UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION

Petitioners

v.

CONCERT PHARMACEUTICALS, INC.

Patent Owner

U.S. Patent No. 10,561,659
Filing Date: May 4, 2017
Issue Date: February 8, 2020

Case No. PGR2021-00006

PETITION FOR POST-GRANT REVIEW

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I. Introduction

Erroneously believing that "Compound (I)" recited in the claims was novel, the Examiner allowed Concert's U.S. Patent No. 10,561,659 (EX1001, "the '659 Patent") without a single rejection. Despite two interviews and an RCE, there is no evidence that Concert ever corrected the Examiner's misunderstanding.

The patent covers a formulation comprising Compound (I), an octa-deuterated analog of ruxolitinib, and method of using Compound (I) to treat hair loss disorders including alopecia areata. Compound (I) is not novel. It was disclosed with formulations and dosages in Concert's prior art U.S. Patent No. 9,249,149 to Silverman (EX1002 ("*Silverman*")) and was found obvious in IPR2017-01256 by the PTAB in 2019. The therapeutic use of ruxolitinib to regrow hair in alopecia areata patients is also not novel. It was publicly disclosed by *Christiano* (EX1005 ("*Christiano"*)) and demonstrated clinically in *Xing* to provide "near-complete hair regrowth" (EX1003 ("*Xing*")).

At best, the '659 patent claims cover the obvious substitution of one drug (ruxolitinib) for its known pharmacodynamic equivalent (Compound (I)) at doses within narrow ranges taught to be efficacious. This "substitut[ing] [of] one equivalent for another" would have been obvious even without an express suggestion. *In re Fout*, 675 F.2d 297, 301 (CCPA 1982). But *Silverman* expressly

taught the use of Compound (I) for treating "a disease that is beneficially treated by ruxolitinib" and both *Christiano* and *Xing* taught that ruxolitinib treated alopecia areata. It would have been expected that Compound (I), differing from ruxolitinib only by deuteration, would have had the same efficacy in treating alopecia areata. As Concert's CEO explained, "At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'" EX1011, 5.

U.S. Patent No. 10,561,659 should never have issued. Petitioner Incyte Corporation respectfully submits this PGR should be instituted and all claims held unpatentable.

II. Statement of Precise Relief Requested

Petitioner requests cancellation of claims 1−21 of U.S. Patent No. 10,561,659 (the "'659 Patent") on the following grounds.

Ground	
1	Claims 1−21 obvious under AIA 35 U.S.C. § 103 over *Silverman* in view of *Xing* and *Ruxolitinib Prescribing Information* (EX1004).
2	Claims 1−21 obvious under AIA 35 U.S.C. § 103 over *Silverman* (EX1002) in view of *Christiano* (EX1005) and *Ni* (EX1006).

3	Claim 8 anticipated under AIA 35 U.S.C. § 102(a) by *Silverman* (EX1002).

III. Scope and Content of the Prior Art

As of May 4, 2016, the filing date of the '659 Patent's earliest priority application, a Person of Skill in the Art ("POSA") would have known that (**A**) Janus kinase Inhibitors ("JAK") inhibitors—including ruxolitinib—treated alopecia areata ("AA") and (**B**) Compound (I), a deuterated analog of ruxolitinib, had been disclosed, specifically claimed, and reported to have improved metabolic properties relative to ruxolitinib and other deuterated analogs of ruxolitinib.

A. Ruxolitinib Treatment of Alopecia Areata

The '659 patent purports to disclose "a method of treating in a subject hair loss disorders that are beneficially treated by administering a JAK1 and/or JAK2 inhibitor." EX1001, Abstract. Such JAK inhibitors, including ruxolitinib, however, were known to treat hair loss disorders such Alopecia Areata ("AA"), an autoimmune diseases where hair loss results from damage caused by inflammatory T-cells regulated by the JAK-Signal Transducers and Activators of Transcription ("STAT") ("JAK-STAT") pathway. EX1005, 1:63−2:8, 78:36−55; EX1012, 6; EX1003, 8−9; EX1013, 1−2; EX1009, ¶¶19–28; EX1014, 3, Fig. 1; *cf*. EX1001, 2:51–3:2. Ruxolitinib in particular had been taught for the treatment of AA hair loss

and been clinically demonstrated to provide "near-complete hair regrowth within 3 to 5 months of oral treatment" using 20 mg twice per day. EX1003, 5, 10; EX1005, 1:63−2:8, 78:36−55; *see also* EX1013, 1; EX1015, 9; *see also* EX1016, 8. By March 2015, "reports on the possible usefulness of Ruxolitinib to treat AA" led clinicians to treat AA starting with ruxolitinib doses of 5 mg/day—the lowest dose taught for its FDA-approved indications—followed by gradual titration to higher doses. EX1017, 31; EX1004, 5 (*e.g.*, § 2.4, table 4); *see also* EX1009, ¶¶29–30, 33–43.

The following references provide examples of the state of the art relating to JAK inhibitors for AA.

a. *Xing* (EX1003)

Xing, titled "Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition," was published in August of 2014 and is prior art under AIA 35 U.S.C. § 102(a)(1). EX1003; EX1018, 1; *see also* EX1007, ¶¶88−92. Its prior art public accessibility is evidenced at least by (1) its date of online publication, August 17, 2014 (EX1003, 5); (2) date stamp from UC Berkley Library, reporting it was received in September 2014 and scheduled for circulation in October 2014 (EX1003, 1) and (3) publication in a well-known and reputable journal, *Nature Medicine* (EX1019, 5, available at https://www.nature.com/nature-research/about/journal-metrics (last accessed October 28, 2020) (reporting 5-year

impact factor of 36.230). *See Hulu, LLC v. Sound View Innovations, LLC*, IPR2018-01039, Paper 29 at 19–20 (PTAB Dec. 20, 2019) (precedential) ("[T]he book is a textbook from an established publisher, O'Reilly, and a well-known book series."). Moreover, *Xing* was cited by several skilled artisans before May 4, 2016, further evidencing its prior art public accessibility. EX1020, 25; EX1021, 5; EX1022, 11; EX1015, 15; *see also Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1350 (Fed. Cir. 2016) ("[A] published article with an express citation to the potentially invalidating reference would similarly provide the necessary guidance.") (citation omitted). Patent Owner also represented in both IPR2017-01256 and in an IDS submitted during prosecution of the '659 patent that *Xing* was published as of 2014. EX1023, 2; EX1047, 1522; *see also Grunenthal GmbH v. Antecip Bioventures II LLC*, PGR2018-00062, Paper 36 at 5 (PTAB Apr. 17, 2020).

b. *Ruxolitinib Prescribing Information* (EX1004)

Ruxolitinib Prescribing Information (EX1004), an excerpt from the 2015 Physician's Desk Reference, 69th edition, is prior art under AIA 35U.S.C § 102(a)(1). *Ruxolitinib Prescribing Information* addressed the FDA-approved uses of ruxolitinib phosphate (Jakafi®) to treat myelofibrosis and polycythemia vera. EX1004, 4; *see also* EX1007, ¶¶68−71. *Ruxolitinib Prescribing Information* disclosed, *inter alia*, ruxolitinib formulation information,

pharmacodynamic and pharmacokinetic data, clinical trial results, and dosing recommendations of 5 mg/day to 50 mg/day, with specific daily doses of 5 mg (5 mg QD), 10 mg (5 mg BID), 20 mg (10 mg BID), 30 mg (15 mg BID), 40 mg (20 mg BID), and 50 (25 mg BID). EX1004, 4, 5 (*e.g.*, § 2.4, table 4, § 2.7). *Ruxolitinib Prescribing Information* also taught increased drug exposure and dose reduction where of ruxolitinib where metabolism was inhibited. EX1004, 5−7 (*e.g.*, §§ 2.7, 7.1).

The Physicians' Desk Reference is an annually published compilation of prescribing information for prescription drugs, well known to the POSA. EX1009, ¶29, n. 28; *see also Frontier Therapeutics, LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, IPR2016-00649, Paper 10 at 21–22 (PTAB Sept. 1, 2016) (finding Physicians' Desk Reference is a printed publication "published on the date[] indicated on the documents"). *Ruxolitinib Prescribing Information* includes a date stamp of January 6, 2015 from Social Law Library (Boston, MA) (EX1004, 1), indicating it was publicly accessible at least as of that date. EX1024. The 2015 Physicians' Desk Reference provides a copyright of 2014 and was cited prior to May 4, 2016, further evidencing its prior art public availability. *E.g.*, EX1004, 3; EX1025, 2.

c. *Christiano* (EX1005)

Christiano, U.S. Patent No. 9,198,911 titled "Methods of Treating Hair Loss Disorders," issued on December 1, 2015 based on applications filed from 2010-2013. EX1005, cover. It is prior art under AIA 35U.S.C §§ 102(a)(1), (2).

Christiano taught the use of ruxolitinib (referred to as "INCB018424") to treat hair loss disorders, including alopecia areata. EX1005, 2:2−8. It disclosed results showing an association between CD8+ T-cells, proinflammatory cytokines (IFN-γ), the JAK-STAT pathway in AA patients, and other data supporting the use of JAK inhibitors to treat AA. *E.g.*, EX1005, 4:21−12:39 (citing, *inter alia*, Petukhova 2010 (EX1026)); *see also* EX1007, ¶¶57−61.

d. *Ni* (EX1006)

Ni, U.S. Published Patent Application No. 2014/0135350 titled "Sustained-Release Dosage Forms of Ruxolitinib" published on May 15, 2014. It is prior art under AIA 35U.S.C §§ 102(a)(1), (2). EX1006, cover.

Ni disclosed that "Ruxolitinib… is the first FDA approved Janus kinase (JAK) inhibitor" and that "[i]mmediate-release dosage forms of ruxolitinib phosphate can be obtained commercially in 5, 10, 15, 20, and 25 mg doses as the drug product Jakafi® (ruxolitinib phosphate (tablets)) (NDA no. N202192)." EX1006, [0002], [0124]; *see also* EX1007, ¶¶72−74.

e. *Craiglow 2016* (EX1027)

Craiglow 2016, "Topical Ruxolitinib for the Treatment of Alopecia Universalis," published in *JAMA Dermatology.* *Craiglow 2016* is prior art under AIA 35U.S.C § 102(a)(1) as it was publicly accessible at least as of its date of online publication, December 9, 2015 (EX1027, 4) and further as of its date of publication in the April 2016 version of *JAMA Dermatology* (*id.*); *see also* EX1028. Indeed, Patent Owner identified *Craiglow 2016* using the same citation as evidenced on the face of this publication in an IDS during prosecution of the '659 patent. EX1047, 1521; *see also Grunenthal*, PGR2018-00062, Paper 36 at 5.

Craiglow 2016 explains that "[i]n light of the recent successful treatment of alopecia areata and variants with the JAK inhibitors tofacitinib and ruxolitinib, these were discussed as therapeutic options." EX1027, 4. The article reports that in an AA patient "[a]fter 12 weeks of [topical] treatment [of ruxolitinib], the eyebrows were nearly normal… there was growth of about 10% of scalp hair" and that "[t]he patient tolerated the medication without adverse effects." *Id*.; *see also* EX1007, ¶¶62−64.

f. *Harris* (EX1031)

Harris, "Rapid Skin Repigmentation on Oral Ruxolitinib in a Patient with Coexistent Vitiligo and Alopecia Areata (AA)," is AIA 35U.S.C § 102(a)(1) prior

art as it was publicly accessible before May 4, 2016, as evidenced by its date of online publication of February 2016. EX1031, 9; EX1032, 1. Records from the U.S. Copyright Office reporting a date of first publication of January 28, 2016 further confirm that *Harris* was publicly available before May 4, 2016. EX1029. Further still, Patent Owner identified *Harris* as being published in February 2016 in an IDS submitted during prosecution of the '659 patent. EX1047, 1521; *see also Grunenthal*, PGR2018-00062, Paper 36 at 5. *Harris* reports on an AA patient treated with 20 mg oral ruxolitinib in the same trial addressed by *Xing*. EX1031, 9; *id*. at 10, ref. 2. At four weeks, the patient experienced "some hair regrowth on his frontoparietal scalp, and after 12 weeks he had significant improvement…." *Id*.; *see also* EX1007, ¶¶65−67.

g. *Pieri* (EX1012)

Pieri, "Ruxolitinib-Induced Reversal of Alopecia Universalis in a Patient with Essential Thrombocythemia," is prior art under AIA 35U.S.C § 102(a)(1), as evidenced by its date of cataloguing by the National Library of Medicine on September 22, 2015 (EX1012, cover page), citation by skilled artisans before May 4, 2016 (EX1015; EX1021), and date of publication from the U.S. Copyright Office of January 19, 2015 (EX1030). Moreover, Patent Owner, in an IDS submitted

during prosecution of the ’659 patent, also identified *Pieri* as being published as of 2015. EX1047, 1522; *see also Grunenthal*, PGR2018-00062, Paper 36 at 5.

Pieri describes treatment of an AA patient with 15 mg of oral ruxolitinib BID that provided “durable” hair regrowth. EX1012, 6−7. Referencing *Xing* (EX1003), *Pieri* states: “[r]ecent data suggest that the list of autoimmune disorders in which ruxolitinib may be efficacious should include alopecia areata.” EX1012, 6; *see also* EX1007, ¶¶75−78.

h. *Silvestri* (EX1017)

Silvestri reports the prior art use of ruxolitinib “off label” to treat AA that began in March 2015 with a dose of 5 mg/day and was gradually raised to 20 mg/day. EX1017, 31. The treatment in *Silvestri* was prompted by “first reports [on the web] on the possible usefulness of Ruxolitinib to treat AA.” *Id*. The reported result over sixteen weeks (four months) was “a progressive regrowth of hair until a complete recovery.” *Id*.

Silvestri was published ten days after the earliest priority date of the ’659 Patent but documents “the level of ordinary skill in the art to which the invention pertained” and demonstrates ruxolitinib doses that would have been “worthy of investigation as of the priority date.” *Yeda Research & Dev. Co. v. Mylan Pharm., Inc.*, 906 F.3d 1031, 1041 (Fed. Cir. 2018); *see also Thomas & Betts Corp. v. Litton*

Sys., Inc., 720 F.2d 1572, 1581 (Fed. Cir. 1983); *In re Farrenkopf*, 713 F.2d 714, 719−20 (Fed. Cir. 1983); EX1007, ¶¶32, 177; EX1009, ¶43.

B. Compound (I): A Deuterated Analog of Ruxolitinib

Compound (I) in the '659 patent is a deuterated analog of ruxolitinib, the active agent in Jakafi® approved by the FDA in 2011. EX1001, 3:9-30; EX1004, 4. Deuterium substitution or "deuteration" entails replacing hydrogen substituents on a drug with deuterium to slow the drug's metabolism while retaining its efficacy, potentially lowering the overall dose and/or dosing frequency. *E.g.*, EX1007, ¶¶38−52; EX1033, 7−10; EX1034,[1] 1−3; EX1002, 2:5−20; EX1035, 5−6; EX1036, 1; EX1038, 2. It has been used widely to try to improve FDA-approved drugs, including by numerous companies dedicated to this strategy. *E.g.*, EX1007, ¶¶51−56; EX1037, 4; EX1033, 6−7, 16−17; EX1039; EX1040; EX1041, 1−3; EX1011, 1−2. Given its "utterly predictable" nature (EX1033, 17), deuterating FDA-approved drugs can bypass much of the time and expense associated with

[1] *See also* EX1093, ¶3 (Shelton Declaration from IPR2017-01256, referring to Ex. 1006 of IPR2017-01256); *Incyte Corp. v. Concert Pharm., Inc.*, IPR2017-01256, Paper 119 (PTAB Apr. 9, 2018) at 14−19 (finding that Ex. 1006 of IPR2017-01256 is a printed publication).

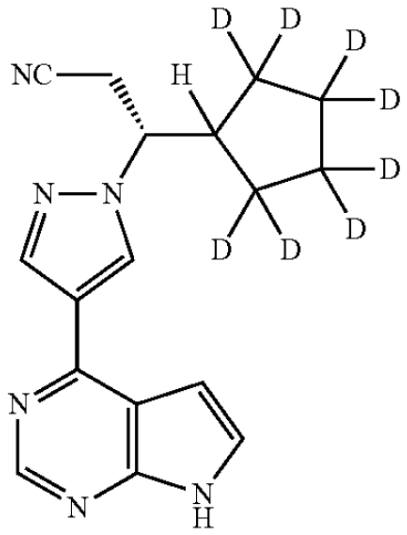
traditional drug development by leveraging data generated for their FDA-approved non-deuterium parent. EX1007, ¶¶54−56; EX1033, 16−17; *see also* EX1042, 16 (Auspex's NDA for deuterated-tetrabenazine relies on "certain nonclinical and clinical safety findings made by the FDA in its approval of" tetrabenazine.); EX1043, 26, 54−56; EX1044, 1.

Compound (I) was disclosed and claimed in Patent Owner's prior-art *Silverman* patent (issued in February 2016 with priority claims to December 2013), which also recognized deuteration as "[a] potentially attractive strategy for improving a drug's metabolic properties…." EX1002, 2:5−20. All claims of *Silverman* were found unpatentable based on the obviousness of Compound (I) in *Incyte Corp. v. Concert Pharm., Inc.*, IPR2017-01256 ("*Incyte*"), Paper 119 at 37 (PTAB Apr. 8, 2019).[2]

Compound (I) is disclosed and claimed in *Silverman* using the designation "Compound 111":

[2] IPR2017-01256 was remanded from the Federal Circuit in view of *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), *reh'g en banc denied*, 953 F.3d 760 (Fed. Cir. 2020), *cert. granted*, *Arthrex, Inc v. Smith & Nephew, Inc., et al.*, No. 19-1458, 2020 WL 6037208 (U.S. Oct. 13, 2020), and is currently stayed.

Compound 111



EX1002, 36:66−37:43; *id*., 7:7−8:43.

Silverman also disclosed:

- "a compound of this invention and the use of such compositions in methods of treating diseases and conditions that are beneficially treated by administering an inhibitor of Janus-associated kinase with selectivity for subtypes 1 and 2 (JAK1/JAK2)" (*id.*, 3:28–32);
- "97% deuterium incorporation" (*id*., 4:7−17);
- "pharmaceutically acceptable salts thus include… phosphate" (*id*., 5:6−8);
- "pharmaceutical compositions comprising an effective amount of a compound of Formula I… or a pharmaceutically acceptable salt of said

compound… [and] a pharmaceutically acceptable carrier" (*id*., 16:23−27);

- "pharmaceutical compositions of the invention include those suitable for oral… administration" (*id*., 17:18−21);
- "unit dosage form[s], e.g., tablets" (*id*., 17:3−5);
- co-administered with a "a second therapeutic agent… "[p]referably… useful in the treatment or prevention of… alopecia areata") (*id.*, 19:34−50);
- "an effective amount of a compound of this invention can range from… 10 mg to 25 mg, from 10 mg to 20 mg,… and from 5 to 10 mg" (*id*., 20:9–17);
- doses can be administered either once or twice a day (*id*., 20:17–28);
- "guidance for selecting an effective dose can be determined by reference to the prescribing information for ruxolitinib" (*id*., 20:25–27); and
- "a method of treating a disease that is beneficially treated by ruxolitinib in a subject in need thereof, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention" (*id*., 20:57–62). *See also* EX1007, ¶¶79−87.

During the prosecution leading to *Silverman*, applicant (Concert) submitted *in vitro* data comparing the relative metabolic stability of two tetra-deuterated ruxolitinib analogs and the octa-deuterated "Compound 111" (claimed Compound (I)) to ruxolitinib to overcome an obviousness rejection based on deuteration of ruxolitinib.[3] EX1045, 108–116 (examiner rejection), 375–377 (applicant response), 414–415 (declaration). Concert's data showed that, relative to ruxolitinib, the half-life ("$t_{1/2}$") of Compound 111 was 75% longer than ruxolitinib in the CYP3A4 supersome assay and 80% longer in the human liver microsome ("HLM") assay. EX1045, 407.

IV. The '659 Patent

U.S. Patent No. 10,561,659 issued February 18, 2020, based on a PCT application filed May 4, 2017. EX1001, 1. Its earliest referenced priority application (App. No. 62/331,827) was filed May 4, 2016. *Id.*

[3] The File History of *Silverman* (EX1045 "*Silverman File History*") was a public record as of at least August 27, 2015, when U.S. Patent Application No. 14/707,912, from which *Silverman* issued, was published as US2015/0239896. *See* EX1002, 1; EX1046, cover; 37 C.F.R. § 1.11(a).

A. The Specification

The "Background of the Invention" recognizes that

> ***[a] potentially attractive strategy for improving a drug's metabolic properties is deuterium modification***… replacing one or more hydrogen atoms with deuterium atoms… because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by ***deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen***.[4]

EX1001, 2:7–24. The specification does not mention that Compound (I), an octa-deuterated analog of ruxolitinib, had already been disclosed and claimed in *Silverman* based on this same premise. *See* EX1002, 7:7−8:43; 36:66−37:43.

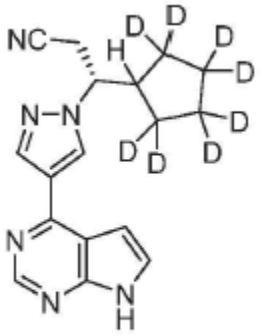
B. Claimed Subject Matter

The claims of the '659 Patent recite use of Compound (I) in methods of treating hair loss disorders (Claims 1−7, 9−21) and a pharmaceutical composition (claim 8). *See* EX1007, ¶¶93−100.

There are three independent method claims: 1, 9, and 11. The broadest, Claim 1, recites:

> 1. A method of treating a hair loss disorder in a mammalian subject, the method comprising administering to the subject 16 mg/day or 24 mg/day of a compound represented by the following structural formula:

[4] ***Bolded italics*** herein denote emphasis added.



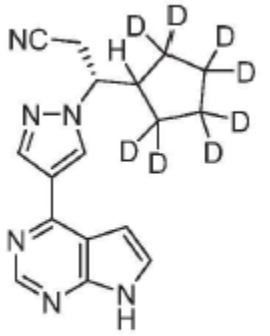
Compound (I)

or a pharmaceutically acceptable salt thereof, wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium.

Claims 9 and 11 are identical except that they require, respectively, administering 8 mg (Claim 9) or 12 mg (Claim 11) of Compound (I) twice daily. The dependent claims further recite treating "alopecia areata" (Claims 2, 15, 18), "wherein the compound is administered orally" (3, 16, 19), "administered as a pharmaceutical formulation which is a tablet" (4), "once a day" (5), "twice a day" (6), natural isotopic abundance for non-deuterium atoms (7), 10.5 or 15.8 mg dose of Compound (I) phosphate salt (10, 12), 97% deuterium incorporation (13, 17, 20), 8 or 12 mg twice per day (14), and to human subjects (21). *See also infra*, § V.C.

Finally, the only composition claim, independent Claim 8, recites:

8. A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and 8 mg or 12 mg of a compound represented by the following structural formula:



Compound (I)

or a pharmaceutically acceptable salt thereof, wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium.

C. Prosecution History

The patent application leading to the '659 Patent was filed on November 11, 2018, based on the May 4, 2017, PCT Application No. US2017/031142, which claims priority to several provisional applications dating from May 4, 2016 through May 1, 2017. EX1001, cover page.

Without making any rejections, the Examiner issued a Notice of Allowance on September 6, 2019. EX1047, 165. In the Reasons for Allowance, the Examiner explained:

> The examiner performed a chemical structure as well as an inventor and classification search to identify any potential prior art. While he [sic] 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.

Id., 170−71. The Examiner further noted that "No IDS were cited by the Applicants in this application nor were any prior art documents cited by the Examiner." *Id.*, 172.

Rather than pay the issue fee, Applicant initiated an interview with the Examiner. The Examiner's interview summary states:

> Applicants plan to file a Request for Continued Examination in the present application and amend the scope of the claims with regards to the dosing seen in the present claims. Applicants intend to file an IDS with the RCE which will help further clarify the amendments.

Id., 187. The summary also states that no prior art was discussed. *Id*.

On October 29, 2019, Concert filed an RCE with a preliminary amendment and an IDS listing several references. *Id*., 1521−24. With no discussion of these newly disclosed references or any rejections, the Examiner allowed all claims for the same reasons as before. *Id*., 1544−45.

As evidenced by the prosecution history, no prior art was "the basis for rejection" and no patentability arguments were previously "evaluated during examination." *Oticon Medical AB v. Cochlear Limited,* IPR2019-00975, Paper 15 at 10 (PTAB Oct. 16, 2019) (precedential); 35 U.S.C. § 325(d).

D. Person of Skill in the Art

A POSA with respect to the subject matter of the '659 Patent as of May 4, 2016, would have had a Ph.D. in chemistry, pharmaceutical sciences, molecular

biology, or a similar field, or an M.D. with similar background. A POSA would also have had at least several years of experience with drug design, drug development, clinical trials, or access to other individuals with that knowledge and experience. Likewise, a POSA would have had knowledge and experience in treating hair loss disorders, or access to a person with that knowledge and experience. EX1007, ¶¶101−102; *see also* EX1009, ¶¶15−18.

E. Claim Construction

In light of the intrinsic record and the state of the art as of the effective filing date of the '659 Patent, a POSA would have understood the following claim terms to be construed as proposed below by Petitioner. Regardless of how the claims are construed, however, all of the challenged claims would have been obvious and anticipated for the reasons set forth herein.

1. "[A] compound represented by [Compound (I)]… wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium" or "at least 97% incorporation of deuterium" (Claims 1−21)

Claims 1−12, 14−16, 18−19, and 21 recite "a compound represented by [Compound (I)] wherein each position designated as deuterium has at least 95% incorporation of deuterium." Claim 13, 17, and 20 further limit the deuterium incorporation to "at least 97%." Based on the context of the claim and the express definitions in the specification, a POSA would understand ***claims 1−12, 14−16,***

18−19, and 21 to read on collections of molecules having as little as 66% simultaneously having a deuterium at all eight positions. EX1007, ¶¶103−105, 107−111. Likewise, a POSA would understand that ***claims 13, 17, and 20 read on collections of molecules having as little as 78% simultaneously having a deuterium at all eight positions***. EX1007, ¶¶112−116.

First, rather than use "compound" or "deuterium" according to their ordinary meanings, both are defined terms in the '659 Patent. "Compound" is defined as

> a collection of molecules having an identical chemical structure, except that there may be isotopic variation among the constituent atoms of the molecules.

EX1001, 2:56−60. The specification further explains that

> a compound represented by a particular chemical structure containing indicated deuterium atoms, will also contain lesser amounts of isotopologues having hydrogen atoms at one or more of the designated deuterium positions in that structure.

Id., 2:60−65; *see also id*., 2:65−7:3 (including "isotopologues" within the collection of compounds). For the claim term "deuterium," the specification states that

> unless otherwise stated, when a position is designated specifically as "D" or "deuterium," the position is understood to have deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (*i.e.*, at least 45% incorporation of deuterium).

Id., 2:33−38. These definitions and disclosures are identical to those in *Silverman.* EX1002, 1:65−2:3, 2:21−41.

Second, considering the claim limitations "***each position*** in Compound (I) designated specifically as deuterium" in view of the express definitions, a POSA would have understood the percent deuterium incorporation (*i.e.*, 95% or 97%) to refer ***independently*** to deuterium at "***each position*** designated as deuterium" rather than to the deuterium content of the molecule as a whole. EX1007, ¶¶108−109; *MicroStrategy Inc. v. Bus. Objects, S.A.*, 429 F.3d 1344, 1351–52 (Fed. Cir. 2005) ("'[E]ach' reaffirm[s] that these claims require individual… association[s]."). That is, the first D will independently have at least 95% (or 97%) deuterium, the second D also will independently have at least 95% (or 97%) deuterium, etc. EX1007, ¶¶108−110, 112.

Because deuterium incorporation at each of the eight positions is considered independently, a POSA would have further understood that as little as 66% ($=95\%^8$) (for Claims 1−12, 14−16, 18−19, and 21) or 78% ($=97\%^8$) (for Claims 13, 17, and 20) of the collection of molecules necessarily have deuterium atoms simultaneously at all eight positions. EX1007, ¶¶111, 113. The remainder could be isotopologues of the octa-deuterated compound. *Id*.

Concert's concession in *Incyte*, where the same definitions and percentage of deuterium incorporation were in issue, confirms these constructions. *Incyte*, Paper 84, 6 (PTAB Nov. 15, 2018) ("If all of the eight positions designated as deuterium

had 95% deuterium enrichment, the amount of octa-deuterated molecules required by the proposed claims, would be at least 66%, with the balance comprising deuterated isotopologues." (citations omitted)); *see also Microsoft Corp. v. Multi-Tech Sys., Inc.*, 357 F.3d 1340, 1349−50 (Fed. Cir. 2004) (relying on patentee's statement in a related application for claim construction).

2. "Treating a hair loss disorder" (Claims 1−7, 9−21)

Claims 1−7 and 9−21 recite a method of "treating a hair loss disorder." The specification states that "treatment of a hair loss disorder includes regrowth of hair, prevention of further hair loss, or diminishing the rate of hair loss." EX1001, 5:66–6:5.

Accordingly, "treating a hair loss disorder" should be construed to include "***regrowth of hair, prevention of further hair loss, or diminishing the rate of hair loss***." EX1007, ¶106; *see also* EX1009, ¶15; *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999) ("[O]nly those terms need be construed that are in controversy, and only to the extent necessary to resolve the controversy.").

V. Grounds 1 and 2: Claims 1–21 of the '659 Patent Would Have Been Obvious

The claims of '659 Patent are directed to treating a hair loss disorder, including AA, with 16 mg or 24 mg/day of Compound (I) and to a pharmaceutical formulation comprising 8 mg or 12 mg of Compound (I). EX1001, 24:30−26:46.

This claimed subject matter is nothing more than the obvious substitution of Compound (I), in the treatment of a disease clinically established to be treated by ruxolitinib, at doses in a known range. EX1007, ¶¶126−135; *In re Fout*, 675 F.2d at 301 (CCPA 1982) ("substitut[ing] one equivalent for another" obvious even without express suggestion); *In re Ruff*, 256 F.2d 590, 594 (CCPA 1958) (obvious to substitute where equivalence is taught in the prior art); *Coalition for Affordable Drugs IX LLC v. Bristol-Myers Squibb Co.*, IPR2015-01723, Paper 10 at 15 (PTAB Feb. 22, 2016) ("*In re Ruff* stands for the proposition that a patent claim is invalid where the prior art teaches the functional equivalency between the claimed compound(s) and the prior art compounds.").

Additional limitations, such as isotopic purity and administration as a phosphate salt, are added in certain claims but do not impart patentability. EX1007, ¶¶159−165, 210−214. Taking all limitations together (with their source claims cited in brackets), all claims read on the following method or composition species:

1) "A method of treating" [1−7, 9−21] "alopecia areata" [2, 15, 18] in "a human" [21] "comprising"
    a) "administer[ing] orally" [3, 16, 19] a "a pharmaceutical formulation which is a tablet" [4] comprising "Compound (I)" [1−7, 9−21] "phosphate salt" [10, 12]

b) where each deuterium "has at least 97% incorporation of deuterium" [13, 17, 20] and "any atom not designated as deuterium is present at its natural isotopic abundance" [7],

c) with doses of "16 mg/day or 24 mg/day" [1−7, 9−21] either

i) "administered once a day" [5] or

ii) "administered twice a day" [6, 14] using either "10.5 mg" [10] or "15.8 mg" [12] Compound (I) "phosphate salt"; or

2) a "pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and 8 mg or 12 mg of" Compound 1 wherein each deuterium "has at least 95% incorporation of deuterium" [8].

As shown below, this common subject matter would have been obvious based on Ground 1[5] and Ground 2[6] in view of the state of the art. *E.g.*, EX1007, ¶¶11−14, 117−121, 247−263; *see also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007)

[5] *Silverman* (EX1002), *Xing* (EX1003), and *Ruxolitinib Prescribing Information* (EX1004), collectively the "Ground 1 References." *See* §§V.A, III

[6] *Silverman* (EX1002), *Christiano* (EX1005), and *Ni* (EX1006), collectively the "Ground 2 References." *See* §§V.B, III.

("In determining whether the subject matter of a patent claim is obvious… [w]hat matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under § 103."); *see also Atlas Powder Co. v. IRECO, Inc*., 190 F.3d 1342, 1346 (Fed. Cir. 1999) ("[A] single prior art species within the patent's claimed genus reads on the generic claim….").

A. Ground 1: Claims 1−21 Would Have Been Obvious Over *Silverman* in View of *Xing* and *Ruxolitinib Prescribing Information*

As shown in the claim chart in § V.C, *infra*, all limitations of claims 1–21 are taught by *Silverman*, *Xing* and *Ruxolitinib Prescribing Information.* Exemplary disclosures of the Ground 1 References and the differences between the claims of the '659 Patent and the prior art are summarized below in § V.A.1. As explained further in Sections V.A.2−V.A.3 below, a POSA would have been motivated with a reasonable expectation of success to combine *Silverman*'s teaching of Compound (I)—deuterated ruxolitinib—with *Xing*'s use of ruxolitinib for AA, further guided by *Ruxolitinib Prescribing Information*'s dosing and forms of administration, to obtain an at least equally efficacious alternative treatment for AA, and would have been further motivated by the potential improvements on ruxolitinib offered by deuteration. *Infra*, §§ V.A.2−V.A.3.

1. *Silverman* in View of *Xing* and *Ruxolitinib Prescribing Information* Rendered Obvious All Claims

Claim 1 recites a method treating "a hair loss disorder in a mammalian subject" with Compound (I) or a pharmaceutically acceptable salt thereof. EX1001, 24:30−53. *Xing* disclosed treatment of AA, which is a hair loss disorder, with ruxolitinib (EX1003, 5, 10) and *Silverman* disclosed that Compound (I) was effective for "treating a disease that is beneficially treated by ruxolitinib" (EX1002, 20:57–59); *infra*, § V.A.2.a.

Claim 1 requires administration of "16 mg/day or 24 mg/day" of Compound (I). EX1001, 24:30−53. These doses fall within narrow "effective amounts" ranges of "10 mg to 20 mg" and "5 mg to 25 mg" taught by *Silverman* for Compound (I). EX1002, 20:9–15. *Silverman* further directed that "guidance for selecting an effective dose can be determined by reference to the prescribing information for ruxolitinib," (*id*., 20:25–27) which disclosed ranges of 5 to 50 mg per day (EX1004, 4, 5 (*e.g.*, §§ 2.4, 2.7) that also narrowly encompass the claimed doses. *Infra*, § V.A.2.b.

Claim 1 further requires "wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium." *Silverman* taught the use of Compound (I) having "an isotopic enrichment factor for each

designated deuterium atom of… at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation)." EX1002, 4:7−17; *infra*, § V.A.2.a.

The other two independent method of treatment claims (Claims 9 and 11) are identical to Claim 1 except they require "administering to the subject twice a day 8 mg" (Claim 9; EX1001, 25:23−46) and "administering to the subject twice per day 12 mg" (Claim 11; EX1001, 26:1−23) of Compound (I). These doses are encompassed by the narrow ranges disclosed by *Silverman* for Compound (I) (EX1002, 20:9–15) and the *Ruxolitinib Prescribing Information* for ruxolitinib (EX1004, 4−5). And all three Ground 1 references disclosed twice-daily administration, including *Silverman* for Compound (I) (EX1002, 20:17−18), *Ruxolitinib Prescribing Information* for ruxolitinib (EX1004, 4−5), and *Xing* for ruxolitinib to treat AA (EX1003, 10). *Infra*, § V.A.2.b.

Independent Claim 8 recites a pharmaceutical composition "comprising a pharmaceutically acceptable carrier or diluent and 8 mg or 12 mg" of 95% incorporated Compound (I). EX1001, 25:1−22. *Silverman* disclosed "pharmaceutical compositions comprising an effective amount of a compound of

Formula I"—which include Compound (I)[7]—"or a pharmaceutically acceptable salt of said compound… [and] a pharmaceutically acceptable carrier" with narrow ranges of "5 mg to 10 mg" and "10 mg to 20 mg" that encompass the claimed amounts of Compound (I). EX1002, 16:23−27, 19:65−20:18. Similarly, *Ruxolitinib Prescribing Information* disclosed that "Each tablet contains ruxolitinib phosphate… together with" carriers and diluents. EX1004, 7 (§ 11). *Infra*, § V.A.2.c.

Silverman in view of *Xing* and *Ruxolitinib Prescribing Information* also taught and would have rendered obvious all the dependent claims.

Claims 2, 15, and 18 recite that "the hair loss disorder is alopecia areata." EX1001, 24:54–55, 26:32–33, 26:38–39. As noted above for Claim 1, *Xing* disclosed treatment of AA with ruxolitinib (EX1003, 5, 10) and *Silverman* disclosed that Compound (I) can be used for diseases treated by ruxolitinib (EX1002, 20:57–59). *Infra*, § V.A.2.a.

Claims 3, 16, and 19 require oral administration (EX1001, 24:56–57, 26:33–34, 26:40–41), which was disclosed by all three Ground 1 references, including for

[7] As detailed in §VI, *infra*, Compound 111 is encompassed within *Silverman*'s Formula I. *See also* EX1007, ¶¶272–275.

Compound (I) (EX1002, 17:18−21), for ruxolitinib (EX1004, 4, 6 (*e.g.*, § 2.9), 7 (*e.g.*, § 11)) and ruxolitinib for the treatment of AA (EX1003, 10). Likewise, administration as a tablet (Claim 4; EX1001, 24:58–60) and administration to a human (Claim 21; EX1001, 26:45–46) were disclosed by each of the references. EX1002, 17:19−25 (tablet), 5:51−52 ("In another embodiment, the mammal is a human."); EX1003, 5, 10 (using commercially available ruxolitinib for treating human AA patients); EX1004, 7 ("ruxolitinib Tablets are for oral administration"), 8−10 (disclosing human clinical trials of FDA-approved ruxolitinib); *Infra*, § V.A.2.b.

Claim 5 requires once daily administration. EX1001, 24:61–62. *Silverman* disclosed that the "effective amount" of Compound (I) "administered once a day" (EX1002, 20:15−17) and *Ruxolitinib Prescribing Information* disclosed "For patients on 5 mg once daily [of ruxolitinib], maintain dose at 5 mg once daily" (EX1004, 5. Claims 6 and 14 require twice-daily administration (EX1001, 24:63–64, 26:29–31), which, as noted above, was disclosed by all three Ground 1 references. *Infra*, § V.A.2.b.

Claim 7 recites "Any atom not designated as deuterium is present at its natural isotopic abundance." This limitation is disclosed verbatim by *Silverman* for Compound (I). EX1002, 9:28−30, 12:20−21. Similarly, 97% deuterium

incorporation (Claim 13, 17, 20; EX1001, 26:26–28, 26:35–37, 26:42–44) is expressly disclosed by *Silverman* for Compound (I). EX1002, 4:7−17; *infra*, § V.A.2.a.

Claims 10 and 12 require administration of Compound (I) as a phosphate salt. EX1001, 25:47–48, 26:24–25. *Silverman* taught Compound (I) as a pharmaceutically acceptable salt and expressly disclosed "Such pharmaceutically acceptable salts thus include… phosphate…." EX1002, 5:6–24. *Ruxolitinib Prescribing Information* disclosed "Each tablet contains ruxolitinib phosphate" (EX1004, 7) and *Xing* disclosed treating AA with "FDA-approved" ruxolitinib, (EX1003, 10), which is ruxolitinib phosphate (EX1004, 7 (*e.g.*, § 11). *See* EX1009, ¶29. The amounts recited in claims 10 and 12 (equivalent to 8 mg and 12 mg of ruxolitinib free base) are encompassed by the narrow ranges disclosed by *Silverman* and *Ruxolitinib Prescribing Information*, noted above for claim 1. *Infra*, § V.A.2.b.

Concert may assert that the express disclosures of the Ground 1 References differ from the claims of the '659 Patent in:

1) substituting orally administered tablets of Compound (I) phosphate for tablets of orally administered ruxolitinib phosphate in the treatment of AA (Claims 1−7, 9−21); and

2) using Compound (I) to treat AA at specific doses of 16 mg/day or 24 mg/day (Claims 1−7, 9−21) as QD dosing (Claim 5), 8 mg BID dosing (Claims 6, 9−10), or 12 mg BID dosing (Claims 11−12) with 8 or 12 mg pharmaceutical compositions (Claim 8).

These alleged differences, however, are encompassed by the general conditions in the prior art and would have been obvious at least because "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (citations omitted); EX1007, ¶¶ 126−134, 170−209. Indeed, there is a "presumption of obviousness" where, as here, the claimed dosing regimens fall within those already known in the art. *E.I. DuPont*, 904 F.3d at 1006.

Even without these controlling presumptions, all claims would have been obvious at least because, as explained below, a POSA would have been motivated, with a reasonable expectation of success, to combine the teachings of the Ground 1 References to achieve the claimed methods of treatment and pharmaceutical formulations.

2. A POSA Would Have Been Motivated to Combine *Silverman*, *Xing*, and *Ruxolitinib Prescribing Information*

A POSA would have been motivated to use Compound (I), the deuterated analog of ruxolitinib from *Silverman*, to treat AA, which *Xing* taught could be treated with ruxolitinib, to obtain at least the same efficacy as ruxolitinib and/or potentially improved pharmacokinetic properties in that treatment. *E.g.*, EX1007, ¶¶126−135. The POSA would have been motivated to use the claimed dosing regimen and compositions, all of which fall within narrow ranges taught by *Silverman* and *Ruxolitinib Prescribing Information* and were further suggested by the state of the art. *See supra*, § III.

a. Motivation to Substitute Compound (I) for Ruxolitinib

A POSA would have been motivated to orally administer tablets of Compound (I) according to *Silverman* to treat AA, which *Xing* taught could be treated in humans with orally administered tablets of ruxolitinib, (1) based on the express teaching of *Silverman*, (2) based on the expectation of obtaining at least the same efficacy as ruxolitinib, and/or (3) to obtain improved pharmacokinetic properties via deuteration. EX1007, ¶¶38−43, 126−135 (citing, *inter alia*, EX1048); *see also* EX1049, 6 (recognizing that *Craiglow 2014* (EX1050), *Pieri* (EX1012), and *Jabbari 2015* (EX1021), among others, "provid[ed] a strong rationale for clinical develop of oral and/or topical JAK inhibitors for the treatment of AA").

Silverman disclosed Compound (I) as useful in "treating diseases and conditions… beneficially treated by ruxolitinib in a subject in need thereof, comprising the step of administering to the subject an effective amount." EX1002, 3:27−32, 20:57−61. Compound (I) would have been "a natural choice for further development," *Altana Pharma AG v. Teva Pharm. USA, Inc*., 566 F.3d 999, 1008 (Fed. Cir. 2009), in treating AA, as taught by *Xing* for ruxolitinib, at least because it was:

- specifically disclosed by *Silverman* (EX1002, 8:10−23);
- one of only three compounds specifically claimed in *Silverman* (*id*., 37:30−40); and
- reported to be "substantially more stable metabolically than ruxolitinib in both the CYP3A4 supersome assay and the HLM assay"[8] as well as superior to the other two specifically-claimed analogs of ruxolitinib (EX1045, 377, 416).

[8] Increased metabolic stability would have been expected since Compound (I) deuterated ruxolitinib's known "metabolic hot spots." EX1007, ¶¶151−158; *see also Incyte*, Paper 119 at 23−24, 31−32.

.

EX1007, ¶¶126−158; *Novartis Pharm. Corp. v. West-Ward Pharm. Int'l Ltd.*, 923 F.3d 1051, 1060 (Fed. Cir. 2019) ("[The] question [of motivation] was answered affirmatively when the district court found that a person of ordinary skill 'would have been motivated to pursue [the known compound] as one of several potential treatment options….'" (citation omitted)).

Moreover, given that *Xing* taught that AA was "beneficially treated by ruxolitinib" (EX1002, 20:57−61), a POSA would have been motivated to use its deuterated analog—particularly Compound (I)—to achieve at least equally efficacious treatment of AA. EX1007, ¶¶122−126. The POSA would have expected at least equal efficacy based on *Silverman*'s disclosure that

> because the size and shape of deuterium are essentially identical to those of hydrogen, replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity that contains only hydrogen.

EX1002, 2:15−20; EX1007, ¶¶ 47−56, 129−135. *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 973 (Fed. Cir. 2014) (motivation based on expectation of similar properties).

The POSA's expectation that deuterated Compound (I) would have had the same biological effects (*e.g.*, efficacy against AA) as its hydrogen-analog ruxolitinib—and hence the motivation to substitute—is also admitted in the '659

Patent and elsewhere by Patent Owner. *E.g.*, EX1001, 2:7−24; EX1011, 5 (Patent Owner's CEO stating that "[a]t Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'"); EX1051, 1 ("According to Roger Tung, president and [CEO] of Concert… 'We have demonstrated repeatedly in human clinical trials that deuterium has the potential to change the properties of a compound, such as absorption, distribution and toxicology, while retaining its original potency and selectivity.'").

The expectation was further reflected in the art as a whole, *e.g.*:

- "When deuterium is substituted into molecules in place of hydrogen, ***in most respects the deuterated compound is quite similar to the all-hydrogen compound***. Since the electron clouds of the atoms define the shape of a molecule, deuterated compounds have shapes and sizes that are ***very similar to their all-hydrogen analogs***." (EX1043, 68);
- "The molecular structures and pharmacologic activities of deuterated compounds, and even the structure and function of fully substituted enzymes are ***extremely similar to their all hydrogen analogs***.") (EX1052, 1);

- "***As expected***, the deuterated analogs of nintedanib remain in an almost equal inhibitory activity against the three kinases tested compared with its parent drug." (EX1053, 3);
- "CTP-499 (deuterium-modified HDX) is… structurally identical to the primary major active metabolite of pentoxifylline (HDX), except for the deuterium modification. ***These molecules have similar physical, chemical, and pharmacological properties; however, deuterium modification has been shown to stabilize the compound in vivo*** and as a result may enhance its antifibrotic and anti-inflammatory effects." (EX1054, 10);
- "Aside from their different pharmacokinetics, however, these deuterated compounds are ***virtually indistinguishable from their hydrogen equivalent drugs***…." (EX1011, 5).

Further, a POSA would have been motivated to use Compound (I) in place of ruxolitinib to treat AA by potential improvements in metabolic properties resulting from deuterium substitution at ruxolitinib's metabolic hot spots. EX1007, ¶¶153−157; *see also* EX1011, 3 ("The latest retro rage in the pharmaceutical world is deuterium substitution… firms large and small are banking on its potential to

improve existing drugs."). The motivation to use deuterated ruxolitinib for this reason was specifically addressed in *Silverman*:

> A potentially attractive strategy for improving a drug's metabolic properties is deuterium modification… replacing one or more hydrogen atoms with deuterium atoms…. In select cases, the increased bond strength imparted by deuterium can positively impact the ADME properties of a drug, creating the potential for improved drug efficacy, safety, and/or tolerability….
>
> Despite the beneficial activities of ruxolitinib, there is a continuing need for new compounds to treat the aforementioned diseases and conditions.

EX1002, 2:5–20, 3:19–21, 20:57–61; *see also* EX1007, ¶¶126−131; *Par Pharm., Inc. v. Novartis AG*, IPR2016-00084, Paper 73 at 16–19 (PTAB Jan. 11, 2018) (explaining that a desire to improve a known drug provides motivation to modify).

The motivation to use Compound (I) in place of ruxolitinib was further reflected in Concert's representations and the state of the art, which taught that deuterium had the potential to reduce the overall dose and/or frequency at which a drug is administered. For example:

- Deuterium substitution "offers a number of potential clinical benefits" including "improved therapeutic window," "Reduced C_{max}-driven side effects," "Improved efficacy convenience and compliance," "improved safety, tolerability and efficacy" (EX1034, 2);

- "[I]mprovement of half-life can do more than simply make a drug last longer. Increased half-life, if it translates to less frequent dosing, improves patient compliance and hence both efficacy and safety indirectly. Longer half-life should lead to decreased discontinuation effects (read, 'withdrawal') in many agents, again a safety improvement." (EX1033, 10);
- "[D]euteration can reduce the rate of systemic clearance resulting in a longer half-life. It can even maintain similar systemic exposure with decreased peak levels and increased trough levels. Finally, decreased pre-systemic metabolism results in higher bioavailability of unmetabolized drug, which means a smaller dosage can achieve the same exposure." (EX1053, 1–2);
- "The goal of such [deuterium substitution] strategies includes extension of elimination half-life, optimization of dose and dosing regimen…." (EX1044, 1);
- "Our approach to tramadol analogs took advantage of the primary kinetic isotope effect to slow CYP450-mediated metabolism. Replacing hydrogen with deuterium at metabolically active sites can result in a slower metabolism due to the reduced rate of cleavage of a

> C–D bond relative to a C–H bond. This approach has been shown to be effective for a number of pharmacological agents including amphetamine, butethal, and morphine." (EX1036, 1).

The motivation to use Compound (I) would have been reinforced by the POSA's understanding that ruxolitinib's properties made it an ideal candidate for improvement by deuteration. EX1007, ¶¶135−150; *Incyte*, Paper 119 at 22–23 ("ruxolitinib contained well-identified sites of oxidative metabolism in *in vivo* metabolism") (citation omitted); EX1055, 8 ("The primary metabolic pathways for [ruxolitinib] in humans… occur[s] on the cyclopentyl moiety."); *id*., 6. This expectation was amplified by the fact that Compound (I) deuterated ruxolitinib's metabolic "hot spots" and had shown improved *in vitro* metabolism over ruxolitinib. EX1007, ¶¶151−157; EX1034, 4–5; *Incyte*, Paper 119 at 23–24, 27. EX1045, 407, 416; *see also* EX1056, 1–2.

A POSA would have been further motivated to use Compound (I) in place of ruxolitinib based on the expectation that gains in metabolic stability were unlikely to be masked *in vivo* by metabolic switching (EX1007, ¶¶136−141; EX1057, 1–2), alternative routes of clearance (EX1007, ¶¶142−144; EX1058, 8; EX1059, 10), or the rate of blood flow relative to clearance (EX1007, ¶¶145−147; EX1058, 8; EX1059, 10). *Ni* also disclosed a flattened (lower C_{max}) and extended (longer $t_{½}$)

drug plasma concentration curve for ruxolitinib via an extended release formulation—the same profile that would have been reasonably expected with lower doses of Compound (I) due to its greater metabolic stability—that retained therapeutic efficacy while reducing side effects. *E.g.*, EX1006, [0005], [0008]–[0011], [0151]–[0163], Figs. 1–4; EX1007, ¶¶132−134. And, contrary to Patent Owner's previous assertions, "dose-limiting toxic side effects" did not teach away from "ADME modification" of ruxolitinib (*Incyte*, Paper 27 at 47 (PTAB July 2, 2018). EX1007, ¶¶148−150; EX1060, 1 ("All study doses of ruxolitinib were generally safe and well tolerated" with co-administration of CYP inhibitors); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738–39 (Fed. Cir. 2013) (dose-dependent side effects did not teach away from increased dose); *Incyte*, Paper 119 at 25–27 (same).

A POSA also would have been motivated to use at least 97% deuterium incorporation at the site of deuteration (EX1001, Claims 13, 17, 20) to maximize the potential benefit of deuterium substitution.[9] EX1007, ¶¶159−165. Reflecting this,

[9] The remainder of the claims only require the broader "at least 95% incorporation of deuterium" and would been obvious for the same reasons as the narrower 97% limitation. *See Comaper Corp. v. Antec, Inc.*, 596 F.3d 1343, 1350 (Fed. Cir. 2010)

Silverman taught that "a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of… at least 6466.7 (97% deuterium incorporation)." EX1002, 4:7−17. And in exemplary syntheses, *Silverman* used commercially available intermediates with greater than 97% deuterium incorporation. EX1002, 24:49−54, 28:16−22, 32:16−22; EX1007, ¶161. Consistent with *Silverman*, practice in the art shows that a POSA would have been motivated to use levels of deuterium incorporation over 97% to maximize the desired effect of inhibiting metabolism. EX1007, ¶¶162−164; EX1061, 1, 6 (Concert using 99.5% deuterium incorporation to "enhance[] pharmacokinetic properties" of boceprevir); EX1058, 1−2 (using >99% deuterium incorporation for the "pharmacokinetic application of deuterium isotope effects"); EX1052, 2 (99.7% isotopic purity in deuterated analogs of paroxetines).

Additionally, as demonstrated by these examples, a POSA would have been motivated to have any atom not designated as deuterium at its natural isotopic

("A broader independent claim cannot be nonobvious where a dependent claim stemming from that independent claim is invalid for obviousness.") (citation omitted)).

abundance (EX1001, claim 7). EX1007, ¶¶166−169; EX1002, 8:4−42, 9:28−30, 12:20−21.

b. Motivation to Optimize Dosing Regimen

A POSA would have been motivated with a reasonable expectation of success to use Compound (I) in the treatment of AA with the claimed dosing regimen, *i.e.*, orally administered (Claims 3, 16, 19) tablets (Claim 4) of 16 mg/day or 24 mg/day (Claims 1−7, 9−21) QD (Claim 5), 8 mg BID (Claims 6, 9−10), and 12 mg BID (Claims 11−12), with 8 and 12 mg pharmaceutical compositions (Claim 8).

i. Oral Doses of 16 and 24 mg/day Administered in Tablet Form

The claimed 16 and 24 mg/day doses (1) fall within the narrow range disclosed by *Silverman* and *Ruxolitinib Prescribing Information*; (2) were suggested based on the strong clinical response seen at 30 and 40 mg per day of ruxolitinib; (3) fall within a narrow range suggested by the dose-response relationships for ruxolitinib and closely-related baricitinib; and (4) were suggested by the potential for reduced dosing due to deuterium-inhibited metabolism. EX1007, ¶¶170−204.

First, *Silverman* disclosed that "an effective amount of a compound of this invention"—which includes Compound (I)—"can range from… from 10 mg to 25 mg [and] from 10 mg to 20 mg…." EX1002, 20:9–15. *Silverman* further taught that "guidance for selecting an effective dose can be determined by reference to the

prescribing information for ruxolitinib" (*id*., 20:25–27) and *Ruxolitinib Prescribing Information*, the prescribing information for ruxolitinib, disclosed total daily doses of 5 to 50 mg and titrating doses up or down "based on safety and efficacy." (EX1004, 4–6). EX1007, ¶¶170−177.

As the Federal Circuit has explained, "[o]rdinarily, 'where there is a range disclosed in the prior art, and the claimed invention falls within that range,'" as is the case here, "there is a presumption of obviousness." *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372–73 (Fed. Cir. 2011) (quoting *Iron Grip Barbell Co. v. USA Sports, Inc.*, 392 F.3d 1317, 1322 (Fed. Cir. 2004)). The CAFC has repeatedly found doses obvious where they fell within similarly narrow (and even broader) ranges. *E.g.*, *Warner Chilcott Co. v. Teva Pharm. USA, Inc.*, 642 F. App'x. 996, 999 (Fed. Cir. 2016) (100 mg obvious over range of 20−175 mg); *Tyco Healthcare*, 642 F.3d at 1373, 1377 (7.5 mg obvious over range of 5−15 mg); *see also In re Sebela Patent Litig.*, Civ. A. No. 14-6414 (CCC) (MF) 2017 WL 3449054, at *24–26 (D.N.J. Aug. 11, 2017) (7.5 mg obvious over range of 0.9−20 mg); *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, Civ. A. No. 14-882-LPS 2017 WL 1199767, at *32–33 (D. Del. Mar. 31, 2017) (10 mg BID obvious over range of total daily dose of 20–40 mg), *aff'd*, 903 F.3d 1310 (Fed. Cir. 2018), *cert. denied*, 140 S. Ct. 111 (2019).

The POSA's motivation to rely on the *Ruxolitinib Prescribing Information* is reflected in the state and level of skill in the art. As Dr. Shapiro explains, off-label prescribing—specifically in the context of AA—is guided by the doses at which a drug is prescribed for its approved indications. EX1009, ¶¶32, 35–43; EX1062, 2–3; EX1063, 4; EX1064, 8; EX1065, 6. Indeed, Dr. Shapiro prescribed, and continues to prescribe, tofacitinib (a JAK inhibitor) for AA within the ranges of its FDA-approved doses. EX1009, ¶¶35–36; EX1066, 1; *see also* EX1067, 1; EX1068, 1.

The POSA's motivation to titrate individual AA patients within this 5 mg/day (5 mg QD) to 50 mg/day (25 mg BID) range was further evidenced by *Silvestri*, which reported on treatment of AA starting with 5 mg/day of ruxolitinib that began in March 2015, prompted by "first reports [on the web] on the possible usefulness of Ruxolitinib to treat AA." EX1017, 31; *see also* EX1009, ¶43; EX1007, ¶177; *Yeda Research*, 906 F.3d at 1041 ("[R]eliance on Khan 2009 is permissible, as it supports and explains [petitioner's expert's] position that a POSITA would have thought less frequent dosing worthy of investigation as of the priority date."); *Thomas & Betts Corp. v. Litton Sys*., *Inc.*, 720 F.2d 1572, 1580−81 (Fed. Cir. 1983) ("unpublished internal criteria" [were] "properly used as indicators of the level of ordinary skill in the art to which the invention pertained").

Second, a POSA would have expected efficacy with total daily doses of Compound (I) lower than 30 mg/day since 30 mg/day and 40 mg/day of ruxolitinib provided "durable" and "near complete" hair regrowth (*supra*, § III.A) and ruxolitinib had a proportional dose-exposure profile. EX1004, 7 (§ 12.3) ("[m]ean ruxolitinib C_{max} and total exposure (AUC) increased proportionally"); EX1059, 6; *see also* EX1007, ¶¶178–180; EX1009, ¶49. A POSA also would have preferred to use the lowest dose and dosing frequency sufficient to achieve effective therapy. EX1007, ¶180; EX1009, ¶¶33–34, 44, 46–47. Thus, a POSA would have been motivated to use Compound (I) at doses lower than 30 mg, including the claimed 16 mg and 24 mg doses per day. EX1007, ¶¶170–180; EX1009, ¶¶31–43; *see also Titanium Metals Corp. of Am. v. Banner*, 778 F.2d 775, 783 (Fed. Cir. 1985) ("The proportions are so close that prima facie one skilled in the art would have expected them to have the same properties.").

Third, the claimed doses of Compound (I) would have been obvious from available dose-response data, which provided a reasonable expectation that total daily doses of ruxolitinib as low as ~6–7 to ~30 mg/day would provide clinically effective JAK inhibition that would at least "regrow[] hair, prevent[] further hair loss, or diminish[] the rate of hair loss" (EX1001, 5:66–6:5). EX1007, ¶¶181–197; EX1009, ¶15; EX1069, 12, 18–19 ("exposure-response relationships [] can guide

therapy, suggest efficacy or safety, dose and dosing intervals"); EX1070, 2. Given that the "PK/PD relationship"[10] and the "[e]xposure profile responsible for efficacy (e.g., AUC vs C_{max} effect)" will "not generally exhibit a clinically measurable change when switching from a C−H bond to a C−D bond" (EX1033, 8–9), a POSA also would have reasonably expected that Compound (I) would treat AA at doses as low as ~6–7 mg/day. EX1007, ¶¶178–179.

More specifically, in selecting doses for Compound (I), a POSA also would have considered the AA data for baricitinib,[11] where 7 mg QD resulted in "remarkable improvement in the patient's AA." EX1021, 3. As Dr. Patterson explains, ~21–23 mg/day of ruxolitinib would have been reasonably expected to provide similar levels of JAK inhibition and AA efficacy, based on comparing the

[10] Pharmacokinetic ("PK")/Pharmacodynamic ("PD").

[11] Baricitinib dose-response relationships would have been considered because baricitinib is structurally similar to ruxolitinib (EX1007, ¶183), has the same JAK 1/2 inhibition mechanism of action (EX1071, 9; EX1072, 1), also provides dose proportional exposure (*id*., 6), and had been studied in AA and similar autoimmune diseases (EX1021, 1; EX1073, 1; EX1074, 1). EX1007, ¶¶182–195; EX1075, 2, 4–5; EX1076, 10–12; EX1077, 5; (EX1078, 16; *see also* EX1079; EX1016, 8).

ruxolitinib:baricitinib IC_{50}-weighted drug concentrations. EX1007, ¶¶182–191, pp. 136–142; EX1080, 2, 5; EX1081, 5. A POSA thus would have reasonably expected "remarkable improvement"—*i.e.*, results equivalent to those seen with 7 mg/day baricitinib—with ~21–23 mg/day ruxolitinib or Compound (I) as well as efficacy at lower doses. EX1007, ¶192.

Data for baricitinib in AA's "sister diseases" (EX1005, 12:43–53) rheumatoid arthritis (RA) and psoriasis (PS), which like AA are mediated by the JAK/STAT pathway and characterized by a prominent IFN-γ signature, would have reasonably suggested ~6–7 mg/day as the lower end of the AA effective range.[12] EX1007, ¶¶193−194; *see also* EX1014, 1–2; EX1050, 1. The minimum effective dose of baricitinib (*i.e.*, the dose showing some level of clinical efficacy) in both RA and PS

[12] *See, e.g.*, EX1005, 17:10–12 ("Indeed positive studies in any one of these autoimmune diseases [RA and PS] that share a common cause can serve as the basis for common treatments."); EX1082, 13 ("Studies in etiologically or pathophysiologically related conditions, or studies of a symptom common to several diseases (e.g., pain) can support each other…."); EX1050, 1 ("JAK inhibition has myriad effects on T-lymphocytes, and therefore it is not surprising that this medication may be useful in the treatment of many inflammatory diseases.");

patients was ~2 mg, which a POSA would have reasonably expected to equate to ~6–7 mg/day of ruxolitinib. EX1073, 4; EX1074, 5; EX1007, ¶¶193−194; *see also* EX1079. The reasonable expectation of clinical efficacy at ~6–7 mg/day ruxolitinib is consistent with, and is reinforced by, ruxolitinib's reported clinical effects at ≤10 mg/day in myelofibrosis patients (EX1083, 3–4)[13] and *Ruxolitinib Prescribing Information*'s direction to use 5 mg/day ruxolitinib in certain patient populations (EX1004, 5 (§§ 2.4, 2.7)). EX1007, ¶¶195−196.

Thus, guided by dose-response data for ruxolitinib and baricitinib, a POSA would have reasonably expected that doses of ruxolitinib and Compound (I) of ~6–7 to ~30 mg/day would treat AA. EX1007, ¶¶181−197. Selecting appropriate doses within this range would have been a matter of routine optimization. EX1007, ¶197; *see, e.g.*, *Warner Chilcott*, 642 F. App'x. at 999; *Tyco Healthcare*, 642 F.3d at 1372−73.

Fourth, the potential for improved *in vivo* metabolic stability, as was already seen *in vitro* (*supra*, §§ III.B, V.A.2.a), would have further motivated using Compound (I) to treat AA at lower doses and frequencies than those clinically

[13] EX1083 (Verstovsek 2014), 3–4 (reporting a 10.4% decrease in spleen volume at ≤10 mg/day of ruxolitinib compared with a 9.2% increase in the placebo group).

demonstrated in *Xing* and *Pieri* with ruxolitinib. EX1007, ¶¶198−203. Indeed, achieving equivalent efficacy with lower doses and/or frequencies was one of the primary reasons for inhibiting metabolism with deuterium. *Supra*, § III.B; EX1007, ¶¶51−53; *see also* EX1084, 1 ("Once-daily dosing of 50 mg of CTP-730 [deuterated apremilast]… demonstrated similar steady-state exposure to historical data for 30 mg of apremilast administered twice daily."); EX1085, 1 ("In this Phase 1 trial, CTP-656 [deuterated Kalydeco] provided several advantages compared to Kalydeco including a reduced rate of clearance, longer half-life, substantially increased exposure and greater plasma levels at 12 and 24 hours."); EX1086, 1 ("The equipotent dose of D_3-L-DOPA, for example, was estimated to be 60% of L-DOPA"); EX1053, 1 ("[D]ecreased pre-systemic metabolism results in higher bioavailability of unmetabolized drug, which means a smaller dosage can achieve the same exposure.").

Moreover, Ruxolitinib Prescribing Information taught increased drug exposure and dose reduction where of ruxolitinib where metabolism was inhibited, as would be the case with deuteration. *E.g.*, EX1004, 5−7 (*e.g.*, §§ 2.7, 7.1); EX1007, ¶¶201−203. Based on this, a POSA would have been motivated to reduce the effective doses of *Xing* and *Pieri* and arriving at the claimed doses of 16 mg and 24 mg of Compound (I) would have required no more than routine optimization.

E.g., EX1007, ¶¶201−204; *Titanium Metals*, 778 F.2d at 783; *Warner Chilcott*, 642 F. App'x. at 999; *Tyco Healthcare*, 642 F.3d at 1372−73.

Finally, it would have been obvious to provide these AA treatments using orally administered tablets, which was taught by *Silverman*, *Xing*, and *Ruxolitinib Prescribing Information.* EX1002, 16:64−17:7, 17:19−25, 17:29−42; EX1003, 10; EX1004, 4, 6 (*e.g.*, § 2.9), 7 (*e.g.*, § 11). Given that "formulations issues" and "delivery options" "*will not generally exhibit a clinically measurable change when switching from a C−H bond to a C−D bond*" (EX1033, 8−9), a POSA would have been motivated to use Compound (I) with oral tablets as was used for ruxolitinib in *Xing* and *Ruxolitinib Prescribing Information*. EX1007, ¶¶215−219, ¶¶231−234; *see also* EX1011, 5 ("The easiest way to find a drug is to start with one.").

ii. QD and BID Dosing

A POSA also would have been motivated to administer the claimed doses QD and BID. EX1007, ¶¶205−209; EX1009, ¶¶44−47. These common frequencies, taught by the Ground 1 References, represented "a finite number of identified, predictable solutions." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1350 (Fed. Cir. 2009); *see also In re Copaxone Consol.*, 906 F.3d 1013, 1026 (Fed. Cir. 2018) ("[T]hese still represent a limited number of discrete permutations…. [T]he prior art clearly indicated that less frequent doses should be

explored.…"); *Boehringer Ingelheim Int'l GMBH v. AbbVie Biotech. Ltd.*, IPR2016-00408, Paper 46 at 23−34 (PTAB July 6, 2017) (holding claims to biweekly dosing obvious over reference disclosing weekly dosing), *aff'd sub nom. AbbVie Biotech., Ltd. v. United States*, 789 F. App'x 879 (Fed. Cir. 2020).

Xing specifically disclosed treating AA using BID dosing and would have motivated using Compound (I) at the same frequency already shown effective for AA with ruxolitinib. EX1003, 10; EX1007, ¶¶205−209. *Silverman* and *Ruxolitinib Prescribing Information* also taught, and would have motivated, administering Compound (I) BID. EX1002, 20:16−18; EX1004, 4−6 (disclosing 5, 10, 15, 20, and 25 mg BID dosing); EX1009, ¶45.

A POSA would have been motivated to administer Compound (I) less frequently, *i.e.*, QD taught by *Silverman* and *Ruxolitinib Prescribing Information*, at least to improve patient compliance. EX1009, ¶¶46−47; EX1002, 20:15−18; EX1004, 5 (*e.g.*, §§ 2.4, 2.7) (disclosing 5 mg QD dosing following treatment interruption, maintaining 5 mg QD based on platelet count, and stable doses of 5 mg QD where metabolism is inhibited); *Hoffmann-La Roche Inc. v. Apotex Inc*., 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance…."). This

motivation is reflected in *Ni*, which taught the desirability of "reducing the number of doses required to achieve a therapeutic effect." EX1006, [0005].

A POSA would have been further motivated to reduce the dosing frequency from BID to QD based on deuterium's potential to slow metabolism. EX1007, ¶208. Like reduction in overall dose, reducing the frequency of administration (*e.g.*, to improve patient compliance) was a common goal for, and practiced with, deuterated drugs. *Supra*, § III.B; EX1007, ¶¶51−53; EX1043, 70 ("D8-linezold may have prolonged exposure enabling a once-daily dosing regimen."); EX1041, 2 ("Deutetrabenazine is also dosed twice instead of three times daily…. Ivacaftor is dosed twice daily, whereas [deuterated ivacaftor] can be dosed just once a day."). This motivation would have been reinforced by *Ni*'s disclosure of clinically effective JAK inhibition with QD dosing where the drug plasma concentration of ruxolitinib was flattened (lower C_{max}) and extended (longer $t_{½}$), as would also have been expected for lower doses of Compound (I). *E.g.*, EX1006, [0008]−[0011], [0151]−[0163], Figs. 1−4; EX1007, ¶¶132−134.

iii. Phosphate Salt

A POSA would have been motivated to administer Compound (I) as a phosphate salt at doses of 10.5 mg and 15.8 mg (Claims 10, 12), which correspond to 8 mg and 12 mg of Compound (I) free base together with the additional phosphate

salt mass. EX1001, 17:15–18:13; EX1007, ¶¶210−214. A POSA would have been motivated to use the phosphate salt form, disclosed for Compound (I) in *Silverman*,[14] at least because *Ruxolitinib Prescribing Information* showed phosphate salt to provide FDA-approved safety and efficacy with ruxolitinib and "salt form" would "*not generally exhibit a clinically measurable change when switching from a C−H bond to a C−D bond*." EX1033, 8. Because phosphate worked for ruxolitinib as known from *Ruxolitinib Prescribing Information*, a POSA would have been motivated to use the phosphate salt of Compound (I) due to the expectation of obtaining the same physical properties as the FDA-approved Jakafi® product. EX1007, ¶213; *see also Pfizer, Inc. v. Apotex, Inc*., 480 F.3d 1348, 1363–64, 1372 (Fed. Cir. 2007) (finding specific salt form obvious over disclosure of fifty-three pharmaceutically acceptable salts).

c. Pharmaceutical Composition Claim 8

The pharmaceutical composition of Claim 8, comprising a pharmaceutically acceptable carrier or diluent and 8 mg or 12 mg of at least 95% deuterium-incorporated Compound (I), would also have been obvious over the Ground 1

[14] EX1002, 4:62–5:8; *see also id*. at claim 7 (claiming Compound (I) "or a pharmaceutically acceptable salt").

References. EX1007, ¶¶225−230; *see also infra*, § VI. There would have been motivation for such compositions at least because they fall within the narrow conditions of *Silverman* and would have been reasonably expected to treat AA. EX1007, ¶¶226−227; *supra*, §§ V.A−V.A.2.b.i; EX1087, 7.

For example, *Silverman* disclosed "pharmaceutical compositions comprising an effective amount of a compound of Formula I"—which include Compound (I)[15]—"or a pharmaceutically acceptable salt of said compound… [and] a pharmaceutically acceptable carrier." EX1002, 16:23−27; *see also id*., 18:9−48, 19:65−67, 20:28−33, 37:44−45 ("A pharmaceutical composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier."). These effective amounts included the narrow ranges of "5 mg to 10 mg" and "10 mg to 20 mg," which encompassed the claimed amounts. EX1002, 19:65−20:18; EX1007, ¶227. Suitable pharmaceutically acceptable carriers and diluents are disclosed in both *Silverman* for Compound (I) and in *Ruxolitinib Prescribing Information* for

[15] As described above in § VI, *infra*, Compound 111 is encompassed within *Silverman*'s Formula I.

ruxolitinib. [16] EX1002, 16:32−45, 17:29−35 (*e.g.*, lactose, cellulose-based substances, colloidal silica); EX1004, 7 (§ 11) ("ruxolitinib phosphate… together with microcrystalline cellulose, lactose monohydrate… colloidal silicon dioxide, sodium starch glycolate… and hydroxypropyl cellulose"); *see also* EX1001, 15:19−33.

Administration of the obvious doses of 8 mg and 12 mg of Compound (I) for treatment of AA (*see supra*, § V.A.2.b.i) using pharmaceutical compositions comprising 8 or 12 mg of the active Compound (1) (as opposed to, *e.g.*, eight separate 1 mg compositions) would have been obvious at least for patient convenience. EX1007, ¶229; EX1009, ¶44; EX1048, 386. It was also consistent with *Ruxolitinib Prescribing Information*, which provides individual tablets containing the appropriate amount of ruxolitinib for each administration. EX1004, 7 (*e.g.*, § 11); EX1007, ¶229. And a POSA also knew from *Ruxolitinib Prescribing Information* that tablets within the 5−25 mg range could be readily formulated and

[16] It would have been obvious to use the ruxolitinib excipients with Compound (I) because the art taught that, like salt selection, "[f]ormulation issues" "*will not generally exhibit a clinically measurable change when switching from a C−H bond to a C−D bond*." EX1033, 8.

reasonably expected the same for Compound (1). EX1004, 4, 7 (*e.g.*, § 11); EX1006, [0124]; EX1007, ¶228.

Thus, especially given the obviousness of 8 mg and 12 mg BID doses of Compound (I) for treatment of AA (*supra*, §§ V.A.2.a−V.A.2.b), a POSA would have been motivated to prepare the claimed pharmaceutical formulations comprising Compound (I) and a pharmaceutically acceptable carrier or diluent in doses of 8 mg and 12 mg. EX1007, ¶¶225-230.

3. There Would Have Been a Reasonable Expectation of Success for the Claimed Methods and Formulation

In addition to the reasonable expectation of success underlying the motivations discussed above, a POSA would have had a reasonable expectation of success in achieving claimed methods and compositions based on the Ground 1 References in view of the state of the art. *See supra*, § III; EX1007, ¶¶235−246.

a. Compound (I) Would be Effective to Treat AA

Orally administered tablets of ruxolitinib phosphate were known to effectively treat AA in humans. *Supra*, § III.A; EX1003, 10; EX1088, 13; EX1012, 6; EX1031, 9; EX1009, ¶¶19−28; EX1007, ¶¶22−37. A POSA would have expected that orally administered tablets of Compound (I) phosphate—which differs structurally from ruxolitinib only in the replacement of eight hydrogens with deuterium—would likewise have been effective in treating AA in humans. EX1007, ¶¶235−239;

EX1009, ¶¶48−51; EX1002, 2:15−20 ("replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity of the drug as compared to the original chemical entity"); EX1038, 5 ("[N]ot only is the replacement of one or a few hydrogens in a drug molecule by deuterium the smallest structural change that can be made but also such a change will have negligible steric consequences or influence on physicochemical properties…."); *see also supra*, § V.A.2.a.

The expectation would have applied equally where each deuterium in Compound (I) has an isotopic purity of least 97% and all other atoms are present at their natural isotopic abundance. EX1007, ¶¶164, 235. Any level of deuterium incorporation less than 100% would simply mean that some molecules are even more similar to ruxolitinib, which treated AA. EX1007, ¶ 49−51, 55−56, 168. Likewise, the expectation of similar properties applies to Claim 7's "any atom not designated" limitation, which simply means that all other atoms are the same as ruxolitinib. EX1007, ¶¶166−169.[17]

[17] A POSA would have reasonably expected to synthesize and formulate Compound (I) based at least on *Silverman*'s disclosure of the same. EX1002, 12:22−26

b. Compound (I) Would Have Been Expected to Treat AA at the Claimed Doses and Dosing Frequencies

The Ground 1 References and the state of the art (*e.g.*, *supra*, § III) demonstrate that a POSA would have had a reasonable expectation of success for treating AA with Compound (I) at the claimed doses and frequencies, including doses of 16 mg and 24 mg administered QD or BID and phosphate equivalents (10.5 or 15.8 mg) administered BID. *See, e.g.*, *supra*, § V.A.2.b; EX1007, ¶¶240−244; EX1009, ¶¶48−51. The expectation would have been high, given that the claimed "treating a hair loss disorder" requires no more than "regrowth of hair, prevention of further hair loss, or diminishing the rate of hair loss." EX1001, 5:66−6:5; *supra*, § IV.E.2.

First, there would have been a reasonable expectation of success as the claimed doses fall within narrow ranges of 5 to 25 mg/day for Compound (I) taught by *Silverman* and 5 to 50 mg/day taught by *Ruxolitinib Prescribing Information* for ruxolitinib. E.g., *supra*, § V.A.2.b.i; *Tyco Healthcare*, 642 F.3d at 1372−73 ("Ordinarily, 'where there is a range disclosed in the prior art, and the claimed

(synthesis); *id*. at 16:22−20:50 (formulation)); EX1007, ¶160−161, 245; *see also* EX1001, 14:4−8 (relying on *Silverman* for synthesis of Compound (I)).

invention falls within that range, there is a presumption of obviousness'" (citations omitted).

Second, ruxolitinib was highly effective in AA patients at both 30 mg/day (15 mg BID) and 40 mg/day (20 mg BID). *Supra*, §§ III.A; EX1009, ¶49. Given that a total daily dose of 30 mg resulted in durable hair regrowth in AA, and that doses of as low as 5−10 mg/day were taught to be effective for treatment via JAK1/2 inhibition, a POSA would have reasonably expected that doses of Compound (I) in the range of ~10 mg/day to 50 mg/day would at least have provided "regrowth of hair, prevention of further, hair loss, or diminishing the rate of hair loss." (EX1001, 5:66−6:5). EX1009, ¶¶48−51; EX1007, ¶¶179−180, 195−197.

Third, the POSA's expectation that ~10 to 50 mg/day of Compound (I) would treat AA also followed from the expected dose-response relationships for ruxolitinib and baricitinib. EX1007, ¶241; *supra*, § V.A.2.b.i. This reasonable expectation of success was reinforced by the fact that total daily doses of ≤10 mg ruxolitinib (or equivalent doses of baricitinib) resulted in a clinical response to JAK inhibition in MF, RA, and PS patients and that Compound (I) would have been reasonably expected to be at least equally effective. EX1007, ¶¶195−197; EX1009, ¶50; EX1033, 8−9; *see also supra*, § V.A.2.b.i.

The expectation of treating AA at the claimed doses was even higher for Compound (I) as deuterium was expected to slow the metabolism of ruxolitinib. EX1007, ¶242; *see also supra*, III.B. Such an expectation was consistent with the disclosures of the *Silverman File History*—where the *in vitro* data showed Compound (I) was more metabolically stable than ruxolitinib—*Ruxolitinib Prescribing Information*, which taught a reduction in dose where metabolism is slowed for ruxolitinib, and the numerous deuterated drugs that showed equal efficacy at doses lower than their parent compounds. *Supra*, §§ III.B, V.A.2.a.

The reasonable expectation of success at the claimed dose regimens also would have applied to the equivalent phosphate doses of 10.5 mg and 15.8 mg. EX1007, ¶¶212−213, 245. FDA-approved ruxolitinib had shown success in AA administered as a phosphate salt; given that "salt form selection" was not expected to change with deuterium (EX1033, 8−9), a POSA would have expected that the phosphate salt of Compound (I) would treat AA. EX1007, ¶¶49, 245; *see also supra*, § V.A.2.b.iii.

Likewise, there was a reasonable expectation that both QD and BID administration of Compound (I) at the claimed doses would have treated AA for the same reasons a POSA would have been motivated to use these dosing intervals. EX1007, ¶¶243−244; *see also supra* § V.A.2.b.ii.

B. Ground 2: Claims 1-21 Would Have Been Obvious Over *Silverman* in View of *Christiano* and *Ni* Obviousness

As shown in the claim chart in § V.C, *infra*, all limitations of claims 1–21 are also taught by *Silverman* in view of *Christiano* (EX1005) and *Ni* (EX1006). As explained further in Sections V.B.1−V.B.3 below, a POSA would have been motivated to combine *Silverman*'s teaching of Compound (I)—deuterated ruxolitinib—with *Christiano*'s use of ruxolitinib for AA, further guided by *Ni's* dosing and forms of administration, to obtain an at least equally efficacious alternative treatment for AA and by the potential improvements on ruxolitinib offered by deuteration. *Infra*, §§ V.B.1−V.B.3.

1. Substituting Orally Administered Tablets of Compound (I) to Treat AA Would Have Been Obvious

As explained, *Silverman* disclosed Compound (I) and the claimed levels of deuterium incorporation. *Supra*, §§ V.A. As also described, a POSA would have been motivated to select Compound (I) from *Silverman* to "treat[] a disease that is beneficially treated by ruxolitinib in a subject in need thereof," such as AA, as it was (1) deuterated at ruxolitinib's "metabolic hotspots," (2) amongst the compounds showing the greatest potential for improvement in metabolic stability, and (3) one of three compounds specifically claimed by *Silverman*. EX1002, 20:51−62; EX1007, ¶251; *supra*, §§ V.A.2, V.A.2.a.

A POSA would have been motivated to combine *Silverman*'s Compound (I)—a JAK inhibitor—with *Christiano* to treat AA in view of *Christiano's* disclosure of using ruxolitinib [18] specifically and JAK inhibitors generally to treat AA. EX1005, 2:1−9, 4:21−12:39, 113:1−6, 271:30−39; EX1007, ¶¶248−250; *see also supra*, §§ V.A.2, V.A.3.a. A POSA would have been further motivated to combine the references by *Silverman*'s disclosure that Compound (I) was useful for diseases "beneficially treated by administering an inhibitor of Janus-associated kinase with selectivity for subtypes 1 and 2 (JAK1/JAK2)… [and] beneficially treated by ruxolitinib." EX1002, 3:27−32, 20:57−61. And a POSA would have been still further motivated to use Compound (I) in place of ruxolitinib in *Christiano* due to the potential for improved metabolic characteristics offered by deuterium. *Supra*, § V.A.3.a; EX1007, ¶¶44−53, 250−251 (citing, *inter alia*, EX1048).

2. The Claimed Dosing Regimen Would Have Been Obvious

A POSA also would have been motivated to treat AA using orally administered tablets of Compound (I) as claimed at least because these elements

[18] *Christiano* refers to ruxolitinib as "INCB018424." EX1005, 36−55 (showing ruxolitinib is "INCB018424"); EX1007, ¶26, n. 21.

were taught to be effective for ruxolitinib, and "formulations issues" and "delivery options" would not have been expected to be affected by the deuterium substitution in Compound (I). EX1033, 8−9; EX1007, ¶¶49, 260−263; *see also supra*, § V.A.2.b−V.A.2.b.iii; *infra*, § V.C. For example, *Ni* disclosed oral administration of tableted ruxolitinib to humans (EX1006, [0003], [0098], [0120]–[0124], [0127], [0151]−[0164]) and *Christiano* disclosed these limitations for ruxolitinib to treat AA (EX1005, 78:37–39, 94:15−18, 100:56−61, 101:50−55).

The claimed daily doses of 16 mg and 24 mg would have been presumptively obvious over *Silverman*'s disclosed range of 5−25 mg. *Supra*, § V.A.2.b.i; EX1007, ¶¶254−256; *see also* EX1005, 103:51−56 ("Toxicity and therapeutic efficacy of therapeutic compositions of the present invention can be determined by standard pharmaceutical procedures…."). The claimed doses fall within, and would have been further obvious from, *Ni*'s disclosure that "ruxolitinib phosphate can be obtained commercially in 5, 10, 15, 20, and 25 mg doses as the drug product Jakafi® (ruxolitinib phosphate (tablets)) (NDA no. N202192)." EX1006, [0124], [0137]-[0163]. *Ni*'s disclosure would have been particularly relevant in view of *Silverman*'s direction that "guidance for selecting an effective dose can be determined by reference to the prescribing information for ruxolitinib" (EX1002, 20:25−27). *Supra*, §§ V.A.2.b.i, V.A.3.b.

Moreover, as discussed, the motivation and expectation of success for the claimed doses would have been bolstered by (1) the strong hair growth seen at 30 and 40 mg/day of ruxolitinib, which suggested lower doses would have been effective; (2) the dose response data for ruxolitinib and baricitinib, which would have suggested that lower and/or fewer doses would be effective; and (3) the expected effect of deuterium in slowing ruxolitinib's metabolism and thus providing equivalent efficacy of Compound (I) at lower doses and/or frequencies. *Supra*, §§ V.A.2.b.i, V.A.3.b; EX1007, ¶256; EX1009, ¶¶31−51.

A POSA also would have been motivated and had a reasonable expectation of success to administer the claimed daily doses using QD and BID dosing frequencies. EX1007, ¶¶257−258; EX1009, ¶¶44−47; *supra*, §§ V.A.2.b.ii, V.A.3.b. Notably, *Christiano* taught QD and BID dosing for JAK inhibitors, which would have included and provided motivation for QD and BID dosing of Compound (I), a JAK inhibitor. EX1005, 93:40−44. *Silverman* and *Ni* also disclosed, and would have motivated, using QD and BID dosing. EX1002, 20:15−18; EX1006, [0147], [0157]; EX1007, ¶¶257−258. Indeed, *Ni* disclosed "a need for new and improved formulations of ruxolitinib that not only mitigate adverse side-effects in patients, but still achieve therapeutic efficacy, and also facilitate administration of the drug, such as by reducing the number of doses required to achieve a therapeutic effect," and

taught the therapeutic efficacy with reduced side effects of sustained release QD ruxolitinib where (relative to immediate release ruxolitinib) the drug plasma concentration is flattened (lower C_{max}) and extended (longer $t_{½}$) as would have been expected for Compound (I). *E.g.*, EX1006, [0005], [0008]−[0011], [0151]−[0163], Figs. 1−4; EX1007, ¶¶132−134; *see also supra*, §§ V.A.2.b.ii, V.A.3.b.

The motivation and reasonable expectation of success would also have been reflected in the art, which showed that ruxolitinib BID successfully treated AA. EX1007, ¶248; EX1009, ¶¶19−27; *supra*, § III.A. Knowing BID provided highly effective treatment, a POSA would have been motivated to use the same effective dosing frequency and also less frequent dosing (*i.e.*, QD) at least to improve patient compliance. *See Hoffmann-La Roche*, 748 F.3d at 1329; EX1006, [0005]; EX1009, ¶¶33−48; *see also supra*, § V.A.2.b.ii, V.A.3.b.

A POSA would have been motivated to administer Compound (I) as a phosphate salt at doses of 10.5 and 15.8 mg BID. EX1007, ¶259; *supra*, §§ V.A.2.b.iii, V.A.3.b. *Silverman* disclosed Compound (I) and taught the use of its compounds as phosphate salts. EX1002, 5:6–24; *see also KSR*, 550 U.S. at 417; *Pfizer*, 480 F.3d at 1363–64, 1372; *Ex Parte Francois Guyon*, No. 2011-011455, 2013 WL 5496996, at *1–3 (PTAB Sept. 27, 2013). *Ni* disclosed that "ruxolitinib phosphate can be obtained commercially." EX1006, [0124]. As "salt form" would

not have been expected to be effected by deuteration (EX1033, 8), a POSA would have been motivated to use the same salt as shown to work for FDA-approved ruxolitinib. EX1007, ¶259; *see also supra*, §§ V.A.2.b.iii, V.A.3.b.

A POSA also would have reasonably expected that the use of Compound (I) as claimed would at least "treat" AA as defined by the '659 Patent. EX1007, ¶¶248−250; *see also* EX1009, ¶¶48−51; *supra*, § V.A.3. *Christiano*'s successful use of ruxolitinib and tofacitinib to treat AA in mice models (*e.g.*, EX1005, 6:38−48, 7:36−39) and the art as whole—which showed effective treatment of AA with ruxolitinib, tofacitinib, and baricitinib in human studies (*supra*, § III.A; EX1068, 1; EX1021, 2, 4)—demonstrated there would have been more than a reasonable expectation that ruxolitinib would treat AA. EX1007, ¶¶252−253; EX1009, ¶¶31−43, 48−51; *supra*, § V.A.3. *Silverman*'s disclosure that "replacement of hydrogen by deuterium would not be expected to affect the biochemical potency and selectivity" of Compound (I) (EX1002, 2:15−20) and the state of the art (*supra*, § III.B) would have provided a POSA with the expectation that Compound (I) would likewise be effective in treating AA. EX1007, ¶¶47−53; *supra*, § V.A.3. Thus, there would have been a reasonable expectation of success that Compound (I) as claimed would treat AA. EX1007, ¶¶235−239, 248; *supra*, § V.A.3.

3. A Pharmaceutical Composition Comprising Compound (I) Would Have Been Obvious

The pharmaceutical composition of Claim 8 also would have been obvious over the Ground 2 References. EX1007, ¶261. There would have been motivation for such dosage forms at least because they fall within the general conditions of *Silverman* and because they would have been reasonably expected to be useful to treat AA, as discussed above. EX1007, ¶¶262−263; *supra*, §§ V.B−V.B.2; *see also supra*, § V.A.2.c.

Silverman disclosed and specifically claimed pharmaceutical compositions comprising Compound (I). EX1002, 16:23−27, 37:44−45, 38:43−44. The "effective amount" of Compound (I) comprising these compositions (EX1002, 16:23−27) included narrow ranges encompassing the claimed dosage amounts. EX1002, 19:65−20:18; EX1007, ¶¶254−255; *supra*, § V.A.2.c. Selecting the dosages within these ranges would have been a matter of routine optimization. *See supra*, §§ V.A.2.b.i, V.B.2.

Ni disclosed the use of pharmaceutical compositions containing ruxolitinib with carriers and/or diluents. EX1006, [0120]−[0124]; EX1007, ¶262. As the art taught that "[f]ormulation issues" would not have been expected to be effected by deuteration (EX1033, 8−9), a POSA would have been motivated with a reasonable

expectation of success to use the same ruxolitinib formulations of *Ni* for deuterated ruxolitinib, *i.e.*, Compound (I). EX1007, ¶¶261−263; *see also supra*, § V.A.2.c.

And as explained, treating AA with the 8 and 12 mg BID doses (*supra*, §§ V.A.2.b.i, V.B.2) using pharmaceutical compositions comprising 8 and 12 mg of Compound (I) would have been obvious at least from (1) patient convenience considerations, (2) *Ni*'s disclosure of individual tablets containing the appropriate amount of ruxolitinib for each administration (EX1006, [0124]), and (3) a POSA's knowledge that pharmaceutical compositions within this range (5, 10, and 20 mg) could have been readily formulated (*id.*). EX1007, ¶261; *supra*, § V.A.2.c.

C. Summary of Elements Taught by the Ground 1 and Ground 2 References

The charts below provide exemplary teachings in the Ground 1 and Ground 2 References of the limitations of Claims 1−21. *See also* EX1007, pp. 143−156. The disclosures for each dependent claim incorporate those of the independent and any other dependent claims from which they depend.

<table>
<tr><th colspan="3">Independent Claim 1</th></tr>
<tr><th>Claim Limitations</th><th colspan="2">Grounds 1 and 2 Prior Art Disclosures</th></tr>
<tr><td rowspan="2">[1.1] "A method of treating a hair loss disorder in a mammalian subject,"</td><td colspan="2">EX1002, 20:57−61 ("[The] invention provides a method of treating a disease that is beneficially treated by ruxolitinib.").</td></tr>
<tr><td>Ground 1</td><td>Ground 2</td></tr>
</table>

<table>
<tr><td></td><td>EX1003, 10 (“All three ruxolitinib-treated patients exhibited near-complete hair regrowth within 3 to 5 months of oral treatment.”).

See also EX1003, 5.</td><td>EX1005, 271:30−33 (“A method of treating a hair-loss disorder in a mammalian subject in need thereof, the method comprising administering to the subject INCB018424.”).

See also EX1005, 1:63−2:3, 5:1−10, 16:38−48, 113:1−6.</td></tr>
<tr><td rowspan="3">[1.2] “the method comprising administering to the subject 16 mg/day or 24 mg/day of”</td><td colspan="2">EX1002, 20:9–15 (“[E]ffective amount of a compound of this invention can range from… 10 mg to 25 mg, from 10 mg to 20 mg….”).</td></tr>
<tr><td>Ground 1</td><td>Ground 2</td></tr>
<tr><td>EX1004, 5 (starting doses of 20 mg, 15 mg, and 5 mg twice daily).

EX1004, 5 (5 mg once-daily).</td><td>EX1006, [0124] (“Immediate-release dosage forms of ruxolitinib phosphate can be obtained commercially in 5, 10, 15, 20, and 25 mg doses as the drug product Jakafi® (ruxolitinib phosphate (tablets)) (NDA no. N202192).”).

EX1005, 103:51−56 (“Toxicity and therapeutic efficacy of therapeutic compositions of the present invention can be determined by standard pharmaceutical procedures….).</td></tr>
</table>

<table>
<tr><td></td><td></td><td>See also EX1005, 102:14−21.</td></tr>
<tr><td rowspan="3">[1.3] “a compound represented by the following structural formula [Compound (I)] or a pharmaceutically acceptable salt thereof”</td><td colspan="2">EX1002, 7:7−8:43, 36:66−37:43 (disclosing Compound (I) (“compound 111”)).

EX1002, 16:23−27 (“The invention also provides… pharmaceutical compositions comprising an effective amount of a compound of Formula I… or a pharmaceutically acceptable salt of said compound… [and] a pharmaceutically acceptable carrier.”).</td></tr>
<tr><td>Ground 1</td><td>Ground 2</td></tr>
<tr><td>EX1004, 7 (“Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base….”).

EX1003, 10 (“[T]reated three patients with moderate to severe disease orally with ruxolitinib, 20 mg twice daily. Ruxolitinib is currently FDA-approved….”).</td><td>EX1006, [0125] (“A relative bioavailability study of the sustained release and immediate formulations of ruxolitinib phosphate was conducted in healthy adult volunteers.”).

EX1005, 104:36−65 (“JAK1/2 inhibitors in clinical development include a) INCB018424, topical and oral….”).

EX1005, 94:15−18 (“They can be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and</td></tr>
</table>

		standard pharmaceutical practice.”).
[1.4] “wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium.”	EX1002, 4:7−17 (“[A] compound of this invention has an isotopic enrichment factor for each designated deuterium atom of… at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation)….”). EX1002, 24:49−54, 28:16−22, 32:16−22 (exemplary synthesize using at least 97% incorporated starting materials).	

Claim 2 (depends from 1)		
’659 Claim Limitation(s)	**Prior Art Disclosures**	
[2] “The method of claim 1, wherein the hair loss disorder is alopecia areata.”	EX1002, 20:57−62 (“[A] method of treating a disease that is beneficially treated by ruxolitinib in a subject in need thereof, comprising the step of administering to the subject an effective amount of a compound or a composition of this invention….”). EX1002, 19:34−50 (“The second therapeutic agent may be selected from any compound or therapeutic agent known to have or that demonstrates advantageous properties when administered with a compound having the same mechanism of action as ruxolitinib…. Preferably, the second therapeutic agent is an agent useful in the treatment or prevention of a disease or condition selected from… alopecia areata.”).	
	Ground 1	**Ground 2**
	EX1003, 5 (“Notably, three patients treated with oral	EX1005, 271:30−43 (“1. A method of treating a

	ruxolitinib, an inhibitor of JAK1 and JAK2, achieved near-complete hair regrowth within 5 months of treatment…."). *See also* EX1003, 10.	hair-loss disorder in a mammalian subject in need thereof, the method comprising administering to the subject INCB018424…. 5. The method of claim 1 wherein the hair loss-disorder is alopecia areata."). EX1005, 6:38−48, 7:36−39 (treatment with ruxolitinib in preclinical models of AA). *See also* EX1005, 2:1−8.

<table>
<tr><td colspan="3">Claim 3 (depends from 1)</td></tr>
<tr><td>'659 Claim Limitation(s)</td><td colspan="2">Prior Art Disclosures</td></tr>
<tr><td rowspan="3">[3] "wherein the compound is administered orally."</td><td colspan="2">EX1002, 17:18−21 ("In certain embodiments, the compound is administered orally. Compositions of the present invention suitable for oral administration may be presented as discrete units such as capsules, sachets, or tablets.").</td></tr>
<tr><td>Ground 1</td><td>Ground 2</td></tr>
<tr><td>EX1003, 10 ("To test the efficacy of JAK inhibitors in human subjects with AA, we treated three patients with moderate to severe disease orally with ruxolitinib, 20 mg twice daily.").</td><td>EX1005, 100:56−61 ("[The] pharmaceutical composition of the invention is formulated to be compatible with its intended route of administration. Examples of routes of administration</td></tr>
</table>

	EX1004, 7 ("Jakafi (ruxolitinib) Tablets are for oral administration."). *See also* EX1004, 4−6.	include parenteral e.g., …oral…."). EX1006, [0127] ("Dosing was administered orally…."). *See also* EX1005, 101:50−55.

Claim 4 (depends from 1)		
'659 Claim Limitation(s)	**Prior Art Disclosures**	
[4] "wherein the compound is administered in a pharmaceutical formulation which is a tablet."	EX1002, 17:19−25 ("Compositions of the present invention suitable for oral administration may be presented as discrete units such as… tablets."). *See also* EX1002, 17:3−9, 17:29−30.	
	Ground 1	**Ground 2**
	EX1004, 4 ("DOSAGE FORMS AND STRENGTHS: Tablets: 5 mg, 10 mg, 15 mg, 20 mg and 25 mg."). EX1003, 10 ("[T]reated three patients with moderate to severe disease orally with ruxolitinib.... Ruxolitinib is currently FDA-approved…."). *See also* EX1004, 6−7, 9−10.	EX1006, [0124] ("Immediate-release dosage forms of ruxolitinib phosphate can be obtained commercially in 5, 10, 15, 20, and 25 mg doses as the drug product Jakafi® (ruxolitinib phosphate (tablets))."). EX1005, 101:50−55 ("Oral compositions generally include an inert diluent or an edible

		carrier. They can be enclosed in gelatin capsules or compressed into tablets. For the purpose of oral therapeutic administration, the active compound can be incorporated with excipients and used in the form of tablets, troches, or capsules."). *See also* EX1006, [0026], [0126]−[0127], [0132], [0140], [0143].

<table>
<tr><td colspan="3">Claim 5 (depends from 1)</td></tr>
<tr><td>’659 Claim Limitation(s)</td><td colspan="2">Prior Art Disclosures</td></tr>
<tr><td rowspan="3">[5] “wherein the compound is administered once a day.”</td><td colspan="2">EX1002, 20:15−17 (“In one embodiment, a dose… is administered once a day.”).</td></tr>
<tr><td>Ground 1</td><td>Ground 2</td></tr>
<tr><td>EX1004, 4 (“For patients on 5 mg once daily, maintain dose, 5 mg once daily.”).

EX1004, 4 (“For patients on 5 mg twice daily, decrease the dose to 5 mg once daily.”).</td><td>EX1006, [0143] (“Ruxolitinib phosphate tablets (5 and 25 mg) were administered as oral doses… qd.”).

EX1005, 93:40−44 (“[C]ompounds can be administered once or twice daily to a subject in need thereof….”).</td></tr>
</table>

		See also EX1005, 3:59−64.

Claim 6 (depends from 1)		
'659 Claim Limitation(s)	**Prior Art Disclosures**	
[6] "wherein the compound is administered twice a day."	EX1002, 20:17−18 ("In one embodiment a dose… is administered twice a day.").	
	Ground 1	**Ground 2**
	EX1004, 5 (starting doses of 5, 10, 15, and 20 mg "given orally twice daily"). EX1003, 10 ("To test the efficacy of JAK inhibitors in human subjects with AA, we treated three patients with moderate to severe disease orally with ruxolitinib, 20 mg twice daily."). *See also* EX1004, 4.	EX1006, [0157] ("patients… were randomly assigned to twice-daily oral, immediate-release"). EX1005, 93:40−44 ("Jak 1, Jak 2, Jak3, Stat 1 or Stat 2 modulating compounds can be administered once or twice daily to a subject in need thereof…."). *See also* EX1005, 122:26−29; EX1006, [0137], [0143], [0157], [0161].

Claim 7 (depends from 1)	
'659 Claim Limitation(s)	**Prior Art Disclosures**

[7] "wherein in Compound (I), any atom not designated as deuterium is present at its natural isotopic abundance."	EX1002, 12:20−21 ("[W]herein any atom not designated as deuterium is present at its natural isotopic abundance."). EX1002, 9:28−30 ("In another set of embodiments, any atom not designated as deuterium in any of the embodiments set forth above is present at its natural isotopic abundance."). *See also* EX1002, 8:4−42.

Independent Claim 8		
'659 Claim Limitation(s)	**Prior Art Disclosures**	
[8.1] "A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and"	EX1002, 16:23−31 ("The invention also provides… pharmaceutical compositions comprising an effective amount of a compound of Formula I… or a pharmaceutically acceptable salt of said compound… [and] a pharmaceutically acceptable carrier."). *See also* EX1002, 36:66−37:43.	
	Ground 1	**Ground 2**
	EX1004, 7 ("Each tablet contains ruxolitinib phosphate equivalent to 5 mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base together with microcrystalline cellulose, lactose monohydrate, magnesium stearate, colloidal silicon dioxide, sodium starch glycolate, povidone and hydroxypropyl cellulose.").	EX1005, 100:25−30 ("An inhibitor or agonist of the invention can be incorporated into pharmaceutical compositions suitable for administration, for example the inhibitor and a pharmaceutically acceptable carrier."). EX1005, 101:59−102:2 ("Pharmaceutically

	See also EX1003, 10.	compatible binding agents, and/or adjuvant materials can be included as part of the composition. The tablets, pills, capsules, troches and the like can contain any of the following ingredients [carriers and diluents]…."). *See also* EX1005, 94:35−43, 95:20−35, 100:31−55; EX1006, [0098], p. 8 (table 1), p. 15 (claim 32).
[8.2] "8 mg or 12 mg of [Compound (I)] or a pharmaceutically acceptable salt thereof"	*See supra*, [1.2].	
[8.3]"wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium."	*See supra*, [1.4].	

Independent Claim 9	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[9.1] "A method of treating a hair loss disorder in a mammalian subject"	*See supra*, [1.1].

[9.2] "the method comprising administering to the subject twice per day 12 mg"	*See supra*, [1.2], [6].
[9.3] "a compound represented by the following structural formula [Compound 1] or a pharmaceutically acceptable salt thereof"	*See supra*, [1.3].
[9.4] "wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium."	*See supra*, [1.4].

Claim 10 (depends from 9)		
'659 Claim Limitation(s)	**Prior Art Disclosures**	
[10] "wherein Compound (I) is administered as 10.5 mg of the phosphate salt twice per day."	EX1002, 5:6–24 ("Such pharmaceutically acceptable salts thus include… phosphate…."). EX1002, 16:23−27 (pharmaceutical composition). *See supra*, [1.2] (10.5 mg), [6] (twice per day). *See also* EX1002, 2:53–3:6.	
	Ground 1	**Ground 2**
	EX1004, 7 ("Each tablet contains ruxolitinib phosphate equivalent to 5	EX1006, [0126] ("This study was performed to evaluate pharmacokinetic

	mg, 10 mg, 15 mg, 20 mg and 25 mg of ruxolitinib free base…."). *See also*; EX1003, 10.	performance of two ruxolitinib phosphate Sustained release (SR) formulations compared to the ruxolitinib phosphate immediate release (IR) tablets."). EX1006, [0143] ("Ruxolitinib phosphate tablets (5 and 25 mg) were administered as oral doses with water in an outpatient setting."). *See also* EX1006, [0012]–[0013], [0023]–[0025], [0066].

Independent Claim 11	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[11.1] "A method of treating a hair loss disorder in a mammalian subject,"	*See supra*, [1.1].
[11.2] "the method comprising administering to the subject twice per day 12 mg of"	*See supra*, [1.2] (12 mg), [6] (twice per day).
[11.3] "a compound represented by the following structural formula [Compound 1]	*See supra*, [1.3].

or a pharmaceutically acceptable salt thereof,"	
[11.4] "wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium."	*See supra*, [1.4].

Claim 12 (depends from 11)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[12] "wherein Compound (I) is administered as 15.8 mg of the phosphate salt twice per day."	*See supra*, [10].

Claim 13 (depends from 1)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[13] "wherein each position in Compound (I) designated specifically as deuterium has at least 97% incorporation of deuterium."	*See supra*, [1.4].

Claim 14 (depends from 1)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[14] "wherein the step of administering	*See supra*, [1.2] (8 mg or 12 mg), [6] (twice per day).

comprises administering to the subject 8 mg twice per day or 12 mg twice per day of Compound (I)."	

Claim 15 (depends from 9)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[15] "wherein the hair loss disorder is alopecia areata."	*See supra*, [2].

Claim 16 (depends from 9)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[16] "wherein the compound is administered orally."	*See supra*, [3].

Claim 17 (depends from 9)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[17] "wherein each position in Compound (I) designated specifically as deuterium has at least 97% incorporation of deuterium."	*See supra*, [1.4].
Claim 18 (depends from 11)	
'659 Claim Limitation(s)	**Prior Art Disclosures**

[18] "wherein the hair loss disorder is alopecia areata."	*See supra*, [1.4].

Claim 19 (depends from 11)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[19] "wherein compound is administered orally."	*See supra*, [3].

Claim 20 (depends from 11)	
'659 Claim Limitation(s)	**Prior Art Disclosures**
[20] "wherein each position in Compound (I) designated specifically as deuterium has at least 97% incorporation of deuterium."	*See supra*, [1.4].

Claim 21 (depends from 14)		
'659 Claim Limitation(s)	**Prior Art Disclosures**	
[21] "wherein the subject is a human."	EX1002, 1:20–3:21 (referring to "patients"). EX1002, 4:50−53 (defining "pharmaceutically acceptable" as "a component that is… suitable for use in contact with the tissues of humans"). EX1002, 5:51−52 ("In another embodiment, the mammal is a human.").	
	Ground 1	**Ground 2**

	EX1004, 8−10 (disclosing clinical trials of FDA-approved ruxolitinib). EX1003, 10 ("To test the efficacy of JAK inhibitors in human subjects with AA, we treated three patients with moderate to severe disease orally with ruxolitinib, 20 mg twice daily.").	EX1006, [0003] (disclosing use of ruxolitinib in humans). EX1006, [0120]–[0164] (disclosing exemplary clinical studies in humans). EX1005, 78:37–39 ("JAK1/2 inhibitors in clinical development include a) INCB018424…"). *See also* EX1005, 115:41−43, 115:66−116:1, 117:5−10.

D. No Secondary Indicia

No unexpected results or other secondary indicia of nonobviousness were relied upon during prosecution of the '659 Patent. Petitioner reserves the right to rebut any alleged secondary indicia presented by Patent Owner in response to this Petition. To the extent that Patent Owner relies on the purported secondary indicia it presented in the *inter partes* review of *Silverman*, they should be rejected as they were rejected previously. *See Incyte*, Paper 119 at 33−37.

Phase II trial results for Compound (I) were submitted during prosecution of the '659 Patent[19] but not relied upon as evidence of, and are in fact not probative of, nonobviousness, as any differences are not "unexpected and significant." *Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006). For example, Concert's Phase II AA trial of CTP-543 (Compound (I)) tested doses of 8 and 12 mg BID and assessed the change in the patient's Severity of Alopecia Tool ("SALT") score at baseline, week 12, and week 24. EX1089, 4; EX1009, ¶¶54−55. *Xing* tested ruxolitinib at 20 mg BID using the similar efficacy measures. EX1049, 2, 6; EX1009, ¶¶54−55. The results of the two studies, summarized below in Figures 1 and 2, show a standard dose response—*i.e.*, the lower doses of CTP-543 were less effective than the higher doses of both CTP-543 and ruxolitinib. EX1009, ¶¶ 52−53, 56−62.

[19] *Silverman*'s Compound 111, *i.e.*, Compound (I) of the '659 Patent, is the active ingredient in "CTP-543." *Incyte*, Paper 119 at 33 n.12.

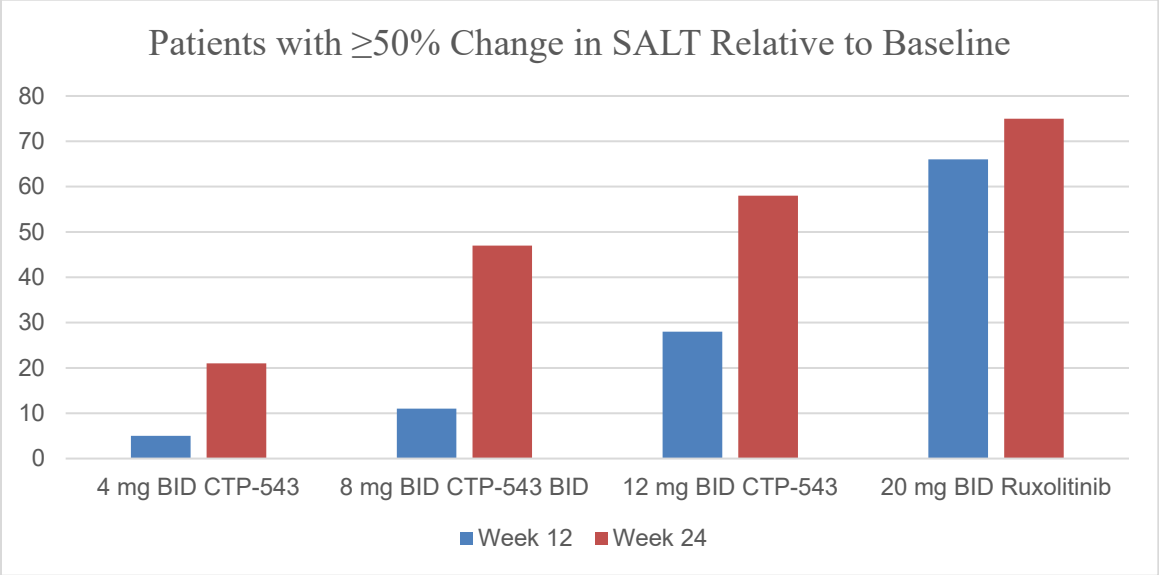


Figure 1

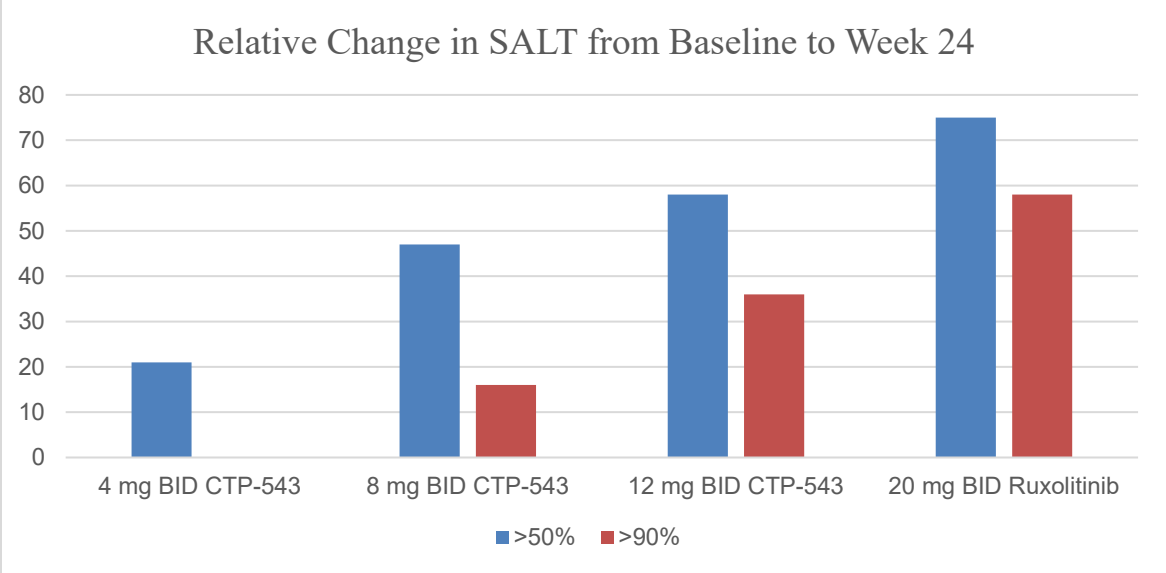


Figure 2

Adverse events rates were also similar. *Compare* EX1049, 4, *with* EX1089, 7−8; EX1009, ¶63; *see also* EX1049, 5−6 (noting that ruxolitinib was "well tolerated" and that adverse events were "consistent with findings from use of tofacitinib in the treatment of patients with psoriasis"); *see also* EX1068, 1; EX1067, 1.

VI. Ground 3: Claim 8 Is Anticipated by *Silverman*

Claim 8 of the '659 Patent recites:

> A pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent and 8 mg or 12 mg of [Compound (I)] or a pharmaceutically acceptable salt thereof, wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium.

Silverman taught this composition. EX1007, ¶¶264−281.

Silverman disclosed "pharmaceutical compositions comprising an effective amount of a compound Formula I… and a pharmaceutically acceptable carrier." EX1002, 16:23−27; *see also id*., 16:32−45, 16:64−17:1, 19:65−67. *Silverman* further taught that an "Exemplary Embodiment[] of Formula I" is "Compound 111," which is "Compound (I)" claimed in the '659 Patent:

Formula I

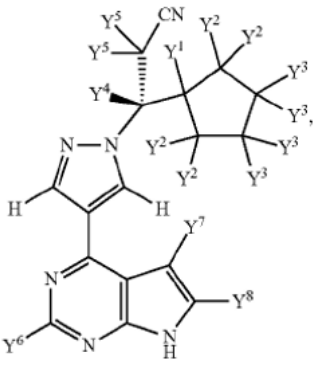


TABLE 1

Exemplary Embodiments of Formula I

Cmpd	Y^1	Each Y^2	Each Y^3	Y^4	each Y^5
100	H	H	H	D	H
101	H	H	H	H	D
102	H	H	H	D	D
103	H	H	D	H	H
104	H	H	D	D	H
105	H	H	D	H	D
106	H	H	D	D	D
107	H	D	H	H	H
108	H	D	H	D	H
109	H	D	H	H	D
110	H	D	H	D	D
111	H	D	D	H	H

EX1002, 8:10−23; EX1001, 24:30−50; EX1007, ¶¶272−275. *Silverman*'s "pharmaceutically acceptable carriers" are likewise described *ipsis verbis* as those in the '659 Patent. EX1002, 16:32−45; EX1001, 14:58−62; EX1007, ¶¶266−271.

These teachings are repeated and reinforced in *Silverman*'s claims, which recite "Compound 111" and a "pharmaceutical composition comprising a pharmaceutically acceptable carrier or diluent." *See* EX1002, Claims 1, 7 ("The compound of claim 1, in which the compound is selected from the group consisting of… Compound 111…."), and 8 ("A pharmaceutical composition comprising the compound of claim 1.").

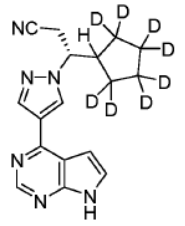
The limitation "wherein each position in Compound (I) designated specifically as deuterium has at least 95% incorporation of deuterium" is also expressly taught by *Silverman.* EX1007, ¶¶279−281. *Silverman* taught that "a compound of this invention has an isotopic enrichment factor for each designated deuterium atom of… at least 6333.3 (95% deuterium incorporation), at least 6466.7 (97% deuterium incorporation), at least 6600 (99% deuterium incorporation), or at least 6633.3 (99.5% deuterium incorporation)." EX1002, 4:7–17. Claimed Compound (I) was a "compound of the invention" within the meaning of *Silverman.* EX1007, ¶¶272−275.

Regarding the amount of drug to include in such formulations, *Silverman* taught that "[i]n the pharmaceutical compositions of the invention, the compound of the present invention is present in an effective amount" and that "an effective amount of a compound of this invention can range… from 10 mg to 20 mg… and from 5 mg

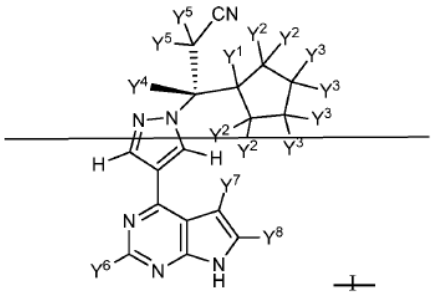
to 10 mg." EX1002, 19:65–20:15. These ranges represent only eleven and six 1 mg alternatives, respectively, and the claimed pharmaceutical formulations with 8 and 12 mg of Compound (I) are encompassed and taught by these narrow ranges. EX1007, ¶¶276−278; *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (holding claimed species of less than 50 ppm anticipated by prior art that disclosed "150 ppm or less")); *Ortho McNeil Pharm., Inc. v. Barr Labs.*, *Inc*., Civ. A. No. 03-4678 (SRC), 2006 WL 3019555, at *3–5 (D.N.J. Oct. 23, 2006) (denying patentee's motion for summary judgment that its claims directed to a contraception pill requiring a 25 microgram dosage of estrogen were not anticipated by a prior art reference disclosing an estrogen dosage range of 20 to 50 micrograms).

Silverman's disclosure of the claimed formulation is further reflected in Concert's prosecution of U.S. Patent Application No. 16/298,795, which contains the same disclosure and priority as *Silverman.* EX1090, 21–64. In a June 28, 2019, Preliminary Amendment, Concert amended Claim 1 to specifically recite "Compound 111" with "at least 97% incorporation of deuterium":

1. (Currently Amended) A compound represented by the following structural formula ~~of Formula I~~:



Compound 111



~~I~~

or a pharmaceutically acceptable salt thereof, ~~wherein:~~ wherein each position in the compound designated specifically as deuterium has at least 97% incorporation of deuterium.

EX1090, 75. Claim 3 in this pending Concert patent application then recites "[a] pharmaceutical composition comprising the compound of claim 1, and a pharmaceutically acceptable carrier." *Id*., 76. As support for the amendment of Claim 1 "to recite Compound 111 or a salt thereof, wherein the deuterium incorporation is at least 97% at each position designated as deuterium," Concert cited to paragraph [0021] in the specification, which corresponds to *Silverman*'s column 4, lines 7–17, addressed above. EX1090, 79, *see also id.*, 26. EX1002, 4:7–17. Notably, this claim stands rejected, based on June 11, 2020 Office Action, as obvious over a host of prior art pre-dating *Silverman.* EX1090, 39–41; EX1092, 3–14.

Thus, *Silverman* taught the claimed pharmaceutical composition comprising an acceptable carrier or diluent and 8 or 12 mg of Compound (I) where each as deuterium has at least 95% incorporation of deuterium.

VII. Mandatory Notices Under 37 C.F.R. § 42.8

A. Real Parties-in-Interest

Pursuant to 37 C.F.R. § 42.8(b)(1), Incyte Corporation as Petitioner is the real party-in-interest.

B. Related Matters

U.S. Application No. 16/704,402 is pending and claims benefit of priority to U.S. Application No. 16/098,338, the application which led to U.S. Patent No. 10,561,659.

IPR2017-01256 against Patent Owner's U.S. Patent No. 9,249,149 is pending, as it was remanded in light of *Arthrex, Inc. v. Smith & Nephew, Inc.*, 941 F.3d 1320 (Fed. Cir. 2019), *cert. granted*, *Arthrex, Inc v. Smith & Nephew, Inc., et al.*, No. 19-1458, 2020 WL 6037208 (U.S. Oct. 13, 2020), and then stayed by the PTAB.

C. Lead and Back-Up Counsel

Lead Counsel	**Back-Up Counsel**
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D. Service of Information

Please send all correspondence to the lead and back-up counsel at the addresses shown above. Petitioner consents to service by e-mail at the addresses of lead and back-up counsel shown above as well as FinneganIncyte-PGR2020@finnegan.com.

VIII. Grounds for Standing

Pursuant to 37 C.F.R. § 42.204(a), Petitioner certifies that the '659 Patent is available for PGR and that Petitioner is not barred or estopped from requesting PGR on the grounds identified in this Petition. Specifically: (1) neither Petitioner nor any of its privies own the '659 Patent; and (2) neither Petitioner nor any of its privies have filed a U.S. civil action challenging the validity of any claim of the '659 Patent.

Respectfully submitted,

Dated: October 28, 2020

By: /Thomas L. Irving/
Thomas L. Irving, Reg. No. 28,619
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP

Counsel for Petitioner
Incyte Corporation.

CERTIFICATION UNDER 37 C.F.R. § 42.24(d)

Pursuant to 37 C.F.R. § 42.24(a)(1)(ii), the undersigned hereby certifies that the foregoing PETITION FOR POST-GRANT REVIEW contains 17,040 words, excluding the parts of this petition that are exempted under 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

/Thomas L. Irving/
Thomas L. Irving, Reg. No. 28,619
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, LLP

Counsel for Petitioner
Incyte Corporation.

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.205(a), the undersigned certifies that on October 28, 2020, a copy of the foregoing **Petition for Post-Grant Review** and **Petitioner's Power of Attorney** were served by FedEx on the correspondence address of record indicated in the Patent Office's public PAIR system for U.S. Patent No. 10,561,659:

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Date: October 28, 2020

By: /William Esper/
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Legal Assistant

FINNEGAN, HENDERSON, FARABOW,
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