UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION
Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,
Patent Owner

Case: IPR2017-01256
Patent No. 9,249,149

CONCERT PHARMACEUTICALS, INC.'S PATENT OWNER RESPONSE

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I. INTRODUCTION

U.S. Patent No. 9,249,149 ("the '149 Patent") claims novel deuterated ruxolitinib compounds. Patent Owner Concert Pharmaceuticals, Inc. ("Concert") is developing one of these compounds, CTP-543, for the treatment of alopecia areata ("AA"), a serious autoimmune disease that causes hair loss on the scalp, face, and other areas of the body. AA patients often suffer great distress, and the disease is associated with high rates of depression, generalized anxiety disorder, and obsessive-compulsive disorder. As explained by leading AA specialist Dr. Mackay-Wiggan, AA patients commonly report a variety of responses to their disease that include loneliness, loss, grief, fear, embarrassment, and guilt. (Ex. 2048 ¶23; Ex. 2069, 1-3.) There is currently no cure or FDA-approved treatment for AA. Ruxolitinib itself is approved for treatment of two types of blood cancer, but not for treatment of AA.

Concert invented deuterated ruxolitinib compounds, including CTP-543 in which eight of the hydrogens of ruxolitinib have been replaced by deuterium. The metabolic effects of deuteration are highly unpredictable, particularly in living systems. As explained by Concert's experts Drs. Baillie and Ortiz de Montellano, experts in drug metabolism, including the use of deuterium substitution, deuteration of different drugs can have a variety of effects on how the drug is

metabolized by the body, which in turn can lead to a variety of effects on clinical utility. In a Phase 1 human clinical trial, CTP-543 has shown unexpectedly favorable pharmacokinetic properties, some of which are particularly desirable for treating AA.

Petitioner oversimplifies the state of the art and argues that three of the claimed deuterated compounds, including CTP-543, would have been obvious. The Board initially denied the petition. On reconsideration, the Board instituted on a single ground, and then expanded the grounds following the *SAS* decision.[1] The Board has now instituted review of claims 1-15 as obvious over (1) Concert Backgrounder, Shilling, and Jakafi® Label (Ground 1); and (2) Concert Backgrounder, Shilling, and Rodgers (Ground 3). Whereas at the institution stage the Board was required to view disputed facts in the light most favorable to Petitioner, the full record now demonstrates that Petitioner has inaccurately

[1] Even in its decision on reconsideration, the Board did not institute Ground 1, finding that Petitioner had not made a threshold showing that Jakafi® Label was a printed publication. Grounds 1 and 2 were added only after *SAS Inst. Inc. v. Iancu*, 138 S. Ct. 1348 (2018) was decided. The parties submitted a joint motion to limit the petition to exclude Ground 2.

characterized the complex nature of the prior art, and has failed to show by a preponderance of the evidence that the claimed compounds would have been obvious.

As set forth below, Concert's arguments are dispositive of both Grounds. As an initial matter, Petitioner has not met its burden to show that two of its references (the Concert Backgrounder and Jakafi® Label) are printed publications. Regardless, there was an affirmative motivation ***not*** to combine the deuteration approach mentioned in the Concert Backgrounder with the teachings of the other references. Petitioner relies only on a general motivation to deuterate all compounds. But POSAs would not have been motivated to modify ruxolitinib to make it more metabolically stable because doing so would be likely to exacerbate the known, significant hematologic toxicities of ruxolitinib. The mechanism of action responsible for ruxolitinib's efficacy—inhibition of JAK kinases—is the very same mechanism responsible for these toxicities, and these toxicities are dose-dependent. POSAs therefore would have recognized that even if they could increase the metabolic stability of ruxolitinib by deuteration, it would likely not improve the risk-benefit profile of the drug, because it could increase toxicity. This would have motivated POSAs to affirmatively reject ruxolitinib as a candidate for deuteration.

Further, POSAs would have had no reasonable expectation that the pharmacokinetics of deuterated ruxolitinib would be positively differentiated from those of ruxolitinib. The improvements demonstrated in Concert's Phase 1 clinical study would not have been expected in combining the deuteration approach mentioned in the Concert Backgrounder with the teachings about ruxolitinib in the cited references. Contrary to Petitioner's oversimplified assertions, POSAs would have understood that the deuterium effect on overall metabolism, if any, is unpredictable. POSAs would have known that the unpredictability arose both on the enzymatic level and from the complexities of drug clearance in living systems. Accordingly, POSAs would have had no reasonable expectation that deuteration of ruxolitinib would provide any benefit, let alone the particularly unexpected pharmacokinetic improvements observed in the Phase 1 clinical study.

Objective indicia confirm the non-obviousness of the invention claimed in the '149 Patent. CTP-543 demonstrates unexpected benefits over ruxolitinib. The Phase 1 clinical data comparing CTP-543 and ruxolitinib in a head-to-head human crossover study showed that the pharmacokinetic profile of CTP-543 is superior to that of ruxolitinib in two ways, neither of which could have been expected.

The first advantage of CTP-543 over ruxolitinib is the potential for CTP-543 to stay within the therapeutic window for treating AA for a longer time; that is, to

be above the level required for efficacy while being below the level where toxicity is likely. The ability of CTP-543 to stay within the therapeutic window for AA longer means that CTP-543 has greater potential than ruxolitinib to provide therapeutic benefits without adverse effects. The therapeutic window results from the different mechanism by which ruxolitinib treats AA as compared to the mechanism by which it treats the cancers and causes toxicity. For these two mechanisms, Concert found that ruxolitinib and CTP-543 are more potent inhibitors of the cytokine interferon-gamma (IFN-γ) pathway than of the cytokine erythropoietin (EPO) pathway. IFN-γ matters greatly in AA, but not in the cancers, where the EPO pathway is more relevant. An understanding of the different potency that ruxolitinib has for these pathways was not in the prior art. Concert's study showed the ability of CTP-543 to maintain plasma concentrations in the therapeutic window longer than an equivalent dose of ruxolitinib.

The second unexpected advantage is that the relative improvement in half-life ($t_{1/2}$) between CTP-543 and ruxolitinib was greatest in those subjects who most rapidly metabolized ruxolitinib. The greater improvement in half-life for people who more rapidly metabolize ruxolitinib means that patients receiving CTP-543 are more likely to achieve therapeutic levels than those receiving an equivalent dose of ruxolitinib. These surprising clinical advantages are particularly

meaningful for AA, a serious condition for which there is no cure, and conclusively support the '149 Patent's non-obviousness.

Finally, CTP-543 has the potential to fill the long-felt need for an AA treatment with a tolerable side-effect profile. The significance of these results has been recognized by Dr. Mackay-Wiggan. FDA's decision to fast-track CTP-543 for expedited review demonstrates the severity of this need and the dearth of available treatments, and the non-obvious nature of the '149 Patent's claimed inventions.

In sum, the record overwhelmingly demonstrates the patentability of the challenged claims.

II. STATE OF THE ART

A. Alopecia Areata

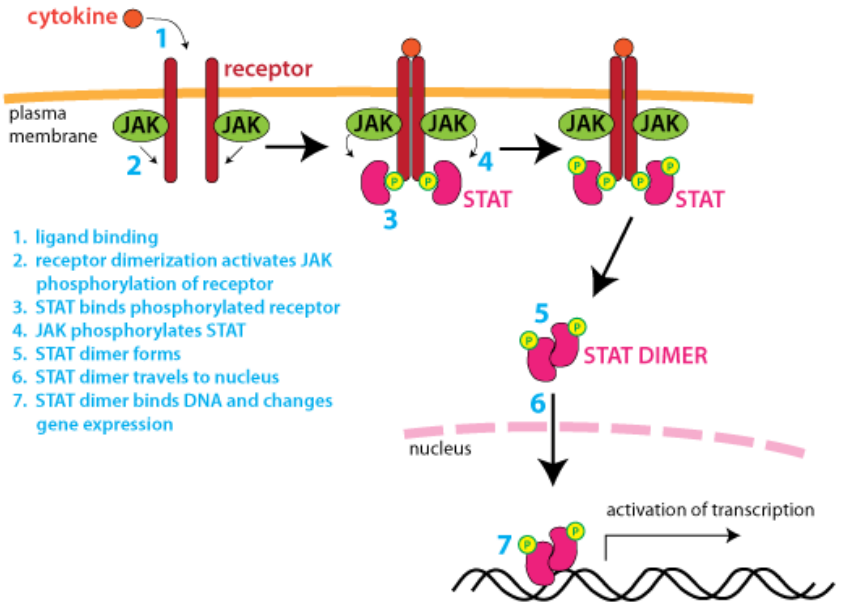
It is believed that in AA, one of the most prevalent autoimmune diseases in the United States, the patient's immune system attacks hair follicles, resulting in unpredictable and sometimes permanent hair loss. (Ex. 2009, 1; Ex. 2048, ¶¶2-23.) AA patients suffer severe psychosocial consequences as a result of their disease. (Ex. 2048 ¶23 (citing Ex. 2069, 1-3).) AA is a chronic, lifelong condition for which there is no approved cure. (*Id.*, ¶37.) In 2012, as today, there were few treatment options, with only limited efficacy. (*Id.*, ¶24.)

B. Ruxolitinib, JAK Inhibitors, and JAK/STAT Signaling

Ruxolitinib inhibits Janus kinases (JAK), part of a family of intracellular tyrosine kinases that play a central role in signaling for many cytokines (signaling proteins). (Ex. 1001, 2:53-65.) Specifically, ruxolitinib potently inhibits Janus kinases 1 and 2 (JAK1/2), which are subtypes of JAK kinases. Jakafi® (ruxolitinib) is FDA-approved for the treatment of two types of cancer affecting the production of red blood cells, myelofibrosis and polycythemia vera. (Ex. 1001, 2:66-3:6.)

The receptors associated with JAK proteins are embedded within cellular membranes. As depicted in Figure 1, when a cytokine binds to this receptor on the extracellular surface, JAK proteins inside the cell associated with the intracellular side of the receptor dimerize and phosphorylate (activate) STAT proteins. The phosphorylated STAT (pSTAT) proteins then selectively activate gene transcription, which leads to further biological effects.

Figure 1: The JAK/STAT signaling pathway



(Ex. 2028, 1.) A JAK inhibitor like ruxolitinib prevents JAK proteins from phosphorylating STAT proteins, thereby preventing downstream biological effects.

While inhibition of JAK/STAT signaling explains how CTP-543 and ruxolitinib can be used to treat both the blood cancers and AA, there are important differences in how the mechanism operates for treatment of the two different disease types. Ruxolitinib's mechanism of action for treating the blood cancers is generally believed to be due to JAK2 inhibition, which in turn prevents JAK2/JAK2 homodimers from activating their corresponding STAT proteins. (Ex. 2002, ¶38.) This JAK2 inhibition also causes anemia, however, by suppressing the activity of EPO, which is necessary for the production of red blood cells. (*Id.*) In other words, the efficacy of ruxolitinib in treating blood cancers and its toxicity are

caused by the same mechanism of action. In AA, on the other hand, the relevant mechanistic pathway for efficacy is believed to be IFN-γ signaling through a JAK1/JAK2 heterodimer. (Ex. 2076, Fig. 1.) The potential efficacy of CTP-543 in AA is believed to result from the inhibition of the JAK1/JAK2 heterodimer, which suppresses IFN-γ signaling. (*Id*.) Thus, unlike blood cancer treatment, for treatment of AA, the mechanisms for efficacy and toxicity (anemia) are mediated by *different* JAK/STAT signaling pathways.

Concert discovered that ruxolitinib and CTP-543 were much more potent inhibitors of the IFN-γ signaling pathway relative to their inhibitory effect on the EPO pathway. Concert thus recognized the opportunity to treat AA while having less impact on the EPO pathway that causes anemia. CTP-543 is now in clinical development and could represent a major advance for AA patients.

More than 20% of myelofibrosis and polycythemia vera patients who take ruxolitinib develop anemia. (Ex. 2006, 5, 7; Ex. 2053, 10.) While this side effect may be acceptable for a cancer indication, it is much less acceptable for diseases like AA that, while quite serious, are not life-threatening. (Ex. 2048, ¶¶26-27.) The divergent JAK/STAT pathway for efficacy in AA somewhat mitigates the risk of anemia. Nevertheless, it would be desirable to have a JAK inhibitor that

controls aberrant IFN-γ activity for AA treatment while further minimizing EPO inhibition to mitigate the risk of hematological toxicities. (Ex. 2048, ¶39.)

C. Toxic Side Effects of Ruxolitinib Make Deuteration Undesirable

Petitioner offers no specific reason why POSAs would choose to deuterate ruxolitinib, and the evidence suggests that POSAs would have believed that deuteration of this particular compound would have been undesirable. Because the beneficial effect of ruxolitinib for treating cancer and its side effects occur through the same mechanism, there is no obvious way deuteration could improve ruxolitinib. A potential effect of deuteration would be to inhibit metabolism, thereby increasing drug exposure.[2]

Ruxolitinib was known to cause hematological toxicities, including anemia, thrombocytopenia (low blood platelet count), neutropenia (low white blood cell count), and lowered hemoglobin. (Ex. 2057, ¶40; Ex. 2009, 4; Ex. 2053, 3, 10; Ex. 2054, 4.) Both the thrombocytopenia and anemia were severe enough to require

[2] To the extent the Board finds the Jakafi® (ruxolitinib) product label to be prior art, it expressly warns against administering the drug with strong metabolic inhibitors due to the risk of exposure-related adverse reactions. (Ex. 1004, 4.) POSAs would have realized that deuteration would have a similar risk.

dose reduction, interruption of treatment, or transfusion of packed red blood cells in some patients. (Ex. 2057, ¶40; Ex. 2048, ¶26; Ex. 2054, 3, 11.) In a clinical study of ruxolitinib for the treatment of myelofibrosis, more than 40% of patients required dose reduction or interruption due to thrombocytopenia. (Ex. 2054, 11-12.) POSAs would have believed that, to the extent they could slow down metabolism by deuteration, deuterating ruxolitinib posed a significant risk of making these side effects worse. (Ex. 2057, ¶41.)

D. Drug Metabolism and the Unpredictable Effect of Deuterium Substitution

In 2012 and today, it was known that the biological processes involved in drug metabolism are staggeringly complex and unpredictable. (*Infra* Sections II.D.1-6.) As discussed below, because of this complexity, conclusions about how a deuterated drug will behave cannot be drawn *a priori* and, furthermore, any clinical impact is highly uncertain. (*Id.*) Petitioner's oversimplified depiction of the state of the art does not acknowledge the many unknowns that would have prevented POSAs from reasonably predicting the pharmacokinetic result of deuterating a drug compound. (*Id.*)

1. The Role of ADME in Determining Clinical Efficacy

The clinical utility of a drug depends on many factors. At a minimum, the drug must have adequate pharmacodynamics, which is typically described by its

selectivity (how preferentially a drug interacts with its intended target) and potency (how strongly the drug interacts with its target). (Ex. 2057, ¶47.)

Favorable pharmacodynamics alone, however, are not sufficient to ensure safety and efficacy. (*Id.*) As Petitioner's expert Dr. Guengerich concedes, a drug must also exhibit appropriate absorption, distribution, metabolism, and excretion (ADME) properties. (Ex. 2047, 162:12-16.) For example, it will be difficult (if not impossible) to achieve a therapeutic benefit if a drug has good pharmacodynamics but is excreted from the body too rapidly to work. (Ex. 2057, ¶48.) Similarly, an otherwise promising drug with limited absorption and/or distribution may have correspondingly little clinical effect. (*Id.*) Indeed, poor ADME qualities are major reasons why drugs fail during clinical trials. (Ex. 1001, 1:20-23; Ex. 1040, 1.)

2. Deuteration and the Unpredictability of an *In Vitro* KIE

Deuteration is a method of replacing one or more hydrogen atoms in a drug with deuterium. Deuterium is a hydrogen isotope that forms stronger bonds with carbon, such that it requires more energy for an enzyme to cleave a C-D bond than a C-H bond. (*See* Ex. 1001, 2:10-12.) Even in simple *in vitro* systems, deuteration can unpredictably impact (or not impact) a drug's rate of metabolism by CYP450 enzymes. (Ex. 2057, ¶29.) In cases where deuteration results in a metabolic

change, this phenomenon is called a kinetic isotope effect, or "KIE."[3] (Ex. 1002, ¶¶ 50-52.)

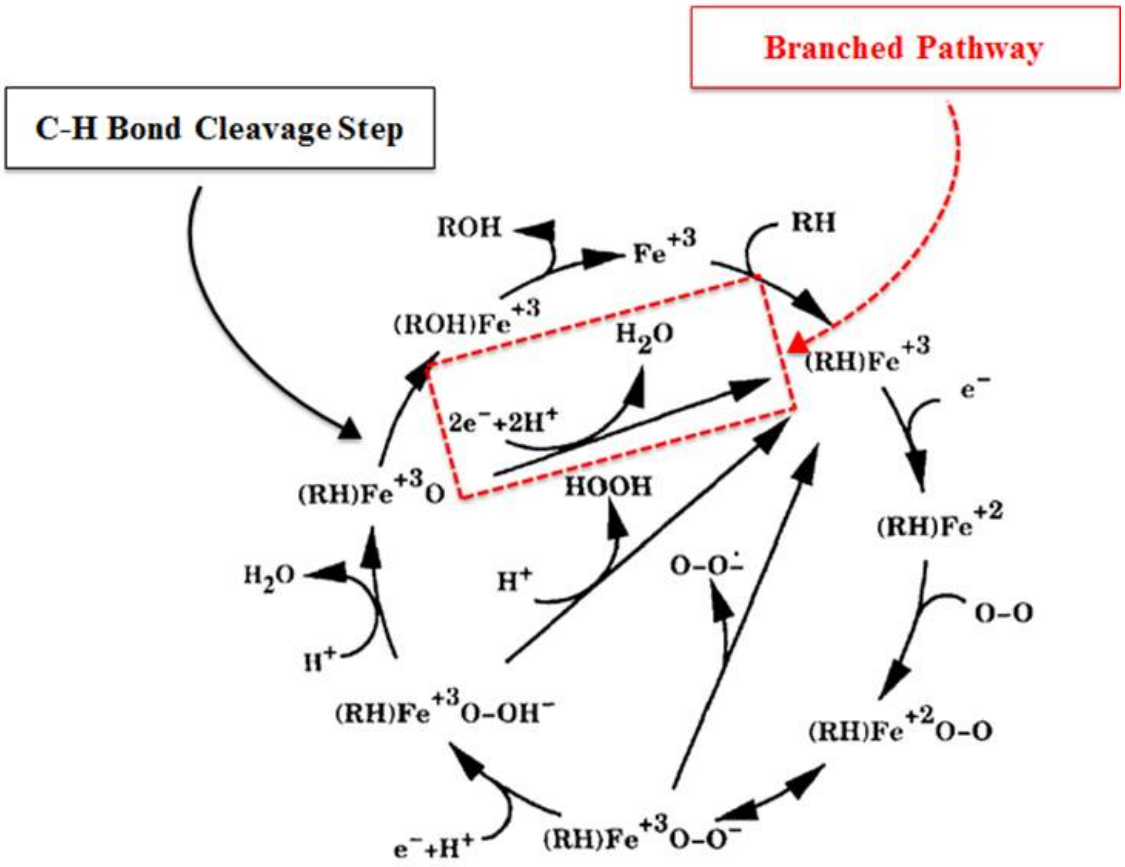
3. Unpredictability of CYP450 Drug Metabolism at the Enzymatic Level

Drug metabolism involves many variables. The most common metabolic pathway of drug clearance starts with oxidative metabolism by CYP450 enzymes. There are at least 57 different human CYP450 enzymes, each having different properties and reaction kinetics. (Ex. 1012, 1; Ex. 1034, 1.) For drugs metabolized by CYP450 enzymes, the unpredictability of the deuterium effect starts at the level of the CYP450 enzyme. As other ADME processes are layered in, the complexity of drug clearance increases, further escalating the unpredictability of the deuterium effect. (Ex. 2057, ¶45.)

Figure 2 below shows the CYP450 catalytic cycle. Metabolic oxidation proceeds through a series of major steps through which the substrate (RH) is oxidized into a metabolite (ROH). One of the last steps in the cycle is cleaving a carbon-hydrogen (C-H) bond.

[3] The terms KIE and "DIE" (deuterium isotope effect) are used interchangeably herein.

Figure 2: CYP450 Catalytic Cycle



(Ex. 2062, 9 (annotations added).)

The overall rate metabolism by CYP450 is determined by the slowest step in the reaction, called the rate-limiting step.[4] (Ex. 2057, ¶32.) Petitioner's simplified view is that deuteration should slow C-H bond breaking and thereby slow metabolism. However, this view wrongly assumes that C-H bond breaking is

[4] Consider a 3-step process. If Step 2 is the slowest step, then relatively small variations in the rates of Steps 1 or 3 will not impact the overall rate of the process.

almost always at least partially rate limiting, and it ignores other, more important, mechanistic aspects.

Contrary to the assertion of Dr. Guengerich that C-H bond cleavage is almost always at least partially rate limiting, the prior art teaches that the C-H bond breaking step is not generally rate limiting. As a rate-limiting step, it would serve as a bottleneck in the catalytic cycle, and the intermediate species preceding this bottleneck would be expected to build up. (Ex. 2057, ¶32; Ex. 2047, 187:11-189:10.) Researchers have found that the intermediate immediately preceding the C-H bond-breaking step does not accumulate, and mechanistic studies have suggested that the intermediate rapidly transforms to the product. (Ex. 2043, 1, 4.) The weight of this evidence thus strongly suggests that the C-H bond breaking step is not in fact rate-limiting. Therefore, whether deuterium modification will result in a meaningful KIE is much more complicated than the over-simplified picture that Dr. Guengerich describes.

Instead, the prior art taught that the existence and strength of KIE *varies* depending on the catalytic cycle for the relevant substrate and CYP450 enzyme. (Ex. 2057, ¶35; Ex. 2062, 9.) The prior art teaches that for a KIE to be observed there must exist an alternative branched pathway in the CYP450 cycle just before the C-H bond breaking step. (Ex. 2057, ¶¶32-34.) As shown in Figure 2, there are

sometimes, though not always, three branched pathways whereby the reaction can be shifted back to an earlier point in the catalytic cycle without oxidizing (metabolizing) the substrate. (*Id.*, ¶; Ex. 2062, 9.) One of these branched pathways (depicted in red in Figure 2), immediately preceding the C-H bond cleavage step, produces water and diverts away from oxidation of the substrate. (Ex. 2057, ¶¶29-30; Ex. 2062, 6, 8-9.) The observation of a KIE, if any, is unpredictable without experimentation because it depends entirely on whether this branched pathway exists for a given CYP450 enzyme and substrate combination, as well as the magnitude and relative kinetics of that branched pathway. (Ex. 2057, ¶35; Ex. 2062, 6, 8-9.) Whether or not such a branched pathway existed for the metabolism of ruxolitinib was not known in the prior art.

In view of the complexity of CYP450 metabolism at the enzymatic level, POSAs would not have been able to predict how deuterium modification would affect the compound. (Ex. 2057, ¶35.)

4. Metabolic Switching

Another complexity Petitioner dismisses too easily is the phenomenon of metabolic switching. When deuterium is substituted at one metabolic site on a drug molecule, enzymatic metabolism can "switch" to act on a different site. (*Id.*; ¶38; Ex. 2047, 109:14-18; Ex. 2023, 2.) The metabolites and their ratio can change

when metabolic switching occurs. (Ex. 2057, ¶38; Ex. 1033, 5; *see also* Ex. 2047, 119:22-120:9, 121:5-122:5, 123:20-125:8 (noting that following deuteration of 7-ethoxycoumarin at a methylene position, the authors reported formation of a previously unreported metabolite).) Such a change in the metabolite ratio can result in no observable change in the overall rate of drug metabolism, or in the increased formation of undesirable or even toxic metabolites. (Ex. 2057, ¶50; Ex. 1010, 6.)

POSAs would have known that metabolic switching contributes to the unpredictability of deuteration. It has frequently been observed in deuterium isotope studies, including by Dr. Guengerich himself. (Ex. 1033, 4 (discussing different ratios of metabolites formed with deuteration and without); Ex. 1035, 2 (Dr. Guengerich reports partial switching following deuteration of testosterone); Ex. 1039, 3 (discussing examples of metabolic switching reported in the literature); Ex. 2023, 3 (same); Ex. 2047, 125:9-11, 134:3-22, 216:11-218:9.) Indeed, metabolic switching can occur even when the alternative metabolic site (to which metabolism is switched after deuteration) is normally only a minor metabolic pathway. (Ex. 2057, ¶38.)

Dr. Guengerich acknowledges metabolic switching, but asserts that there would not be appreciable switching to a minor metabolite unless it is "generally

present in a much larger amount than less than 5%" of the parent compound. (Ex. 1002, ¶106.) This proposition is contradicted by the very reference on which Dr. Guengerich relies, Ex. 1033 ("Harada"). (Ex. 2057, ¶38.) Harada reports that although deuteration of the relevant drug resulted in a "dramatic decrease" in the rate of C-H bond breaking (Ex. 1033, 1, 5), the overall reaction rate was unchanged because of metabolic switching to a minor metabolite that represented only about 5% of the metabolite mixture before deuterium substitution. (*Id.*, 1.) After deuteration, this metabolite increased about 5-fold. (*Id.*, 1, 4; Ex. 2047, 123:20-124:11.) This large increase in the production of such a minor metabolite (which Harada characterized as a "trace" metabolite), is contrary to Petitioner's assertion that metabolic switching is not observed when the alternative metabolic site is only a minor metabolic pathway. (Ex. 2057, ¶38.)

5. Even Where a KIE is Observed *In Vitro*, It Can Be Masked *In Vivo*

POSAs would have appreciated that even if a KIE is observed in a purified enzyme system, it is unpredictable whether an *in vivo* KIE will also result. The complexity of biological systems means that KIE is often masked by competing effects. (Ex. 1008, 49; Ex. 1027, 3 ("The complexity of biological systems and the number of competing effects that can mask the DIE have made the application of deuterium to drug discovery highly unpredictable and challenging."); Ex. 1040, 2.)

The prior art confirms that whether a KIE would be observed *in vivo* cannot be predicted *a priori*. (Ex. 2057, ¶¶19-22.)

Petitioner and its expert acknowledge that an *in vitro* KIE may not be "probative of how" a deuterated drug "would actually perform *in vivo*." (Petition, 40; Ex. 1002, ¶¶118, 123.) For example, Dr. Guengerich asserts that experimental parameters can cause "misleading" *in vitro* results that would not carry through to an *in vivo* environment, and that an *in vitro* KIE "is not necessarily relevant to the 'success' of a deuterated analog; in that what is rate limiting *in vivo* may differ from the *in vitro* results." (Ex. 1002, ¶¶108, 118, 123.) He also acknowledges that where a drug is metabolized by multiple enzymes, deuterium substitution can cause metabolism to switch to a different metabolic pathway. (Ex. 2047, 117:10-119:10; *see* Ex. 2057, ¶22.) This can mask the *in vivo* KIE. (Ex. 2057, ¶¶21-22.)

KIE can be masked *in vivo* by competing biological effects. If this occurs, deuterium substitution will not affect the overall rate of metabolism of the drug in human subjects. (Ex. 1008, 50; Ex. 2057, ¶38.)

6. The Unpredictable Effect of Deuteration on the Clinical Profile

Dr. Guengerich admits that "even if expressed *in vivo*, the KIE that results from deuteration must have [some] effect on a pharmacokinetic parameter of … interest in order to make deuterium substitution useful." (Ex. 1012, 4; Ex. 2047,

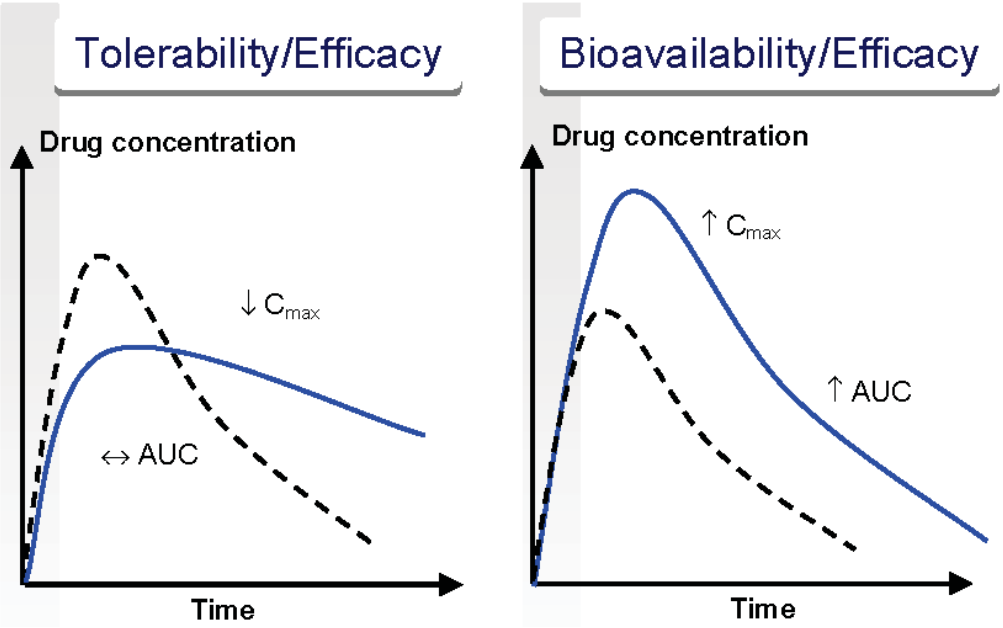
157:21-158:5.) But POSAs would not have been able to predict what type of changes—if any—deuteration would cause in a drug's clinical pharmacokinetic profile. (Ex. 2057, ¶¶20-22.) Deuteration only results in KIE in some cases, and as described below, only some KIEs translate into positive ADME or pharmacokinetic changes.[5] Dr. Guengerich's declaration is devoid of any real evidence demonstrating that POSAs would have expected deuterated ruxolitinib to have a beneficial impact on any relevant pharmacokinetic parameter.

A drug's efficacy and safety depends on both its pharmacodynamic and pharmacokinetic properties. (Ex. 2057, ¶18.) Pharmacodynamic measurements include potency and selectivity. (Ex. 2047, 36:16-37:17.) Pharmacokinetic properties include sufficient ADME. (*Id.*, 36:7-15, 37:8-21.) ADME properties are evaluated using pharmacokinetic measures such as maximum plasma concentration (C_{max}), rate of decrease in plasma concentration (measured as half-life, "$t_{½}$"), and total drug exposure (area under the curve, "AUC"). (Ex. 2057, ¶¶18-19; Ex. 2047, 36:7-15.)

[5] As described above, whether an ADME change is "positive" will depend on the drug, and varies based on characteristics like side effect profile. (*Supra* Section II.D.2.)

Dr. Guengerich's declaration addresses solely the expected pharmacodynamic properties of a deuterated drug. He wrote that deuterated analogs were known to "perform" at least as well as their undeuterated analogs and have the same efficacy (Ex. 1002, ¶91), but at deposition he clarified that in view of the limited scope of work done with deuterated drugs in humans, the opinion he rendered was limited to pharmacodynamic properties and *in vitro* performance. (Ex. 2047, 160:22-162:4.) Yet as Dr. Guengerich admitted, drug safety and efficacy depend on more than just pharmacodynamic properties—they depend on appropriate ADME properties as well. (Ex. 2047, 162:12-16.) Dr. Guengerich did not address these in his declaration. The impact of KIE on ADME as measured by pharmacokinetic parameters is variable and unpredictable. (Ex. 2057, ¶¶21-22; Ex. 1027, 2 ("It is difficult to predict *a priori* which effect deuterium may have on a drug's metabolism."); Ex. 1006, 3 ("[T]he magnitude and nature of the deuterium benefit cannot be predicted *a priori*.").)

Even if a KIE is observed *in vivo*, POSAs could not know the resulting clinical effects. The Concert Backgrounder, relied upon by the Petitioner and its expert, illustrates two possible, but opposite, scenarios of KIE-induced changes to a drug's pharmacokinetic profile, where the solid line shows the effect of deuteration on C_{max} and AUC:



(Ex. 1006, 2.) The hypothetical plasma concentration-time curve on the left shows a *lower* C_{max} with the same total drug exposure (AUC), while the curve on the right shows an *increase* in C_{max} with increased AUC. (Ex. 1002 ¶50 (citing Ex. 1006); Petition at 14; Ex. 2047, 178:21-179:11.) As Dr. Guengerich concedes, these are merely two examples of possible outcomes of deuteration. (Ex. 2047, 180:15-181:6.) Neither Petitioner nor Dr. Guengerich addressed what effect the deuteration of ruxolitinib would have been expected to have on the pharmacokinetic profile of ruxolitinib, and for good reason: it cannot be predicted *a priori* if one of these possibilities—or a different possibility altogether—would result. (Ex. 2057, ¶¶18-22.)

Moreover, even these illustrative scenarios can each have positive or negative effects on safety and efficacy, depending on the characteristics of the relevant drug, such as its side effects. For example, if deuteration results in increased C_{max} as shown in the curve on the right, dose-dependent adverse events may increase. (Ex. 2057, ¶50; Ex. 2047, 179:22-180:4.) This would not be a favorable outcome for a drug such as ruxolitinib, which has dose-dependent side effects. (Ex. 2057, ¶41.)

E. Examples of Unpredictable Results from Deuterating Drugs

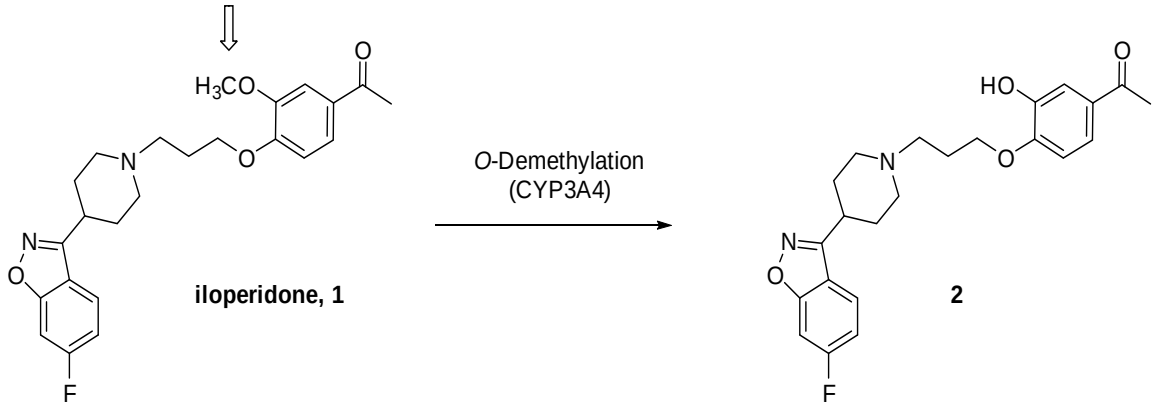
The prior art demonstrates that "the application of deuterium to drug discovery [was] highly unpredictable and challenging." (Ex. 1008, 50 (citation omitted).) Below are just a few prior art examples showing that deuterium modification of drugs, even at "metabolic hotspots," does not improve pharmacokinetic properties in a predictable manner.[6] These are real world examples that help illustrate why experimentation is required before one can know what effect, if any, deuterium modification will have on overall metabolism.

[6] As Dr. Guengerich acknowledged, failures in drug discovery tend to be under-reported, suggesting that there are likely other examples as well. (Ex. 2047 171:21-172:15.)

The first three examples show that deuterium modification can actually decrease metabolic stability, having a different effect from what Petitioner claims would have been expected. The fourth example shows that *in vitro* results do not always carry over into an *in vivo* setting.

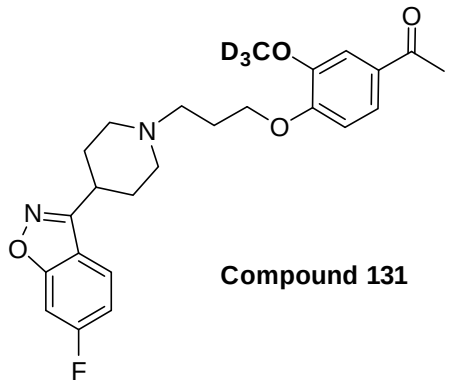
1. Deuterated Iloperidone

Fanapt® (iloperidone) is approved for the treatment of schizophrenia. (Ex. 2029.) In human liver microsomes ("HLM"), CYP3A4 metabolizes iloperidone at the methoxy moiety of the phenyl ring, as indicated by the arrow below:



(Ex. 2020, Fig.1.)

Concert prepared a deuterated iloperidone compound (Compound 131), which was deuterated at this "metabolic hotspot":



Compound 131

(Ex. 2024, ¶5.) As shown below, Concert observed that deuteration at the known metabolic site resulted in *less* metabolic stability compared to iloperidone, *i.e.*, the deuterated compound showed a *shorter* half-life. If this KIE were not masked or otherwise modified *in vivo*, this would translate into a *decrease* in the drug's residence in the body.

***In Vitro* $t_{1/2}$ in HLM**	
Compound	Average $t_{1/2}$ (min)
Iloperidone	59.0
Compound 131	35.4

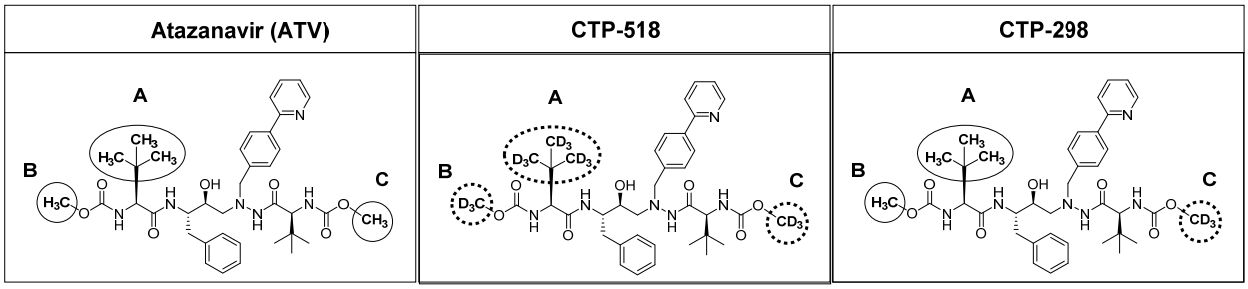
(*Id.*, 7.)

2. Deuterated Atazanavir

Reyataz® (atazanavir) is approved for the treatment of human immunodeficiency virus ("HIV"). (Ex. 1008, 55.) To improve metabolic stability, Reyataz® is dosed with the metabolic inhibitor ritonavir. (*Id.*) Petitioner touts deuterated Reyataz® (atazanavir) as a deuteration "success" in the years

immediately preceding Concert's invention of deuterated ruxolitinib. (Petition, 16.) However, as it moved forward with deuterated atazanavir, Concert encountered unanticipated effects in humans.

Concert prepared deuterated atazanavir compounds, including the clinical candidates CTP-518 and CTP-298, which were each deuterated at known "metabolic hotspots." (Ex. 2001, ¶¶19-22.) The structures of atazanavir ("ATV"), CTP-518, and CTP-298 are shown below:



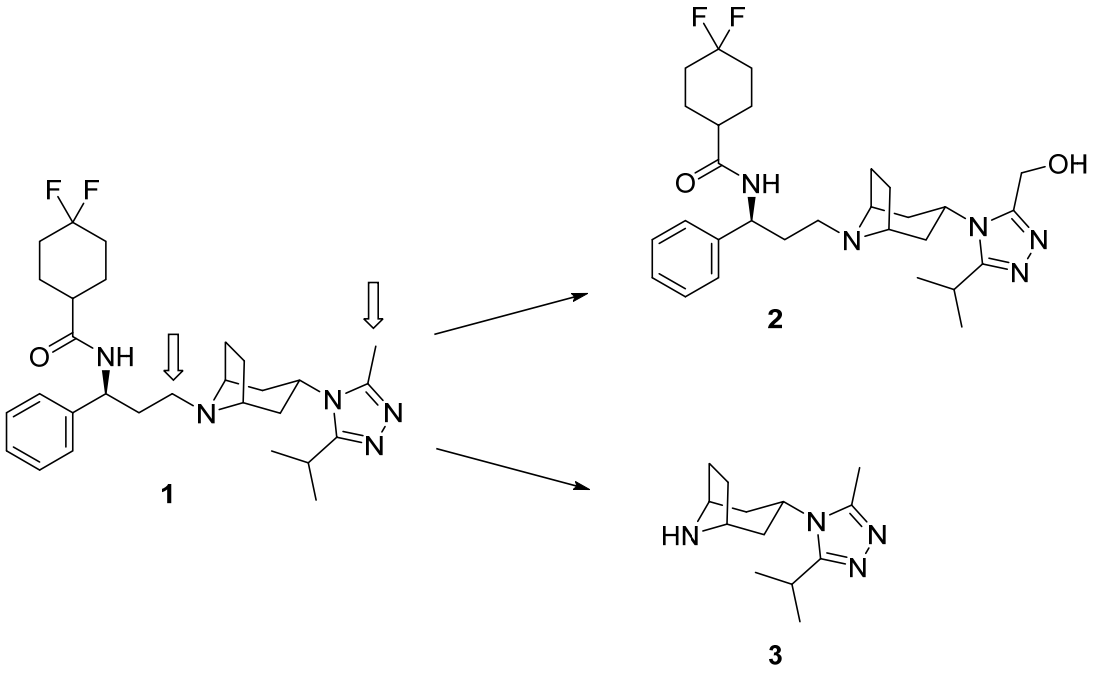
(*Id.*, ¶19.) In Concert's HLM studies, the $t_{½}$ of CTP-518 compared to ATV was extended by 60%, while the $t_{1/2}$ of CTP-298 was extended by only 12%. (*Id.*, ¶21.)

Concert then compared CTP-518 and CTP-298 in two pharmacokinetic crossover studies in healthy human volunteers. (*Id.*, ¶¶23-25.) In these studies, CTP-298 surprisingly proved to be more metabolically stable in humans than either CTP-518 or ATV, while CTP-518 was *considerably worse* than ATV in terms of plasma exposure. (*Id.*) Because CTP-518 has deuteration at the metabolic hotspots labeled as "A" and "B" in the above figure and CTP-298 does not, the

clinical data for CTP-518 was thus the ***opposite*** of what Petitioner asserts would have been expected. (Ex. 2002, ¶64.) Accordingly, the atazanavir example cited in the Petition evidences that deuterium substitution at a drug's known "metabolic hotspots" is not predictable. Deuterating at all three known metabolic hotspots did not improve metabolic stability. Surprisingly, enhanced metabolic stability was observed only for a compound that was deuterated at only one of the known hotspots.

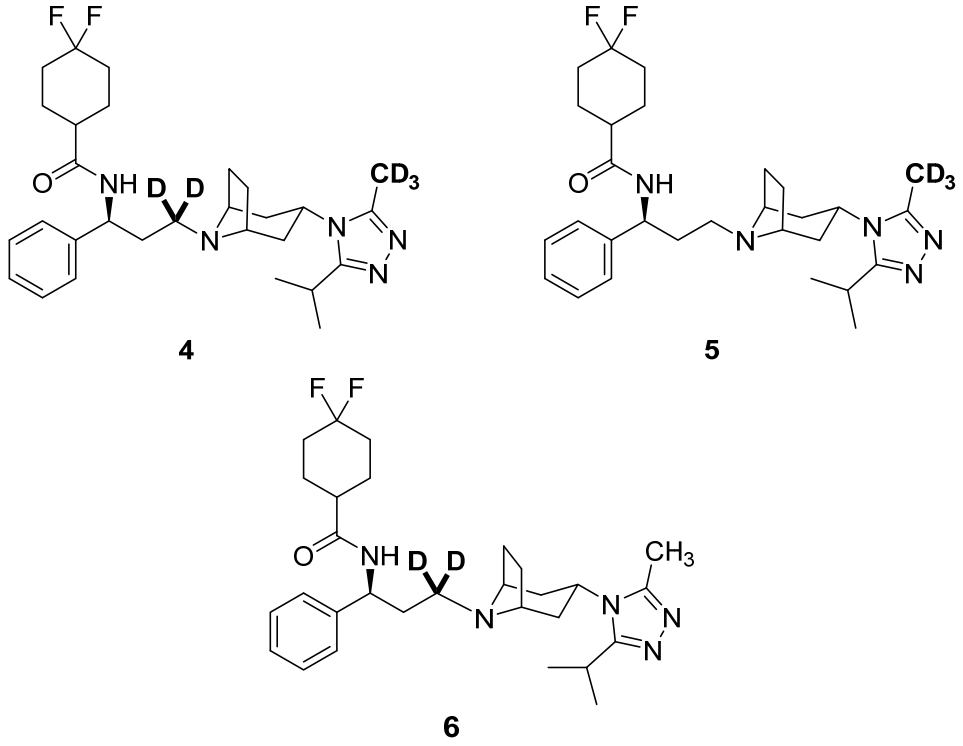
3. Deuterated Maraviroc

Selzentry® (maraviroc) (compound **1** below) is approved for the treatment of HIV infection. (Ex. 2030.) Two of the major metabolic pathways for maraviroc are: (1) oxidation of the methyl group to afford compound **2**; and (2) *N*-dealkylation of the tropane ring to afford compound **3** (arrows indicate metabolic sites):



(Ex. 2021, Fig. 5.)

Concert prepared deuterated compounds **4**, **5,** and **6**:



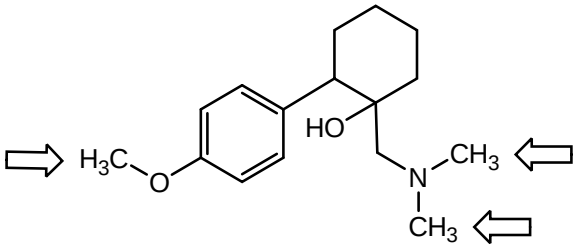
(Ex. 2022, 6.) In HLM studies, only deuteration at both of the metabolic sites (compound **4**) increased $t_{1/2}$ compared with maraviroc, while deuteration at only the methyl group (compound **5**) actually decreased $t_{1/2}$:

***In Vitro* $t_{1/2}$ in HLM**	
Compound	Average $t_{1/2}$ (min)
Maraviroc	97.2
Compound 4	145.5
Compound 5	45.5
Compound 6	95.5

(*Id*., 7; Ex. 2002, ¶70.) Again, a compound deuterated at "metabolic hotspots" actually demonstrated the ***opposite*** effect than that predicted by Petitioner. Moreover, deuteration at only the methylene group (compound **6**), which Petitioner asserts always results in at least some KIE, resulted in little or no change in $t_{1/2}$.

4. Deuterated Tramadol

Even if deuteration increases half-life *in vitro*, there may be no *in vivo* effect. For example, Shao attempted to slow CYP450-mediated metabolism of tramadol by replacing hydrogen with deuterium at metabolically active sites (at the O-methyl and N-methyl groups indicated below by the arrows):



Tramadol

(*See* Exhibit 2025, 3 (describing chemical illustrated above).) Although some of the deuterated compounds exhibited reduced *in vitro* metabolism, clearance was not reduced and *in vivo* half-life was not increased. (*Id.,* 3-4.)

Contrary to Dr. Guengerich's assertion that a KIE will always be observed when deuterating, particularly at a methylene, these examples demonstrate the unpredictability of deuteration, even when deuterating at a methylene. Indeed, Dr. Guengerich himself observed no KIE in deuterating cholesterol at a methylene. (Ex. 1036, 1; Ex. 2047, 201:13-202:12.) Other literature also shows that deuteration at methylenes has not led to meaningful KIEs. (Ex. 2068 (describing *in vivo* study with no meaningful KIE for deuterated tolbutamide); Ex. 2077 (providing *in vitro* data for deuterated tolbutamide); *see also* Ex. 2078 (reporting *in vitro* and *in vivo* data for deuterated nerispirdine).

III. DEUTERIUM-MODIFIED RUXOLITINIB HAS AN UNEXPECTED, CLINICALLY SUPERIOR PHARMACOKINETIC PROFILE COMPARED TO RUXOLITINIB

In view of the state of the art, the properties of the claimed deuterated ruxolitinib compounds are unexpected. Concert compared the pharmacokinetic

profiles of CTP-543 and ruxolitinib by conducting a Phase 1 crossover study in healthy human volunteers. In the study, each subject received one drug followed by the other, with a short break in between. The results of this study, which were not discussed in the Petition, revealed that CTP-543 is clinically superior to ruxolitinib in two different ways, each of which is unexpected and potentially beneficial to treatment of patients. As will be discussed further in Section IX.A below, these attributes are unexpected and favor patentability.

A. CTP-543 Has an Unexpectedly Longer Time in the Therapeutic Window

The first way that CTP-543 showed clinical superiority was in the flattening of the pharmacokinetic curve, showing the prolonged time that drug concentrations of CTP-543 remain in the therapeutic window for treatment of AA.

Concert discovered that ruxolitinib is a more potent inhibitor of the IFN-γ pathway than it is of the EPO pathway. For inhibition of the IFN-γ pathway that provides efficacy for AA, ruxolitinib and deuterated analogs have an IC_{50} (concentration to inhibit 50%) of about 50 nM.[7] (Ex. 2001, ¶¶16-17.) As drug plasma levels drop below about 50 nM, the compounds are expected to become

[7] IC_{50} is a commonly-used benchmark of activity and is useful for comparison purposes.

less effective for treating AA. For inhibition of the EPO pathway that causes unwanted anemia, the compounds have an IC_{50} of about 677 nM. (Ex. 2001, Table 1.) As drug plasma levels rise above about 670 nM, the risk of anemia-associated side effects is expected to increase. As depicted in Figure 3a below, the therapeutic window for the plasma concentration, therefore, is between about 50 nM and about 677 nM.

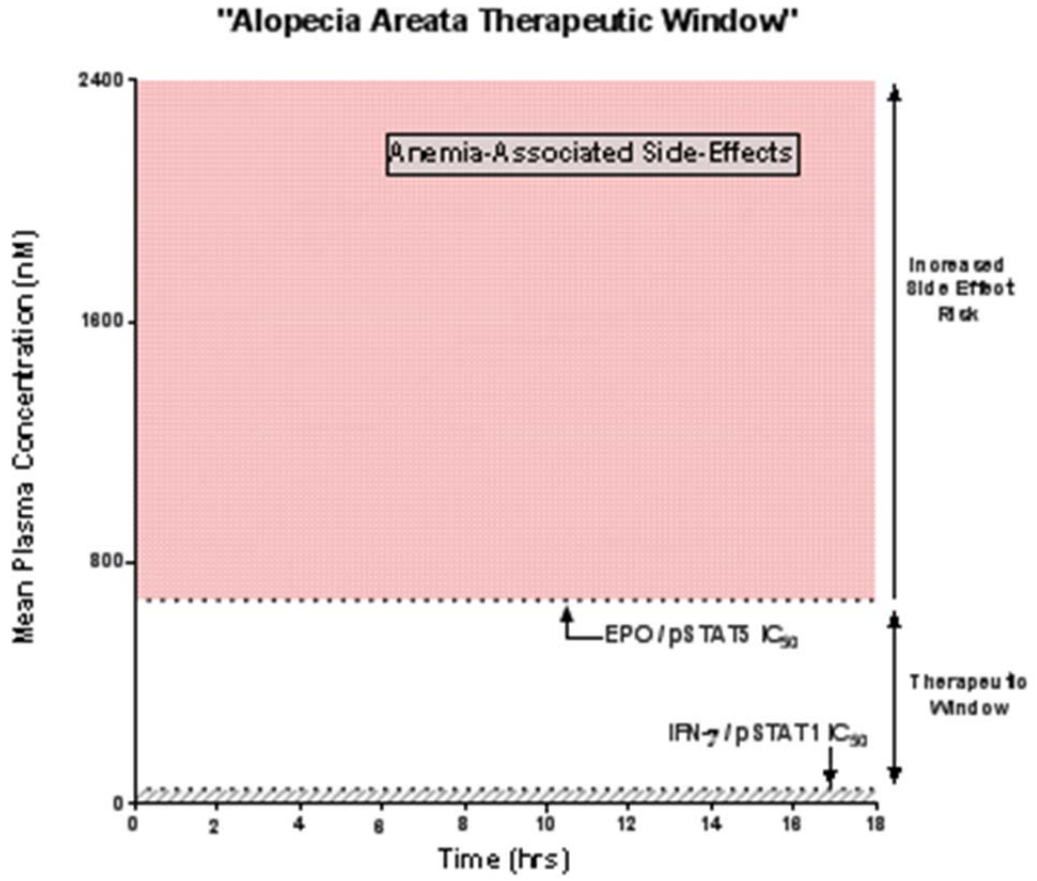


Figure 3a.

(Ex. 2071, ¶5.)

For AA, it is desirable to have a JAK inhibitor that maintains a plasma concentration within this therapeutic window for as long as possible. After ruxolitinib administration, the plasma concentration of drug rises rapidly, reaching a peak level (C_{max}) within 1-2 hours post-dose. (Ex. 2006, 9.) The half-life is about 3 hours. (Ex. 2001, ¶12, Table 3.) Increasing the dose of ruxolitinib, in an effort to prolong the time plasma concentrations are at therapeutically effective levels, would also increase C_{max} and increase the risk of toxicity. (Ex. 2048, ¶33.)

As summarized in Table 4 below, in Concert's Phase 1 study, based on a dose-normalized comparison of CTP-543 and ruxolitinib,[8] CTP-543 showed statistically significant increases in plasma exposure measured by AUC_{inf}, plasma concentration at 12 hours (C_{12hr}), $t_{1/2}$, and a slower rate of drug clearance (CL/F). (Ex. 2001, ¶13.) Importantly, there was no statistically significant change in C_{max}. (*Id.*)

[8] The pharmacokinetic factors were dose normalized to correct for the difference in dosing between ruxolitinib and CTP-543. (Ex. 2001, ¶12.)

Table 4: Comparison of CTP-543 and Ruxolitinib Pharmacokinetic (PK) Parameters		
PK Parameter	**p-value**	**Statistically different ($p < 0.05$)**
C_{max}	0.0941	No
AUC_{inf}	0.0006	Yes
C_{12hr}	0.007	Yes
$t_{1/2}$	0.003	Yes
CL/F	0.0001	Yes

(Ex. 2001, ¶13.) CTP-543 thus demonstrated a flatter pharmacokinetic curve (longer half-life with comparable C_{max}) compared to ruxolitinib, and better potential for maintaining plasma levels within the therapeutic window for AA. (Ex. 2002, ¶50.) The comparison demonstrates that CTP-543 could inhibit the IFN-γ pathway as effectively as ruxolitinib, but for a longer time or with a lower dose. (*Id.*, ¶¶51-52.)

Specifically, CTP-543 achieved plasma concentrations above the IC_{50} level for IFN-γ for 14.9 hours, 2.2 hours longer than did ruxolitinib. (Ex. 2001, ¶17.) Concert modeled how much ruxolitinib would be needed to similarly inhibit the IFN-γ pathway for as long as the single 16 mg dose of CTP-543. The model showed that 27 mg of ruxolitinib would provide the same inhibitory levels as 16 mg of CTP-543. (*Id.*) These results are shown below in Figure 3b:

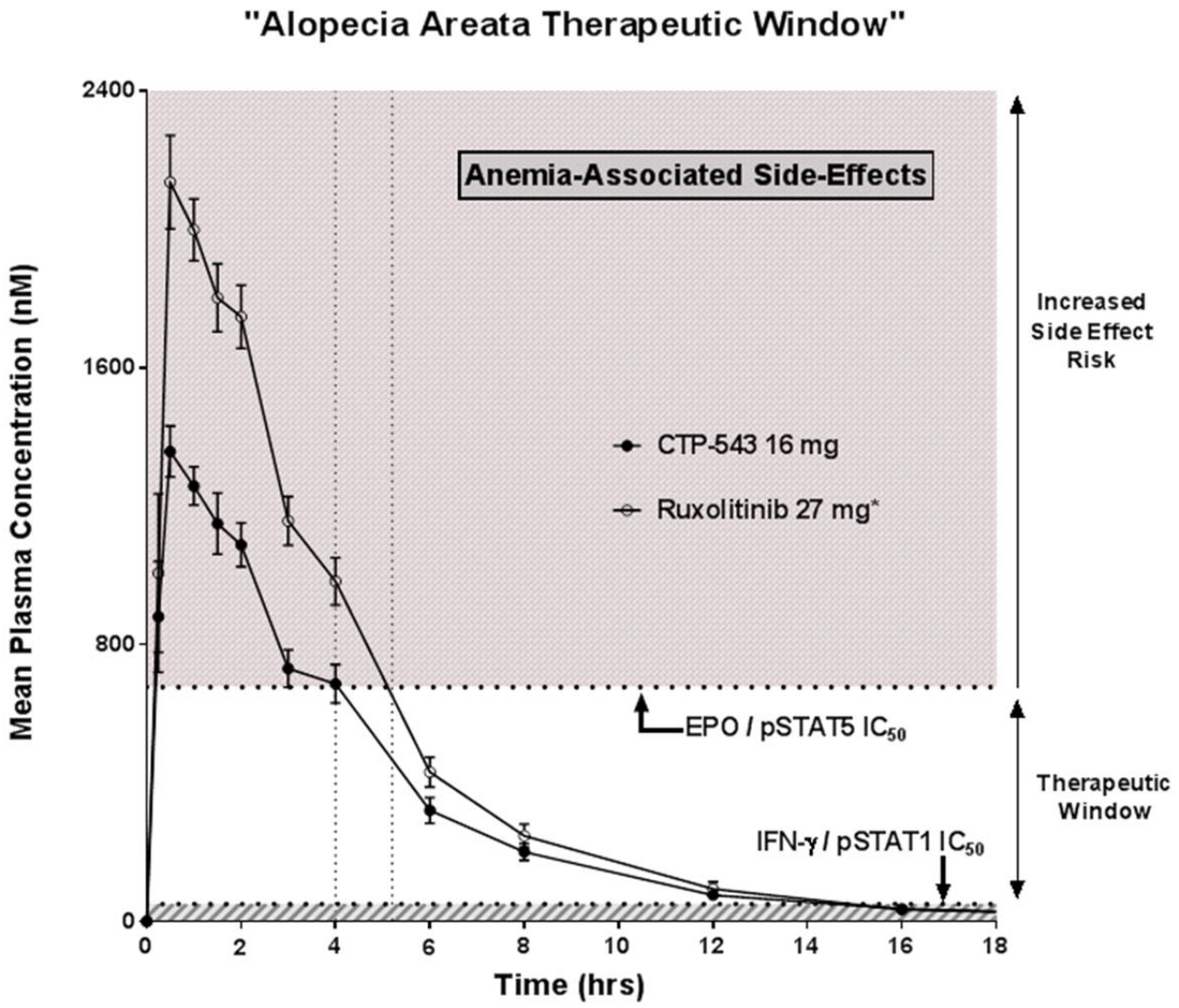


Figure 3b

(Ex. 2071, ¶6.) The flatter pharmacokinetic curve for CTP-543 resulting from an increase in half-life with no statistical change in C_{max} provides CTP-543 with a better potential to maintain plasma levels within the therapeutic window for alopecia areata for longer than ruxolitinib (as indicated by the vertical lines in Figure 3b). (Ex. 2071, ¶¶6-7.) CTP-543 is the first CYP450-metabolized

deuterated drug Concert has encountered that, when compared to the protio compound, has a significantly increased half-life in human subjects without a significant increase in C_{max}. (Ex. 2071, ¶8.) These pharmacokinetics show the potential for a clinical benefit. (Ex. 2048, ¶38.) Specifically, this finding means that doses of CTP-543 that are likely to be effective for AA are less likely to cause C_{max}-related side effects such as anemia compared to similarly-effective doses of ruxolitinib. (*Id.*, ¶39.)

B. CTP-543 Demonstrates a Significant and Unexpected Benefit for Patients Who Rapidly Metabolize Ruxolitinib

The Phase 1 study demonstrated an unexpected, and unexplained, greater benefit for subjects who rapidly metabolize ruxolitinib. The more rapidly a subject metabolized ruxolitinib, the greater the relative increase in half-life that was observed when the subject was given CTP-543. (Ex. 2001, ¶14; Ex. 2002, ¶49.) This greater relative half-life improvement was statistically significant. (Ex. 2001, ¶14.)

The clinical significance of this advantage of CTP-543 is that a greater percentage of the patient population will have drug levels within the therapeutic window for a longer time. Because a shorter $t_{½}$ results in a steeper decline in plasma concentrations, the more rapid metabolizers are likely to have less therapeutic response from a dose of ruxolitinib. (*See* Ex. 2013, 56-60.) Thus,

patients who would rapidly metabolize ruxolitinib are more likely to obtain a clinical response with CTP-543. (Ex. 2048, ¶34.)

This advantage of CTP-543 was unexpected. Concert's declarants are not aware of another example where a comparison of a CYP450-metabolized deuterated drug to a non-deuterated drug showed an inverse relationship between the magnitude of half-life improvement and the half-life for the non-deuterated drug. (Ex. 2001, ¶15; Ex. 2002, ¶53.) POSAs would have expected that if deuteration results in increased half-life, the amount of increase would be similar across subjects. (Ex. 2057, ¶51.) For example, if deuteration slows the rate of overall metabolism such that a normal metabolizers experience a 5% longer half-life, POSAs would have no reason to expect that more rapid metabolizer's increase in half-life would be statistically significantly longer than 5%. (*Id.*) The mechanism for the significant difference between half-life improvement for slower ruxolitinib metabolizers and more rapid metabolizers observed in Concert's CTP-543 study is not taught in the prior art.

In sum, the clinical advantages of CTP-543 over ruxolitinib include (1) the mitigation of dose-limiting toxicity, (2) the ease of determining a dose that balances safety and efficacy, and (3) the potential to treat a greater percentage of the patient population with a dose that is both safe and effective. (Ex. 2048, ¶40.)

C. CTP-543 Satisfies the Long-Felt Need for an FDA-Approved, Evidence-Based Alopecia Areata Treatment

As described above, there has been a long-felt need for an evidence-based AA treatment that does not have unacceptable side effects. (*Supra* Section II.A.) AA patients cannot tolerate the same side-effects that can accompany treatment of life-threatening diseases. (Ex. 2057, ¶53.) While debilitating, AA is not life-threatening. (Ex. 2048, ¶26-27.) A drug that causes severe side effects will therefore be less tolerable for an AA patient than for a cancer patient. (*Id.*, ¶37; Ex. 2057, ¶53.) Furthermore, AA can be a chronic, lifelong condition. (Ex. 2048, ¶27.) Side-effects that may otherwise be tolerable for treating a disease of short duration can be untenable for indefinite maintenance treatment. (*Id.*) There has been a long-felt need for an effective AA treatment with a tolerable long-term side effect profile. (*Id.*, ¶37.)

Concert's clinical studies have shown that CTP-543 is a promising drug to fill this unmet need. Whereas ruxolitinib poses a significant risk of anemia, CTP-543 shows the potential to mitigate this risk with an improved pharmacokinetic and ADME profile resulting in a longer amount of time following each dose wherein plasma concentrations are within the safe and effective treatment window. (*Supra* Sections II.B, II.D.6; Ex. 2048, ¶35.) CTP-543 therefore stands to exhibit a much more tolerable side-effect profile for AA patients than ruxolitinib. (Ex. 2048, ¶36.)

Indeed, in January 2018, the FDA granted CTP-543 a "*Fast Track*" designation, which expedites the review of drugs that treat serious conditions and fill an unmet medical need. (Ex. 2071, ¶9.)

IV. THE '149 PATENT

The '149 Patent issued on February 2, 2016, and claims priority through a chain of applications to an initial provisional application filed on June 15, 2012. The '149 Patent discloses specific deuterated ruxolitinib compounds, including CTP-543.

While the challenged claims cover various deuterated compounds, Petitioner focuses only on octa-deuterated ruxolitinib, 3,3,4,4-tetra-deuterated ruxolitinib, and 2,2,5,5-tetra-deuterated ruxolitinib (Petition, 8-9)—the three compounds recited in claim 7. Accordingly, Concert does the same here.

V. PERSON OF ORDINARY SKILL IN THE ART

Patent Owner proposes the following definition for a POSA:

> A person of ordinary skill in the art would typically have had a master's degree or a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, physical organic chemistry or a related discipline. Alternatively, the person of ordinary skill in the art may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a person of ordinary skill in the art may have collaborated with others of skill in the art, such

> that the individual and/or team collectively would have had experience in synthesizing and analyzing complex organic compounds, developing drugs for human use, including analyzing human pharmacokinetic, pharmacodynamic, and ADME parameters and conducting and evaluating *in vitro* testing, human *in vivo* testing, and/or treating JAK1 or JAK2-mediated diseases and disorders in humans.

(Ex. 2048, ¶5.)

This definition differs from Petitioner's by including human drug development experience, which, based on the cited prior art, is a necessary part of the POSA definition.

VI. PETITIONER HAS NOT SHOWN THAT JAKAFI® LABEL OR CONCERT BACKGROUNDER ARE PRINTED PUBLICATIONS

Petitioner has failed to carry its burden of proving that either Jakafi® label (Ground 1) or Concert Backgrounder (Grounds 1 and 3) are prior art printed publications. 35 U.S.C. § 311(b); *Dynamic Drinkware, LLC v. Nat'l Graphics, Inc.*, 800 F.3d 1375, 1378-79 (Fed. Cir. 2015). On this basis alone, the Board should find that Petitioner has not met its burden to show unpatentability of the challenged claims.

The Board has found that Petitioner has not met its burden of proving that Jakafi® Label (Ex. 1004) is a printed publication. (Institution Decision ("ID"), 12-15.) That decision was correct and should be adopted in a final decision.

With respect to the Concert Backgrounder, while the Board found that Petitioner met its initial burden of production, the Board specifically noted that it did "not make a final determination as to the public accessibility of Concert Backgrounder." (ID, 16-18.) Petitioner has not and cannot make the required showing.

Petitioner relies solely on the document's purported availability on a "cached WebCite® page" to demonstrate public accessibility. (Petition, 27-29.) Even taking this at face value, Petitioner has at most established that the Concert Backgrounder was available at a specific location on www.webcitation.org. But availability on the internet alone is not sufficient to show public accessibility. *Blue Calypso, LLC v. Groupon, Inc.*, 815 F.3d 1331, 1349 (Fed. Cir. 2016). Petitioner must also demonstrate that the document was publicly accessible to POSAs, *e.g.*, by showing that it was disseminated or otherwise made available such that POSAs exercising reasonable diligence could locate it. *Id.* at 1348-49; *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006); *Hospitality Core*

Servs. LLC v. Nomadix Inc., IPR2016-00052, Paper 8, 8-11 (P.T.A.B. Apr. 27, 2016).

When, as here, a challenger asserts that a document was "publicly accessible" by virtue of its presence on a website, the Board and Federal Circuit look to whether the website was adequately indexed. *See Adobe Sys. Inc. v. Grecia*, IPR2018-00418, Paper No. 7 at 8-10 (P.T.A.B. June 21, 2018) (collecting cases); *id.* at 11 ("To determine a date on which [the reference] was publicly accessible, we look to evidence of . . . any search capability of the library's website."). In *Blue Calypso*, the Federal Circuit affirmed the Board's finding that petitioner failed to establish that POSAs, exercising reasonable diligence, would have a located a report ("Ratsimor") that was published on a webpage. 815 F.3d at 1350-51. That outcome was compelled because the "record [was] devoid of any evidence that a query of a search engine before the critical date, using any combination of search words, would have led to Ratsimor appearing in the search results." *Id*. at 1349-50.

Similarly, in *SRI*, the Federal Circuit vacated summary judgment of invalidity where there was insufficient evidence to show that a document purportedly published on a file transfer protocol (FTP) server was publicly accessible. *SRI Int'l, Inc. v. Internet Sec. Sys., Inc.*, 511 F.3d 1186, 1195 (Fed. Cir.

2008). In *SRI*, there was no evidence that the FTP server contained "an index or catalogue or other tools for customary and meaningful research." *Id.* at 1196. The Federal Circuit found it insufficient evidence that one person had accessed the document on the FTP server, pointing to a prior case in which knowledge of a document's publication by three people was not enough to show printed publication status. *Id.* 1195-96 (citing *Application of Bayer*, 568 F.2d 1357, 1358-59 (C.C.P.A. 1978)). It was also important that the one person in *SRI* who knew of the document had been provided with the document's full FTP address, instead of having searched the FTP to locate it. *Id.* at 1196. Thus, the Federal Circuit concluded that the record "d[id] not show that an anonymous user skilled in the art . . . would have gained access to the FTP server and would have freely navigated through the directory structure to find the [document]." *Id.*

Here, too, there is no evidence that WebCite® was catalogued or indexed such that POSAs would have been able to access the Concert Backgrounder on WebCite®, whether through search engine results or by a search of WebCite® itself. Indeed, the evidence affirmatively indicates that this was *not* the case. WebCite®'s internal search function appears to be limited to URL, date, and "snapshot ID" (unique numeric ID) searches. (Ex. 2026, 1, 9.) The apparent lack of ability to perform keyword searches suggests that documents hosted on WebCite® are not

indexed for text searchability internally on WebCite® or externally on a search engine. Thus, not only is the record "devoid of any evidence that a query of a search engine before the critical date, using any combination of search words, would have led to" Concert Backgrounder on WebCite®, *Blue Calypso*, 815 F.3d at 1350, but the apparent lack of text searchability also affirmatively suggests that Concert Backgrounder on WebCite® would *not* have been located using a search engine query or an internal search of the website. *See Adobe*, IPR2018-00418, Paper No. 7 at 10-12 (denying institution where affidavit from the "Wayback Machine" Internet Archive did "not indicate that the archived files are searchable through a subject matter index or catalog").

Petitioner contends that the public accessibility is "evidenced by its use in a law review article published in 2009, which cited the same WebCite® page used in th[e] petition" and/or by its use in an International Search Report (ISR) for a Concert patent application. (Petition, 28.) Again, this at most establishes that the document was available on WebCite®. The Federal Circuit has found that even specific knowledge of the relevant document by one to three individuals does not demonstrate public accessibility of a document hosted in an un-indexed, un-catalogued location. *See SRI*, 511 F.3d at 1195-96. On the face of the law review article and the ISR, both the author and examiner possessed the full WebCite®

address for the Concert Backgrounder (http://www.webcitation.org/5e81SGCnl). *See* Ex. 1018, 45; Ex. 1021, 3. Thus, even if there *were* any evidence that WebCite® is indexed or catalogued, there is no evidence that either the law review author or the examiner found the Concert Backgrounder by searching for it, the way a POSA would have to, as opposed to by having been provided with the full web address (as was the case in *SRI*). As in *SRI*, the record here "does not show that an anonymous user skilled in the art" in 2012 "would have gained access to" WebCite® "and would have freely navigated through the directory structure to find" Concert Backgrounder.[9] 511 F.3d at 1196. Petitioner has not shown how or why POSAs, exercising reasonable diligence, could have located it.[10]

[9] Moreover, Petitioner has not established that the Concert Backgrounder cited in the ISR is the same as Ex. 1016. The ISR references a document cached on 26.01.2009, while Ex. 1016 was purportedly cached on 27.01.2009. (*Compare* Ex. 1021, 3 *with* Ex. 1016, 1.)

[10] Petitioner asserts that other patent applicants have also cited the Concert Backgrounder. (Petition at 28 n.2.) Two of the cited patents have purported priority dates after the '149 Patent priority date, and thus fail to inform whether the Concert Backgrounder is prior art to the '149 Patent claims. The other two patents

In sum, Petitioner has not established that POSAs, doing the type of searches POSAs would have performed, would have located this marketing document. While the Board found that Petitioner satisfied its initial burden of production, Petitioner's corroborating evidence falls far short of meeting its burden of persuasion, which is fatal to both instituted Grounds.

VII. THE CHALLENGED CLAIMS ARE NOT OBVIOUS BECAUSE THERE WAS AFFIRMATIVE MOTIVATION NOT TO DEUTERATE RUXOLITINIB

Petitioner cannot demonstrate unpatentability because it cannot show motivation to combine the asserted references to arrive at the claimed compounds. Indeed, the full record now demonstrates that not only was there no motivation for POSAs to deuterate ruxolitinib, but the state of the art actually provided affirmative reasons *not* to do this. This evidence was not before the Board when it instituted IPR.

At institution, the Board was required to credit Petitioner's expert testimony that POSAs would have expected similar properties for deuterated and protio ruxolitinib. Under the Federal Circuit's structural similarity cases (*Aventis* and

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issued after the '149 Patent's priority date, and Petitioner has not shown when the document became part of the prosecution histories.

Dillon), the Board concluded that this was a sufficient showing of motivation for institution. (ID, 21-23.) Now, the contrary evidence and expert testimony that Concert newly provides here disproves the notion that similar functionality under *Aventis* would have been expected between deuterated and protio ruxolitinib, which was the sole basis for the Board's agreement with Petitioner's assertion of motivation.

A. POSAs Would Have Been Affirmatively Motivated Not to Attempt Modifying Ruxolitinib's Metabolism Through Deuteration

The state of the art in 2012 does not support a motivation for POSAs to arrive at the claimed compounds. In fact, the prior art taught that ruxolitinib had dose-limiting toxic side effects that could be exacerbated by slowing its metabolism, providing POSAs with affirmative motivation *not* to attempt ADME modification. (Ex. 2047, 92:5-11 (acknowledging that thrombocytopenia is dose-dependent, and that dose-dependent side effects increase as dose increases.) Dr. Guengerich did not address adverse events or the effect of ruxolitinib deuteration on adverse events. (*Id.*, 91:10-20.) Nor did he offer an opinion on whether ruxolitinib's known side effects were caused by the parent drug or any of its metabolites. (*Id.*) This is fatal to Petitioner's argument. *InTouch Techs., Inc. v. VGO Commc'ns, Inc.*, 751 F.3d 1327, 1348-49 (Fed. Cir. 2014).

As described above, ruxolitinib was known to have toxic side effects caused by the same mechanism of action responsible for its activity. (*Supra* Section II.C.) POSAs thus would have been affirmatively motivated *not* to undertake deuterium substitution for ruxolitinib, due to its concomitant risk of increasing toxicity. (Ex. 2057, ¶41.)

POSAs' affirmative motivation not to arrive at the claimed compounds demonstrates that they are not obvious. *Millennium Pharms. v. Sandoz Inc.*, 862 F.3d 1356, 1366 (Fed. Cir. 2017) (POSAs would have avoided modifying prior art given "evidence that the chemical modification of [prior art compound] would have been unattractive to a person of ordinary skill for fear of disturbing the chemical properties whereby [the compound] function[ed] effectively"); *DePuy Spine v. Medtronic Sofamor Danek*, 567 F.3d 1314, 1326 (Fed. Cir. 2009) ("An inference of nonobviousness is especially strong where the prior art's teachings undermine the very reason being proffered as to why a person of ordinary skill would have combined the known elements."). Here, ruxolitinib's dose-dependent toxicity would have dissuaded POSAs from trying to change the metabolic profile via deuteration.

A preexisting compound (here, ruxolitinib) will only support the obviousness of a new, modified compound where there is a motivation to make the

particular modifications that result in the claimed invention (here, deuteration). *Takeda Chem. Indus. v. Alphapharm Pty.*, 492 F.3d 1350, 1356 (Fed. Cir. 2007) ("[I]n order to find a prima facie case of unpatentability . . . , a showing that the prior art would have suggested making *the specific molecular modifications necessary to achieve the claimed invention* [i]s also required." (emphasis added) (citation omitted)). Petitioner cannot make this showing, and its obviousness challenges should also be rejected on that basis. Deuteration is relatively expensive and highly unpredictable. (Ex. 2057, ¶39.) POSAs would have pursued other clinically-validated strategies for increasing a drug's metabolic stability instead of deuteration, such as the use of extended release dosage forms. (Ex. 2057, ¶43.) As of 2012, use of extended release dosage forms were routine, and such dosage forms were much more reliable than deuteration for lowering C_{max}. (*Id.*, ¶44.) In fact, after the priority date of the '149 patent, Petitioner itself took this approach to mitigate the side effects of ruxolitinib. (*See generally* Ex. 2056.)

Petitioner has made no showing of why POSAs would have been motivated to modify ruxolitinib's metabolism by deuteration, rather than other available methods for modifying metabolic profile. At best, the Petition merely sets forth some general reasons why POSAs might have been motivated to deuterate drugs *generally*, but provides no justification for why POSAs would have been motivated

to deuterate ruxolitinib *in particular* to arrive at the claimed compounds.[11] But to prevail, Petitioner must show "that the prior art would have suggested making the *specific* molecular modifications necessary to achieve the claimed invention"—*i.e.*, deuterating ruxolitinib to arrive at the claimed octa- and tetra-deuterated compounds.[12] *Takeda*, 492 F.3d at 1356 (emphasis added).

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[11] Under Petitioner's logic, POSAs would have been motivated to deuterate the vast majority of FDA-approved drug molecules. According to Dr. Guengerich, CYP450 enzymes are involved in the metabolism of "75% of all drugs used today." (Ex. 1002, ¶45.) Further, nearly all FDA-approved drugs have metabolic hotspots, known efficacy and safety, and address clinically-validated targets. (Ex. 2047, 172:16-175:1.) The standard for demonstrating motivation under *KSR* will not support such a blanket conclusion. *Takeda*, 492 F.3d at 1356-57 (noting the "importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does'" (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 418 (2007)).

[12] Even if POSAs were motivated to deuterate ruxolitinib, Petitioner has not established any motivation to prepare the two tetra-deuterated compounds

B. POSAs Would Not Have Been Motivated to Arrive at the Claimed Compounds Based on Structural Similarity to Ruxolitinib

Petitioner has not met its burden to show that POSAs would have been motivated to create the claimed compounds. In its Petition (and in the Institute Decision), the sole basis for such a motivation derived from the Federal Circuit's cases finding that motivation to produce a claimed compound can be based on structural similarity to a prior art compound (*Aventis* and *Dillon*). *Aventis* and *Dillon* require that, before motivation can be assumed, POSAs would need to expect similar properties of the prior art and claimed compounds. *Aventis Pharma Deutschland GmbH v. Lupin, Ltd.*, 499 F.3d 1293, 1301 (Fed. Cir. 2007) (quoting *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990)). Petitioner has not made this showing.

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discussed in the Petition. In both compounds, deuterium is absent at either position 2 or 3 of the cyclopentyl ring, but Shilling teaches that metabolic oxidation occurs at ***both*** positions. (Ex. 1005, 6, 8; Ex. 1002, ¶70.) Moreover, POSAs would have had no reasonable expectation of success that this partial deuterium substitution would result in a significant KIE, due to the possibility of metabolic switching. (Ex. 1002, ¶¶72-75.)

At institution, the Board was required to resolve factual disputes in Petitioner's favor, and thus the Board credited Dr. Guengerich's assertion that POSAs would "expect at least the same efficacy" from deuterated and protio ruxolitinib. (ID, 21-23.) It was this assertion that satisfied the Board that Petitioner had met its initial burden to show motivation under *Aventis* and *Dillon*. (*Id.*) But it is clear on the record now before the Board that this assertion is incorrect.

Motivation to arrive at a modified new compound can be shown by a "sufficiently close" structural relationship to a prior art compound *only where* POSAs would have had "'an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis*, 499 F.3d at 1301 (quoting *Dillon*, 919 F.2d at 692). In *Aventis*, the Federal Circuit found that patent claims directed to a particular stereoisomer[13] isolated from a mixture of stereoisomers were obvious. *Id.* The Court explained that "[o]rdinarily, one expects a concentrated or purified ingredient to retain the same properties it exhibited in a mixture," and noted that "isolation of interesting compounds is a

[13] Stereoisomers are molecules with the same chemical formula that differ only in the spatial arrangement of their atoms. *Aventis*, 499 F.3d at 1295.

mainstay of the chemist's art." *Id.* at 1302. The result in *Aventis* (that motivation could be assumed) relied on the *known* properties of a stereoisomer based on the *known* properties of the prior art mixture.

As an initial matter, this case is factually different from *Aventis* and *Dillon*. In *Aventis*, the blood pressure drug ramipril in pure stereoisomer form was found to be *prima facie* obvious because it was known in the prior art in a less pure form, and the prior art "provide[d] sufficient reason" to believe the claimed stereoisomer was the active form. *Aventis*, 499 F.3d at 1302. In *Dillon*, the claim to a fuel additive containing a tetra-orthoester was found to be *prima facie* obvious over the prior art fuel additive having instead a tri-orthoester. The *Dillon* court relied on the *known* equivalence of the tri- and tetra-orthoester in finding obviousness. *Dillon*, 919 F.2d at 694. Here, the claimed deuterated ruxolitinib compounds did not exist in the prior art, and Petitioner has not established an expectation of the similar properties that were dispositive in *Aventis* and *Dillon*.

Aventis does not broadly stand for the proposition that a showing of motivation is unnecessary for structurally-similar compounds. Instead, Petitioner must show some reason why POSAs would expect a deuterated drug to have similar properties to the protio compound in order for an assumed motivation under *Aventis* and *Dillon* to apply. *See also Rhone Poulenc Agro, S.A. v. DeKalb*

Genetics Corp., 272 F.3d 1335, 1357 (Fed. Cir. 2001) (vacated on unrelated grounds) (before assuming motivation, first requiring challenger to demonstrate that the claimed composition would be expected to have "similar properties" to a structurally-similar prior art compound). The Federal Circuit recently explained that "the chemical arts are unpredictable and that similar structures do not always result in similar properties." *Anacor Pharm., Inc. v. Iancu*, 889 F.3d 1372, 1385 (Fed. Cir. 2018) (citing *Eisai Co. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1359 (Fed. Cir. 2008)). Accordingly, even where a claimed compound is structurally similar to a prior art compound, the "obviousness inquiry often depends on whether there is evidence demonstrating *a nexus between* structural similarities (or dissimilarities) and ***functional similarities (or dissimilarities)***." *Id.* (emphasis added).

On the full record before the Board, POSAs would *not* have had an expectation that the claimed deuterated compounds would have had "functional similarities" to protio ruxolitinib. Far from a "concentrated or purified ingredient" that would have been expected to "to retain the same properties" that the *same ingredient* "exhibited in a mixture" (*Aventis*, 499 F.3d at 1301), a deuterated drug

is a *different molecule* from the protio compound.[14] A drug's properties include not only pharmacodynamic measures such as potency and selectivity, but pharmacokinetic and ADME properties as well. As explained above, while the expectation is that a deuterated drug will have similar pharmacodynamic properties as the protio drug, whether a deuterated drug's ADME and pharmacokinetic properties would become better, worse, or stay the same after deuteration was entirely unpredictable. Petitioner itself has pointed to the Concert Backgrounder which describes the possibility of dissimilar properties. As discussed, in some cases, the dissimilar properties resulting from deuteration would be detrimental, as, for example, when the C_{max} of a drug with dose-dependent toxicities is increased for the deuterated drug. (*Supra* Sections II.D.6.) In light of this unpredictability, POSAs would not have been able to form any "expectation" about whether the claimed deuterated compounds would have had functional similarities to protio ruxolitinib. (Ex. 2057, ¶45.)

[14] Even further, the FDA has determined that a deuterated version of an existing drug is a New Chemical Entity that requires its own clinical evidence of safety and efficacy. (Ex. 2074.)

As its only support for motivation under *Aventis*, Petitioner relies on Dr. Guengerich's assertion that deuterated drugs have "selectivity and potency comparable to their hydrogen analogs." (Petition, 30-31; Ex. 1002, ¶55.) In turn, Dr. Guengerich's sole support is a quotation from Concert's CEO saying, "[W]e've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it." (Ex. 1002, ¶¶55, 88.) But Dr. Guengerich conceded that a drug's safety and efficacy depend on more than sufficient selectivity and potency. (Ex. 2047, 36:7-37:17.) Dr. Guengerich thus does not even assert that POSAs would have expected that *all* the relevant properties would be similar. Accordingly, Petitioner's "'conclusory statements' alone are insufficient" to show motivation, which "must be supported by a 'reasoned explanation.'" *In re Nuvasive, Inc.*, 842 F.3d 1376, 1383 (Fed. Cir. 2016) (citation omitted).

Petitioner's mere reference to similar selectivity and potency therefore falls far short of its burden to show that POSAs would have had an "expectation, in light of the totality of the prior art" that the claimed deuterated compounds would have had "functional similarities" to protio ruxolitinib. *Aventis*, 499 F.3d at 1301; *Anacor*, 889 F.3d at 1385.

VIII. THE CHALLENGED CLAIMS ARE NOT OBVIOUS BECAUSE POSAs WOULD NOT HAVE HAD A REASONABLE EXPECTATION OF SUCCESS IN ARRIVING AT THE CLAIMED INVENTIONS

Even if Petitioner were able to show that POSAs would have been motivated to use deuteration in an attempt to modify ruxolitinib's metabolism, Petitioner cannot carry its burden to show that POSAs would have had a reasonable expectation of success in doing so. To establish obviousness of a new compound, Petitioner must show a reasonable expectation of its advantageous properties. *Mylan Labs. Ltd. v. Aventis Pharma S.A.*, IPR2016-00627, Paper 10, at 11 (P.T.A.B. Aug. 23, 2016) (quoting *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012)); *Neptune Generics, LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25, at 19 (P.T.A.B. Dec. 9, 2015) (denying institution on a patent to a deuterated drug, where the prior art supported the unpredictability of deuteration on pharmacology and toxicity).

The full record now demonstrates that POSAs would not have had a reasonable expectation of success in achieving advantageous properties. As explained above, there was unpredictability of the deuterium effect at each level of metabolism and drug clearance—(1) whether deuteration would result in an *in vitro* KIE, which depended on the characteristics of the catalytic cycle for the CYP450 enzyme(s) and drug involved, (2) whether an *in vitro* KIE would be

expressed *in vivo* or would be masked by competing biological effects, and (3) what ADME changes, if any, would result from an *in vivo* KIE. (*Supra* Sections II.D.)

Petitioner's reasonable expectation of success argument is founded on the incorrect assumption that deuterating at metabolic hotspots "predictably" leads to "altered" metabolism. (Petition, 35.) Petitioner's arguments are at odds with the state of the art. Appreciating the complexity of each stage of deuteration, in view of examples such as those described in Section II.D, POSAs would have known that deuterating "hotspots" does not predictably lead to a compound having both increased metabolic stability and adequate safety and efficacy.

A. POSAs Would Not Have Had a Reasonable Expectation of Achieving an *in Vitro* KIE From Deuterating Ruxolitinib

As described above, whether an *in vitro* KIE will result from deuteration is complicated and unpredictable. (*Supra* Sections II.D.3, 4.) In 2012, POSAs would have known that KIE expression was not simply a function of whether C-H bond breaking is rate-limiting. (*Id.*) Instead, it was known that the existence and magnitude of *in vitro* KIE was more complex and varied, requiring a branched pathway immediately before the C-H bond breaking step in the catalytic cycle for the relevant enzyme(s) and the relevant drug. (*Id.*)

Petitioner asserts that POSAs would have expected deuteration of ruxolitinib at its methylenes to result in a KIE because the C-H bond breaking step in the CYP450 catalytic cycle is purportedly always at least partially rate-limiting when methylenes are involved. (Ex. 2002, ¶53.) This assertion is contrary to the state of the art showing that C-H bond breaking is not generally rate limiting. (Ex. 2057, ¶32.) Petitioner's view is refuted by findings that the intermediate immediately preceding the C-H bond-breaking step does not accumulate and mechanistic studies that have suggested the transformation from that intermediate to the product is rapid. (Ex. 2043, 1, 4.) The weight of this evidence strongly suggests that the C-H bond breaking step is not in fact rate-limiting. (Ex. 2057, ¶32.) Therefore, whether deuterium modification will result in meaningful KIE is much more complicated than the over-simplified and incorrect picture that Dr. Guengerich describes. Concert's own examples of deuteration of drugs yielding unpredictable KIE's is indicative of this complexity. (*Supra* Section II.E.)

Dr. Guengerich admitted that nothing in the prior art expressly teaches the supposed maxim that where a C-D bond is a methylene, you will always see KIE. (Ex. 2047, 156:17-157:19.) As he acknowledged in his prior art publications, "exactly which of the individual steps . . . is rate limiting has been debated for many years." (Ex. 2045, 12.) While Dr. Guengerich asserted at deposition that the

debate was resolved following his 2013 review article (Ex. 2047, 155:6-156:16), that paper published in 2013 and is therefore not prior art. (Ex. 1012.) Further, Dr. Guengerich is not aware of any acknowledgement that the debate about identity of the rate-limiting step had been resolved, in view of his review paper or otherwise. (Ex. 2047, 200:1-201:5.) In addition, he admitted that in 2012, others in the art held the view that the electron reduction steps, not the C-H bond breaking step, were rate-limiting. (*Id.*, 201:7-21.) Indeed, in 2011 Dr. Guengerich himself published work on deuterated cholesterol showing that the C-H bond-breaking step was not rate-limiting, despite the fact that the bond was a methylene. (*Id.*, 201:13-203:3.)

Whether or not a KIE is observed (and its magnitude) is entirely unpredictable. (Ex. 2057, ¶29.) Where the C-H bond breaking step is not rate-limiting, generally, there will be no meaningful KIE observed. (Ex. 2057, ¶29) In the handful of instances where Dr. Guengerich has observed a KIE, the prior art explains that this can happen when there is an alternative branched pathway in the CYP450 cycle just before the C-H bond breaking step. (Ex. 2057, ¶32.) As shown in Figure 2 above (*supra* at 14), there are sometimes, though not always, three branched pathways whereby the reaction can be shifted back to an earlier point in the catalytic cycle without oxidizing (metabolizing) the substrate. (Ex. 2057, ¶30;

Ex. 2062, 9.) One of these branched pathways (depicted in red in Figure 2), immediately preceding the C-H bond cleavage step, produces water and diverts away from oxidation of the substrate. (Ex. 2057, ¶33; Ex. 2062, 6, 8-9.) There is no measure of predictability about whether or not a KIE will be observed, and the magnitude of such a KIE, if any, which will depend entirely on whether this branched pathway exists for a given CYP450 enzyme and substrate combination, and its magnitude and relative kinetics. (Ex. 2057, ¶35.) This is entirely unpredictable without experimentation. (*Id.*)

Dr. Guengerich's declaration includes a cursory paragraph briefly acknowledging this complexity of the CYP450 catalytic cycle before improperly dismissing it. He notes the prior art teaching that "there must be a 'branch'" in the catalytic cycle "to observe an isotope effect when a C-H bond is broken." (Ex. 1002, ¶113), and he acknowledged at deposition that whether this water formation pathway occurs depends on the particular substrate. (Ex. 2047, 211:21-212:6, 212:22-213:11.) But he makes no attempt to describe the extent to which it was known whether the alternative branch exists for the metabolism of ruxolitinib. (Ex. 2057, ¶29; Ex. 2062, 9.) Before actually deuterating a compound like ruxolitinib, POSAs in 2012 (or today) would not know whether the branched pathway exists in the catalytic cycle for the compound and relevant CYP450

enzyme(s), or if it exists, how significant the branched pathway is in that reaction. (Ex. 2057, ¶26.) The prior art taught that these unknowns are together responsible for the unpredictable existence and extent of KIE. (*Id.* ¶22.)

Dr. Guengerich himself acknowledged this uncertainty in his own prior art publication: "Relatively little information is available regarding what step is rate-limiting in P4503A4 reactions. . . . [W]ithout information on the extent to which chemical steps (e.g. substrate oxidation) limit catalysis, it will not be possible to understand or predict the behavior of this system."[15] (Ex. 1035, 1.) He also personally observed at least two instances where C-H bond breaking was not rate-limiting. In the metabolism of testosterone, he concluded that C-H bond breaking "is not rate-limiting," and that "other steps in the catalytic cycle make major rate-limiting contributions." (*Id.*, 9, 10 (also noting that the C-H bond breaking step

[15] Dr. Guengerich asserted at deposition that between 2005 and 2012, new information became available that indicated that C-H bond breaking in P450 3A4 is rate-limiting—specifically, his 2005 paper relating to testosterone. (Ex. 2047, 136:11-22.) But this 2005 paper expressly stated that the C-H bond-breaking step was *not* rate-limiting, and his litigation-inspired effort to disavow the clear statements in his prior-art publication should be rejected. (*Id.*, 145:7-146:10.)

"appears to be less rate-limiting in P450 3A4 reactions than with several reactions catalyzed by other mammalian P450s . . . .").) For cholesterol, he concluded that the electron transfer reduction steps, not the C-H bond-breaking step, were rate-limiting. (Ex. 1036, 1; Ex. 2047, 201:13-202:12.)

POSAs would not have had a reasonable expectation of achieving an *in vitro* KIE from deuterating ruxolitinib without knowing what CYP450 enzymes are responsible for metabolism and, for each such enzyme, how significant the branched pathways are. (Ex. 2057, ¶¶33-35.) Dr. Guengerich cites only to Jakafi® Label—which, the Board found, has not been shown to be a printed publication—as support for the alleged knowledge that ruxolitinib was described "as metabolized by CYP3A4 and to a lesser extent by CYP2C9." (Ex. 1002, ¶46.) But the Jakafi® Label Dr. Guengerich cites does not mention CYP2C9 (Ex. 2047, 80:3-81:3), nor does any other reference in the Grounds identify any relevant enzyme(s) whatsoever. (*Id.*, 94:12-15 (admitting that Shilling does not specify which CYP450 enzymes are involved in ruxolitinib's metabolism). Rather, CYP2C9 was not identified in the Jakafi® Label until after the priority date (Ex. 2006, 9), meaning that the prior art picture for ruxolitinib metabolism was incomplete. Further, even if POSAs would have believed that ruxolitinib was primarily metabolized by CYP3A4, Dr. Guengerich's own publication suggested it would

"not be possible to understand or predict the behavior of this system" because the rate-limiting step for CYP3A4 metabolism was unknown. (Ex. 1035, 1.)

Petitioner's theory that a KIE will be observed if the breaking of the C-H bond is at least partially rate-limiting in ruxolitinib metabolism oversimplifies CYP450 metabolism and ignores disagreement in the art about the rate-limiting step. (*Supra* Section II.D.3.) Regardless, even if Petitioner's theory is accepted, POSAs would not have known or been able to predict whether the breaking of the C-H bond would have been the rate-limiting step in the metabolic oxidation of ruxolitinib. (*Supra* Section II.D.)

Finally, even if a KIE is observed, metabolic switching to other parts of the molecule can mask the *in vitro* KIE. (*See, e.g.*, Ex. 1040, 4; Ex. 1027, 4; Ex. 1008, 50; Ex. 2023, 2.) Petitioner cites no prior art that taught whether metabolic switching would occur with deuterated ruxolitinib. Petitioner suggests that the degree of metabolism at an alternate site will influence whether this phenomenon occurs (Petition, 38), but as discussed above, this is contradicted by the Harada reference on which Dr. Guengerich relies. (*Supra* at 18; Ex. 1033, 1, 5.) Rather, it is the relationship between the topology of the enzyme's active site and the structure of the substrate that drives metabolic switching. (Ex. 2023, 1-2.)

Petitioner has not posited any prior art information about this relationship with respect to ruxolitinib.

B. Even if an *in Vitro* KIE Were Demonstrated, POSAs Would Not Have Had a Reasonable Expectation of Achieving an *in Vivo* KIE from Deuterating Ruxolitinib

Petitioner and Dr. Guengerich agree that POSAs cannot expect the expression of an *in vivo* KIE, even where a KIE is present *in vitro*. The art cited in the Petition consistently refers to the unpredictability of producing an *in vivo* KIE from deuteration. (*See, e.g.*, Ex. 1008, 50 ("The complexity of biological systems and the number of competing effects in enzyme-catalyzed reactions that can mask the DIE have made the application of deuterium to drug discovery highly unpredictable and challenging."); Ex. 1027, 3-4 (same); Ex. 1010, 3 ("[Deuteration] might be a bit rockier than expected. Blocking a site of *in vitro* metabolism with a deuterium atom may not improve half-life because the metabolic profile may be different *in vivo*, or metabolic switching might shunt metabolism toward a (previously) minor pathway.").) And Dr. Guengerich argues that CTP-543's unexpected *in vitro* KIE was "not probative of how" the drug "would actually perform *in vivo*." (Ex. 1002, ¶¶118-129; Petition, 40.) He also acknowledges that "what is rate limiting *in vivo* may differ from the *in vitro* results." (Ex. 1002, ¶108.)

Beyond the complexity inherent in CYP450 metabolism on the enzyme level, ADME processes lend much greater uncertainty to the fate of the drug *in vivo*. Deuteration can lead to metabolic switching, which can cause further unpredictability. (*Supra* Section II.D.4.) In many cases, molecules are metabolized by multiple different enzymes. (Ex. 2047, 110:18-111:9.) As Dr. Guengerich acknowledged, not only can it be difficult to determine exactly which enzymes are responsible for metabolism *in vivo*, but other factors such as substrate concentration and enzyme saturation come into play. (*Id.*, 33:11-:22.) If deuteration inhibits metabolism at a preferred site, metabolism may switch to another metabolic pathway, which can mask an *in vivo* KIE. (*Id.*, 34:16-35:1; Ex. 2057, ¶¶21-22; *supra* Section II.D.5.) As noted above, the prior art does not provide a full picture of the metabolism of ruxolitinib, and Dr. Guengerich concedes that to be able to predict whether a KIE observed *in vivo* will cause any change in the relative prevalence of different metabolic pathways, a prerequisite is to know what metabolic pathways are implicated for a particular drug. (Ex. 2047, 117:10-118:2.)

C. POSAs Would Not Have Predicted the Effect of Deuteration on the Clinical Profile

As discussed above (Section II.D.6), even where an *in vivo* KIE is observed, POSAs would not have been able to predict *a priori* what effect it would have on

the clinical profile of the drug. The field is far from being as predictable as Petitioner suggests. The Concert Backgrounder, upon which Petitioner relies, describes very different possible clinical profiles when there is an *in vivo* KIE. (Ex. 2057, ¶¶46-50.) Further when Concert studied deuterated atazanavir in human volunteers, another example Petitioner points to, deuteration was found to *shorten* half-life (*supra* at 25), thereby producing the opposite effect to the one Petitioner argues POSAs would have expected.

Dr. Guengerich asserts that any isotope effect would be expected to result in a pharmacokinetic change (Ex. 2047, 191:3-10), but his declaration does not describe *how* the pharmacokinetics would change. As such, Petitioner has not demonstrated that POSAs would have expected that deuterating ruxolitinib would result in a safe and efficacious new drug, and thus has not carried it burden of demonstrating obviousness.

IX. OBJECTIVE INDICIA OF NONOBVIOUSNESS SUPPORT THE PATENTABILITY OF THE CHALLENGED CLAIMS

The non-obviousness of the claims is also supported by secondary considerations of non-obviousness, including unexpected results and satisfaction of a long-felt need.

A. Unexpected Results

As discussed above, two important and clinically meaningful unexpected advantages of CTP-543 over ruxolitinib were not addressed in the Petition: (a) an increased time in the therapeutic window, and (b) increased clinical response at a given dose. *Procter & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009) (evidence "that the claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" strongly supports non-obviousness); *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

1. Increased Time in the Therapeutic Window

Both non-clinical and clinical studies show that, relative to ruxolitinib, CTP-543 has the potential to demonstrate an unexpected clinical benefit by maintaining safe and effective drug levels for a longer period. This increased time in the therapeutic window is due to pharmacokinetic differences between the drugs that are especially favorable for CTP-543 with respect to its potential to treat AA. (Ex. 2002, ¶50.) In particular, as discussed above, doses of CTP-543 that are likely to be effective in the treatment of AA are less likely to cause anemia than similarly-effective doses of ruxolitinib. (*Supra* Section III.A.)

Neither Shilling nor the Concert Backgrounder explain this increased time in the therapeutic window or suggest why it would have been expected. While the

Concert Backgrounder provides two model illustrations for how deuteration might possibly change pharmacokinetic and ADME properties, there is no way a POSA would know which one, if any, to expect. The scenario that illustrates an increase in C_{max} would be detrimental due to the increased risk of side effects. (Ex. 1006, 2.) Petitioner's analogy to torcetrapib is likewise inapposite, because that argument also relies on the lowering of C_{max}, which is not the case for CTP-543.

2. Greater Clinical Response for Patients Who Rapidly Metabolize Ruxolitinib

Another unexpected advantage of CTP-543 is the potential for an increased clinical response at a given dose. (*Supra* Section III.B.) Patient populations are heterogeneous and display a range of pharmacokinetic profiles for a given dose of drug. (Ex. 2002, ¶49.) As a result, not all patients receiving drug will benefit to the same degree. (*Id.*) As described above, individuals in Concert's Phase 1 study with the shortest ruxolitinib $t_{1/2}$ values unexpectedly had the greatest improvement in $t_{1/2}$ values when given CTP-543. (*Supra* Section III.B.) An increased clinical response at a given dose would be clinically meaningful because a patient would be more likely to benefit from treatment. (Ex. 2048, ¶¶40-41.)

Petitioner does not cite any prior art disclosure showing that deuterium modification can provide a greater benefit in $t_{1/2}$ to more rapid CYP3A4 metabolizers, much less any reason why POSAs would have expected to observe

such a benefit for any drug, let alone for deuterated ruxolitinib. Patent Owner and Dr. Baillie are not aware of any other reported examples where a deuterated compound of a CYP3A4-metabolized drug provides a proportionately greater benefit in $t_{1/2}$ to those subjects with the shortest $t_{1/2}$ for the protio drug. (Ex. 2001, ¶15; Ex. 2002, ¶53.) These unexpected clinical benefits are highly probative of nonobviousness.

B. Long-Felt Need

Concert is developing CTP-543 as a first-in-class treatment satisfying the long-felt need for a safe and effective AA treatment. As described above, existing treatment options for AA patients in 2012 promised little efficacy and carried potentially significant side effects. (*Supra* Sections II.A, III.C.) For example, ruxolitinib is known to suppress IFN-γ immune function and as such, may have potential use in moderating AA. (Ex. 2009, 1-2.) But ruxolitinib poses a risk of anemia and thrombocytopenia due to its inhibition of the EPO pathway. (*Supra* Section II.B.) These side effects are already undesirable in the context of treating the blood cancers for which ruxolitinib is FDA-approved. They would become even more burdensome in the context of chronic, maintenance treatment for AA. (Ex. 2048, ¶27.) There has been a long-felt need for an AA treatment that is not only effective, but also safe for prolonged use. (*Id.*, ¶40.)

CTP-543's unexpected clinical improvements over ruxolitinib make it uniquely suited to meet this need. Because of deuterium modifications, CTP-543 has a longer half-life than ruxolitinib, and plasma concentrations of CTP-543 therefore spend a longer time in the therapeutic window for AA treatment. (*Supra* Section II.D.6.) This increased time in the therapeutic window and potential for greater therapeutic response at a given dose show the promise of CTP-543 to help AA patients while mitigating the risk of undesirable side effects posed by ruxolitinib. (Ex. 2048, ¶38; Ex. 2002, ¶54.) The FDA's award of a "*Fast Track*" designation to CTP-543 underscores the importance of the need satisfied by the octa-deuterated compound of the '149 patent. (Ex. 2071, ¶9.) Petitioner's hindsight-driven narrative that the challenged claims were merely the result of ordinary skill cannot be reconciled with the longstanding need that the '149 invention satisfied. *WBIP*, *LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016) ("Evidence of a long felt but unresolved need tends to show non-obviousness because it is reasonable to infer that the need would have not persisted had the solution been obvious.").

X. CONCLUSION

As demonstrated herein, Petitioner has failed to carry its burden of proving that the challenged claims are unpatentable by a preponderance of the evidence,

and the Board should therefore reject Petitioner's challenges to claims 1-15 of the '149 patent and refuse to cancel the claims.

Respectfully submitted,

Date: July 2, 2018

By: /*Cynthia Lambert Hardman*/

Cynthia Lambert Hardman (Reg. No. 53,179)
Marta Delsignore (Reg. No. 32,689)
GOODWIN PROCTER LLP
The New York Times Building
620 Eighth Avenue
New York, NY 10018-1405
Tel: 212-813-8800
Fax: 212-355-3333
chardman@goodwinlaw.com
mdelsignore@goodwinlaw.com

Daryl K. Wiesen (*pro hac vice* request to be filed)
Emily Rapalino (*pro hac vice* request to be filed))
Sarah J. Fischer (Reg. No. 74,104)
GOODWIN PROCTER LLP
100 Northern Avenue
Boston MA 02210-1980
Tel: 617-570-1000
Fax: 617-523-1231
dwiesen@goodwinlaw.com
erapalino@goodwinlaw.com
sfischer@goodwinlaw.com

CERTIFICATE OF COMPLIANCE

This Paper contains 13,867 words, excluding the portions exempted by 37 C.F.R. ¶42.24(a)(1). Accordingly, this Paper complies with the requirements of 37 C.F.R. § 42.24(b)(1).

Respectfully submitted,

Date: July 2, 2018

By: /*Cynthia Lambert Hardman*/
Cynthia Lambert Hardman
Registration No. 53,179

CERTIFICATE OF SERVICE

The undersigned hereby certifies that the foregoing document captioned "**PATENT OWNER RESPONSE**," including Exhibits 2032-2065, 2068-2071, and 2074-2079 cited therein, was served electronically via e-mail on this 2nd day of July, 2018, as follows:

Stephen B. Maebuis
Michele M. Simkin
Foley & Lardner LLP
3000 K St. NW, Ste. 600
Washington, D.C., 20007
smaebius@foley.com
msimkin@foley.com
incyte_concert_ipr@foley.com

Thomas L. Irving
Mark Feldstein
Maureen Queler
Christopher McDavid
Finnegan, Henderson, Farabow, Garrett & Dunner, LLP
tom.irving@finnegan.com
mark.feldstein@finnegan.com
maureen.queler@finnegan.com
christopher.mcdavid@finnegan.com

Counsel for Petitioner Incyte Corp.

/*Cynthia Lambert Hardman*/
Cynthia Lambert Hardman
Registration No. 53,179