UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

INCYTE CORPORATION,

Petitioner,

v.

CONCERT PHARMACEUTICALS, INC.,

Patent Owner.

Case IPR 2017-01256

Patent 9,249,149

PETITION FOR *INTER PARTES* REVIEW OF CLAIMS 1 – 15 OF U.S. PATENT NO. 9,249,149

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1027	Harbeson, et al., Deuterium in Drug Discovery and Development, *Annual Report Med. Chem*., vol. 46, pp. 403-417 (2011)

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1028	Concert Declarations filed August 18, 2011 in US SN 12/150,107 and August 6, 2009 in US SN 11/957,442
1029	Morgan, et al., Design and Synthesis of Deuterated Analogs of Ivacaftor With Enhanced Pharmacokinetic Properties (2012)
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1035	Krauser, J.A., and Guengerich, F.P., "Cytochrome P450 3A4-Catalyzed Testosterone 6β -Hydroxylation: Stereochemistry, Kinetic Deuterium Isotope Effects, and Rate-limiting Steps," *J. Biol. Chem. 280,* pp. 19496-19506 (2005)
1036	Shinkyo, R., and Guengerich, F.P., "Cytochrome P450 7A1 Cholesterol 7α-Hydroxylation. Individual Reaction Steps in the Catalytic Cycle and Rate-limiting Ferric Iron Reduction." *J. Biol. Chem. 286*, pp. 4632-4643 (2011)

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1039	Foster, A.B., "Deuterium isotope effects in studies of drug metabolism" *Trends in Pharmacological Sciences*, *5*, pp. 524-527 (1984)
1040	Fisher et al., *Curr. Opinion in Drug Discovery & Dev*., 9, pp. 101-109 (2006)
1041	Foster, A.B., *Advances in Drug Research*, 14, pp. 1-40 (1985)

I. Mandatory Notices

A. Real Party-In-Interest (37 C.F.R. § 42.8(b)(1))

The real-party-in-interest for this petition is Incyte Corporation.

B. Related Matters (37 C.F.R. § 42.8(b)(2))

Pending U.S. Patent Application No. 14/570,954 was filed on December 15, 2014 and remains pending. U.S. Pat. No. 9,249,149 (the "'149 Patent," Ex. 1001) is a continuation of U.S. Patent Application No. 14/570,954.

C. Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	Back-up Counsel
Stephen B. Maebius Registration No. 35,264 (202) 672-5569 smaebius@foley.com	Michele M. Simkin Registration No. 34,717 (202) 672-5538 msimkin@foley.com

D. Notice of Service Information (37 C.F.R. § 42.8(b)(4))

Please direct all correspondence regarding this Petition to counsel at the following address:

incyte_concert_ipr@foley.com.

Petitioner consents to service by email at the addresses above.

II. Requirements for *Inter Partes* Review

A. Payment of Fees

This petition is accompanied by payment of $23,000.

B. Grounds For Standing

Petitioner certifies that the ’149 Patent is available for *inter partes* review and that the petitioner is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition. The ’149 Patent claims priority to pre-AIA priority documents (earliest filing date June 15, 2012), and was treated by the U.S. Patent Office as a pre-AIA patent. For the purposes of this *inter partes* review petition, Petitioner does not dispute the claim to priority; and thus, the ’149 Patent is subject to *inter partes* review as of its date of grant. 37 C.F.R. § 42.102(a)(2).

C. Statement of Precise Relief Requested

All claims of the ’149 Patent should be held unpatentable under 35 U.S.C. § 103(a) as obvious over:

(1) Jakafi® (ruxolitinib) Prescribing Information (Ex. 1004), Shilling et al., "Metabolism, excretion, and pharmacokinetics of [14C]INCB018424, a selective Janus tyrosine kinase 1/2 inhibitor, in humans," *Drug Metabolism and Disposition*, 38(11): 2023-2031 (2010) (“Shilling,” Ex. 1005), and the Concert Precision Deuterium Chemistry Backgrounder (2007) (“Concert Backgrounder,” Ex. 1006); and

(2) U.S. Pat. No. 7,598,257 to Rodgers et al. (“Rodgers,” Ex. 1007), Shilling (Ex. 1005), and the Concert Backgrounder (Ex. 1006).

All claims of the ’149 Patent should also be held unpatentable under 35 U.S.C. § 102(b) as anticipated by:

Rodgers (Ex. 1007).

The specific grounds are:

Ground	Claims	Description
1	1-15	Obvious under §103 over Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder
2	1-15	Anticipated under §102 by Rodgers
3	1-15	Obvious under §103 over Rodgers, Shilling, and the Concert Backgrounder

As explained below, Jakafi® (ruxolitinib) Prescribing Information is prior art under Section 102(a), and Shilling, the Concert Backgrounder, and Rodgers are each prior art under at least Section 102(b).

D. Threshold Requirement For *Inter Partes* Review

This petition demonstrates the required “reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a).

E. Statement of Reasons For Relief Requested

The Board should institute review of all claims of the ’149 Patent because all of the claims would have been anticipated and/or obvious over the cited prior art based on the grounds specified above. Anticipation is due to the disclosure of the subject matter of all claims of the ’149 Patent in the Rodgers reference.

Obviousness is due to a *prima facie* case that all claims of the ’149 Patent are rendered obvious over the prior art, and by a lack of sufficient evidence of secondary considerations to overcome the *prima facie* case of obviousness. This petition presents two grounds of obviousness and one ground of anticipation.

Petitioner urges institution of review on all grounds in this petition because certain references asserted in the petition are prior art under Section 102(a) and potentially subject to antedating.

III. Introduction

Incyte Corporation (“Incyte” or “Petitioner”) requests review of U.S. Patent No. 9,249,149 (“the ’149 Patent,” Ex. 1001) by Silverman et al., entitled “Deuterated derivatives of ruxolitinib,” issued on February 2, 2016. U.S. Patent Office records indicate the ’149 Patent is assigned to Concert Pharmaceuticals, Inc. (“Concert” or “Patent Owner”). This Petition demonstrates a reasonable likelihood that claims 1-15 of the ’149 Patent are unpatentable in view of the identified prior art.

This petition relies on a Declaration by Professor F. Peter Guengerich, Ph.D. (“Guengerich Declaration,” Ex. 1002). Prof. Guengerich is the Tadashi Inagami Professor of Biochemistry in the Department of Biochemistry at the Vanderbilt University School of Medicine. Ex. 1002, ¶ 1. Prof. Guengerich has been a professor at the Vanderbilt University School of Medicine for over 40 years.

During his career, Prof. Guengerich and his research group have made numerous contributions to the field of biochemistry and medicinal chemistry, with a particular emphasis on mechanisms of activation and detoxication of chemical carcinogens and toxicants, as well as characterization of enzymes involved in these processes. Prof. Guengerich's work has included significant contributions in the topics relevant to the technology relating to the '149 Patent. As summarized in his declaration and *curriculum vitae,* Prof. Guengerich has many further qualifications, including almost 700 original peer-reviewed scientific articles and more than 200 invited reviews and chapters, along with numerous positions on editorial boards, professional memberships and consulting positions. Ex. 1002, ¶¶ 2-12; Ex. 1003.

Prof. Guengerich's testimony, along with several references used in the present grounds, were not before the U.S. Patent Office during prosecution of the application leading to the '149 Patent.

IV. The '149 Patent Claims

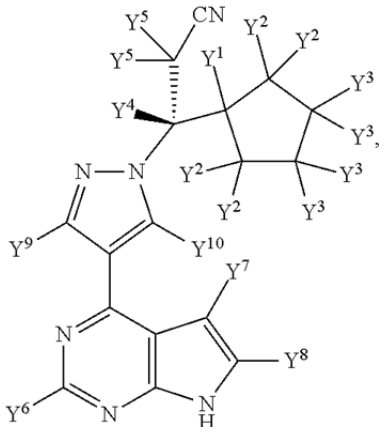
The claims of the '149 Patent recite deuterated analogs of the FDA-approved, small-molecule pharmaceutical, ruxolitinib and pharmaceutical compositions comprising these deuterated analogs. Ex. 1001, 36:16-48:44; Ex. 1002, ¶¶ 32-40; Ex. 1004.

The '149 Patent has two independent claims: claims 1 and 9.

Claim 1 recites:

1. A compound of Formula A:

Formula A



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each $Y^2$is the same;

each Y^3 is selected from hydrogen and deuterium, and each $Y^3$is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7, Y^8 , $Y^{9,}$ and Y^{10} are each independently selected from hydrogen and deuterium; provided that:

each Y^2 is deuterium; or

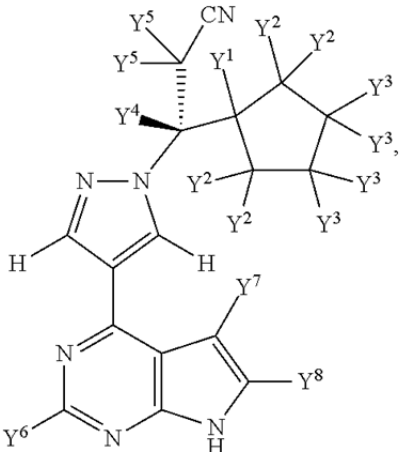
each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

Claim 9 recites a slightly more limited genus as follows:

9. A compound of Formula I:

Formula I



or a pharmaceutically acceptable salt thereof, wherein:

Y^1 is hydrogen;

each Y^2 is selected from hydrogen and deuterium, and each Y^2 is the same;

each Y^3 is selected from hydrogen and deuterium, and each Y^3 is the same;

Y^4 is selected from hydrogen and deuterium;

each Y^5 is the same and is selected from hydrogen and deuterium; and

Y^6, Y^7 and Y^8 are each independently selected from hydrogen and deuterium; provided that:

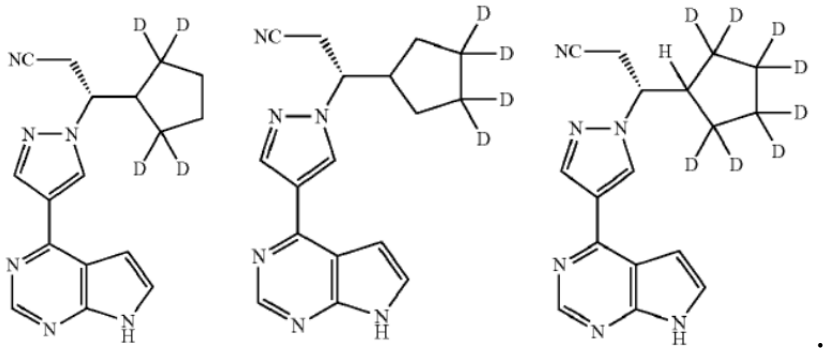
each Y^2 is deuterium; or

each Y^3 is deuterium; or

each Y^2 and each Y^3 is deuterium.

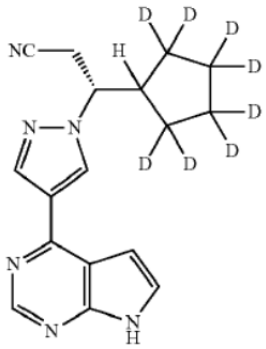
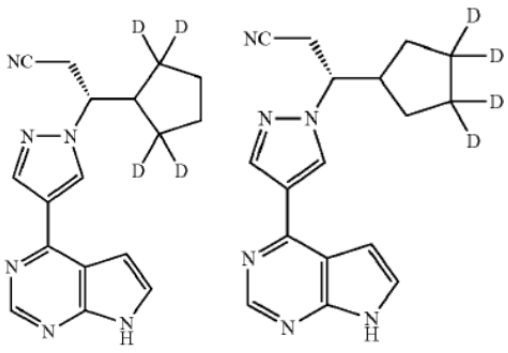
Ex. 1001, 36:15-54, 38:1-32.

Claims 2-7 and 9-14 depend directly or indirectly from claim 1 or 9, and recite a number of different deuteration patterns of ruxolitinib. However, each claim encompasses at least one of the following three compounds:



Ex. 1002, ¶ 33. Claims 1, 2, 5-7, 9, 10, 13, and 14 each read on the following "octa-deuterated" ruxolitinib analog, and claims 1-4, 6, 7, 9-12, and 14 each read on the following "tetra-deuterated" ruxolitinib analogs. Ex. 1002, ¶¶ 33-39.

For the sake of efficiency, this Petition focuses on the patentability of these three ruxolitinib derivatives, which will be referred to as follows:

	
"octa-deuterated ruxolitinib"	"tetra-deuterated ruxolitinib"

Finally, claims 8 and 15 recite pharmaceutical compositions comprising the compound of either claim 1 or 9 and a pharmaceutically acceptable carrier.

None of the claims is directed to a particular method of use or treatment with the deuterated analogs of ruxolitinib. Ex. 1002, ¶ 40.

V. Person of Ordinary Skill in the Art

A Person of Ordinary Skill in the Art ("POSA") is a hypothetical person who is presumed to be aware of all the pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the subject matter of the '149 Patent, as of June 15, 2012 (*i.e.*, the earliest filing date of the '149 Patent) a POSA 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 POSA may have had a lesser degree in one of those fields, but accompanied by more experience. To the extent necessary, a POSA 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. Ex. 1002, ¶¶ 15-18.

VI. Background Knowledge in the Art Prior to June 15, 2012

The background publications discussed below, along with those relied on by Prof. Guengerich, reflect general knowledge a POSA may have brought to bear in reading and interpreting the prior art as of the earliest filing date of the '149 Patent,

and thereby assist in understanding why one would have been motivated to combine or modify the references asserted in this Petition.

In short, as of June 15, 2012, the following fundamental concepts were well established in the art: (A) the oxidative metabolism of pharmaceutical compounds; (B) the deuteration of pharmaceutical compounds to slow metabolism; and (C) ruxolitinib and its established utility. Ex. 1002, ¶ 42. This portion of the petition addresses each in turn.

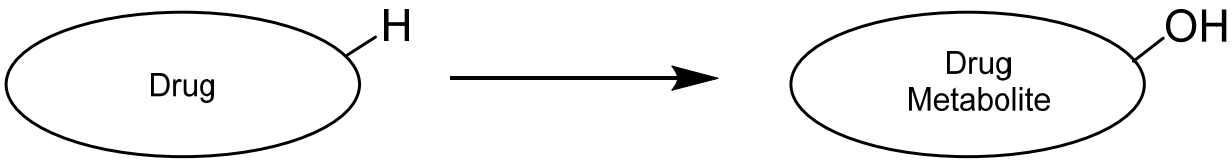
A. Oxidative Metabolism, Including Cytochrome P450 Enzymatic Oxidation

Well before June 15, 2012, it was understood that drugs and other environmental chemicals that enter the body are modified by a vast array of enzymes. Ex. 1002, ¶ 43. The biochemical transformations performed by these enzymes can alter the compound to render it beneficial, harmful, or simply ineffective. The processes by which biochemical reactions alter drugs within the body are collectively called drug metabolism or drug biotransformation. *Id*.

Orally administered drugs are often absorbed in the gastrointestinal ("GI") tract and transported directly to the liver via the portal circulation. Ex. 1002, ¶ 44. In this manner, the liver has the opportunity to metabolize drugs before they reach the systemic circulation, and consequently, before they reach their target organs. *Id*. This so-called "first-pass effect" must be taken into account when designing

dosing regimens because, if hepatic (liver) metabolism is extensive, the amount of drug that reaches the target tissue may be much less than the amount (dose) that is administered orally. *Id*.

An example of a common hepatic metabolism mechanism is an oxidation reaction of the compound by membrane-associated enzymes expressed in the endoplasmic reticulum of liver cells. For example, it has been understood for many decades that a common process in drug metabolism is the oxidation of a C–H group in a molecule to form a C–OH group. Ex. 1002, ¶¶ 47-48. This change in the compound structure is depicted in the simplified diagram below, and in many cases, allows the body to more efficiently eliminate the compound. *Id*.



The enzymes that catalyze these reactions are typically oxidases; the majority of these enzymes are hemeprotein monooxygenases of the cyochrome P450 class (often referred to generally as P450s). Ex. 1002, ¶¶ 45-48. Cytochrome P450 (sometimes abbreviated "CYP") enzymes are involved in the metabolism of approximately 75% of all drugs used today that are cleared by metabolism. Ex. 1002, ¶ 45. Cytochrome P450 enzymes are numerous, and

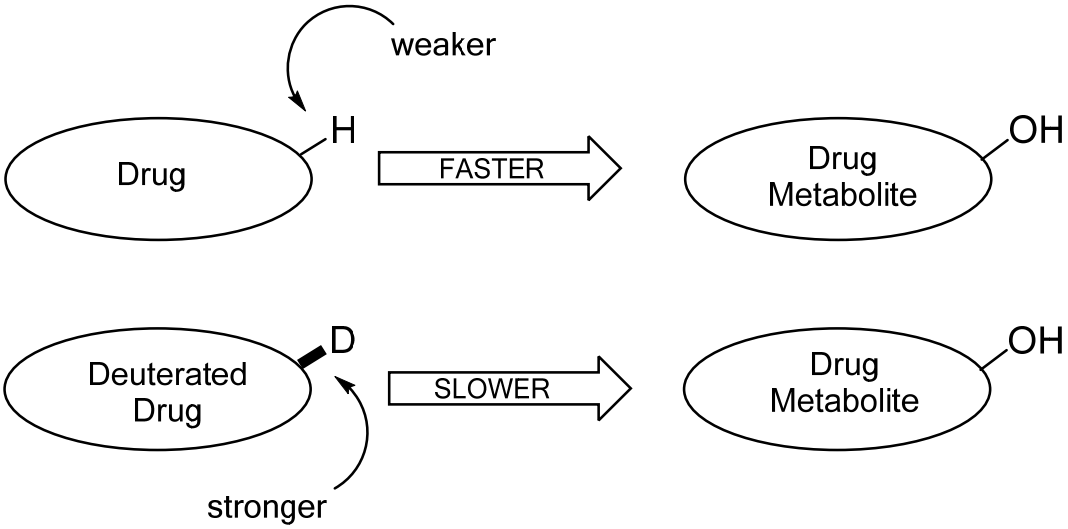
specific cytochrome P450 enzymes, such as CYP3A4 and CYP2C9, were known in the art prior to June 15, 2012. Ex. 1002, ¶ 46.

B. Deuterated Analogs of Known Active Compounds

Replacing a protium hydrogen ("H" also commonly referred to as "^{1}H") in a C–H bond with deuterium ("D" also commonly referred to as "^{2}H") forms a *9-times* stronger C–D bond that both (1) makes a stronger bond, and (2) gives rise to what is termed a kinetic (deuterium) isotope effect ("KIE"). Ex. 1002, ¶¶ 50-53. This concept was first discovered in the early part of the twentieth century, and has been applied to pharmaceutical compounds for over half a century. Ex. 1002, ¶ 52.

One common motive for placing a deuterium atom in a drug molecule is to affect the "ADME" (Adsorption, Distribution, Metabolism, and Excretion) characteristics of the compound. Ex. 1002, ¶ 50. For example, a deuterium atom may slow the metabolism, and therefore, the clearance of a drug. *Id.* An alternate benefit, in some cases, is to slow processes that lead to the formation of toxic by-products of the drug *in vivo*. *Id.* The underlying fundamental basis of these ADME effects is the KIE. That is, if the rate of the breaking of a C–H bond is at least partially "rate-limiting" in the overall process of drug metabolism and/or elimination, then a drug will be cleared more slowly from the body when the protium hydrogen is substituted with deuterium due to the stronger C–D bond, which is more difficult to break. Ex. 1002, ¶¶ 50, 53.

Returning to the visual aid used in the previous section, a common process in drug metabolism is the oxidation of a C–H group in a molecule to form a C–OH group. Thus, if the intent is to slow drug metabolism, then there is a potential benefit to strengthening a C–H bond that is susceptible to metabolism to make it more difficult to break or oxidize. Ex. 1002, ¶ 54. This may be referred to by a number of terms, including "site-selective deuteration." See Ex. 1008 p. 49.



The basic effect of a KIE (due to deuterium substitution) is to slow a hydroxylation reaction, catalyzed by an oxidase enzyme such as cytochrome P450, monoamine oxidase, or aldehyde oxidase. Ex. 1002, ¶ 54. As acknowledged in the art, deuterium and hydrogen are very similar in size and electronic properties. Ex. 1002, ¶ 55; Ex. 1006. Thus, deuterium-substituted compounds retain their molecular shape and their basic electronic properties of the hydrogen analogs, and therefore, have selectivity and potency comparable to their hydrogen analogs. Ex.

1002, ¶ 55; see also Ex. 1013, p. 5 ("At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'").

However, as mentioned above, because deuterium is heavier than hydrogen it forms significantly stronger bonds with carbon resulting in differentiated ADME characteristics. This offers a number of potential clinical benefits, including: (i) improved safety by inhibiting the formation of toxic metabolites and reducing drug-drug interactions, (ii) better tolerability through reduction of overall dose and C_{max} (maximum plasma concentration of drug achieved), and (iii) enhanced efficacy by increasing bioavailability, AUC (area under the curve for drug), and C_{min} (minimum blood plasma concentration for drug) with minimal impact on C_{max}. Ex. 1002, ¶ 50. Deuteration may also block elimination pathways enhancing the formation of active metabolites. Ex. 1002, ¶¶ 49-55.

In the years preceding 2012, there was a renewed interest in deuterated analogs of known pharmacologically active compounds. Ex. 1002, ¶¶ 56-62; Ex. 1008; Ex. 1013. For example, a textbook published in 2010 provided context of the increased interest in deuterated drugs in terms of new patent application filings:

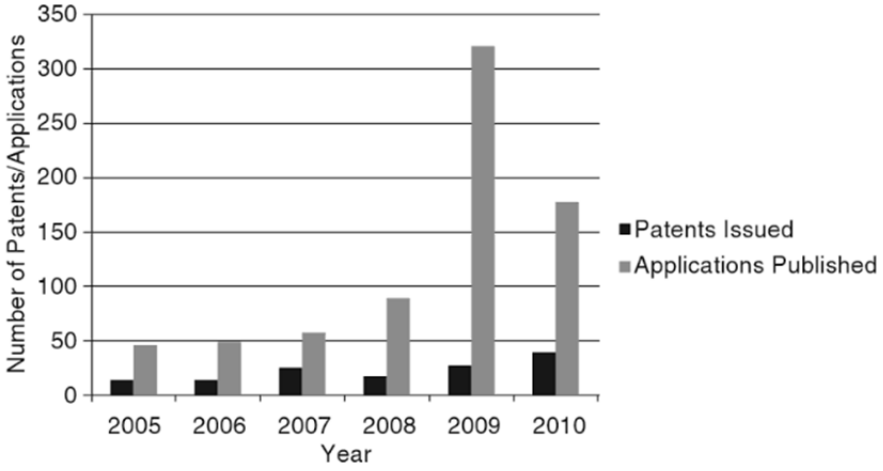


FIGURE 10.4. Issued patents and published applications containing "deuterium" or "deuterated" in the claims and "pharmaceutical" in any field for 2005–2010.

Morgan et al. (Ex. 100, p. 51). In many instances, however, the patents that included deuterated analogs of pharmacologically active compounds relied on the novelty of the pharmacologically active compound, and thus, the chart does not suggest that deuterated analogs were *per se* patentable purely based on deuteration. Ex. 1002, ¶ 59.

Further, a popular trade journal – *Chemical & Engineering News* (see above) – stated in 2009 that the "latest retro rage in the pharmaceutical world is deuterium substitution, a drug-design strategy that has faded in and out of vogue over the years." *See* A. Yarnell, "Heavy-Hydrogen Drugs Turn Heads, Again," *Chem. Eng. News, 87*(25):36-39 (2009) (Ex. 1013, p.1); see also Ex. 1002, ¶ 56. In fact, the article highlights three startup companies – Auspex Pharmaceuticals, Protia, LLC, and Concert – each of which based their business model on synthesizing deuterated analogs of known pharmaceutical compounds. As the CEO of Auspex is quoted as

saying, "[t]he easiest way to find a drug is to start with one." Ex. 1013, p. 5; Ex. 1002, ¶ 58.

In addition to increased interest, there were a number of purported "successes" in deuteration strategy in the years immediately preceding the earliest possible priority date of the '149 Patent. For example, in 2009 Concert agreed to license a deuterated version of Bristol-Myers Squibb's ("BMS") HIV protease inhibitor Reyataz® to BMS for $35 million up front, and up to $1 billion in milestone payments in addition to double-digit royalty percentages if a marketed product resulted. Ex. 1013, p. 3; Ex. 1002, ¶ 57. Further, each of Auspex, Protia, and Concert reported successful deuteration results for a number of other known pharmaceutical compounds prior to the earliest possible priority date of the '149 Patent. Ex. 1002, ¶ 58.

In fact, much of Concert's portfolio of pending and granted patents is directed to deuteration of known compounds, as summarized in the table below providing a non-exhaustive list of Concert patent families describing and/or claiming deuterated forms of compounds known prior to filing of the respective patent or patent application. The patent families in the chart are listed in order of publication date, starting in 2007 – *e.g.*, well before the priority date of the '149 patent.

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
7,514,068	Biphenyl-pyrazolecarboxamide compounds	Nov 8, 2005	Mar 22, 2007 US 2007/0066657 A1	Compound 1 (rimonabant also known as N-(piperidin-1-yl)-5-(4-chlorophenyl)-1-(2,4-dichlorophenyl)-4-methyl-1H-- pyrazole-3-carboxamide); U.S. Pat. No. 6,344,474; and Compound 1A (Surinabant also known as 5-(4-bromophenyl)-1-(2,4-dichlorophenyl)-4-ethyl-N-(1-piperidinyl)-1H-pyr-azole-3-carboxamide); WO 2005/046689
7,678,914 8,450,492	Deuterated benzo[D][1,3]-dioxol derivatives	Jul 29, 2005	Aug 16, 2007 US 2007/0191432 A1 Sep 2, 2010 US 2010/0222589 A1	Compound 1 (paroxetine (Paxil®))
7,863,274	Deuterium enriched analogues of tadalafil as PDE5 inhibitors	Jul 29, 2005	Aug 16, 2007 US 2007/0191381 A1	Tadalafil
8,343,950	Quinazoline derivatives	Dec 15, 2006	Jul 10, 2008 US	Erlotinib

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
	and methods of treatment		2008/0166358 A1	
8,552,008	Deuterated 3-(dihydro-1H-pyrazolo[4,3-D]pyrimidin-5-yl)-4-propoxybenzenesulfon-amide derivatives and methods of use	Oct 20, 2006	Aug 7, 2008 US 2008/0188496 A1	Udenafil
8,759,383 9,233,938	Inhibitors of cholesterol ester transfer protein	Mar. 16, 2007	Oct 2, 2008 US 2008/0242711 A1	Anacetrapib
8,198,305	1,2-benzisoxazol-3-yl compounds	Apr 13, 2007	Oct 16, 2008 US 2008/0255194 A1	Iloperidone
7,528,131	Substituted morpholinyl compounds	Apr 19, 2007	Oct 23, 2008 US 2008/0261983 A1	Mosapride, known as Gasmotin®
7,820,666	Tetrahydrotriazolo-pyrazine derivatives and uses thereof	May 8, 2007	Nov 13, 2008 US 2008/0280913 A1	Sitagliptin
7,608,737	Naphthyl(eth	May 1,	Nov 13, 2008	Agomelatine

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
	yl) Acetamides	2007	US 2008/0280908 A1	
7,973,049 8,188,110 8,541,436 8,710,072 9,314,440 9,072,711	Morphinan compounds	May 1, 2007	Nov 13, 2008 US 2008/0280936 A1 Dec 15, 2011 US 2011/0306627 A1 Oct 20, 2011 US 2011/0257214 A1	Dextromethorphan, marketed as Zenvia® and Neurodex®
7,943,620	Anti-anginal compounds	Mar 7, 2007	Dec 25, 2008 US 2008/0318969 A1	Ranolazine
8,071,596 8,080,549	Endothelin receptor antagonists	Jan 12, 2007	Jan 1, 2009 US 2009/0005394 A1	Bosentan
8,013,007	Alpha 1A-adrenoceptor antagonists	Feb 26, 2007	Jan 8, 2009 US 2009/0012112 A1	Silodosin
7,687,509	Pyrimidinecarboxamide derivatives	Jul 9, 2007	Feb 5, 2009 US 2009/003532	Raltegravir

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
			4 A1	
8,796,267	Oxazolidinone derivatives and methods of use	Oct 23, 2006	Apr 9, 2009 US 2009/0093422 A1	Linezolid
8,410,124	Deuterated etravirine	Oct 18, 2007	Apr 23, 2009 US 2009/0105147 A1	Etravirine
7,985,750	Substituted oxazolidinone derivatives	Aug 14, 2007	May 28, 2009 US 2009/0137535 A1	Rivaroxaban
7,994,194	4-oxoquinoline derivatives	Sep 12, 2007	Jun 4, 2009 US 2009/0143427 A1	Elvitegravir
8,338,425	Heterocyclic kinase inhibitors	Dec 10, 2007	Jun 11, 2009 US 2009/0149399 A1	Dasatinib
7,855,204 9,133,137	Derivatives of gefitinib	Jan 22, 2008	Jul 23, 2009 US 2009/0185999 A1 Mar 10, 2011 US 2011/0059046 A1	Gefitinib
8,084,464	Tetrahydroisoquinoline	Dec 18, 2007	Jul 30, 2009 US	Almorexant

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
	derivatives		2009/0192188 A1	
8,367,674	Piperazine derivatives	Apr 17, 2008	Oct 29, 2009 US 2009/0270336 A1	Vicriviroc
8,592,487	Deuterated darunavir	Oct 26, 2007	May 6, 2010 US 2010/0113589 A1	Darunavir
8,318,754 9,107,922	Pyrimidinecarboxamide derivatives	Jul 9, 2007	Jun 17, 2010 US 2010/0152214 A1	Raltegravir
8,349,817 8,357,674 8,765,723	Analogues of cilostazol	Apr 25, 2007	Sep 30, 2010 US 2010/0249079 A1	Cilostazol
8,158,805 8,258,309	Azapeptide derivatives	Jun 12, 2007	Jan 13, 2011 US 2011/0009355 A1	Atazanavir
8,952,016 9,035,050 9,492,457 9,493,463	Substituted xanthine derivatives	Feb 29, 2008	Mar 10, 2011 US 2011/0059995 A1	pentoxifylline and its metabolites
8,501,738	Substituted triazolo-pyridazine derivatives	Jun 23, 2009	Mar 17, 2011 US 2011/0065711 A1	TPA-023
8,609,673	Vandetanib derivatives	Jan 22, 2008	May 19, 2011	Vandetanib

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
8,278,460	Substituted benzimidazoles	Oct 15, 2009	Jul 14, 2011 US 2011/0172280 A1	NS11394
8,513,434 8,575,361 9,273,009	Tetrahydronaphthalene derivatives	Mar 2, 2010	Sep 29, 2011 US 2011/0237635 A1	Mibefradil
8,704,001 9,108,902	Deuterated 2-amino-3-hydroxypropanoic acid derivatives	Sep 16, 2008	Oct 13, 2011 US 2011/0251131 A1	Lacosamide
8,575,221	Derivatives of dimethylcurcumin	Mar 17, 2010	Oct 20, 2011 US 2011/0257271 A1	Dimethylcurcumin
8,227,464	Substituted oxazolidinone derivatives	Aug 14, 2007	Nov 17, 2011 US 2011/0281828 A1	Rivaroxaban
9,045,453	Substituted dioxopiperidinyl phthalimide derivatives	Nov 14, 2008	Nov 24, 2011 US 2011/0288126 A1	Lenalidomide
8,461,197 9,051,261 9,309,182	4-hydroxybutyric acid analogs	Apr 23, 2009	May 17, 2012 US 2012/0122952 A1	sodium oxybate marketed as Xyrem®
8,563,554 9,199,986	Deuterated pyrazino[2,1-	Mar. 17,	Jun 14, 2012 US	Praziquantel

Table of Concert Pharm Patents and Patent Applications Describing and/or Claiming Deuterated Forms of Compounds Known Prior to the Respective Patent/Patent Application Filing Date				
Patent No.	**Title**	**Earliest Priority Date**	**Exemplary publication**	**Known Compound deuterated and then claimed and/or described by Concert**
9,206,179	a]isoquinolines for the treatment of diseases and/or conditions	2009	2012/0149709 A1	
8,410,082	Fluorinated diaryl urea derivatives	May 22, 2009	Sep 20, 2012 US 2012/0237474 A1	Sorafenib
8,404,737 9,296,689	Substituted isoindoline-1,3-dione derivatives	Jun 18, 2009	Oct 4, 2012 US 2012/0252864 A1	Apremilast

Thus, as of the earliest priority date for the ’149 Patent, so-called “site-selective deuteration” had become a standard strategic approach for both drug repositioning and discovery. Ex. 1002, ¶¶ 61-62; see also Ex. 1008; Ex. 1027.

C. Ruxolitinib

At the earliest possible priority date of the ’149 Patent, ruxolitinib was a well-established, pharmaceutical first approved by the FDA in November 2011 under the tradename Jakafi®. Ex. 1004; Ex. 1002, ¶ 63. Ruxolitinib was recognized as a kinase inhibitor indicated for treatment of patients with

intermediate or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. *Id.*

Ruxolitinib was also recognized as being active against alopecia prior to the earliest possible priority date of the '149 Patent. Indeed, a physician at Columbia University was developing ruxolitinib for the treatment of alopecia, and had shown success in *in vivo* rodent models. *See* Ex. 1002, ¶ 64 (*discussing* Ex. 1014, published May 10, 2012 (Example 6, ¶ [0358], page 130, which discloses *in vivo* preclinical studies using ruxolitinib (also referred to as INCB018424) in a mouse model for disease)). Although the claims of the '149 Patent do not recite a specific use, Concert is developing deuterated ruxolitinib for the treatment of the same indication: alopecia. Ex. 1002, ¶ 65; see also Ex. 1015.

VII. Claim Construction

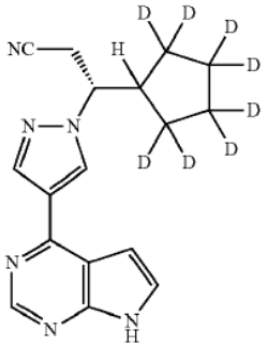
In an *inter partes* review, a claim in an unexpired patent is given its broadest reasonable construction in light of the specification. 37 C.F.R. § 42.100(b). One claim term requires a definition other than "plain and ordinary meaning." "D" or "deuterium" is defined in the '149 Patent as meaning that the position has "deuterium at an abundance that is at least 3000 times greater than the natural abundance of deuterium, which is 0.015% (*i.e.*, at least 45% incorporation of deuterium)." Ex. 1001, 3:65-4:3. Petitioner does not believe any other term in the

claims requires explicit construction, and therefore should be given their ordinary and customary meaning in view of the specification.

VIII. Detailed Explanation of Grounds for Unpatentability

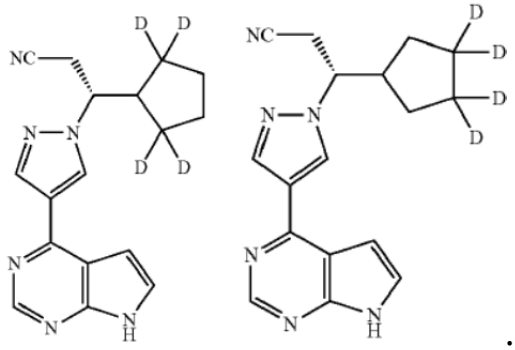
Petitioner requests *inter partes* review of each claim of the '149 Patent based on the grounds for unpatentability listed in the index below. Per 37 C.F.R. § 42.6(d), copies of the cited references for each ground of unpatentability are filed herewith

Claims 1, 2, 5-7, 9, 10, 13, and 14 each read on the following "octa-deuterated" ruxolitinib analog:



. Ex. 1002, ¶ 39.

Claims 1-4, 6, 7, 9-12 and 14 each read on the following "tetra-deuterated" ruxolitinib analogs:



. *Id.*

Claims 8 and 15 each recite a pharmaceutical composition comprising a compound that reads on any of the three octa-deuterated and tetra-deuterated compounds above, and a pharmaceutical carrier. Ex. 1002, ¶¶ 35-39

These claims would have been anticipated by, or obvious over, the references in the following three grounds.

Ground	Claims	Description
1	1-15	Obvious under §103 over Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder
2	1-15	Anticipated under §102 by U.S. Pat. No. 7,598,257
3	1-15	Obvious under §103 over U.S. Pat. No. 7,598,257, Shilling, and the Concert Backgrounder

The detailed explanation that follows establishes a reasonable likelihood that claims 1-15 would have been anticipated and/or obvious to a POSA based on the above-cited references.

A. Ground 1: Claims 1-15 are obvious over Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder

Claims 1-15 are invalid under pre-AIA 35 U.S.C. § 103(a) as obvious over the combination of Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder. More specifically, each of (1) the "octa-deuterated" ruxolitinib analog, (2) the "tetra-deuterated" ruxolitinib analogs, and (3) a pharmaceutical composition comprising one of these compounds and a pharmaceutical carrier would have been obvious over the combination of Jakafi®

(ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder, and thus, each of claims 1-15 is invalid.

1. Cited Prior Art

The Jakafi® (ruxolitinib) Prescribing Information (Ex. 1004) was first published in November of 2011. Thus, the publication is prior art under at least pre-AIA 35 U.S.C. § 102(a).[1] This reference is listed in the list of considered references on the face of the '149 Patent. However, the reference was not cited in any rejection during prosecution of the application leading to the '149 Patent.

Shilling (Ex. 1005) was published by at least November of 2010. Thus, the reference is prior art under at least pre-AIA 35 U.S.C. § 102(b). This reference is listed in the list of considered references on the face of the '149 Patent. However, the reference was not cited in any rejection during prosecution of the application leading to the '149 Patent.

The Concert Backgrounder (Ex. 1006) was publically accessible by at least January 27, 2009, as shown in the cached WebCite® page (Ex. 1016; also available

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[1] While the Jakafi® (ruxolitinib) Prescribing Information is prior art under at least pre-AIA 35 U.S.C. § 102(a), the understanding that ruxolitinib was an effective pharmaceutical compound was shown in printed publications well over a year before the earliest effective filing date, for example, in Shilling (Ex. 1005).

at http://www.webcitation.org/5e81SGCnl). The cached WebCite® page was readily accessible to the public as indicated by the WebCite® description of its services (Ex. 1017).

The public accessibility of the Concert Backgrounder via the cached WebCite® page is further evidenced by its use in a law review article published in 2009, which cited the same WebCite® page used in this Petition. Ex. 1018, p. 66, n. 268. Likewise, the International Search Authority ("ISA") for a Concert PCT application directed to deuterated analogs of the known drug rilpivirine (PCT/US2011/025472) cited the Concert Backgrounder based on the same WebCite® page used in this Petition. Ex. 1021. As indicated in the International Search Report that published on August 21, 2011, the WebCite® page was accessed by the ISA on May 12, 2011. Ex. 1021, p. 3.[2] Despite the fact that this reference

[2] Multiple other applicants have cited the same Concert Backgrounder. For example:

US9,290,475 filed Mar 2014; issued Mar 2016; priority 2013; assignee DeuteRx, LLC

US9,540,340 filed Jan 2014; issued Jan 2017; priority 2013; assignee DeuteRx, LLC

was cited against Concert's other patent applications covering deuterated analogs of known drugs, Concert did not cite this reference during the prosecution of the '149 Patent, and therefore this reference is not listed in the list of considered references on the face of the '149 Patent and presumably was not considered by the Examiner. Thus, the reference is prior art under at least pre-AIA 35 U.S.C. § 102(b).

2. Teachings of the Art and Motivation to Combine

Jakafi® (ruxolitinib) Prescribing Information demonstrates that, not only was ruxolitinib a known compound as of June 15, 2012, but it was an *FDA-approved* known compound. Ex. 1004. Thus, a POSA would have understood the compound to be a particularly effective and relatively safe compound for use in a pharmaceutical composition. Ex. 1002, ¶ 67; Ex.1004; Ex. 1005.

While the Jakafi® (ruxolitinib) Prescribing Information may not explicitly disclose a deuterated form of ruxolitinib, it is well established in the chemical arts that "structural similarity between claimed and prior art subject matter, proved by

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US9,090,585 filed Mar 2012; issued July 2015; priority 2011; assignee DeuteRx, LLC

US8,940,727 filed Oct 2010; issued Jan 2015; priority 2009; assignee Otsuka Pharmaceutical Co. Ltd.

combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990). "The 'reason or motivation' need not be an explicit teaching that the claimed compound will have a particular utility; it is sufficient to show that the claimed and prior art compounds possess a 'sufficiently close relationship … to create an expectation,' in light of the totality of the prior art, that the new compound will have 'similar properties' to the old." *Aventis Pharma Deutschland GmbH v. Lupin Ltd*., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (*citing Dillon*, 919 F.2d at 692).

In the present case, tetra- and octa-deuterated ruxolitinib analogs and ruxolitinib differ only by the deuteration of the cyclopentyl ring (*i.e.*, different isotopes of the same atom). Ex. 1002 , ¶ 33. As explained by Prof. Guengerich, it was well understood that deuterium and hydrogen are very similar in size and electronic properties, and that deuterium-substituted compounds retain their molecular shape and their basic electronic properties, and therefore, have selectivity and potency comparable to their hydrogen analogs. Ex. 1002, ¶ 55; *see also* Ex. 1013, p. 5 ("At Concert, 'we've never seen any biologically relevant differences in target selectivity or potency of a drug when we deuterate it.'").

This alone is sufficient "to create an expectation … that the new compound will have similar properties to the old," and thus, to set forth a *prima facie* rejection. *Aventis Pharma*, 499 F.3d 1293, 1301; *Dillon*, 919 F.2d at 692.

Shilling and the Concert Backgrounder, however, give additional reason or motivation to make the specific tetra- and octa-deuterated ruxolitinib analogs and compositions because these references provide an expectation that these ruxolitinib analogs may display superior ADME properties as compared to non-deuterated ruxolitinib.

Specifically, Shilling discloses known metabolites of ruxolitinib that result when the drug is administered to a human. Ex. 1002, ¶¶ 68-70; Ex. 1005. The dominant metabolites are those in which ruxolitinib *has been oxidized on the cyclopentyl ring*. Ex. 1002, ¶ 69; Ex. 1005.

Meanwhile, the Concert Backgrounder explains to a POSA that deuterium substitution has the potential to create new chemical entities with improved safety, tolerability, and efficacy. Ex. 1006, p. 2; Ex. 1002, ¶¶ 71-73, 136. The deuterated compounds useful for this technique are "based on drugs with known efficacy and safety that address clinically validated targets." Ex. 1006, p.3. Further, in Concert's own words, this technique allows one to "rapidly create novel, differentiated compounds with substantially reduced R&D risk, time, and expense." Ex. 1006, p. 3. Thus, the Concert Backgrounder provides motivation to

a POSA to select for deuteration an approved drug with known efficacy and safety that addresses clinically validated targets potentially to obtain superior ADME properties. Ex. 1002, ¶¶ 83-84, 136.

A POSA also would have understood from the Concert Backgrounder that compounds should be selected that have known "metabolic hotspots" (*i.e.*, "drugs with identified sites of oxidative metabolism, as shown in literature reports of *in vivo* metabolism"), and that these compounds should be deuterated at some or all of the known metabolic hotspots. Ex. 1002, ¶¶ 74, 83-85; Ex. 1006, p. 4.

Thus, a POSA would have been motivated to apply the techniques disclosed in the Concert Backgrounder to ruxolitinib because ruxolitinib was an FDA-approved drug with known efficacy and safety that addresses clinically validated targets as taught by Jakafi® (ruxolitinib) Prescribing Information, and ruxolitinib contained well-identified sites of *in vivo* oxidative metabolism, as shown by Shilling. Ex. 1002, ¶¶ 83-85.

3. Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success in combining Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder to reach the claimed subject matter of the '149 Patent.

As Prof. Guengerich explains, the synthesis of the octa- and tetra-deuterated ruxolitinib analogs was well within the abilities of a POSA from commercially

available starting materials. Ex. 1002, ¶¶ 104-105. Furthermore, deuterated analogs of drugs were known generally in the art to perform *at least* as well as their undertreated counterparts. Ex. 1002, ¶¶ 91-93; Ex. 1013. Thus, given the known efficacy and safety of ruxolitinib, the deuterated analogs claimed in the '149 Patent would have been expected to possess at least a similar efficacy and safety profile. Ex. 1002, ¶ 92. Indeed, Concert had admitted that they had "never seen any biologically relevant differences in target selectivity or potency of a drug when [they] deuterate it." Ex. 1013, p. 5. It is also of note that Concert has since determined that the *in vivo* safety and exposure of a deuterated analog of ruxolitinib in humans appears comparable to the reported exposure for ruxolitinib. Ex. 1015; Ex. 1002, ¶ 92. Thus, a POSA at the earliest priority date of the '149 Patent would have expected the tetra- and octa-deuterated ruxolitinib analogs to perform *at least* as well as ruxolitinib, and later evidence confirms that deuterated ruxolitinib, in fact, worked about the same as ruxolitinib. Ex. 1002, ¶¶ 91-92.

As noted above, this is a sufficient expectation to render the claims *prima facie* obvious. *Aventis Pharma*, 499 F.3d 1293, 1301; *Dillon*, 919 F.2d at 692.

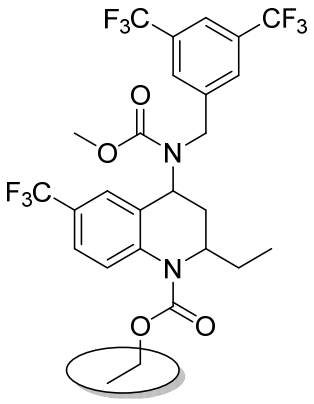
Nevertheless, the following explanation provides additional reasons why a POSA would have had a reasonable expectation that at least the octa- and tetra-deuterated ruxolitinib analogs would have provided improved metabolic stability

over ruxolitinib based on Shilling and the Concert Backgrounder. See Ex. 1002, ¶¶ 93-103.

Shilling shows that ruxolitinib was an ideal candidate for the deuteration strategies in the Concert Backgrounder. Ex. 1002 ,¶¶ 83-84. This is, in part, because the results on metabolism presented by Shilling indicate that the metabolism is largely restricted to the cyclopentyl ring. *Id*. The extent of *in vivo* oxidation at other parts of the molecule (*e.g*., the deazapurine ring system) is minimal (<5%), and the cyclopentyl sites are sp3-hybridized, which is a hybridization that is very capable of producing kinetic isotope effects upon deuteration. Ex. 1002, ¶¶ 83-84, 97-103.

While, on its surface, the Concert Backgrounder states that benefits from deuteration cannot be predicted *a priori*, closer inspection of the document reveals that a POSA would have seen certain patterns that lend themselves to concluding that there is at least a reasonable level of predictability. For example, as explained by Prof. Guengerich, while the Concert Backgrounder shows twelve deuterated analogs of torcetrapib (A-L), and explains how only six showed enhanced metabolic stability, these are the six deuterated analogs that a POSA would have expected to show enhanced metabolic stability based on the known metabolic pathways of torcetrapib. Ex. 1002, ¶¶ 74-77.

Specifically, the Concert Backgrounder purports to discover that deuteration at the position circled in the following figure is required to enhance metabolic stability:



. Ex. 1006, p. 5.

In fact, each metabolite of torcetrapib is metabolized at least at the circled position. Ex. 1002, ¶¶ 74-77. As Prof. Guengerich explains, not deuterating at this position would have been expected not to block metabolism. Ex. 1002, ¶ 77. Predictably, when the circled position is fully deuterated (analogs A to F), metabolism is altered, but when this position is not fully deuterated (analogs G to L), metabolism is not altered. Ex. 1006, p. 5. This suggests that this deuteration strategy is even more predictable than it appears from the Concert Backgrounder. Ex. 1002, ¶ 77.

Indeed, as the reasonable expectation of success would have been implicitly recognized by a POSA as a "substantially reduced R&D risk," which is a result of the relative ease and predictability of producing deuterated analogs of known pharmacologically-active compounds, and suggests a reasonable expectation of

success – even if, as Concert alleges, *a priori* predictability is not present." Ex. 1002 ,¶ 72-73, 101.

As outlined above, there is sufficient evidence of reasonable predictability and a reasonable expectation within the references used in Ground 1. The general information found in the art does not diminish this expectation.

As Concert argued during prosecution, and as Prof. Guengerich discusses, there are a number of theories as to why a deuteration strategy in general might be unpredictable. None of these theories, however, destroys the reasonable expectation of success.

First, Concert cited a number of irrelevant papers during prosecution allegedly showing a lack of reasonable expectation of success. Ex. 1009, pp. 253-261. As Prof. Guengerich explains, none of these papers reasonably suggests to a POSA in June of 2012 that he or she would not have had a reasonable expectation that at least the "octa-deuterated" ruxolitinib analog and the "tetra-deuterated" ruxolitinib analogs would have provided improved metabolic stability. Ex. 1002, ¶¶ 109-117. Instead, the papers are to (1) a mechanistic study relating to single type of P450 that is not suitable for each compound studied (Fukuto et al., *J. Med. Chem*., 34, 2871-2876, (1991); Ex. 1038), (2) a 30-year old conclusion that deuterated analogs were not likely to be used in drug design, which explained that the reason KIE might have been limited was cost and FDA issues, not necessarily

effect (Foster, A.B., *Advances in Drug Research*, 14:1-40 (1985); Ex. 1041); and (3) a 2006 paper that reaches conclusions that are not supported by the cited references relied upon therein (Fisher et al., *Current Opinion in Drug Discovery & Development*, 9, 101-109 (2006); Ex. 1040). Ex. 1002, ¶¶ 109-117.

Furthermore, all of these references were published in 2006 or before. As noted throughout both the petition and Prof. Guengerich's declaration, post-2006 publications provide evidence of the reemergence of deuteration strategy as a viable pathway for new pharmaceutical compounds as described, for example, in the Concert Backgrounder. Ex. 1002, ¶¶ 115-117; *see also* Ex. 1013, p. 1 ("The latest retro rage in the pharmaceutical world is deuterium substitution, a drug-design strategy that has faded in and out of vogue over the years.").

Second, a POSA would have been aware that Concert has previously submitted numerous patent filings on various deuterated analogs of known pharmaceutical compounds. Ex. 1002, ¶ 58; *see also* Ex. 1008 (chart showing increased interest in deuterated drugs in terms of new patent application filings). These past successes would have suggested that the strategy for deuteration outlined in the Concert Backgrounder was applicable to a wide range of compounds in cases where metabolic "hot spots" were known. Ex. 1002, ¶ 58.

Further, as explained by Prof. Guengerich, at least some KIE is seen in almost all compounds, and the art as a whole by June of 2012 would have resulted

in a reasonable expectation of success in deuterating ruxolitinib at known metabolic "hot spots" to obtain improved metabolic stability. Ex. 1002, ¶¶ 53, 95, 102, 117.

Third, as Prof. Guengerich explains, a POSA would not have expected "metabolic switching" to ameliorate the KIE in the octa-deuterated and tetra-deuterated ruxolitinib analogs. Ex. 1002, ¶ 106. For starters, as taught by Shilling, the amount of ruxolitinib that is metabolized only at a position other than the cyclopentyl ring is less than 5 % (*e.g.*, the M49 metabolite). *Id.* A POSA would have understood that, *even if* metabolic switching were to occur as a result of deuterium substitution, the increase would have to be enormous to "switch" completely to the M49 metabolite, in that M49 accounted for only 3% of the parent molecule. *Id*. As Prof. Guengerich explains, the art contains examples of metabolic switching from a major metabolite to a minor metabolite, but the minor metabolite is generally present in a much larger amount than less than 5 %. *Id*.

Fourth, as Prof. Guengerich explains, a POSA would have expected at least some KIE as a result of deuterium substitution in the octa-deuterated and tetra-deuterated ruxolitinib analogs. Ex. 1002, ¶¶ 53, 95, 102, 107-108, 117. This is, in part, because the step in which the un-deuterated ruxolitinib carbon-hydrogen bond is broken by the P450 is at least a partially rate-limiting step. Ex. 1002, ¶¶ 107-108. As Prof. Guengerich explains, with a known hydroxylated metabolism at a

methylene, there is almost always at least some deuterium isotope effect (*e.g.*, the C-H bond breaking step is at least partially rate limiting). *Id*.

The magnitude of this KIE is irrelevant to the *prima facie* determination. Rather, "it is sufficient to show that the claimed and prior art compounds possess a sufficiently close relationship to create an expectation, in light of the totality of the prior art, that the new compound will have similar properties to the old." *Aventis Pharma Deutschland GmbH v. Lupin Ltd*., 499 F.3d 1293, 1301 (Fed. Cir. 2007) (*citing In re Dillon*, 919 F.2d 688, 692 (Fed. Cir.1990))(internal quotations removed).

Furthermore, *even if* there is some unpredictability, "an unexpected result or property does not by itself support a finding of nonobviousness." *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, 769 F.3d 1339, 1350 (Fed. Cir. 2014).

Once a *prima facie* case is established, it falls to the applicant or patentee to rebut it, for example with a showing that the claimed compound has unexpected properties. *In re Dillon*, 919 F.2d 688 at 692. However, as explained below, Patent Owner has failed to meet the burden of rebutting a *prima facie* rejection.

4. Concert has Not Demonstrated Unexpected Results Sufficient to Rebut the *Prima Facie* Obviousness

Concert provided experimental evidence purporting to show unexpected results during prosecution in the declaration of Vinita Uttamsingh, filed July 30, 2015 ("Uttamsingh Declaration"). Ex. 1009, pp. 252-261, 281-288. As Prof. Guengerich explains, these results were not probative of unexpected results because: (1) at least some *in vitro* effect would have been expected from deuterating at the cyclopentyl metabolic "hot spot" of ruxolitinib; (2) the magnitude of the KIE in *in vitro* tests was not unexpectedly superior based on the KIEs shown in the art; and (3) the experimental parameters were not probative of how the tested analogs would actually perform *in vivo*. Ex. 1002, ¶¶ 118-129.

In fact, in a press release dated December 14, 2016, Concert announced Phase I results of its deuterated ruxolitinib analog, CTP-543 and stated "[t]he half-life of CTP-543 was approximately 3.3 hours, **similar to that reported for non-deuterated ruxolitinib**." Ex. 1015 (emphasis added). In addition, the safety and exposure for Concert's deuterated analog, CTP-543, was similar to the reported exposure of a similar dose of non-deuterated ruxolitinib. *Id*.

With these actual *in vivo* results in hand, the results of the *in vitro* tests provided during prosecution are of even less significance. Ex. 1002, ¶ 127.

Nevertheless, Petitioner addresses below the experimental evidence provided during prosecution.

The experimental evidence provided during prosecution was not unexpected because at least some *in vitro* stabilization effect would have been expected from deuterating at the cyclopentyl metabolic "hot spot" of ruxolitinib. Ex. 1002, ¶¶ 118-129. In fact, most compounds metabolized by P450 reactions show at least some primary isotope effect, even if small. Ex. 1002, ¶¶ 102, 103, 107, 116. As Prof. Guengerich explains, the kinetic isotope effects reported in the Uttamsingh Declaration (Ex. 1009, p. 284, Tables 1 and 2) are relatively low (< 2), and are near the point of being statistically insignificant. Ex. 1002, ¶¶ 121-127. As Prof. Guengerich explains, these *in vitro* results say little to nothing about the deuterated ruxolitinib derivatives having an unexpected property, let alone an unexpectedly superior property compared to ruxolitinib. Ex. 1002, ¶ 129.

Further, the experimental evidence provided during prosecution was not probative of how the tested analogs would actually perform *in vivo*. Ex. 1002, ¶¶ 121-122. Indeed, the *in vivo* results released by Concert show little effect as compared to non-deuterated ruxolitinib. Ex. 1015. The experimental evidence in the Uttamsingh Declaration consisted of simple assays (*e.g.*, only a few data points measured, at only a single, substrate concentration), and were not done in a more robust manner, such as a manner that would be used in publication in peer-

reviewed literature. Ex. 1002, ¶ 122. While there is no requirement for experimental results to be completed in the same manner as would be done for peer-reviewed literature, the experimental results must still be reliable enough to be *probative*. Prof. Guengerich explains that the results in the Uttamsingh Declaration do not meet this minimum threshold because, *e.g.*, the simple *in vitro* assays are not a reliable indicator of how the deuterated ruxolitinib derivatives would perform *in vivo*, and in fact, were not conducted in a manner that would be recognized in the art as producing probative results. Ex. 1002, ¶ 122.

Furthermore, *even if* one accepts the *in vitro* half-life ($t_{1/2}$) measurements reported in Table 2 of the Uttamsingh Declaration at face value as accurate half-life measurements for the listed compounds, this measurement is incomplete. Ex. 1002, ¶¶ 123-127. The data has not been standardized, and is subject to variables, such as protein concentration. As Prof. Guengerich explains, once the data is standardized by converting to intrinsic clearance (CL'_{int}) and theoretical systemic clearance (CL_s), the difference between ruxolitinib and compound 111 is minimal, and is not the type of difference that would be expected to impart a large difference on *in vivo* clearance of the drug. Ex. 1002, ¶¶ 123-127.

Thus, based on the deficiencies in the Uttamsingh Declaration along with the later evidence of little or no *in vivo* effect from deuteration of ruxolitinib, Patent Owner has not provided evidence sufficient to rebut the strong *prima facie*

obviousness created by Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder. At best, any minor differences between ruxolitinib and its deuterated analogs constitute a difference in degree, which is insufficient to overcome the *prima facie* obviousness case.

Thus, each of the claims including the octa-deuterated ruxolitinib analog (claims 1, 2, 5-7, 9, 10, 13, and 14) and each of the claims including a tetra-deuterated ruxolitinib analog (claims 1-4, 6, 7, 9-12 and 14) are obvious over the cited references. Further, Jakafi® (ruxolitinib) Prescribing Information, Shilling, and the Concert Backgrounder all disclose a pharmaceutical compositions/uses. Thus, claims 8 and 15 reciting pharmaceutical compositions are also obvious.

B. Ground 2: Claims 1-15 are anticipated by U.S. Pat. No. 7,598,257

Claims 1-15 are invalid under pre-AIA 35 U.S.C. § 102(b) as anticipated by U.S. Pat. No. 7,598,257 to Rodgers et al. ("Rodgers"; Ex. 1007).

Each of (a) the "octa-deuterated" ruxolitinib analog, (b) the "tetra-deuterated" ruxolitinib analogs, and (c) a pharmaceutical composition comprising one of these compounds and a pharmaceutical carrier would have been immediately envisaged upon reading Rodgers.

1. Cited Prior Art

Rodgers issued on Oct. 6, 2009, more than a year prior to the earliest possible filing date of the '149 Patent. Thus, the Rodgers reference is prior art under at least pre-AIA 35 U.S.C. § 102(b).

2. Disclosure from Rodgers

Rodgers is an Orange Book listed patent for Jakafi® (ruxolitinib). Ex. 1019. All 8 claims of Rodgers recite 3-cyclopentyl-3-[4-(7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl]propanenitrile, or a pharmaceutically acceptable salt or specific enantiomer of this compound. One of these specifically recited enantiomers is ruxolitinib. *See, e.g.*, Ex. 1007, Claims 1-8; Ex. 1002, ¶ 130. The specification of Rodgers explains that deuterated forms of the claimed ruxolitinib compounds are within the scope of the invention:

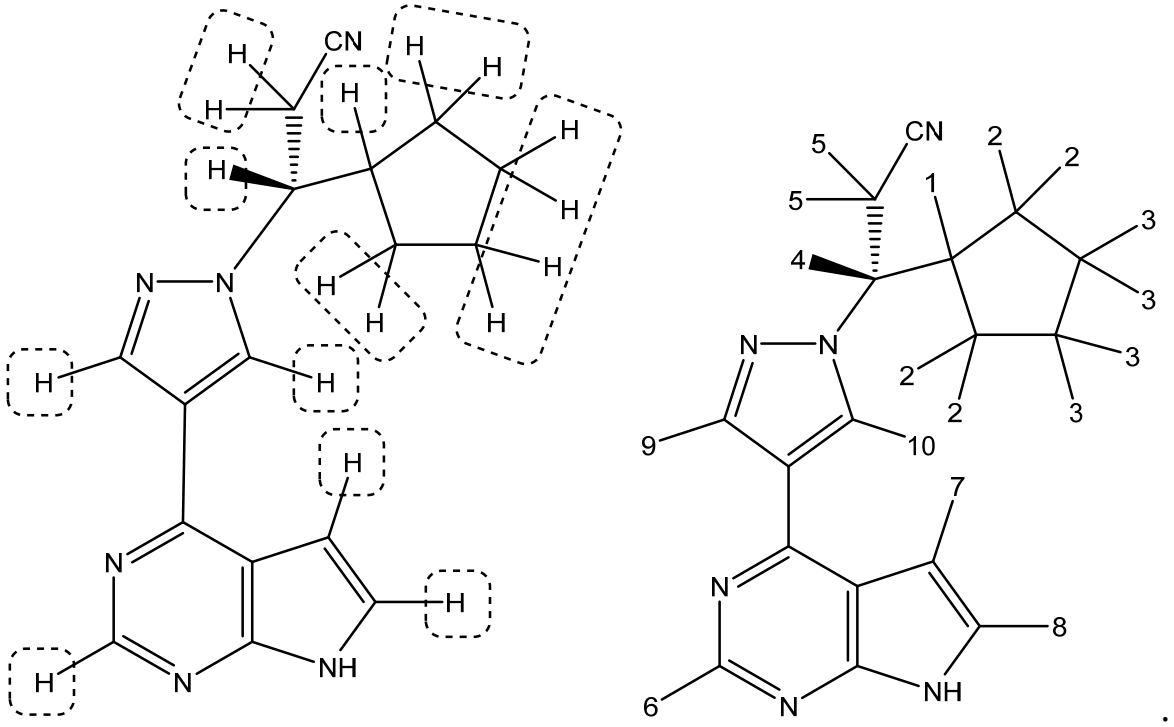
> Compounds of the invention can also include all isotopes of atoms occurring in the intermediates or final compounds. Isotopes include those atoms having the same atomic number but different mass numbers. For example, isotopes of hydrogen include tritium and deuterium.

Ex. 1007, 32:13-17. Thus, Rodgers specifically discloses that compounds of the invention include deuterated analogs (as one of 2 examples of tritium and deuterium isotopes) and further presents ruxolitinib as an inventive compound in the claims. Ex. 1002, ¶¶ 131-132; Ex. 1007. By reading Rodgers as a whole (the

claims and the specification), a POSA would immediately envisage from Rodgers a genus of deuterated ruxolitinib analogs. Ex. 1002, ¶¶ 131-132.

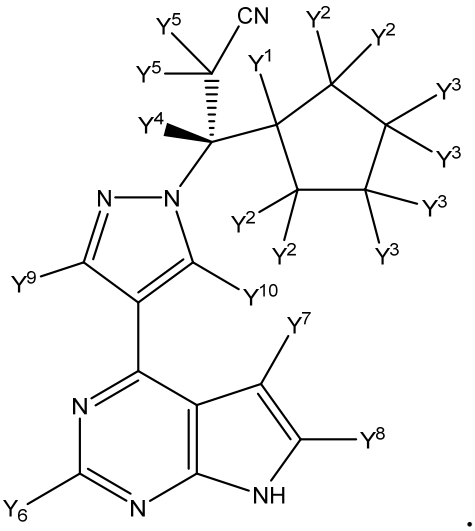
Whether a generic disclosure necessarily anticipates everything within the genus depends on the factual aspects of the specific disclosure and the particular products at issue. *Sanofi-Synthelabo v. Apotex, Inc.,* 550 F.3d 1075, 1083 (Fed. Cir. 2008). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. *In re Petering,* 301 F.2d 676 (CCPA 1962). One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." *Id.*

Despite there being 18 hydrogens in ruxolitinib, a POSA would immediately realize that there are only 10 possible distinct sites of deuteration on ruxolitinib:



Ex. 1002, ¶ 131. As explained by Prof. Guengerich, there is no reason to deuterate only one hydrogen at a given position (*e.g.*, only one of the hydrogens above labeled #2), thus a POSA would understand and at once envisage that the 10 possible sites of deuteration should not be expanded to a number that treats every single hydrogen as a different position to independently deuterate (*i.e.*, the hydrogens labeled #2 would be viewed as one position, not four). Ex. 1002, ¶ 131.

Indeed, it appears that Concert recognized this grouping of hydrogens when drafting the ’149 Patent, as demonstrated by Formula A, which also shows 10 possible distinct sites of deuteration with the same grouping of these sites together:



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Ex. 1002, ¶ 131; Ex. 1001, 6:7-50.

From this, the potential number of deuterated analogs is 2^{10}-1, or 1,023. While this number may seem high, a POSA would be able to envisage at once these compounds because each option is merely a binary choice of "H" or "D." Ex. 1002, ¶ 131. The POSA could have easily, and at once, envisaged these deuterated analogs simply by making a series of binary choices. In fact, Concert does as much in the '149 Patent by constructing tables such as Tables 1 and 2 of the '149 Patent, which list each of the binary choices. Ex. 1001, 8:10-39, 8:50-9:23; Ex. 1002, ¶ 131.

This binary factual situation is different from cases where variable groups are described as having many diverse structural options, such as *In re Petering,* where the prior art disclosed a generic chemical formula "wherein X, Y, Z, P, and R'- represent either hydrogen or alkyl radicals, R a side chain containing

an OH group." 301 F.2d 676, 681 (CCPA 1962). In *Petering*, the Court remarked that "alkyl" was a nebulous limitation that could include perhaps an infinite number of compounds. *Id.* Likewise, cases like *Atofina v. Great Lakes Chemical Corp*., 441 F.3d 991 (Fed. Cir. 2006), are not factually applicable because at issue in that case was a prior art temperature range of 100-500 degrees Celsius, which did not include only whole integer temperature amounts, but rather a spectrum of partial integer temperatures that could again include perhaps an infinite number of temperatures.

Instead, "whether a generic disclosure necessarily anticipates everything within the genus … depends on the factual aspects of the specific disclosure and the particular products at issue." *Atofina*, 441 F.3d at 999. When a generic formula embracing a limited number of compounds closely related to each other in structure and the properties possessed by the compound class of the prior art was that disclosed for the claimed compound, then a POSA would at once envisage the subject matter within the disclosure. *In re Schauman,* 572 F.2d 312 (CCPA 1978).

In the present case, while 1,023 compounds may initially appear to be a large number of compounds, the modification choice is binary (*i.e.*, H or D), and in its simplicity, would have allowed a POSA immediately to envisage each analog much in the same way one can immediately envisage each whole integer number between 1 and 1,023 despite there being many numbers. Ex. 1002, ¶ 131. The

"octa-deuterated" ruxolitinib analog and the "tetra-deuterated" ruxolitinib analogs are members of the disclosed deuterium-substituted ruxolitinib genus of Rodgers and would have been immediately envisaged. Ex. 1002, ¶ 131.

Furthermore, the compounds are all *extremely* closely related to each other in structure, given that the only difference is a different isotopic substitution of the same atom (*i.e.*, H and D). These deuterium-substituted compounds retain the molecular shape and basic electronic properties of the hydrogen analog, and therefore, have selectivity and potency at least comparable to their hydrogen analog. Ex. 1002, ¶¶ 55, 131; Ex. 1013.

In sum, the limited number of binary compounds disclosed in Rodgers, which are closely related to each other in structure and properties possessed by the compound class of the prior art would have allowed a POSA to at once envisage the species within more general disclosure because the . Ex. 1002, ¶¶ 130-132. As discussed above, the binary compounds disclosed in Rodgers are both sufficiently limited and well delineated, and thus, provide anticipatory disclosure of the specific deuterated analogs of ruxolitinib.

Thus, each of the claims including the octa-deuterated ruxolitinib analog (claims 1, 2, 5-7, 9, 10, 13, and 14) and each of the claims including a tetra-deuterated ruxolitinib analog (claims 1-4, 6, 7, 9-12 and 14) are anticipated. Further, Rodgers discloses a pharmaceutical composition comprising a compound

of the invention and a pharmaceutically acceptable carrier. *See, e.g.*, Ex. 1007 at 65:23-68:52, 347:21-25. Thus, claims 8 and 15 reciting pharmaceutical compositions are also anticipated. Ex. 1002, ¶ 131.

C. Ground 3: Claims 1-15 are obvious over Rodgers, Shilling, and the Concert Backgrounder

Claims 1-15 are invalid under pre-AIA 35 U.S.C. § 103(a) as obvious over the combination of Rodgers, Shilling, and the Concert Backgrounder. Each of (a) the "octa-deuterated" ruxolitinib analog, (b) the "tetra-deuterated" ruxolitinib analogs, and (c) a pharmaceutical composition comprising one of these compounds and a pharmaceutical carrier would have been obvious over the combination of Rodgers, Shilling, and the Concert Backgrounder, and thus, each of claims 1-15 is invalid.

1. Cited Prior Art

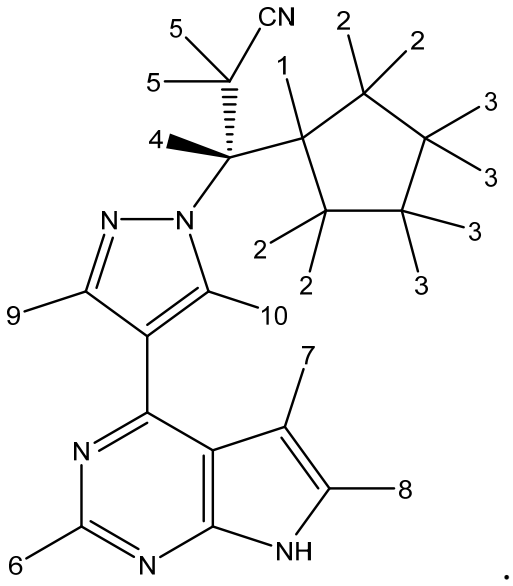
The prior art references of this ground are discussed previously. Each reference is prior art under at least pre-AIA 35 U.S.C. § 102(b).

2. Teachings of the Art and Motivation to Combine

As discussed above, the eight claims of Rodgers recite the compound and isomer that is ruxolitinib, while the specification teaches that compounds of the invention include those in which hydrogen is replaced with deuterium isotopes. *See, e.g.*, Ex. 1007, 3:13-17, Claims 1-3; Ex. 1002, ¶¶ 130, 133. From this disclosure, a POSA would immediately envisage a genus of deuterated ruxolitinib

analogs. Ex. 1002, ¶ 133. Even if (a) the "octa-deuterated" ruxolitinib analog and (b) the "tetra-deuterated" ruxolitinib analogs are not found to be anticipated by Rodgers, they would have been *prima facie* obvious based on Shilling and the Concert Backgrounder.

As noted above, there are 10 possible distinct sites of deuteration on ruxolitinib:



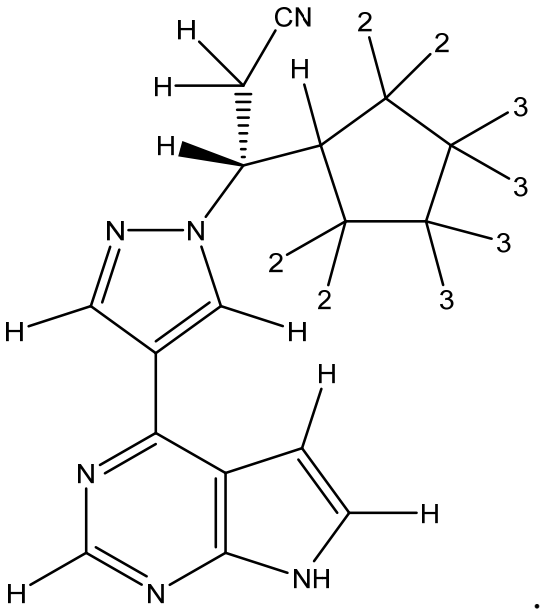
Shilling teaches that oxidative metabolism occurs almost entirely on the cyclopentyl ring at Y^2 and Y^3. Ex. 1002, ¶ 134; Ex. 1005.

The Concert Backgrounder explains that deuterium substitution has the potential to create new chemical entities with improved safety, tolerability, and efficacy. Ex. 1006, p. 2; Ex. 1002, ¶¶ 71-73, 136. The deuterated compounds useful for this technique are "based on drugs with known efficacy and safety that

address clinically validated targets." This, as Concert put it, would allow one to "rapidly create novel, differentiated compounds with substantially reduced R&D risk, time, and expense." Ex. 1002, ¶¶ 71-73, 136; Ex. 1006.

As Prof. Guengerich details, the Concert Backgrounder also explains to a POSA that compounds should be selected that have known "metabolic hotspots" (*i.e.*, drugs with identified sites of oxidative metabolism, as shown in literature reports of *in vivo* metabolism), and should be deuterated at some or all of these metabolic hotspots. Ex. 1002, ¶ 136; Ex. 1006.

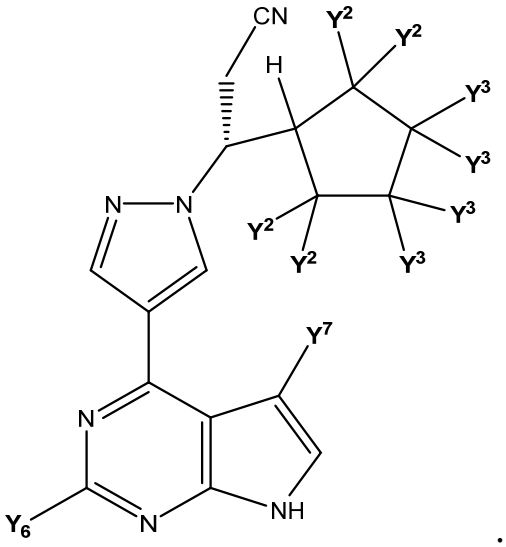
Thus, when a POSA would have considered Rodgers in view of Shilling and the Concert Backgrounder, the genus of deuterated compounds useful for creating chemical entities with improved safety, tolerability, and efficacy becomes:



Ex. 1002, ¶ 134.

Now, the number of potential compounds is 2^2-1, or 3 (*i.e.*, the "octa-deuterated" ruxolitinib analog and the "tetra-deuterated" ruxolitinib analogs). Ex. 1002, ¶ 134.

Even if one were to include the minor metabolite M49, the genus would still be quite limited:



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Ex. 1002, ¶ 134. Under this rubric, there would be four sites of potential metabolism, and thus, 2^4-1, or 15 potential compounds. Of these, a POSA would have understood that the sites at the cyclopentyl ring (Y^2 and Y^3) would be the most logical to deuterate based on the fact that the overwhelming majority of metabolism occurs at these positions. Ex. 1002, ¶ 134.

Furthermore, even if the Board does not agree that Rodgers teaches a genus of deuterated ruxolitinib compounds, there is still a motivation to combine non-

deuterated ruxolitinib of Rodgers with Shilling and the Concert Backgrounder for the same reasons as Ground 1.

Thus, a POSA would have been motivated to apply the techniques disclosed in the Concert Backgrounder to ruxolitinib and/or the deuterated ruxolitinib of Rodgers because ruxolitinib was a claimed compound of the invention in Rodgers, and ruxolitinib contained well-identified sites of oxidative metabolism in *in vivo* metabolism, as shown in Shilling. Ex. 1002, ¶¶ 135-136.

3. Reasonable Expectation of Success

A POSA would have had a reasonable expectation of success in combining Rodgers, Shilling, and the Concert Backgrounder to reach the claimed subject matter of the '149 Patent. This reasonable expectation of success is based on Shilling and the Concert Backgrounder in the same way as for Ground 1 because both the Jakafi® (ruxolitinib) Prescribing Information and Rodgers teach the known compound ruxolitinib. The reasons why a POSA would have a reasonable expectation of success are the same as for Ground 1 (Section VIII(A)(3)), which apply equally to this Ground 3.

4. Concert has Not Demonstrated Unexpected Results Sufficient to Rebut the *Prima Facie* Obviousness

As noted in Ground 1, Patent Owner has failed to demonstrate unexpected results for the claimed subject matter. Thus, the discussion for lack of secondary considerations in Ground 1 (Section VIII(A)(4)) is also relevant to Ground 3.

Thus, each of the claims including the octa-deuterated ruxolitinib analog (claims 1, 2, 5-7, 9, 10, 13, and 14) and each of the claims including a tetra-deuterated ruxolitinib analog (claims 1-4, 6, 7, 9-12 and 14) are obvious over the cited references. Further, Rodgers, Shilling, and the Concert Backgrounder all disclose a pharmaceutical compositions/uses. Thus, claims 8 and 15 reciting pharmaceutical compositions are also obvious.

IX. Conclusion

For the above reasons, claims 1-15 of the '149 Patent are unpatentable over the asserted prior art. Petitioners therefore request institution of an *inter partes* review and that claims 1-15 be canceled.

Respectfully submitted,

Date April 7, 2017 By /Stephen B. Maebius/

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CERTIFICATE OF COMPLIANCE

This Paper contains 9,809 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).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of the foregoing Petition for *Inter Partes* Review together with all exhibits, the power of attorney, and all other papers filed therewith was served on Concert Pharmaceuticals, Inc. by overnight mail by Federal Express service directed to the attorneys of record for the patent at the following addresses:

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