there were no data in the prior art to suggest that the compound was a logical starting point for development. *See id.* The same is true

here. Nothing in Silverman points to Compound 111 as a logical choice for further development.

2. Treatment of AA

Having failed to show why a person of ordinary skill would focus on Silverman's Compound 111, Incyte has also not presented any prior-art disclosures teaching the treatment of AA—or any other hair-loss disorder—with Compound (I) as claimed in the '659 patent. The prior art Incyte *does* rely upon does not fill this significant gap.

Incyte first relies on a portion of the Silverman specification that states that "[a]ccording to an[] embodiment, the invention provides a method of treating a disease that is beneficially treated by ruxolitinib in a subject in need thereof." Ex. 1002 at 20:57-59; *see* Paper 1 at 27. But Incyte fails to cite Silverman's disclosure of the diseases that are "beneficially treated by ruxolitinib"—a list that does *not* include AA. Specifically, Silverman discloses a number of conditions that ruxolitinib was approved to treat, including "myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis," as well as ongoing clinical trials to treat "essential thrombocythemia, pancreatic cancer, prostate cancer, breast cancer, leukemia, non-Hodgkin's lymphoma, multiple myeloma and psoriasis." Ex. 1002 at 2:67-3:6. But it does *not* disclose the use of ruxolitinib or Compound (I) to treat AA. And the

single reference to AA in Silverman is directed to the use of a second therapeutic—not ruxolitinib or the compounds of the invention. Ex. 1002 at 19:34-50 ("Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from [several conditions including] alopecia areata.").

In an effort to piece together a teaching that is not present in the prior art, Incyte relies on a handful of anecdotal reports of hair regrowth in patients taking ruxolitinib: Xing, Higgins, Pieri, and Harris. *See* Paper 1 at 57. But none of these reports involved treatment of AA *with Compound (I)*—a different drug from ruxolitinib. And they certainly do not show treatment of AA at the doses claimed in the '659 patent. 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; in contrast to these prior-art references, the '659 patent claims lower doses that are supported by a placebo-controlled clinical trial in AA. Consider each anecdotal report in turn.

Xing focuses on animal models used to study the mechanism of AA. Ex. 1003. In a single paragraph, Xing discusses 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, *see id.*, and it used a different drug (ruxolitinib) and a higher dose (20 mg twice daily) than those claimed in the '659 patent. Furthermore,

AA is a condition which spontaneously reverses in approximately one third of patients, *see* Ex. 2006 at 1, rendering reports of hair regrowth in a few isolated patients not meaningful in assessing the efficacy of ruxolitinib in AA. All of these differences militate against Incyte's reliance on this study as teaching or suggesting the claimed invention.

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.* In other words, the same patient had experienced full hair regrowth without ruxolitinib. *Id.*

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.*

Harris is a letter to the editor describing observations of hair regrowth in a single patient 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 a single

patient with both AA and vitiligo, with a focus on the patient's vitiligo. *Id.* The patient received 20 mg twice daily. *Id.*

These case reports of a different drug would not have provided a person of ordinary skill in the art any information about dosing, efficacy, pharmacokinetics, pharmacodynamics, or side-effects for Compound (I). 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, 1060-61 (Fed. Cir. 2019) (finding that even Phase 1 data in the prior art was insufficient to support reasonable expectation of efficacy).

3. Dosing Amounts

The claims of the '659 patent disclose specific dose amounts and regimens for use of Compound (I) in the treatment of AA. Incyte has failed to show that those amounts and regimens were known in the prior art. Instead, Incyte relies on the purported 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. 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 indication which range might be applicable to which specific compounds or conditions. *Id.* at 20:11-15. 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). As discussed above (in Section VII.A.1), 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. As discussed above (in Section VII.A.2), Silverman does not disclose the

use of Compound (I) to treat AA, and therefore any 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. Moreover, Silverman's reference to the prior-art dosing information for ruxolitinib relates to blood cancer, not AA. 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 (and it clearly does not), 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 has not met its burden to show that the dosing amounts were disclosed in the prior art, and even if a broader range was disclosed for other indications, the presumption of obviousness should not apply.

B. Incyte Has Failed to Meet its Burden to Show that There Was a Motivation to Substitute Compound (I) for Ruxolitinib

Incyte has also failed to meet its burden to show there was a motivation for a person of ordinary skill in the art to substitute Compound (I) for ruxolitinib.

1. Incyte Improperly Relies on Non-Prior-Art Information to Support Alleged Motivation

As discussed above (in Section V.B), Silverman is not a proper prior-art reference, and even if it were, it contains no data for Compound (I) (or "Compound 111") that would have motivated a person of ordinary skill in the art to select that

compound from among the compounds disclosed. To supply the missing motivation, Incyte improperly relies on non-prior-art data from the Silverman file history. Specifically, Incyte cites assay data from the declaration of Vinita Uttamsingh submitted during the Silverman prosecution (*see supra* Section VII.A.1) to demonstrate that Compound (I) was more stable than ruxolitinib, and that a person of ordinary skill in the art would therefore have selected it for further study. *See* Paper 1 at 15, 34; Ex. 1045, at 414. But, again, the Uttamsingh declaration is not prior art. *See supra* Section V.B.1.

2. Incyte Ignores the Unpredictability of Drug Pharmacokinetics and Pharmacodynamics as they Relate to a Different Disease Like AA

In arguing that there would have been a motivation to substitute Compound (I) for ruxolitinib in the treatment of AA, Incyte relies on the two drugs' similar "potency and selectivity," pharmacodynamic properties[10] of the compounds related to their affinity for the JAK receptor. Paper 1 at 35.[11] But Incyte has not provided

[10] 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.

[11] The argument that a skilled artisan would be motivated to substitute Compound (I) for ruxolitinib in the treatment of AA presupposes that the skilled artisan would have known that ruxolitinib itself was effective to treat AA at the

evidence that there was a known relationship between the pharmacokinetic and pharmacodynamic properties of ruxolitinib, which would have allowed a skilled artisan to predict therapeutically effective doses for the treatment of AA. And it has certainly not shown a known pharmacokinetic/pharmacodynamic relationship for Compound (I). Absent a known relationship between the drug's pharmacokinetics and pharmacodynamics for AA, a person of ordinary skill in the art 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 skilled artisan 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) ("Because all experts and parties agree, however, that skilled artisans did *not* know the PK/PD 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. The district court, therefore, 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.").

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claimed doses. But as discussed above (in Sections VII.A.2 and VII.A.3), Incyte has not met its burden to show that the prior art taught that such use of ruxolitinib was effective for treatment of AA.

3. 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

As discussed above (in Section VII.A.2), Incyte has failed to cite any prior art suggesting effective treatment of AA with ruxolitinib at a dose lower than 30 mg/day, and certainly not at the claimed doses of 16 mg/day or 24 mg/day. In an attempt to fill this gap, Incyte asserts that deuterating a drug predictably allows for lower dosing compared to the non-deuterated compound. *See* Paper 1 at 38-40. But Incyte cherry-picks isolated sentences from a series of references, mischaracterizing the teachings of the art as a whole regarding deuteration. 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:

- "Since the magnitude and nature of the deuterium benefit *cannot be predicted a priori*, CoNCERT must test multiple compounds in a range of assays to identify those that are differentiated." Ex. 1034 at 3 (emphasis added).
- "However, certain types of substitutions just work, and other types just do not work. *No computational chemist or other theoretical scientist has yet come up with a method for predicting which cases will work a priori*. They are still playing 'Jeopardy'; give them the

answer, and they will provide a great question." Ex 1033 at 6 (emphasis added).

- "Although the effect of isotopic substitution on binding to receptors and enzymes has been previously considered negligible, *these more recent data support that they are unpredictable, and can be insignificant, or contribute positively or negatively to measured DIEs*." Ex. 1043 at 69 (emphasis added).
- "For these compounds, marked isotope effects were observed in vitro using liver cytosol; however, in hepatocytes and in vivo, these effects were attenuated by the involvement of other enzyme systems or elimination mechanisms. *In vivo deuterium replacement strategies may be confounded by metabolic switching*." Ex. 1044 at 1 (emphasis added).
- "For deuterated drugs, *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. 1044 at 2 (emphasis added).
- "It is important to note that the effects observed in this study . . . may be quite different from the metabolism-related effects imparted by deuteration of other drugs. . . . *It is hoped that empirical characterization of this expanding class of drugs, using approaches similar to those described in this report, will provide better tools to predict how deuterium substitution can be leveraged in the future and, as a result, to improve the safety and efficacy of existing therapeutic agents*." Ex. 1052 at 11 (emphasis added).

- Xu 2015 provided pharmacokinetic data for three deuterated analogs of nintedanib, and the data show that deuteration can actually cause a *decreased* half-life. Ex. 1053 at 3.

A person of ordinary skill in the art, 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. Instead, the references Incyte relies on show, contrary to Incyte's argument, that a person of ordinary skill in the art would not reliably expect a certain dose of Compound (I) to have the "same biological effects" as a higher dose of ruxolitinib.[12] Paper 1 at 35. 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.

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

[12] While Incyte's argument of predictability is wrong and contrary to its own references, whether or not deuteration results in a predictable effect is not even dispositive: the effect of ruxolitinib itself for treating AA over a dose range that includes the claimed doses was not known or suggested in the prior art. Therefore, Incyte has not even shown how much of a deuterium effect would be needed to bridge the gap to the use of ruxolitinib at higher doses.

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 person of ordinary skill in the art 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 evidence 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 person of ordinary skill in the art would have reasonably expected to achieve a therapeutic effect in AA at the claimed lower doses with Compound (I) in view of the clear teaching in the prior art of the unpredictability resulting from deuteration, 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 specific motivation to

substitute Compound (I) for ruxolitinib at a lower dose to treat AA. *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))). These deficiencies are fatal to Incyte's obviousness argument.

C. Incyte Has Failed to Meet its Burden to Show that There Was a Motivation to Select the Claimed Doses and Regimen

Incyte has further failed to meet its burden to show there was a motivation to use the specific doses claimed in the '659 patent—*i.e.*, 16 mg and 24 mg per day, dosed either once or twice daily—in the treatment of AA. Incyte has provided no evidence in the prior art to support those specific doses for ruxolitinib, let alone for Compound (I). Incyte relies on a mixture of prior art for unrelated drugs and diseases, coupled with anecdotal clinical reports using *higher* doses of ruxolitinib, misstatements about the range taught in Silverman, discussion of non-prior art, and sheer speculation. That is not enough to meet its burden.

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

Incyte relies on information about different drugs, approved for different indications, to argue a motivation for using particular doses of Compound (I) to treat AA. But Incyte fails to support its reasoning with either law or science.

Incyte first introduces the concept of "related" drugs. Paper 1 at 43. Yet Incyte fails to cite a single case finding that motivation for the particular dosing of one drug could be found by relying on the behavior of a *different* drug (let alone in a *different* disease). That is unsurprising: contrary to Incyte's argument, 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) (finding that in the field of chemistry "minor changes in a product or process may yield substantially different results"); *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, No. 99-cv-38, 2001 WL 1397304, at *14 (S.D. Ind. Oct. 29, 2001) ("Small changes in chemical structure may have dramatic and unpredictable biological effects."). 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. Indeed, much smaller changes have been found nonobvious in the chemical arts. *See id.* (finding single substitution of hydrogen for a halogen to be non-obvious).

Nor does Incyte provide any credible scientific basis for making such comparisons. A skilled artisan would readily understand that different drugs differ in their pharmacokinetic behavior and in their pharmacodynamic effects and would readily appreciate that, for even the *same* drug, the pharmacokinetic/pharmacodynamic relationship will impact different diseases in different ways. 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, and Incyte fails to address why a skilled artisan would ignore those principles.

To support its improper reliance on other drugs approved to treat other conditions, Incyte introduces not only the concept of "related" drugs, but also 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, and instead relies 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 person of ordinary skill in the art would have known that dosing of a single drug across different autoimmune conditions was quite variable and could not be predicted a priori. For example, hydroxychloroquine is approved to treat two autoimmune diseases—rheumatoid arthritis and lupus erythematosus—but has markedly different doses for each. For lupus erythematosus, the average initial dose is 400 mg per day, whereas for rheumatoid arthritis, 400 mg is at the lowest end of the recommended initial dose range, which extends up to 600 mg. Ex. 2017 at 7. 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 for treating 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 skilled artisan would look to other drugs 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. In making its "related" drug/"sister disease" argument about several specific JAK inhibitors, Incyte (a) ignores known differences in dosing of JAK inhibitors for different autoimmune conditions, (b) ignores the known differences in metabolism between baricitinib and ruxolitinib, and (c) improperly relies on mathematical dose calculations developed in contexts irrelevant to determining effective dose of a JAK inhibitor, all in a hindsight effort to argue that the claimed doses would have been obvious.

a. Incyte's Reliance on Other JAK Inhibitors for Other Conditions Is an Improper Use of "Related" Drugs in "Sister Diseases"

First, Incyte's reliance on dosing for other JAK inhibitor drugs—ruxolitinib, tofacitinib, and baricitinib—to argue that a person of skill in the art would have been motivated to use the claimed doses of Compound (I) is misplaced. Incyte ignores that each of these drugs is dosed differently depending on the indication. For ruxolitinib, the dose varies depending on the condition of the patient and the disease state, as determined by platelet count, with the starting dose ranging from 5 mg to 20 mg twice a day. *See* Ex. 1004 at 5. Tofacitinib also requires different dosing depending on the indication. For example, whereas for ulcerative colitis, the recommended dose includes an induction dose of 10 mg twice a day or 22 mg once

a day, 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 approved for rheumatoid arthritis at 2 mg daily, and failed to get approval at 4 mg daily due to safety concerns. *See* Ex. 2016 at 1. In light of these differences, Incyte has not established that a person of ordinary skill in the art would look to other drugs, even within the class of JAK inhibitors (none of which was approved for treating AA), in selecting a dose for Compound (I) to treat AA, nor that doing so would lead the skilled artisan to the claimed doses in the '659 patent.

b. Incyte's Reliance on Baricitinib Dosing to Predict Ruxolitinib or Compound (I) Dosing Ignores the Different Metabolism of the Two Drugs

With respect to baricitinib, Incyte has also ignored crucial differences in metabolism between the two drugs. The very references Incyte relies upon show that the metabolism of ruxolitinib is almost entirely metabolized prior to excretion, with less than 1% of unmetabolized drug being excreted unchanged, whereas the majority of a baricitinib dose (64.1%) is excreted in an unmetabolized form. *Compare* Ex. 1004 at 7, *with* Ex. 1072 at 6. Incyte has failed to address these significant differences in metabolism and clearance and has failed to explain why a

person of skill in the art would equate dosing for two different drugs with such different rates and mechanisms for clearance.

c. Incyte Attempts to Rely on Irrelevant Mathematical Calculations to Determine Ruxolitinib Dosing from Baricitinib Dosing

Finally, Incyte improperly relies on an argument in the declaration of Steven Patterson regarding an alleged mathematical model for computing the dose of ruxolitinib based on dosing of baricitinib in AA.[13] *See* Paper 1 at 47-48 (citing Ex. 1007 ¶¶ 182-91). It argues that in determining a ruxolitinib dose from baricitinib, a person of skill in the art would look to references discussing mathematical computations to determine a minimum effective dose.[14] But Incyte provides no basis in either the petition or in Dr. Patterson's declaration to support a motivation to combine Silverman or any other art with these references. For one thing, these references do not relate to ruxolitinib, JAK inhibitors, or treatment of AA, and are therefore not even within the relevant field of endeavor. *See, e.g.*, *In re Clay*, 966

[13] 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.

[14] Inexplicably, Incyte also cites the label for Olumiant (baricitinib), even though it is dated May 31, 2018, making it undeniably post-art. Ex. 1079 at 20.

F.2d 656, 658-60 (Fed. Cir. 1992) (finding that reference was not analogous where it was not from the same field of endeavor and not reasonably pertinent to the problem the inventor sought to address); *K-TEC, Inc. v. Vita-Mix Corp.*, 696 F.3d 1364, 1375 (Fed. Cir. 2012) (same).

Nor are these references in an analogous art, because they do not address the problem to be solved—determining an effective dose of Compound (I) in AA. *See Clay*, 966 F.2d at 658-60; *K-TEC*, 969 F.3d at 1375. Incyte cites Reigner for the so-called "similar drug approach," *see* Paper 1 at 47 n. 11 (citing Ex. 1077), but this reference does not relate to selecting a dose for *effective* treatment of a condition, nor does it relate to treatment of 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.

Tallarida 2010,[15] another reference Incyte relies on, *see* Paper 1 at 47 (citing Ex. 1076) is also irrelevant. That reference relates to mathematical modeling of dosing for drugs to be given *in combination* when the dosing for each drug separately has already been determined. But it does not predict dosing for a single drug. Incyte fails to explain how or why a person of ordinary skill in the art would rely on this modeling to determine the dose of Compound (I) when Tallarida's model depends

[15] Tallarida 2016 also relates to modeling drug combinations. Ex. 1076 at 1.

on prior knowledge of the dosing for individual drugs. Ex. 1076 at 1, 8. Neither Dr. Patterson's declaration nor the petition even mentions that Tallarida is concerned with "combinations" of well-known drugs when the dosing is already known for each separate drug for a given indication, a situation not present here. Compound (I) was not a known drug for a known indication, and the patent at issue does not concern the combination of Compound (I) with any other drug. Incyte has not met its burden to show that a person of ordinary skill in the art would use this sort of calculation to arrive at the claimed dose.

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

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 person of ordinary skill in the art would use 5 mg per day as a starting dose of ruxolitinib for treatment of AA. Paper 1 at 10, 45. But a post-art publication cannot provide the sole motivation to optimize a 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). Here, none of the prior art references Incyte relies on disclose a dose lower than 30 mg per day. Incyte's reliance on non-prior art to fill that gap is improper.

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.[16] Under *Yeda*, a non-prior-art reference like Silvestri may not fill that primary role.

3. The Prior-Art Dosing Disclosures on Which Incyte Relies Would Not Lead a Person of Ordinary Skill in the Art 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 are obvious, Incyte relies on a single reference's finding of adventitious hair regrowth in one patient reportedly taking 30 mg 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 (citing *Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir.

[16] Incyte also offers bare references to its expert declarations, *see* Paper 1 at 45, but it cannot incorporate those declarations by reference. *See infra* Section VIII.C.

1985)). But as discussed above (in Section VII.A.2), 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 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 failed to provide sufficient evidence to show that the difference between the single report of a 30 mg dose of ruxolitinib in the prior art and the claimed doses of 16 mg and 24 mg is not meaningful. Nor has Incyte provided any reason that a skilled artisan 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 782-83. 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.

4. Incyte Misrepresents the Range Taught in Silverman

As discussed above (in Section VII.A.3), Incyte misrepresents the range taught in Silverman in order to draw incorrect conclusions about the obviousness of

the claimed dosing range. Incyte cites several cases to support its contention that this disclosure in Silverman provides a motivation to optimize the dose range, *see* Paper 1 at 44, but its reliance on those cases is fundamentally misplaced.

As an initial matter, the cases Incyte cites are all inapposite. Those cases all 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). That is not case here: as discussed above (in Section VII.A.3), the range in Silverman is not for the treatment of AA.

Furthermore, as discussed above (in Section VII.A.3), even where a range is disclosed in the prior art, that range creates, at best, a rebuttable presumption of obviousness of a subset of doses within that range. *See E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018). Here, that presumption is rebutted in two independent ways. First, Incyte ignores that the prior art on ruxolitinib and Compound (I) related to diseases other than AA, which makes the explicitly claimed benefit of the claimed doses in the '659 patent—treatment of AA—a difference in kind, not in degree. In that regard, Incyte's reliance on *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370 (Fed. Cir. 2011), is inapt. The prior art in *Tyco* provided dosing information for the *same* drug to treat the *same*

condition as in the claims of the patent at issue. *See id.* at 1372-73. Second, even if the ranges in Silverman were specific to AA, where courts have found prior-art dose ranges to create a presumption of obviousness, the prior-art ranges have been much smaller than the ranges in Silverman. *See* Paper 1 at 44 (citing cases with smaller ranges). As discussed above (in Section VII.A.3), Silverman discloses a broader 1-500 mg range, and, although Silverman discloses 12 examples of smaller overlapping ranges, it expresses no preference for any of them. 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 Tyco*, 642 F.3d at 1372-73. Even the broadest prior-art range in *Tyco* of 5 mg to 30 mg is substantially smaller than the overarching 1 mg to 500 mg range at issue here in Silverman. *See also Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 14-cv-882, 2017 WL 1199767, at *32 (D. Del. Mar. 31, 2017) (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 *Sebela*, the prior art disclosed a narrow range that was most preferred. *In re Sebela Patent Litig.*, No. 14-cv-6414, 2017 WL 3449054, at *25 (D.N.J. Aug. 11, 2017). 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., LLC 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.* 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* Ex. 1004 at 5 (providing charts of dosing information depending on condition and disease state, as determined by platelet count); Ex. 1066 at 1 (providing different dosing ranges for tofacitinib when treating psoriatic arthritis versus ulcerative colitis).

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 person of ordinary skill in art regarding dosing for patients suffering from AA. Additionally, the very same paragraph in Silverman that refers to the Ruxolitinib Prescribing Information also 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, the sex, age and general health condition of the subject, excipient usage, the possibility of co-usage with other therapeutic treatments such as use of other agents and the judgment of the treating physician." 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. Based on this teaching, a person of ordinary skill in the art 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.

As of the priority date, ruxolitinib was approved only to treat patients with "intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-

polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis," which are all blood cancers. Ex. 1004 at 4. Incyte has failed to provide any rationale for applying the same dosing regimen for these severe, life-threatening conditions to AA.

Incyte's reliance on its clinical expert, Dr. Shapiro, cannot provide that basis, as 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, whereas ruxolitinib is a JAK1/2 inhibitor. *Compare* Ex. 1050 (disclosing tofacitinib at JAK1/3 inhibitor), 1067 (same), 1068 (same), *with* Ex. 1004 at 7 (disclosing ruxolitinib as JAK1/2 inhibitor). Incyte provides no valid basis for applying prior art regarding a JAK inhibitor with a different set of targets (JAK1/3) to ruxolitinib or Compound (I), which are JAK 1/2 inhibitors. 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* Ex. 1066 at 1 (providing different dosing ranges for tofacitinib when treating psoriatic arthritis versus ulcerative colitis). Incyte has provided no justification for ignoring these differences, and has failed to meet its

burden to show that a person of ordinary skill in the art would look to a different JAK inhibitor approved for a different disease to determine the effective dose of Compound (I) for AA.

5. Generic Motivations to Reduce Dose Are Insufficient to Supply the Requisite Motivation for the Specifically Claimed Doses

Incyte cannot rely on a skilled artisan's general "prefer[ence] to use the lowest dose and dosing frequency sufficient to achieve effective therapy." Paper 1 at 46. Such a general preference does not supply the requisite motivation to use the specific doses claimed specifically for Compound (I) for the treatment of AA. *See Procter & Gamble Co. v. Teva Pharm. USA, Inc*., 566 F.3d 989, 997 (Fed. Cir. 2009) ("[P]atents 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))). This is especially true because the claims of the '659 patent are not generic method-of-treatment claims—they are claims to specific doses in specific regimens for a specific disease.

D. There Was No Reasonable Expectation of Success

Incyte has not met its burden to show that there is a reasonable expectation of success. Incyte cites a handful of clinical reports to support the broad proposition

that ruxolitinib was known "to effectively treat AA in humans." Paper 1 at 57-58. But that is insufficient to provide a reasonable expectation of success in treating patients with AA with ruxolitinib, let alone with Compound (I) at the claimed doses.

Incyte's reliance on Xing, Higgins, Pieri, and Harris is unavailing. Xing, Higgins, and Pieri are not placebo-controlled clinical trials on the treatment of AA—the gold standard to determine efficacy and dosing. They are not even early-stage clinical trials on the treatment of AA, which the Federal Circuit has held did not provide a reasonable expectation of success. *See Novartis Pharm. Corp. v. W.-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060-61 (Fed. Cir. 2019) (affirming a finding that Phase 1 clinical was insufficient to show a reasonable expectation of success). Instead, they are simply a collection of anecdotes at higher doses.

As discussed above (in Section VII.A.2), Xing involved only three patients, who received 20 mg twice daily. Ex. 1003. Higgins was a single patient with AA associated with chronic mucocutaneous candidiasis, who had previously suffered from alopecia followed by full hair regrowth. Ex. 1088 at 13. The patient in Higgins also received 20 mg of ruxolitinib twice a day. Ex. 1088 at 13. Pieri involved a single patient in a Phase 2 clinical trial for thrombocythemia, who noticed improvement of AA symptoms after taking 15 mg of ruxolitinib twice a day. Ex. 1012 at 6-7. Harris involved a research letter where the patient was in a clinical trial regarding ruxolitinib and AA, but it discusses only a single patient with both AA

and vitiligo, with a focus on the patient's vitiligo. Ex. 1031 at 9. Given the high rate of spontaneous hair regrowth in AA, even without any treatment, these anecdotal reports do not demonstrate the efficacy of ruxolitinib in AA. Taken individually or together, these references do not support a reasonable expectation of success, particularly at the claimed doses of 16 mg to 24 mg a day given the lowest reported dose of ruxolitinib that was given was 30 mg per day.[17]

E. The Secondary Considerations Support a Finding of Nonobviousness

Incyte's attempts to discredit any secondary consideration of non-obviousness rely on faulty assumptions and incorrect law. As an initial matter, Incyte's reliance on the vacated IPR proceeding is improper and does not support Incyte's contention that there are no secondary considerations that support non-obviousness. *See infra* Section X.

Substantively, Incyte combines data from different studies, involving different subjects, to arrive at its conclusions regarding the relative efficacy of Compound (I) and ruxolitinib. Paper 1 at 85-86 & figures 1-2. But a person of ordinary skill in the art would not compare data from different sources and different drugs in the same graphical representation. The experimental conditions are not the

[17] Additionally, Incyte ignores the fact that Compound (I) has a higher molecular weight than ruxolitinib and the impact that difference may have on dosing.

same and do not allow for any fair comparison. *See, e.g.*, *Hines v. Wyeth*, No. 2:04-cv-690, 2011 WL 2680814, at *6 (S.D. W. Va. July 8, 2011) ("[I]t does not appear that comparing the results of separate studies with different variables and experimental conditions would be a scientifically sound methodology for evaluating the relative risks of two drugs. Nor does plaintiff, the burden-carrying party, explain why such a methodology should be deemed reliable."). Thus, the information presented by Incyte does not provide repudiation of secondary considerations.

In fact, the evidence supports the unexpected efficacy of Compound (I) in treating AA. *See* Ex. 2026. There is no prior art that provides an effective treatment for AA at the claimed doses using ruxolitinib, let alone Compound (I). Ruxolitinib has only ever been approved at different doses for treating different diseases. *See* Ex. 1004 at 4. The efficacy of Compound (I) in treating AA at the claimed doses is therefore a difference in kind, and not degree, which makes it highly probative of non-obvious. *See Allergan, Inc. v. Sandoz, Inc.*, 796 F.3d 1293, 1306 (Fed. Cir. 2015) (finding nonobviousness where unexpected results differed in kind from what would have been expected); *Coalition for Affordable Drugs VII LLC v. Pozen Inc.*, IPR2015-01718, Paper 40, at 26, 29 (P.T.A.B. Feb. 21, 2017) (same). As of the priority date, not only had no JAK inhibitor been approved for the treatment of AA, but there were no FDA approved treatments for AA at all. Ex. 2006 at 1. Compound (I) at the claimed doses provides an effective treatment for AA using a JAK inhibitor.

In recognition of this difference in kind result demonstrated by Compound (I), the FDA has granted Breakthrough Therapy and Fast Track designations to Concert's Compound (I) (referred to as CTP-543) for treatment of AA. Ex. 2014 at 1.

VIII. INCYTE'S EXPERT DECLARATIONS SHOULD BE GIVEN LITTLE WEIGHT

The Board should give little weight to the declarations provided by Incyte's experts. Dr. Patterson, Incyte's technical expert, does not have the requisite experience to offer opinions related to deuteration or JAK inhibitors. And Dr. Shapiro, Incyte's clinician, has taken positions in this matter that directly contradict his previous statements. Further, Incyte should not be permitted to incorporate by references large portions of Dr. Patterson's declaration without sufficient analysis of those sections.

A. Dr. Patterson Is Not Qualified to Offer the Opinions in His Declaration

The claims of the '659 patent relate to (i) a deuterated JAK inhibitor (ii) for the treatment of AA. Based on Dr. Patterson's description of his own expertise, he is not qualified to opine on either of those topics. *See Sundance, Inc. v. DeMonte Fabricating, Inc.*, 550 F.3d 1356, 1363-64 (Fed. Cir. 2008) (Fed. R. Evid. 702 requires that an expert be "qualified in the pertinent art"). None of his publications listed on his curriculum vitae relate to deuterated drugs, and only one, a mechanistic study, references deuterium at all. Ex. 1008 at 2. Further, there is nothing to indicate

he has any experience with JAK inhibitors. His CV lists a single paper that relates to NAD kinases, an entirely different class of proteins from JAKs. Ex. 1008 at 5. Further, his public faculty profile describes his expertise as "[a]nti-microbial drugs, cancer therapy, antiviral therapy, [and] cyanide antidotes." Ex. 2015 at 1. His listed areas of expertise do not include deuterated compounds, JAK inhibitors, or treatment of AA or other autoimmune disorders. Accordingly, he is not qualified to offer expert testimony on these topics and is not qualified in the pertinent art. For these reasons, the Board should give little weight his declaration.

B. Dr. Shapiro's Declaration Should Be Given Little Weight

Dr. Shapiro has offered contradictory opinions that are plainly litigation-inspired to suit the moment. In his declaration in *Incyte Corp. v. Concert Pharmaceuticals, Inc.*, 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 would have been obvious based on the same half-life information. Ex. 1009 ¶ 51.

Additionally, Dr. Shapiro's declaration should be given little weight because he relies on exhibits that Incyte has not even attempted to show are prior art. *See e.g.*, Ex. 1009 ¶¶ 19-27 (citing Ex. 1067; Ex. 1068). These single-page exhibits do

not include a cover page or table of contents. *See* Ex. 1067; Ex. 1068. One (Ex. 1068) has no date at all, while and the other (Ex. 1067) has a footer that simply reads "May 2016" without any specific information about when it became publicly available. Incyte offers no argument as to whether either of these references is prior art, yet Dr. Shapiro relies upon them as though they were, without any further explanation.

Dr. Shapiro also improperly relies on references related to tofacitinib, without addressing the fact that the references clearly state that tofacitinib is a JAK1/3 inhibitor, not a JAK1/2 inhibitor. Ex. 1009 ¶¶ 35-36, 41-42. Dr. Shapiro does not provide any analysis as to why a JAK1/3 inhibitor is relevant to the dosing of ruxolitinib or Compound (I), which are JAK1/2 inhibitors. *Compare* Ex. 1050 (disclosing tofacitinib as a JAK1/3 inhibitor), 1067 (same), 1068 (same), *with* Ex. 1004 at 7 (disclosing ruxolitinib as a JAK1/2 inhibitor).

For all these reasons, Dr. Shapiro's declaration is not entitled to weight.

C. Incyte's Declaration Testimony Was Improperly Incorporated by Reference and Should Not Be Considered by the Board

In addition to these inherent flaws in Incyte's expert declarations, the Board should also give them little weight because Incyte improperly incorporates them by reference in its petition. *See e.g., Hamilton Techs. LLC v. Tehrani*, IPR2020-01199, Paper 6, at 9 n. 4 (P.T.A.B. Jan. 6, 2021) ("As explained in our Consolidated Trial Practice Guide (CTPG), 'parties that incorporate expert testimony by reference in

their petitions, motions, or replies without providing explanation of such testimony risk having the testimony not considered by the Board.'" (quoting CTPG at 35-36)); *Jiangu Smartsens Tech. Co., Ltd. v. Omnivision Techs., Inc.*, IPR2019-01263, Paper 48, at 25 (P.T.A.B. Dec. 18, 2020) ("Even if Patent Owner had provided some sort of citation to Dr. Theuwissen, there is no discussion of his analysis of conception in the brief itself. Our Rules prohibit incorporation by reference of arguments from one document into another.").

Dr. Patterson's declaration contains a number of paragraphs that relate to the metabolic switching and the specifics of ruxolitinib metabolism. *See* Ex. 1007 ¶¶ 136-41. Incyte cites these paragraphs repeatedly throughout the petition, but does not provide any analysis or explanation on these subjects. Paper 1 at 35, 40. The information contained in Dr. Patterson's declaration that is merely referenced in the petition is not properly before the Board and should not be considered. *See Jiangu*, IPR2019-01263, Paper 48, at 25 (P.T.A.B. Dec. 18, 2020).

Dr. Patterson's declaration also contains a lengthy passage regarding dose response information, as well as an appendix with a significant series of calculations regarding the IC_{50} for ruxolitinib and baricitinib, including the Hill Coefficient. Ex. 1007 ¶¶ 170-204 & Appendix I. Incyte cites these paragraphs without providing any explanation or analysis of the information contained therein. Paper 1 at 43 (citing Ex. 1007 ¶¶ 170-204), 46 (citing Ex. 1007 ¶¶ 170-97), 47 (citing Ex. 1007 ¶¶ 178-

79, 182-95), 49 (citing Ex. 1007 ¶¶ 181-97), 60 (citing Ex. 1007 at ¶¶ 179-80, 195-97). Under similar circumstances, the Board did not allow a party to incorporate appendices from an expert declaration, and Incyte should likewise not be allowed to incorporate this analysis and the calculations contained in Dr. Patterson's declaration appendix. *See Hamilton*, IPR2020-01199, Paper 6, at 9 n. 4 (P.T.A.B. Jan. 6, 2021).

IX. GROUND 3 SHOULD BE DENIED BECAUSE CONCERT HAS DISCLAIMED CLAIM 8

In an effort to streamline this proceeding, Concert has filed a statutory disclaimer of claim 8. Ex. 2020. Because Ground 3 relates only to claim 8, the Board should not consider that Ground in determining whether to institute review. *See* 37 C.F.R. § 42.207(e) ("No post-grant review will be instituted based on disclaimed claims.").

X. INCYTE'S RELIANCE ON A VACATED IPR IS MISPLACED

Incyte repeatedly invokes the final written decision in *Incyte Corp. v. Concert Pharmaceuticals, Inc.*, IPR2017-01256, Paper 119 (P.T.A.B. April 8, 2019). *See, e.g.*, Paper 1 at 11 n. 1, 12, 34, 40, 41, 84, 85 n. 19. On secondary considerations, for example, Incyte argues that "[t]o the extent that [Concert] relies on the purported secondary indicia it presented in the *inter partes* review of *Silverman*, they should be rejected as they were rejected previously." *Id.* at 84. But Incyte's reliance is misplaced, because the panel's decision in *Incyte* was vacated. Specifically, the Federal Circuit "vacated" the panel's decision and "remanded [the case] to the Board

for proceedings consistent with this court's decision in *Arthrex*." Ex. 2024 at 2 (Order, *Concert Pharm., Inc. v. Incyte Corp.*, No. 19-2011 (Fed. Cir. Jan. 24, 2020)). The decision in *Arthrex*, in turn, made clear that an *Arthrex* remand requires "that a new panel of APJs must be designated and a new hearing granted." *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320, 1340 (Fed. Cir. 2019). The Court also "le[ft] to the Board's sound discretion whether it should allow additional briefing or reopen the record in any individual case." *Id.*[18]

When a decision is vacated, it is as if the decision never existed. *See, e.g.*, *Action on Smoking & Health v. C.A.B.*, 713 F.2d 795, 797 (D.C. Cir. 1983) ("[T]he opinion clearly and unequivocally *vacated* the offending portion of [an agency rule]. To 'vacate,' as the parties should well know, means 'to annul; to cancel or rescind; to declare, to make, or to render, void; to defeat; to deprive of force; to make of no authority or validity; to set aside.'"). That is especially true in the case of IPR2017-01256, where the Board cannot simply rubber-stamp its prior decision, but must

[18] The government has sought certiorari in *Concert*, and the Supreme Court is presumably holding the petition in that case pending its resolution of *Arthrex*. *See* Pet. for Cert. 27, No. 20-74, *Iancu v. Luoma* (July 23, 2020). But no party sought to stay the Federal Circuit's mandate in *Concert*, and it therefore issued on April 16, 2020. *See* Ex. 2025 (Mandate, *Concert*, No. 19-2011 (Fed. Cir. April 16, 2020)).

appoint a new panel and hold a new hearing (and has the discretion to allow additional briefing and evidence). Thus, the prior panel decision should be given no weight.

XI. CONCLUSION

For the foregoing reasons, the Board should deny institution.

February 16, 2021

Respectfully submitted,

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

I hereby certify that this "PATENT OWNER'S PRELIMINARY RESPONSE" complies with the word count limitation of 37 C.F.R. § 42.24(a)(1)(ii) and (b)(1) because the preliminary response contains 17,742 words, excluding the cover page, signature block, and the parts of the preliminary response exempted by 37 C.F.R. § 42.24(a)(1).

February 16, 2021

Respectfully submitted,

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document captioned "PATENT OWNER'S PRELIMINARY RESPONSE" and the Patent Owner exhibits cited therein were served electronically via e-mail on this February 16, 2021, as follows:

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