

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GlaxoSmithKline LLC,
Petitioner

v.

FibroGen, Inc.,
Patent Owner

U.S. Patent No. 8,466,172
Appl. No. 12/928,119 filed Dec. 2, 2010
Issued: June 18, 2013

Title: Stabilization of Hypoxia Inducible Factor (HIF) Alpha

IPR Trial No. IPR2016-01315

**PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,466,172
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42.100 ET SEQ.**

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EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. 8,466,172 (filed Dec. 2, 2010) ("the '172 patent")
1002	Declaration of Dr. Paul Schumacker, Ph.D.
1003	Office Action dated Jan.30, 2006 in the file history of U.S. Patent Appl. No. 10/313,551 (filed Dec. 6, 2002)
1004	Office Actions dated July 23, 2009 and June 2, 2010 in the file history of U.S. Patent Appl. No. 11/494,978 (filed July 28, 2006)
1005	Examiner Interview Summary dated Feb. 5, 2013 in the file history of U.S. Patent Appl. No. 12/928,119 (filed Dec. 2, 2010)
1006	Epstein et al., <i>C. elegans EGL-9 and Mammalian Homologs Define a Family of Dioxygenases that Regulate HIF by Prolyl Hydroxylation</i> , Cell, 107:43-54 (Oct. 5, 2001) ("Epstein 2001")
1007	Jaakkola et al., <i>Targeting of HIF-α to the von Hippel-Lindau Ubiquitylation Complex by O₂-Regulated Prolyl Hydroxylation</i> , Science, 292:468-472 (Apr. 20, 2001) ("Jaakkola 2001")
1008	Semenza, <i>Hypoxia-inducible factor 1: master regulator of O₂ homeostasis</i> , Current Opinion in Genetics & Development, 8:588-594 (1998) ("Semenza 1998")
1009	Semenza, <i>HIF-1 and human disease: one highly involved factor</i> , Genes & Development, 14:1983-1991 (2000) ("Semenza 2000")
1010	U.S. Provisional Patent Application No. 60/337,082 (filed Dec. 6, 2001) ("the '082 application")
1011	U.S. Provisional Patent Application No. 60/349,659 (filed Jan. 16, 2002) ("the '659 application")
1012	U.S. Provisional Patent Application No. 60/359,683 (filed Feb. 25, 2002) ("the '683 application")
1013	U.S. Provisional Patent Application No. 60/386,488 (filed June 5, 2002) ("the '488 application")
1014	U.S. Patent Appl. No. 10/313,551 (filed Dec. 6, 2002)
1015	Amendment After Allowability dated Mar. 15, 2013 in the file history of U.S. Patent Appl. No. 12/928,119 (filed Dec. 2, 2010)
1016	Notice of Allowability dated Feb. 20, 2013 in the file history of U.S. Patent Appl. No. 12/928,119 (filed Dec. 2, 2010)
1017	Freidman et al., <i>Prolyl 4-hydroxylase is required for viability and morphogenesis in Caenorhabditis elegans</i> , Proc. Natl. Acad. Sci. USA, 97(8):4736-4741 (Apr. 25, 2000) ("Freidman")
1018	Nwogu et al., <i>Inhibition of collagen synthesis with prolyl 4-</i>

	<i>hydroxylase inhibitor improves left ventricular function and alters the pattern of left ventricular dilatation after myocardial infarction</i> , Circulation, 104:2216-2221 (2001) ("Nwogu")
1019	U.S. Patent No. 6,093,730 (filed Oct. 19, 1998) ("Weidmann")
1020	Franklin et al., <i>Inhibition of prolyl 4-hydroxylase in vitro and in vivo by members of a novel series of phenanthrolinones</i> , Biochem J., 353:333-338 (2001) ("Franklin 2001")
1021	Kivirikko and Myllyharju, <i>Prolyl 4-hydroxylase and their protein disulfide isomerase subunit</i> , Matrix Biol., 16:357-368 (1998) ("Kivirikko")
1022	Chandel et al., <i>Mitochondrial reactive oxygen species triggers hypoxia-induced transcription</i> , Proc. Natl. Acad. Sci. USA, 95:11715-11720 (1998) ("Chandel 1998")
1023	Goldberg et al., <i>Regulation of the Erythropoietin Gene: Evidence That the Oxygen Sensor Is a Heme Protein</i> , Science, 242:1412-1415 (1988) ("Goldberg 1988")
1024	Huang et al., Williams Hematology, 6th Edition at 36 (1998) ("Huang 1998")
1025	Ivan et al. <i>HIFα Targeted for VHL-Mediated Destruction by Proline Hydroxylation: Implications for O₂ Sensing</i> , Science, 292 (Apr. 20, 2001) ("Ivan 2001")
1026	Lee et al., <i>Hypoxia-inducible Factor-1 Mediates Transcriptional Activation of the Heme Oxygenase-1 Gene in Response to Hypoxia</i> , J. Biol. Chem., 272(9):5375-5381 (1997) ("Lee 1997")
1027	Bickel et al., <i>Selective Inhibition of Hepatic Collagen Accumulation in Experimental Liver Fibrosis in Rats by a New Prolyl 4-Hydroxylase Inhibitor</i> , Hepatology, 28(2):404-411 (1998) ("Bickel")
1028	Marti et al., <i>Erythropoietin Gene Expression in Human, Monkey and Murine Brain</i> , European J. of Neuroscience, 8:666-676 (1996) ("Marti 1996")
1029	Maxwell et al., <i>The tumour suppressor protein VHL targets hypoxia-inducible factors for oxygen-dependent proteolysis</i> , Nature, 399:271-275 (May 20, 1999) ("Maxwell 1999")
1030	Listing of the documents reviewed and relied upon by Paul Schumacker in preparing his Declaration (Ex. 1002)
1031	Roberto Bolli, <i>The late phase of preconditioning</i> , Circ. Res., 87(11):972-982 (Nov. 24 2000) ("Bolli")
1032	Melillo et al., <i>Regulation of Inducible Nitric Oxide Synthase</i>

	<i>Expression in IFN-γ-treated Murine Macrophages Cultured Under Hypoxic Conditions</i> , The Journal of Immunology, 157:2638-2644 (1996) ("Melillo")
1033	Semenza, <i>Hypoxia-inducible factor 1: oxygen homeostasis and disease pathology</i> , Trends in Molecular Medicine, 7(8):345-350 (Aug. 2001) ("Semenza 2001")
1034	Pugh et al., <i>Activation of Hypoxia-inducible Factor-1; Definition of Regulatory Domains within the α Subunits</i> , The J. Biol. Chem., 272(17):11205-11214 (1997) ("Pugh 1997")
1035	Jiang et al., <i>Dimerization, DNA binding, and transactivation properties of hypoxia-inducible factor 1</i> , J. Biol. Chem., 271(30):17771-17778 (July 26, 1996) ("Jiang 1996")
1036	Kilic et al., <i>Brain-derived erythropoietin protects from focal cerebral ischemia by dual activation of ERK-1/2 and Akt pathways</i> , The ASEB Journal, 19:2026-2028 (2005) ("Kilic 2005")
1037	Lee et al., <i>Early expression of angiogenesis factors in acute myocardial ischemia and infarction</i> , New Engl. J. Med 342(9):626-633 (Mar. 2, 2000) ("Lee 2000")
1038	Myllyharju and Kivirikko, <i>Characterization of the iron- and 2-oxoglutarate binding sites of human prolyl 4-hydroxylase</i> , EMBO J, 16:1173-1180 (1997) ("Myllyharju")
1039	Bergeron et al., <i>Role of Hypoxia-Inducible Factor-1 in Hypoxia-Induced Ischemic Tolerance in Neonatal Rat Brain</i> , Ann Neurol, 48:285-296 (2000) ("Bergeron 2000")
1040	Stoyanovsky and Cederbaum, <i>Thiol Oxidation and Cytochrome P450-Dependent Metabolism of CCl₄ Triggers Ca²⁺ Release from Liver Microsomes</i> , Biochemistry, 35:15839-15845 (1996) ("Stoyanovsky 1996")
1041	Wasser et al., <i>Liver Fibrosis: effect of Anti-Oxidant Alcohol Withdrawal</i> , Journal of Gastroenterology and Hepatology, 16:1244-1253 (2001) ("Wasser 2001")
1042	Ambrosio et al., <i>Reduction in experimental infarct size by recombinant human superoxide dismutase: insights into the pathophysiology of reperfusion injury</i> , Circulation, 74(6): 1424-1433 (1986) ("Ambrosio 1986")
1043	Reimer and Jennings, <i>Myocardial Ischemia, Hypoxia, and Infraction</i> , Chapter 75, The Heart and Cardiovascular System, 2nd Ed., Raven Press, Ltd. (1992) ("Reimer 1992")

1044	Choi and Alam, <i>Heme Oxygenase-1: Function, Regulation, and Implication of a Novel Stress-inducible Protein in Oxidant-induced Lung Injury</i> , Am. J. Respir. Cell Mol. Biol., 15:9-19 (1996) ("Choi 1996")
1045	Franklin et al., <i>Approaches to the design of anti-fibrotic drugs</i> , Biochemical Society Transactions, 19:812-815 (1991) ("Franklin 1991")
1046	Leff, A.R. and P.T. Schumacker. <i>Respiratory Physiology: Basics and Applications</i> . W.B. Saunders, Philadelphia 1993.
1047	<i>Curriculum Vitae</i> of Paul Schumacker, Ph.D.

GlaxoSmithKline LLC ("GSK" or "Petitioner") requests *inter partes* review under 35 U.S.C. § 312 and 37 C.F.R. § 42.108 of claims 1-8 of U.S. Patent No. 8,466,172 ("the '172 patent"), which issued on June 18, 2013 to Guenzler-Pukall et al. and is assigned to FibroGen, Inc. A petition for *inter partes* review must demonstrate "a 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). This Petition meets this threshold for the reasons outlined below.

I. INTRODUCTION

The '172 patent purports to disclose new methods of treating a hypoxic or ischemic condition or disorder by administering a known class of compounds identified as heterocyclic carboxamides. As claimed, these compounds treat such disorders by stabilizing the alpha subunit of hypoxia inducible factor (HIF- α).¹ However, the prior art taught that heterocyclic carboxamide compounds could be used to stabilize HIF- α and provided motivation to use such compounds to treat hypoxic and ischemic conditions, as reflected by the teachings of Petitioner's prior art references: Weidmann, Ivan 2001, Bickel 1998, and Semenza (see discussions, *infra*). Furthermore, the prior art taught the administration of heterocyclic carboxamide compounds to treat hypoxic and ischemic conditions—which would

¹ Hypoxia inducible factor (HIF) is a protein heterodimer composed of α and β subunits.

inherently stabilize HIF- α . Accordingly, the claims of the '172 patent are also inherently anticipated by the prior art.

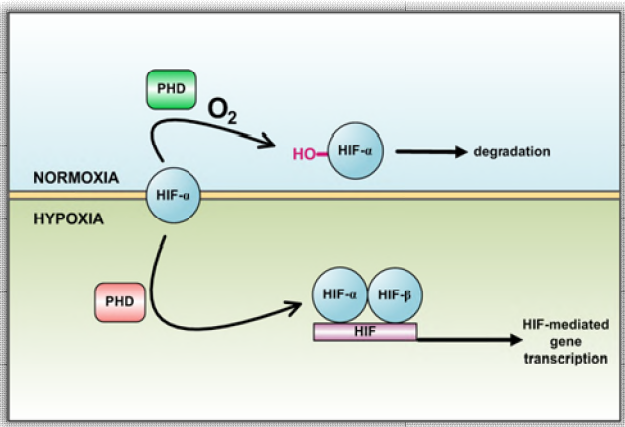


Figure 1 – Prolyl hydroxylase induced degradation of HIF- α under normoxia and accumulation of HIF under hypoxia. Ex. 1002, Schumacker. Decl. ¶ 46

were mediated by HIF. In particular, HIF was known to play a key role in regulating angiogenesis, erythropoiesis, ventilation, and cellular metabolism targeted at increasing oxygen delivery to tissues or reducing oxygen consumption.

It was also known that hypoxia resulted in increased HIF levels or activity. More specifically, it was well known that HIF activity depends on the availability of HIF- α in the body and that the availability of HIF- α is controlled by the enzyme HIF-prolyl hydroxylase (HIF-PHD). More particularly, it was known that in hypoxia, hydroxylation of HIF- α by HIF-PHD decreases, i.e. HIF- α is stabilized, leading to its accumulation and an increase in HIF (conversely, it was known that in normoxia HIF- α is degraded through hydroxylation by HIF-PHD, leading to a decrease in HIF). *See* Figure 1.

Prior to the effective filing date of the '172 patent claims, it was known that hypoxia results in a number of compensatory mechanisms designed to ameliorate the destructive effects of hypoxia, and that these protective responses

Thus, prior to the alleged invention one skilled in the art understood that HIF activity is increased by inhibiting the degradation of HIF- α by HIF-PHD, and that the effects of hypoxia (such as increasing HIF and its subsequent gene transcription) could be mimicked by inhibiting HIF-PHD. The prior art also taught a number of heterocyclic carboxamide compounds known to inhibit HIF-PHD. Thus, it was understood that heterocyclic carboxamide compounds that inhibited HIF-PHD could mimic the effects of hypoxia by increasing HIF and would be useful in the treatment of conditions in which increasing HIF levels is desirable, including hypoxic or ischemic conditions.

Indeed, prior to the effective filing date of the '172 patent, it was known in the art that heterocyclic carboxamide compounds could be used to treat fibrosis—an ischemic condition. It is understood that administration of such compounds inherently stabilizes HIF. Furthermore, it was obvious to a person of ordinary skill in the art that heterocyclic carboxamide compounds stabilize HIF- α and that increasing HIF in a subject would be useful to treat conditions associated with hypoxia or ischemia. Accordingly, for the reasons set out below, the claims of the '172 patent are invalid as either anticipated or obvious in view of the prior art.

II. REQUIREMENTS FOR INTER PARTES REVIEW UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

GSK certifies that the '172 patent is available for *inter partes* review and that GSK is not barred or estopped from requesting an *inter partes* review challenging the patent claims on the grounds identified in this petition.

B. Identification of Challenge (37 C.F.R. § 42.104(b))

GSK respectfully requests that the Board cancel claims 1-8 of U.S. Patent No. 8,466,172 (Ex. 1001) based on the following grounds of unpatentability:

Ground 1. Claims 1, 2, 3, 5, 6 and 8 are unpatentable under 35 U.S.C. § 102 as anticipated by United States Patent No. 6,093,730 to Weidmann et al. ("Weidmann" (Ex. 1019)).

Ground 2. Claims 1, 2, 3, 5, and 6 are unpatentable under 35 U.S.C. § 103(a) as obvious over Ivan 2001 (Ex. 1025) in view of Bickel 1998 (Ex. 1027).

Ground 3. Claim 8 is unpatentable under 35 U.S.C. § 103(a) as obvious over Ivan 2001 (Ex. 1025) in view of Bickel 1998 (Ex. 1027) and Weidmann (Ex. 1019).

Ground 4. Claims 4 and 7 are unpatentable under 35 U.S.C. § 103(a) as obvious over Ivan 2001 (Ex. 1025) in view of Bickel 1998 (Ex. 1027) and Semenza 2000 Ex. 1009).

Pursuant to 37 C.F.R. § 42.204(b), a detailed explanation of the precise relief requested for each challenged claim, including where each element is found in the prior art patents or publications, the relevance of the prior art reference, and the exhibit numbers of the supporting evidence, is provided in Section V below, including detailed claim charts. The proposed construction of the challenged claims is found in Section III.E. Additional explanation and support for each ground of rejection is set forth in the Declaration of Paul Schumacker, Ph.D., Ex. 1002.

III. RELEVANT INFORMATION REGARDING U.S. PATENT NO. 8,466,172

A. Brief Description of the Challenged Patent

The '172 patent was filed as U.S. Patent Application Serial No. 12/928,119 ("the '119 application") on Dec. 2, 2010.² The claims of the '172 patent relate to

² The '119 application is a continuation of U.S. Patent Application No. 11/494,978 ("the '978 application") filed on July 28, 2006, which is a continuation of U.S. Patent Application No. 10/313,551 ("the '551 application") filed on Dec. 6, 2002. These applications claim priority to Provisional Application Nos. 60/386,488 ("the '488 application") filed on June 5, 2002, 60/359,683 ("the 683 application") filed on Feb. 25, 2002, 60/349,659 ("the '659 application") filed on Jan. 16, 2002, and 60/337,082 ("the '082 application") filed on Dec. 6, 2001.

methods for treating hypoxic or ischemic disorders or conditions in a subject by administering a heterocyclic compound that stabilizes HIF- α . Ex. 1001, col. 63, ln. 32-col. 34, ln. 41. The patent describes hypoxia as a "state of reduced oxygen" that "can occur when the lungs are compromised or blood flow is reduced." Ex. 1001, col. 2, lns. 34-35. Ischemia is described as a "reduction in blood flow" that may be caused by a variety of conditions including an obstruction of blood vessels by a clot (thrombus), a foreign circulating object (embolus) or a vascular disorder, such as atherosclerosis. Ex. 1001, col. 2, lns. 35-39.

The specification explains that the compounds of the invention stabilize HIF- α by inhibiting the enzymes responsible for the hydroxylation, and subsequent degradation, of HIF- α . Ex. 1001, col. 3, lns. 64-66. The specification states that the enzymes responsible for hydroxylation of HIF- α are 2-oxoglutarate dioxygenases, Ex. 1001, col. 4, lns. 4-5, and provides examples of 2-oxoglutarate dioxygenase enzymes, including procollagen prolyl 4-hydroxylase and HIF prolyl 4-hydroxylase (HIF-PHD). Ex. 1001, col. 4, lns. 4-15; col. 18, lns. 17-21.

The specification references several prior art compounds and incorporates those compounds by reference for use in the claimed methods, including the compounds tested in Bickel 1998 and Weidmann³, both discussed *infra*. Ex. 1001, col. 26, ln. 10-14 (Bickel 1998); col. 36, lns. 1-6 (Weidmann). The compounds

³ Each inventor of the '730 patent is also an author of Bickel 1998.

used in the invention may be capable of inhibiting both HIF-PHD and procollagen prolyl 4-hydroxylase. Ex. 1001, col. 18, lns. 16-21; col. 42, lns. 49-59. Included in the specification is a description of certain prior art experiments using compounds within the scope of the invention to treat cardiac and liver ischemia. Ex. 1001, col. 54 (Example 6), col. 59 (Example 7). The specification states that Nwogu et al. "reported the use of a compound of the invention following myocardial infarction."⁴ Ex. 1001, col. 54, lns. 45-52. The applicants explain that they have discovered that the benefit shown in Nwogu's experiments "is due to stabilization of HIF α ." Ex. 1001, col. 54, lns. 49-52. Based upon the results disclosed in Nwogu et al., the applicants explain "that the methods of the present invention do reduce reactive cardiac fibrosis over a longer time course." Ex. 1001, col. 58, lns. 28-30.

The specification also describes the prior art experiments disclosed in Bickel 1998 which "reported the use of a compound of the present invention following induction of toxic-ischemic injury in the liver." Ex. 1001, col. 59, lns. 15-40. Bickel's experiments show that "treatment with a compound of the invention produced statistically significant improvement in liver function. . . . The

⁴ The specification describes "ischemic conditions" and "ischemic disorders" as including myocardial infarction. Ex. 1001, col. 21, lns. 29-31.

improvement in the liver function is attributed to stabilization of HIF α by the methods of the invention." Ex. 1001, col. 59, lns. 60-67.

The specification further describes the prior art compounds disclosed in Weidmann. Ex. 1001, col. 36, lns. 1-33. For example, Compound 9 (N-((1-Chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine) of Weidmann, which is the same compound disclosed in the '172 patent as Compound B (N-((1-chloro-4-hydroxy-isoquinoline-3-carbonyl)-amino)-acetic acid, was shown to stabilize HIF- α (Example 1 and 2), induce expression of HIF-target genes (Example 3), treat myocardial infarction (*id.*, Example 6, experiment II), and treat renal ischemia-reperfusion injury (*id.*, Example 8). Ex. 1001, Examples 1, 2, 3, 5, and 8. Compound 9 (i.e., Compound B) is a heterocyclic carboxamide. Ex. 1002, Schumacker Decl. ¶¶ 13-18.

B. Discussion of the File History

The '172 patent issued from a series of applications. During prosecution of these applications, the examiner rejected the claims as failing to comply with 35 U.S.C. §§ 102, 103, and 112. *See, e.g.*, Ex. 1003, Appl. No. 10/313551, Office Action dated Jan. 30, 2006; Ex. 1004, Appl. No. 11/494,978, Office Actions dated July 23, 2009 and June 2, 2010. During the prosecution of the application that led to the issuance of the '172 patent, the examiner and applicants held several discussions. *See, e.g.*, Ex. 1005, Appl. No. 12/928,119, Examiner Interview

Summary dated February 5, 2013. Following these discussions, the applicants amended the claims to limit their scope to heterocyclic carboxamide compounds and treatment of hypoxic or ischemic disorders, and the claims were allowed.⁵ *See* Ex. 1016, Appl. No. 12/928,119, Notice of Allowability dated Feb. 20, 2013.

In the Notice of Allowability, the examiner stated that U.S. Patent No. 5,658,933 to Weidmann et al. ("the '933 patent") was the closest prior art because it "teach[es] heterocyclic carboxamide compounds of formula (i) for use as inhibitors of prolyl hydroxylase for inhibiting collagen synthesis and fibrotic diseases." *Id.* at 5. In allowing the claims, the examiner stated that the claims differed from the '933 patent because "the heterocyclic compounds of [the '933 patent] are targeted for inhibiting prolyl hydroxylase while applicant's compounds have demonstrated to be useful in stabilizing HIF α ." However, this statement does not accurately reflect the teachings of the prior art as of the effective date of the '172 patent and demonstrates that the examiner did not appreciate the link between prolyl hydroxylase inhibition and stabilizing HIF- α . See Ex. 1002, Schumacker Decl. ¶¶ 94-95. In fact, it was recognized in the art that the inhibition of prolyl hydroxylase activity stabilizes HIF- α and, therefore, HIF- α stabilization could be achieved by

⁵ The examiner made an agreed-to Examiner Amendment and the applicants made additional amendments thereafter. Ex. 1015, Amendment after Notice of Allowability dated Mar. 15, 2013.

using HIF-PHD inhibitors, including those disclosed in the '172 patent.⁶ *See* Ex. 1002, Schumacker Decl. ¶¶ 57-64; Ex. 1001, col. 4, ln. 41- col. 5, ln. 6.

C. The Effective Filing Date for Claims 1-8 of the '172 Patent is Dec. 6, 2002

Claim 1 of the '172 patent is the only independent claim. This claim, and the remaining claims that depend from it, require the administration of "a heterocyclic carboxamide" to stabilize HIF- α for the treatment of hypoxic or ischemic disorders. Ex. 1001, col. 63, ln. 1 to col. 63, ln. 42. As such, each claim of the '172 patent will only be supported by a disclosure that addresses the ability of heterocyclic carboxamides as a class of compounds to stabilize HIF- α and treat hypoxic or ischemic disorders or conditions. *See, e.g., New Railhead Mfg., LLC v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002) ("In other words, the specification of the *provisional* must 'contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,' 35 U.S.C. § 112 ¶ 1, to enable an ordinary skilled artisan to practice the invention *claimed* in the *non-provisional* application.") (emphasis in original).

⁶ Applicants incorporated the compounds of Weidmann and the '933 patent by reference, as compounds useful with the claimed method. *See* Ex. 1001, col. 35, ln. 17 to col. 36 ln. 33. Applicants cannot dispute that these compounds stabilized HIF- α through an inhibition of prolyl hydroxylase.

The '551 application is the grandparent of the '119 application that matured into the '172 patent. The '551 application has a filing date of Dec. 6, 2002 and claims priority to four U.S. provisional applications: the '488 application filed on June 5, 2002, the '683 application filed on Feb. 25, 2002, the '659 application filed on Jan. 16, 2002, and the '082 application filed on Dec. 6, 2001. None of the provisional applications provide any disclosure as to the ability of heterocyclic carboxamide compounds as a class to treat hypoxic or ischemic conditions or disorders.⁷

While the majority of the compounds within this genus of heterocyclic carboxamide compounds are defined by the formulas disclosed in the specification of the '172 patent (Ex. 1001, col. 26, lns. 30-40; col. 34, lns. 12-60; col. 36, lns. 35-49; col. 37, lns. 55-64; and col. 38, lns. 35-40), these formulas were not disclosed in the provisional applications. *See* Ex. 1010, Appl. No. 60/337,082; Ex. 1011, Appl. No. 60/349,659; Ex. 1012, Appl. No. 60/359,683; and Ex. 1013, Appl. No. 60/386,488. The applicants first included these formulas in non-provisional application no. 10/313,551 filed on Dec. 6, 2002. *See* Ex. 1014, Appl. No. 10/313,551 at ¶ [0033]; [0035]; [0092].

⁷ *See*, e.g., Ex. 1010, '082 application, p. 5, ln. 21 to p. 6, lns. 26; p. 16, ln. 26 to p. 18, ln. 6; p. 37, lns. 30-31.

The law recognizes that for a claim encompassing a chemical genus, written description of an invention "requires a precise definition, such as a structure, formula [or] chemical name, of the claimed subject matter sufficient to distinguish it from other materials." *Boston Scientific Corp. v. Johnson & Johnson*, 647 F.3d 1353, 1363 (Fed. Cir. 2011) (internal citations and quotations omitted). In light of the absence of any teaching concerning heterocyclic carboxamide compounds as a genus useful in achieving the invention and the failure to include the formulas of the proposed compounds in any of the provisional applications, the provisional applications filed through June 5, 2002 do not provide written description to support the claims of the '172 patent. *See* Ex. 1002, Schumacker Decl. ¶¶ 32-35. Therefore, the earliest filing date that the Board should accord the claims of the '172 patent is Dec. 6, 2002—the filing date of the non-provisional '082 application.

D. Person of Ordinary Skill in the Art

A person of ordinary skill in the art at the time of the effective filing date of the claims of the '172 patent would have had a Ph.D. in physiology or biochemistry (or a related discipline) or an M.D. degree, and one or two years of research experience in cardiology, nephrology, or pulmonology. The research experience may overlap with the period of education. Ex. 1002, Schumacker Decl. ¶ 30.

E. Claim Construction

The Board is charged with applying "the broadest reasonable interpretation consistent with the specification, and . . . claim language should be read in light of the specification as it would be understood by one of ordinary skill in the art." *In re Montgomery*, 677 F.3d 1375, 1379 (Fed. Cir. 2012) quoting *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004) ; *see also In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1275-78 (Fed. Cir. 2015), *aff'd sub nom., Cuozzo Speed Techs., LLC v. Lee*, ___ S. Ct. ___ (2016) (affirming the PTAB's application of the broadest reasonable interpretation standard in an *inter partes* review).

1. Heterocyclic Carboxamide Compound

Under the prevailing standard adopted for *inter partes* review, a person of ordinary skill in the art would construe the term "heterocyclic carboxamide compound" as any compound that contains a heterocyclic ring and a carboxamide moiety. A carboxamide moiety has the general formula R-CO-NR'R" wherein R, R' and R" are organic substituents or hydrogen. Ex. 1002, Schumacker Decl. ¶ 31.

IV. RELEVANT PRIOR ART

A. Technology Background

1. Hypoxia and Ischemia

Hypoxia, a state of reduced oxygen, may occur as a result of reduced flow of blood to tissues. Ex. 1001, col. 21, lns. 50-51. Ex. 1001, col. 21, lns. 18-19.

Given that blood carries oxygen to the cells, a reduction in blood flow (i.e.,

ischemia) may lead to ischemic conditions, which in turn can often result in reduced cellular oxygen. Ex. 1002, Schumacker Decl. ¶¶ 36-37. This can cause a cell to transition from a normoxic condition (i.e., normal oxygen levels) to a hypoxic condition. Ex. 1002, Schumacker Decl. ¶ 38.

Hypoxia and ischemia elicit a number of compensatory local vascular and biochemical responses that result in increased delivery of oxygen to tissue. These responses affect angiogenesis, erythropoiesis, ventilation, and cellular metabolism targeted at increasing oxygen delivery to tissues or reducing oxygen consumption Ex. 1008, Semenza 1998; Ex. 1009, Semenza 2000; Ex. 1002, Schumacker Decl. ¶¶ 39-40. For example, hypoxia and ischemia increase the production of vascular endothelial growth factor ("VEGF") leading to angiogenesis. Ex. 1009, Semenza 2000. Among the systemic adaptations to hypoxia is the increase in production of erythropoietin ("EPO") by the kidneys and liver, which stimulates increased production of red blood cells in the bone marrow. Ex. 1002, Schumacker Decl. ¶¶ 41, 45.

2. Hypoxia-Inducible Factor

HIF is a heterodimer composed of α and β subunits. Ex. 1024, Huang 1998 at 7987 (abstract). As the HIF- β subunit exists in excess in the body, levels of active HIF depend on the availability of the HIF- α subunit. Ex. 1002, Schumacker Decl. ¶¶ 44-46. Therefore, "[i]nduction of HIF-1 α [] appears to be a critical step in

the hypoxic response and occurs via increased stability of the protein."⁸ Ex. 1008, Semenza 1998 at 589, col. 1-2. Furthermore, both hypoxia and ischemia regulate the activity of HIF. Ex. 1009, Semenza 2000 at 1983 ("The regulation of HIF-1 activity occurs at multiple levels. Whereas HIF-1 α mRNA is constitutively expressed in tissue cultures cells, it is markedly induced by hypoxia or ischemia in vivo."); Ex. 1002, Schumacker Decl. ¶ 46.

HIF activates the transcription of genes encoding proteins that play key roles in angiogenesis, vascular reactivity and remodeling, glucose and energy metabolism, cell proliferation and survival, erythropoiesis and iron homeostasis. Ex. 1008, Semenza at 589, Table 1; Ex. 1002, Schumacker Decl. ¶ 45. As a result, the modulation of HIF activity by pharmacological means was proposed as a novel therapeutic approach for a number of pathophysiologic conditions. Ex. 1008, Semenza at 592 ("Manipulation of HIF-1 activity—either pharmacologically or by gene therapy—may represent a novel approach to the treatment of cancer, cerebral and myocardial ischemia.")

⁸ Many publications use the terms HIF and HIF-1. HIF is a broader category of proteins than HIF-1, but it would be understood that any disclosures discussing HIF are equally applicable to HIF-1, and vice versa. Ex. 1002, Schumacker Decl. ¶ 46, n.2.

3. HIF-PHD Activity Regulates the Stability of HIF- α , Which Allows for an Accumulation of HIF

It was well understood by the late 1990s that hypoxia results in the stabilization of HIF- α , which leads to its accumulation in cells; however, the oxygen sensor responsible for regulation of the process was not known. *See* Ex. 1002, Schumacker Decl. ¶ 47. In 2001, in concurrently-published papers in *Science*, scientists from William Kaelin's laboratory and Peter Ratcliffe's laboratory demonstrated that the degradation of HIF- α was regulated by an enzyme, prolyl 4-hydroxylase, that required oxygen for its activity.⁹ Ex. 1025, Ivan 2001 at 467; Ex. 1007, Jaakkola 2001 at 468 (abstract) ("the HIF-1 α subunit is regulated . . . by an enzyme we have termed HIF- α prolyl hydroxylase."); Ex. 1002, Schumacker Decl. ¶¶ 48, 53.

Before the effective filing date of the '172 patent, the art also disclosed that compounds that bond with iron or change its form, such as iron chelators and cobaltous ions, could mimic the action of hypoxia on HIF- α by effectively removing reactive iron from the reaction. Ex. 1007, Jaakkola 2001 at 468, col. 2; Ex. 1025, Ivan 2001 at 464, col. 2. With the understanding that the absence of

⁹ The inhibition of the degradation of HIF- α results in the accumulation of HIF- α in cells. Consequently, more HIF- α will be available to bind with HIF- β to allow for the formation of HIF. Ex. 1002, Schumacker Decl. ¶ 46.

oxygen and iron affected HIF levels, the Kaelin and Ratcliffe laboratories focused on prolyl hydroxylases as a potential degradation pathway because these enzymes require both oxygen and iron to function. Ex. 1025, Ivan 2001 at 465, col. 3; 467, col. 2; Ex. 1007, Jaakkola 2001 at 470, col. 2-3; Ex. 1002, Schumacker Decl. ¶¶ 48, 53. In further investigating this potential pathway, these scientists recognized that prolyl hydroxylase enzymes require 2-oxoglutarate to accomplish hydroxylation, which was confirmed through the testing of 2-oxoglutarate analogs that were found to inhibit the activity of HIF-PHD. Ex. 1007, Jaakkola 2001 at 471, col. 1. *See* Ex. 1002, Schumacker Decl. ¶¶ 48-50.

Armed with the understanding that "the HIF system regulates not only cellular responses to oxygen, but a range of systemic functions such as regulation of angiogenesis, erythropoiesis and vasomotor control," scientists recognized that the identification of HIF-PHD raised therapeutic possibilities. Ex. 1006, Epstein 2001 at 52, col. 2; Ex. 1002, Schumacker Decl. ¶ 54. Indeed, Epstein 2001 points to the ability of "the 2-oxoglutarate analog dimethyloxalylglycine" to strongly induce HIF target genes, and comments that the "design of more specific inhibitors [of HIF prolyl hydroxylases] for therapeutic development" may now be possible. Ex. 1006, Epstein 2001 at 52 (column 2).

4. Existing Prolyl Hydroxylase Inhibitors as Anti-fibrotic Compounds

Before Kaelin and Ratcliffe's laboratories disclosed that HIF-PHD was the

crucial enzyme for the degradation of HIF- α , several other publications had recognized that prolyl hydroxylase inhibitors could act as anti-fibrotic compounds. *See, e.g.,* Ex. 1027, Bickel 1998; Ex. 1017, Freidman 2000; Ex. 1018, Nwogu; Ex. 1020, Franklin 2001; Ex. 1019, Weidmann; Ex. 1002, Schumacker Decl. ¶¶ 59-75. These references suggest the administration of prolyl hydroxylase inhibitors to treat fibrotic diseases of the lung, liver and skin and atherosclerosis¹⁰ (Ex. 1019, Weidmann, col. 1, lns. 25-30); chronic hepatic fibrosis (Ex. 1027, Bickel 1998¹¹); progressive fibro-proliferative diseases (Ex. 1020, Franklin¹²); and myocardial infarction (Ex. 1018, Nwogu).¹³ Ex. 1002, Schumacker Decl. ¶¶ 59, 65, 71, 73.

¹⁰ The '172 patent describes atherosclerosis as a chronic ischemic condition. Ex. 1001, col. 21, lns. 34-35.

¹¹ The '172 patent incorporates the experiments performed by Bickel into the patent and describes the experiment as showing use of a compound of the invention for the treatment of liver ischemia. Ex. 1001, col. 59, lns. 12-67, Example 7.

¹² The '172 patent describes the compounds disclosed in Franklin as compounds that can be used with the present invention. Ex. 1001, col. 26, lns. 10-24.

¹³ The '172 patent describes myocardial infarction as an acute ischemic condition. Ex. 1001, col. 21, lns. 29-31. The patent also incorporates the experiments of Nwogu as examples of using compounds in accordance with the methods of the patent. Ex. 1001, col. 54, Example 6.

In light of (i) the knowledge concerning prolyl hydroxylase inhibitors as anti-fibrotic compounds and (ii) the discovery of the involvement of prolyl hydroxylase in HIF stabilization, Kaelin and his colleagues suggested to others to test these compounds in hypoxic and ischemic conditions. Ex. 1025, Ivan 2001 at 467 ("In principle, drugs that stabilize HIF may augment angiogenesis and the adaption to chronic hypoxia. Several small-molecule proline hydroxylase inhibitors have been developed as antifibrotic agents and can now be tested in ischemia models."). The compounds that Kaelin and his colleagues stated should be tested in ischemia models included the compounds disclosed in Bickel 1998 (Ex. 1027), Kivirikko (Ex. 1021), Freidman (Ex. 1017), and Franklin (Ex. 1020), each of which the '172 patent incorporates by reference as disclosing compounds of the invention. See Ex. 1025, Ivan 2001 at 467-468, end notes 22, 32, 33 and 34; Ex. 1001, col. 26, lns. 10-17.

B. Prior Art References Underlying the Grounds for Rejection

1. Bickel 1998 and Weidmann Disclose Prolyl Hydroxylase Inhibitors (Including Heterocyclic Carboxamides) to Treat Fibrotic Conditions Including Ischemia

(a) Bickel 1998

Bickel 1998 and Weidmann disclose inhibitors of prolyl hydroxylase for treatment of fibrotic conditions. Ex. 1002, Schumacker Decl. ¶¶ 65, 63. Bickel 1998 teaches the administration of prolyl hydroxylase inhibitors for the treatment of liver fibrosis. Ex. 1027, Bickel 1998 at 404; Ex. 1002, Schumacker Decl. ¶ 65.

In particular, the reference describes experiments involving S4682, a heterocyclic carboxamide in the form of a heterocyclic carbonyl glycine that was designed as a 2-oxoglutarate mimetic. Ex. 1027, Bickel 1998 at 404, Figure 1, 405; Ex. 1002, Schumacker Decl. ¶ 65. The results revealed that S4682 directly inhibited purified prolyl 4-hydroxylase. Ex. 1027, Bickel 1998 at 408; Ex. 1002, Schumacker Decl. ¶ 66. Moreover, through this inhibition of prolyl 4-hydroxylase, the compound showed anti-fibrotic properties against liver fibrosis or, as described in the '172 patent, liver ischemia.¹⁴ Ex. 1027, Bickel 1998 at 410; Ex. 1002, Schumacker Decl. ¶¶ 66-68; Ex. 1001, col. 59, Example 7.

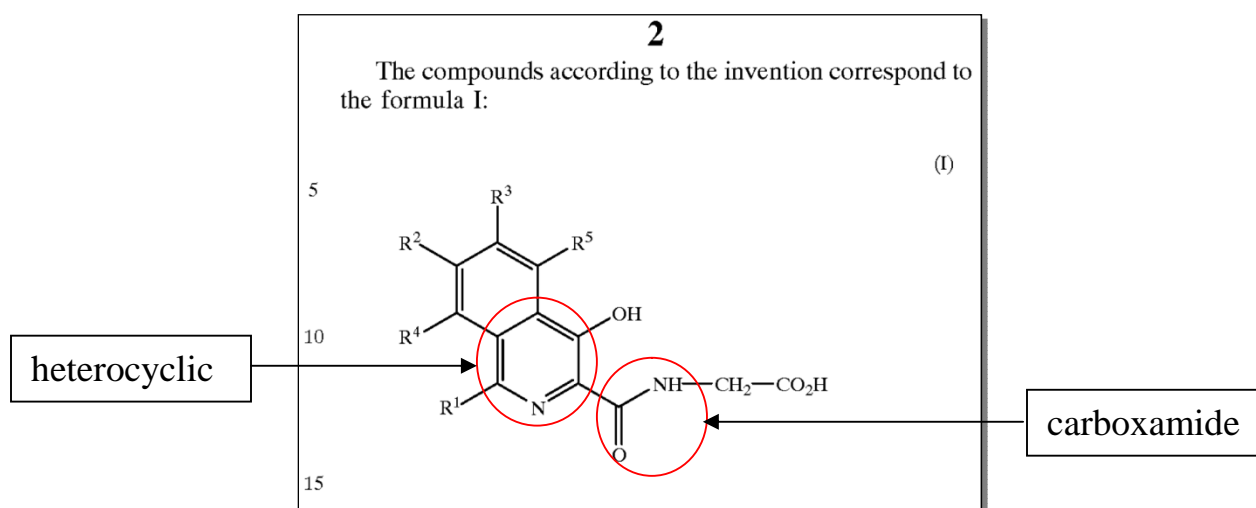
(b) Weidmann

Weidmann¹⁵ teaches administering heterocyclic carboxamide compounds to a subject to treat ischemic conditions. Ex. 1002, Schumacker Decl. ¶¶ 59-64. Specifically, Weidmann discloses substituted isoquinoline-3-carboxamide compounds, their use as inhibitors of prolyl 4-hydroxylase, and their use as pharmaceuticals for the treatment of fibrotic disorders. Ex. 1019, Weidmann, col. 1, lns. 8-11; Ex. 1002, Schumacker Decl. ¶ 59. Weidmann describes pharmaceutical uses for inhibitors of prolyl hydroxylase for treatment of fibroses

¹⁴ Bickel 1998 simulated liver fibrosis by long-term treatment with CCl₄. Ex. 1027, Bickel at 410; Ex. 1002, Schumacker Decl. ¶¶ 66-67.

¹⁵ Weidmann qualifies as prior art under 35 U.S.C. § 102(b).

of the lungs, liver, and skin, and in addition atherosclerosis.¹⁶ Ex. 1019, Weidmann, col. 1, lns. 25-30. The substituted isoquinoline-3-carboxamide compounds include compounds that fall within the scope of Formula I reproduced below. Ex. 1019, Weidmann (abstract), col. 2, lns. 1-15; Ex. 1002, Schumacker Decl. ¶ 60. A compound falling within the scope of Formula I of Weidmann is a heterocyclic carboxamide.¹⁷ Ex. 1002, Schumacker Decl. ¶¶ 59-60.



¹⁶ The '172 patent defines atherosclerosis as an ischemic condition. Ex. 1001, col. 21, lns. 34-35.

¹⁷ These compounds fall within the scope of "heterocyclic carboxamide" as defined in III.E.1 above, because the '172 patent incorporates the compounds of Weidmann ('730 patent) by reference and describes them as examples of compounds within the scope of Formula (Ib). Ex. 1001, col. 36, lns. 1-6; Ex. 1002, Schumacker Decl. ¶ 62.

In addition to the general formula, the patent provides several example compounds that are heterocyclic carboxamide compounds. *See*, e.g., Ex. 1019, Weidmann, col. 13, lns. 13-24 (Example 1, N-((1-Chloro-4-hydroxyl-7-(2-propyloxy)isoquinolin-3-yl)carbonyl)glycine); col. 16, lns. 43-47 (Example 7, N-((6-Benzyloxy-1-chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine); col. 16, lns. 62-65 (Example 8, N-((7-Benzyloxy-1-chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine); col. 17, lns. 12-14 (Example 9, N-((1-Chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine); col. 18, lns. 25-28 (Example 13, N-((7-(1-Butyloxy)-4-hydroxyisoquinolin-3-yl)carbonyl)glycine); Ex. 1002, Schumacker Decl. ¶ 61.¹⁸

¹⁸ The '172 patent lists many of the compounds disclosed in the examples of Weidmann (the '730 patent) and provides nomenclature for referencing those compounds within the specification of the '172 patent. *Id.* For example, Example 7 of the '730 patent is "Compound J" of the '172 patent. Compare Ex. 1019, Weidmann, col. 16, lns. 43-47 to Ex. 1001, col. 36, lns. 14-16. The '172 patent also renamed Example 8 as "Compound L", Example 9 as "Compound B" and Example 13 as "Compound M." Compare Ex. 1019, Weidmann, col. 16, lns. 62-65; col. 17, lns. 12-14; col. 18, lns. 25-28 to Ex. 1001; col. 36, ln. 18-20; col. 36, lns. 10-11; col. 36, lns. 21-22, respectively; Ex. 1002, Schumacker Decl. ¶ 62.

In addition to disclosing use of the compounds to treat ischemic conditions such as liver fibrosis and atherosclerosis, Weidmann provides test data for several of the compounds. Weidmann reports *in vitro* experiments measuring the IC₅₀ of the antifibrotic activity, e.g., compounds of Formula I. Ex. 1019, Weidmann, col. 9, lns. 40-60; Ex. 1002, Schumacker Decl. ¶ 44. Table I includes data for Compounds B, J, L and M of the '172 patent. *See* Ex. 1019, col. 9, lns. 52-58, Examples 9, 7, 8 and 13, respectively. Weidmann further provides *in vivo* data demonstrating the anti-fibrotic activity for the compounds by testing them in CCl₄-model of toxic ischemia of the liver.¹⁹ Ex. 1002, Schumacker Decl. ¶ 64. Table II of Weidmann shows the testing of multiple animals with varying doses for compounds of Formula I. *Id.*, col. 10, lns. 24-34. The compound of Example 9 was tested using a variety of animals and dosages, including via oral administration. *Id.*, col. 10, lns. 24-34. The animals that received the oral dosage showed the highest inhibition of hydroxyproline formation at -71%. *Id.*, col. 10, ln. 32; Ex. 1002, Schumacker Decl. ¶ 64.

Support for the disclosures of Weidmann are found in the '172 patent specification. For instance, the '172 patent provides test data for the compound of

¹⁹ This is the same ischemia model used in Bickel. *See* Ex. 1027, Bickel at 405.

The '172 patent states that this model shows induction of toxic-ischemic injury to the liver. Ex. 1001, col. 59, lns. 16-18.

Example 9 of Weidmann, which is identified as Compound B. *See*, e.g., Ex. 1001, col. 36, lns. 9-11; col. 48, Example 1; col. 49, Example 2; col. 50, Example 3; col. 54, lns. 33-39 (showing results from Example 5, Experiment II); col. 58, lns. 49-54 (discussing Experiment II of Example 6); col. 60, Example 8. The testing of Compound B disclosed in Example 1 of the '172 patent shows that the compound "stabilized HIF α in a normoxic environment in a dose-dependent manner, allowing HIF α to accumulate within the cell." Ex. 1001, col. 48, lns. 59-62.

2. Ivan Discloses the Use of Prolyl Hydroxylase Inhibitors for the Stabilization of HIF- α to Treat Conditions Where It is Desirable to Modulate HIF

Ivan 2001²⁰ is a seminal paper that describes the importance of prolyl hydroxylases as regulators of the degradation of HIF- α under normoxic conditions. Ex. 1025, Ivan 2001; Ex. 1002, Schumacker Decl. ¶ 76. Previous work had established that hypoxic conditions, i.e., low oxygen levels, or iron chelators had the ability to impede the degradation of HIF- α . Ivan 2001 postulated that because prolyl hydroxylases require both molecular oxygen and Fe²⁺, these proteins may play a role in HIF- α degradation. Ex. 1025, Ivan 2001 at 464 (abstract); 467 ("The requirement of molecular oxygen and iron for proline hydroxylase activity would potentially explain the stabilization of HIF under hypoxic conditions or after treatment with agents that eliminate or compete with iron."). Ex. 1002,

²⁰ Ivan 2001 published on Apr. 20, 2001 and is prior art under 35 U.S.C. § 102(b).

Schumacker Decl. ¶ 53. Another component required by prolyl hydroxylases is 2-oxoglutarate. Ex. 1025, Ivan 2001 at 467 ("[prolyl hydroxylases] require Fe^{2+} , molecular oxygen, 2-oxoglutarate . . .").

Based upon the testing performed, Ivan 2001 states that "results indicate that pVHL [von Hippel-Lindau tumor suppressor protein] recognizes a proline-hydroxylated epitope present in HIF-1 α " and, therefore, HIF hydroxylation is carried out by an enzyme that hydroxylates a proline (Pro⁵⁶⁴) on HIF-1 α . *Id.*, Ivan 2001 at 467. Ivan 2001 explains that the authors of the concurrently published article, Jaakkola 2001, came to the same conclusion. *Id.*, Ivan 2001 at 467; Ex. 1002, Schumacker Decl. ¶ 53. Jaakkola 2001 states in its abstract that "the HIF-1 α subunit is regulated through hydroxylation of a proline residue (HIF-1 α P564) by an enzyme we have termed HIF- α prolyl hydroxylase." Ex. 1007, Jaakkola 2001 at 468. Ex. 1002, Schumacker Decl. ¶ 84. Ivan 2001 explains that the knowledge that proline hydroxylation governs HIF turnover should allow a better understanding of HIF regulation, and suggests testing the existing known collagen prolyl hydroxylase inhibitors for the stabilization of HIF to understand their effect on conditions known to be regulated by HIF, in particular, tissue ischemia. Ex. 1025, Ivan 2011 at 467; Ex. 1002, Schumacker Decl. ¶ 85.

3. Semenza 2000 Discloses HIF's Relationship to Hypoxic and Ischemic Events

Semenza 2000²¹ describes the "[i]nvolvement of HIF-1 in key physiological and pathophysiological processes." Ex. 1009, Semenza 2000 at Figure 1; Ex. 1002, Schumacker Decl. ¶ 83. It explains that "under hypoxic conditions, HIF-1 α protein levels increase dramatically and the fraction that is ubiquitinated decreases." *Id.* at 1983. The increase of HIF resulting from increased availability of HIF-1 α leads "to the transcriptional activation of VEGF and several dozen other known target genes." *Id.* Semenza 2000 discloses that "HIF-1 participates in essential developmental and physiological processes" including energy metabolism, cell proliferation/viability, erythropoiesis, iron metabolism, vascular development/remodeling, and vasomotor tone. *Id.* at 1984, Table 1, 1987, Figure 1. According to Semenza 2000, HIF also "contributes to either protective or pathologic responses in several major disease states" including hypoxic and ischemic conditions. *Id.* at 1984-85, 1986. Ex. 1002, Schumacker Decl. ¶ 83. These conditions include ischemic cardiovascular disorders, cerebral ischemia, retinal ischemia, pulmonary hypertension, pregnancy disorders and cancer. Ex. 1009, Semenza 2000 at 1984-1985. Semenza 2000 proposes that therapeutic

²¹ Semenza 2000 published on Aug. 15, 2000 and is prior art under 35 U.S.C. § 102(b).

strategies that increase HIF-1 α expression can promote biological responses that will assist in the treatment of these conditions. *Id.* at 1984. As explained in Semenza 2000, target conditions that could be treated by these therapeutic strategies include atherosclerosis, myocardial infarction and reperfusion injury.²² *Id.* at 1984; Ex. 1002, Schumacker Decl. ¶ 83.

V. STATEMENT OF PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(a))

A. Explanation of Ground 1 for Unpatentability

1. Claims 1, 2, 3, 5, 6 and 8 Are Anticipated by Weidmann

Claim 1 of the '172 patent is directed to a method for treating a hypoxic or ischemic disorder or condition in a subject by administering an effective amount of a heterocyclic carboxamide compound that stabilizes the alpha subunit of hypoxia-inducible factor (HIF- α). Ex. 1001, col. 63, lns. 32-36. Weidmann anticipates claim 1 of the '172 patent because it discloses each limitation of the claim either

²² Semenza 2000 highlights atherosclerosis and myocardial infarction when discussing myocardial ischemia. Ex. 1009, Semenza 2000 at 1984. It also discusses the concept of preconditioning through HIF-1 α up-regulation before a lethal ischemic event. This is a model for assessing reperfusion injury that can be treated through HIF's effect on glucose/energy metabolism and cell proliferation/viability, and on enzymes such as HO-1 and NOS2. Ex. 1002, Schumacker Decl. ¶¶ 67, 83, 93; Ex. 1009, Semenza at 1984, Table 1.

expressly or inherently. *See, e.g., King Pharma., Inc. v. EON Labs, Inc.*, 616 F.3d 1267, 1374 (Fed. Cir. 2010). A reference inherently discloses a limitation if that limitation is necessarily present. *In re Montgomery*, 677 F.3d at 1379-1380. The inherent limitation may inevitably result from following the disclosed steps of a reference. *Id.* at 1380.

Following the steps set out in Weidmann will result in practicing the methods recited in claim 1 of the '172 patent, as Weidmann discloses administering a heterocyclic carboxamide compound to a subject to treat ischemic conditions and it is understood that, upon administration of the compound, HIF- α will be stabilized. In essence, the stabilization of HIF- α is the natural flowing result of practicing the disclosure of Weidmann. *See* Ex. 1002, Schumacker Decl. ¶¶ 87-96.

Specifically, Weidmann teaches the administration of heterocyclic carboxamide compounds, e.g., isoquinoline-3-carboxamides, as inhibitors of prolyl 4-hydroxylase to treat fibrotic disorders. Ex. 1019, Weidmann, col. 1, lns. 8 - 11; Ex. 1002, Schumacker Decl. ¶¶ 59, 89. Weidmann explains that the inhibition of prolyl hydroxylase (involved in the biosynthesis of collagen) reduces the hydroxylation of proline residues on collagen, resulting in a nonfunctional, underhydroxylated collagen molecule. *Id.*, col. 1, lns. 10-20. Due to the ability of prolyl hydroxylase inhibitors to affect collagen synthesis, the patent teaches that these compounds are suitable for treatment of fibrotic diseases of the lung, liver,

and skin, and treatment of atherosclerosis.²³ *Id.*, col. 1, lns. 25-30; Ex. 1002, Schumacker Decl. ¶ 89.

In addition to disclosing use of the compounds to treat ischemic conditions such as liver fibrosis, Weidmann provides test data for several of the compounds that demonstrates the efficacy of the compounds in treating such conditions. Weidmann describes the testing of rats that had been administered carbon tetrachloride (CCl₄) to induce liver fibrosis.²⁴ *Id.*, col. 9, ln. 62 to col. 10, ln. 62; Ex. 1002, Schumacker Decl. ¶¶ 64, 90-93. Weidmann shows that the prolyl hydroxylase inhibitors decrease the extent of liver fibrosis. *Id.*, col. 9, ln. 36 to col. 10, ln. 34. Weidmann concludes that the prolyl hydroxylase inhibitors disclosed were active in the CCl₄ liver fibrosis model in concentrations ranging from 1 to 100 mg/kg. *Id.*, col. 10, lns. 4-8.

Accordingly, Weidmann expressly discloses the administration of a heterocyclic carboxamide compound (e.g., compound of Example 9) in an effective amount (e.g., 1mg/kg to 100 mg/kg) to a subject (rat) by oral

²³ The '172 patent defines chronic ischemic conditions to include atherosclerosis. Ex. 1001, col. 21, lns. 34-35.

²⁴ Similarly, Bickel utilized a CCl₄ model to induce liver injury. Ex. 1027, Bickel 1998 at 404, 401. The '172 patent describes the Bickel tests as showing treatment of liver ischemia. Ex. 1001, col. 59, Example 7.

administration to treat an ischemic condition or disorder (liver fibrosis). Ex. 1019, Weidmann, col. 9, ln.61-col. 10, ln. 34. While Weidmann does not expressly state that the administered heterocyclic carboxamide compound "stabilizes the alpha subunit of hypoxia inducible factor (HIF α)," upon administration of the compound of Example 9 to treat liver ischemia, HIF- α will be stabilized. Ex. 1002, Schumacker Decl. ¶¶ 94-95.

The '172 patent confirms that HIF- α is stabilized as a result of the Weidmann experiments, as the '172 patent states "(Compounds A to F) stabilized HIF α in a normoxic environment in a dose-dependent manner, allowing HIF α to accumulate within the cell." Ex. 1001, col. 48, lns. 59-63. Compound B is the same compound as Compound 9 of Weidmann.²⁵ The other experiments within the '172 patent that recite data for Compound B provide additional support showing that Compound B stabilizes HIF- α . These experiments measure the effect of Compound B on certain physiological processes. Scientists such as Gregg Semenza had previously established that such physiological processes are affected by the up-regulation of HIF through the stabilization of HIF- α . *See* Ex. 1001, col.

²⁵ The '172 patent lists Example 9 as "Compound B". Compare Ex. 1019, Weidmann, col. 16, lns. 62-65; col. 17, lns. 12-14; col. 18, lns. 25-28 to Ex. 1001; col. 36, lns. 18-20; col. 36, lns. 10-11; col. 36, lns. 21-22, respectively; Ex. 1002, Schumacker Decl. ¶ 62.

49, lns. 52-53 (showing the effect on glucose/energy metabolism); col. 50, lns. 4-6 (showing increased expression of VEGF); col. 54, lns. 33-38 (showing increased expression of VEGF); col. 58, ln. 49-col. 59, ln. 11 (showing treatment of myocardial infarction); Ex. 1009, Semenza 2000 at 1983, 1984, Table 1; Ex. 1002, Schumacker Decl. ¶¶ 94-96.

Because the natural flowing result of practicing Weidmann is the stabilization of the alpha subunit of hypoxia inducible factor (HIF- α), this limitation is inherent within Weidmann's disclosure. *See King Pharma.*, 616 F.3d at 1275 ("Such newly discovered benefits are not patentable because they are inherent in the prior art."); *In re Montgomery*, 677 F.3d at 1381. Weidmann inherently anticipates dependent claims 2, 3, 5, 6 and 8 as well, because the analysis for claim 1 applies equally to these additional claims. Ex. 1002, Schumacker Decl. ¶¶ 97-101. Specifically, claim 2 depends from claim 1 and adds the limitation that the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase enzyme activity. Ex. 1001, col. 63, lns. 37-39. This is the natural flowing result of the administration of the compounds of Weidmann, including the compound of Example 9. Ex. 1002, Schumacker Decl. ¶ 97. As discussed above, the '172 patent confirms that the compound of Example 9 of Weidmann, upon

administration, inhibits HIF prolyl hydroxylase enzyme activity as recited in claim 2. Ex. 1001, col. 48, lns. 59-63.²⁶

Claim 3 requires treatment of a disorder or condition associated with an ischemic event. Weidmann discloses administration of the compound of Example 9 to treat an ischemic condition or disorder (liver fibrosis). Ex. 1019, Weidmann, col. 9, ln. 61 to col. 10, ln. 34; Ex. 1002, Schumacker Decl. ¶ 98. The testing described in Weidmann also teaches the limitations of claims 5 and 6, because the testing model simulates an ischemic event associated with a toxic injury (claim 5) and a chronic disorder or condition (claim 6). Ex. 1019, Weidmann, col. 9, ln. 61 to col. 10, ln. 34 (disclosing use of antifibrotic model that utilizes carbon tetrachloride-induced (CCl₄) liver fibrosis); Ex. 1002, Schumacker Decl. ¶¶ 99, 100. This disclosure teaches the limitation of claim 5 because the administration of CCl₄ results in a toxic injury to the liver. Ex. 1002, Schumacker Decl. ¶ 99. The disclosure teaches the limitation of claim 6 because the patent

²⁶ Example 9 of the '730 patent (Ex. 1019 at col. 17, lns. 10-15) is the same compound as Compound B of the '172 patent (Ex. 1001 at col. 36, lns. 9-11). The '172 patent explains that "various compounds of the invention (Compounds A to F) stabilize HIF α in a normoxic environment in a dose-dependent manner, allowing HIF α to accumulate within the cell." Ex. 1001 at col. 48, lns. 59-62 (emphasis added); Ex. 1002, Schumacker Decl. ¶¶ 62-63.

discloses administering CCL₄ twice weekly for 4 weeks. The administration of CCL₄ for 4 weeks induces chronic liver fibrosis. Ex. 1002, Schumacker Decl. ¶ 100.

Lastly, Weidmann inherently anticipates dependent claim 8 which includes the limitation that the administration is oral. *Id.* at Ins. 42-43. The administration of the compound of Example No. 9 to treat liver ischemia is an oral administration. Ex. 1019, Weidmann, col. 10, Ins. 23-35. The oral administration of the disclosed heterocyclic compound to treat ischemia is anticipatory—as such administration would clearly infringe claims 1 and 8 of the '172 patent. Ex. 1002, Schumacker Decl. ¶ 101. *Bristol-Myers Squibb Co. v. Ben Venue Laboratories, Inc.*, 246 F.3d 1368, 1378 (Fed. Cir. 2001) ("Kris's performance of these same steps today would literally infringe the '803 claims; it is axiomatic that that which would literally infringe if later anticipates if earlier.")

Thus, as of the effective filing date of the '172 patent, the prior art Weidmann patent taught the administration of heterocyclic carboxamide compounds to treat hypoxic and ischemic conditions, which would inherently stabilize HIF- α , and thereby anticipate claims 1, 2, 3, 5, 6 and 8 of the '172 patent.

2. The Summary of Anticipation Arguments Regarding Claims 1, 2, 3, 5, 6 and 8 under Ground 1

Claim	Weidmann
1. A method for treating a hypoxic or ischemic disorder or condition in a	"The antifibrotic action was determined in the model of carbon tetrachloride-

Claim	Weidmann																			
subject the method comprising	<p>induced liver fibrosis. For this, rats were treated twice weekly with CCL₄ (1 ml/kg) dissolved in olive oil. The test substance was administered daily, if appropriate even twice daily, orally or intraperitoneally dissolved in a suitable compatible solvent. . . . Substance Administration: Here the experimental animals were treated for two weeks only with carbon tetrachloride, then for the next two weeks with carbon tetrachloride and test substance . . .</p> <p>Results:</p> <div><div>TABLE II</div><div><div>25</div><table><tr><th>Test substance from Example</th><th>Dose [mg/kg] (number of animals)</th><th>Inhibition of hydroxyproline formation</th></tr><tr><td>1</td><td>20 (15)</td><td>-55%</td></tr><tr><td>9</td><td>20 (15)</td><td>-67%</td></tr><tr><td rowspan="3">30</td><td>40 (15)</td><td>-65%</td></tr><tr><td>100 (24)</td><td>-58%</td></tr><tr><td>100* (14)</td><td>-71%</td></tr><tr><td>19</td><td>40 (13)</td><td>-39%</td></tr></table></div><div>*oral administration</div></div> <p>Ex. 1019, Weidmann, col. 9, ln. 62 to col. 10, ln. 51</p>	Test substance from Example	Dose [mg/kg] (number of animals)	Inhibition of hydroxyproline formation	1	20 (15)	-55%	9	20 (15)	-67%	30	40 (15)	-65%	100 (24)	-58%	100* (14)	-71%	19	40 (13)	-39%
Test substance from Example	Dose [mg/kg] (number of animals)	Inhibition of hydroxyproline formation																		
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30	40 (15)	-65%																		
	100 (24)	-58%																		
	100* (14)	-71%																		
19	40 (13)	-39%																		
administering to the subject an effective amount of a heterocyclic carboxamide compound	<p>"The compounds of formulae I and Ia are inhibitors of prolyl 4-hydroxylase." Ex. 1019, Weidmann, col. 9, lns. 36-39.</p> <p>"Example 9 N-((1-Chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine" Ex. 1019, Weidmann, col. 17, lns. 12-50.</p> <p>"The compounds according to the invention were active in this model in a concentration of 1 to 100 mg/kg." Ex. 1019, Weidmann, col. 10, lns. 6-8.</p>																			
that stabilizes the alpha subunit of hypoxia inducible factor (HIF α).	The natural flowing result of administering the compound of Example 9 will be to stabilize HIF- α .																			

Claim	Weidmann
	Ex. 1002, Schumacker Decl. ¶¶ 90-92. The '172 patent confirms that the compound of Example No. 9 stabilizes HIF α because Compound B correspond to the compound of Example No. 9. Ex. 1001, col. 48, lns. 59-63; col. 49, lns. 6-8; Ex. 1002, Schumacker Decl. ¶ 62.
2. The method of claim 1, wherein the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase enzyme activity.	"The compounds of formulae I and Ia are inhibitors of prolyl 4-hydroxylase." Ex. 1019, Weidmann, col. 9, lns. 36-39. "Example 9 N-((1-Chloro-4-hydroxyisoquinolin-3-yl)carbonyl)glycine" Ex. 1019, Weidmann, col. 17, lns. 12-50.
3. The method of claim 1, wherein the hypoxic or ischemic disorder or condition is associated with an ischemic event.	"The antifibrotic action was determined in the model of carbon tetrachloride-induced liver fibrosis. For this, rats were treated twice weekly with CCL ₄ (1 ml/kg) dissolved in olive oil. The test substance was administered daily, if appropriate even twice daily, orally or intraperitoneally dissolved in a suitable compatible solvent. . . ." Ex. 1019, Weidmann, col. 9, ln. 62 to col. 10, ln. 51.
5. The method of claim 3, wherein the ischemic event is associated with surgery, organ transplantation, infarction, trauma, or injury.	"The antifibrotic action was determined in the model of carbon tetrachloride-induced liver fibrosis. For this, rats were treated twice weekly with CCL ₄ (1 ml/kg) dissolved in olive oil. The test substance was administered daily, if appropriate even twice daily, orally or intraperitoneally dissolved in a suitable compatible solvent. . . ." Ex. 1019, Weidmann, col. 9, ln. 62 to col. 10, ln. 51.

Claim	Weidmann																					
	The testing results in an ischemic event associated with an injury. Ex. 1002, Schumacker Decl. ¶¶ 90, 93, 99.																					
6. The method of claim 1, wherein the ischemic disorder or condition is chronic.	<p>"The antifibrotic action was determined in the model of carbon tetrachloride-induced liver fibrosis. For this, rats were treated twice weekly with CCL4 (1 ml/kg) dissolved in olive oil. The test substance was administered daily, if appropriate even twice daily, orally or intraperitoneally dissolved in a suitable compatible solvent. . . .Here the experimental animals were treated for two weeks only with carbon tetrachloride, then for the next two weeks with carbon tetrachloride and test substance" Ex. 1019, Weidmann, col. 9, ln. 62 to col. 10, ln. 51.</p> <p>The 4 week administration of carbon tetrachloride induces chronic liver fibrosis. Ex. 1002, Schumacker Decl. ¶¶ 90, 93, 100.</p>																					
8. The method of claim 1, wherein the administering is oral administration	<div><div>25</div><div><div>TABLE II</div><table><tr><th>Test substance from Example</th><th>Dose [mg/kg] (number of animals)</th><th>Inhibition of hydroxyproline formation</th></tr><tr><td>1</td><td>20 (15)</td><td>-55%</td></tr><tr><td>9</td><td>20 (15)</td><td>-67%</td></tr><tr><td>30</td><td>40 (15)</td><td>-65%</td></tr><tr><td></td><td>100 (24)</td><td>-58%</td></tr><tr><td></td><td>100* (14)</td><td>-71%</td></tr><tr><td>19</td><td>40 (13)</td><td>-39%</td></tr></table></div></div> <div><div>*oral administration</div><div>Ex. 1019, Weidmann, col. 9, ln. 62 – col. 10, ln. 51.</div></div>	Test substance from Example	Dose [mg/kg] (number of animals)	Inhibition of hydroxyproline formation	1	20 (15)	-55%	9	20 (15)	-67%	30	40 (15)	-65%		100 (24)	-58%		100* (14)	-71%	19	40 (13)	-39%
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19	40 (13)	-39%																				

B. Explanation of Ground 2 for Unpatentability – Claims 1, 2, 3, 5, and 6 are Obvious Over Ivan 2001 in View of Bickel 1998

1. Claim 1 is Obvious Over Ivan 2001 in View of Bickel 1998

The method of claim 1—to treat a hypoxic or ischemic disorder by administering a heterocyclic carboxamide compound that stabilizes HIF- α —would have been obvious to a person of ordinary skill in the art over Ivan 2001 in view of Bickel 1998. In particular, the claim is obvious in light of (1) the disclosure by Ivan 2001 that inhibitors of prolyl hydroxylase inhibitors could stabilize HIF- α and be useful in treating conditions where it is desirable to modulate HIF, including ischemia, and (2) Bickel 1998, which teaches the use of a heterocyclic carboxamide compound that inhibits prolyl hydroxylase in the treatment of liver ischemia. Ex. 1002, Schumacker Decl. ¶¶ 103-107.

A person of ordinary skill in the art would be motivated to combine Ivan 2001 and Bickel 1998 because Ivan 2001 directs a person of ordinary skill in the art to test the heterocyclic carboxamide prolyl hydroxylase inhibitors disclosed in Bickel 1998 against ischemic conditions and disorders. Ex. 1025, Ivan 2001 at 467 and 468, n. 32. Ex. 1002, Schumacker Decl. ¶¶ 104, 106. In light of this explicit instruction, Ivan 2001 and Bickel 1998 provide a person of ordinary skill in the art with the motivation to combine the references with a reasonable expectation of success that such compounds will stabilize HIF and thereby treat conditions such as ischemia. Ex. 1002, Schumacker Decl. ¶¶ 104, 106-107.

Combined, these references teach each limitation of claim 1 of the '172 patent. Ivan 2001 identifies that inhibitors of prolyl hydroxylase can prevent the hydroxylation of HIF- α , leading to an accumulation of HIF. *See* Ex. 1025, Ivan 2001 at 467 along with Ivan's citation of Jaakkola 2001 at 468²⁷; Ex. 1002, Schumacker Decl. ¶¶ 76, 77, 104. While Ivan 2001 does not discuss that a heterocyclic carboxamide can be utilized to inhibit prolyl hydroxylase to result in the stabilization of HIF- α , Bickel 1998 does disclose a heterocyclic carboxamide compound developed as an antifibrotic. Ex. 1024, Ivan 2001 at 467-468; Ex. 1002, Schumacker Decl. ¶ 105. Further, Ivan 2001 recognizes that several prolyl hydroxylase inhibitors have been developed as antifibrotic agents, and instructs a person of ordinary skill in the art to test those compounds in ischemia models in hopes that these drugs could be helpful in angiogenesis or hypoxic conditions. Ex. 1025, Ivan at 467; Ex. 1002, Schumacker Decl. ¶ 104.

The prior art "small-molecule proline hydroxylase inhibitors" that Ivan 2001 instructs a person of ordinary skill in the art to test in ischemia models includes the compounds disclosed in prior art references, such as Kivirikko 1998; Bickel 1998, Franklin 2001 and Friedman 2000. Ex. 1025, Ivan 2001 at 467-468, end notes 22, 32, 33 and 34. Ex. 1002, Schumacker Decl. ¶¶ 69-73; 104. The '172 patent

²⁷ "The HIF-1 α subunit is regulated . . . by an enzyme we have termed HIF- α prolyl hydroxylase." Ex. 1007, Jaakkola at 468.

identifies each of these prior art references as disclosing compounds of the invention. Ex. 1001, '172 patent, col. 26, lns. 10-18. Furthermore, the existing prolyl hydroxylase inhibitors that Ivan 2001 suggests testing for stabilization of HIF in ischemia models includes a heterocyclic carboxamide. Ex. 1024, Ivan 2001 at 467-468. Bickel 1998 shows testing of S4682 – a heterocyclic carboxamide. Ex. 1027, Bickel 1998 at 405, Figure 1; Ex. 1002, Schumacker Decl. ¶¶ 54, 69-73; 104.

Considering that Ivan 2001 teaches the administration of a compound that inhibits prolyl hydroxylase to result in the stabilization of HIF- α and suggests the testing of the heterocyclic compounds of Bickel 1998 in ischemia models as potentially effective in angiogenesis and the adaption to chronic hypoxia, a person of ordinary skill in the art, as of the effective filing date of the '172 patent, would have a reasonable expectation that a heterocyclic carboxamide compound would (i) stabilize HIF- α and (ii) treat a subject suffering from a hypoxic or ischemic condition or disorder. Ex. 1002, Schumacker Decl. ¶¶ 103-108.

2. Ivan 2001 and Bickel 1998 Render Claim 2, 3, 5 and 6 Invalid as Obvious

Claim 2 depends from claim 1 and adds the limitation that the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase enzyme activity. Ex. 1001, col. 63, lns. 37-39. Ivan 2001 teaches that the degradation of HIF hydroxylation is carried out by an enzyme that hydroxylates a proline on HIF- α

and notes that Jaakkola 2001 came to the same conclusion. Ex. 1025, Ivan at 467.²⁸ Ivan 2001 proposes that the enzyme is prolyl hydroxylase. Ex. 1026 at 467. In fact, Jaakkola expressly states that "the HIF-1 α subunit is regulated through hydroxylation of a proline residue (HIF-1 α P564) by HIF- α prolyl hydroxylase (HIF-PH)." Ex. 1007, Jaakkola at 468 (Abstract). The disclosure that prolyl hydroxylase enzymes are responsible for the degradation of HIF- α coupled with the analysis for claim 1 discussed *supra* establishes that claim 2 is invalid as obvious. Ex. 1002, Schumacker Decl. ¶ 109.

Claim 3 depends from claim 1 and requires that the disorder or condition be an ischemic event. Ex. 1001, col. 63, lns. 40-4. Bickel 1998 discloses treatment of liver ischemia. Bickel 1998 teaches use of the heterocyclic carboxamide compound to treat liver ischemia induced by the administration of CCl₄. Ex. 1027, Bickel 1998 at 405, Experimental Liver Fibrosis. Treatment with CCl₄ is a model for liver ischemia. Ex. 1002, Schumacker Decl. ¶ 110. The '172 patent acknowledges that Bickel 1998 discloses treatment of liver ischemia. Ex. 1001, col. 59, lns. 12-67.

²⁸ Ivan 2001 and Jaakkola 2001 both published in Issue 292 of Science. Ex. 1025, Ivan 2001; Ex. 1007, Jaakkola 2001. The articles ran on consecutive pages in that issue.

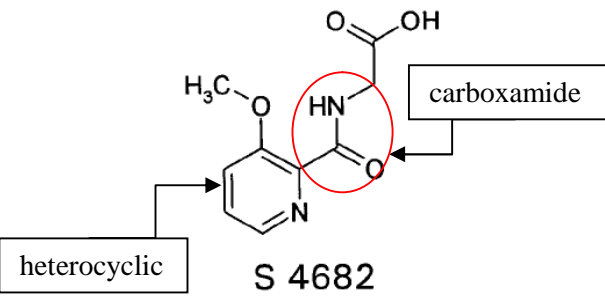
Claim 5 depends from claim 3 and requires the ischemic event is associated with surgery, organ transplantation, infarction, trauma, or injury. The liver ischemia treated in Bickel 1998 is an injury. Ex. 1027, Bickel 1998 at 405, Experimental Liver Fibrosis; Ex. 1002, Schumacker Decl. ¶ 111. In fact, the '172 patent describes the Bickel 1998 testing as "induction of toxic **ischemic injury** in the liver." Ex. 1001, col. 59, lns. 17-19 (emphasis added).

Claim 6 depends from claim 1 and requires treatment of a chronic ischemic disorder or condition. Ex. 1001, col. 64, lns. 35-36. Bickel 1998 teaches treatment of a chronic ischemic disorder because the model utilized shows a chronic ischemic disorder or condition as the CCl₄ was administered for a 9 week period. Ex. 1027, Bickel 1998 at 405; Ex. 1002, Schumacker Decl. ¶ 112.

3. Summary of Obviousness Rejections under Ground 2

Claim	Ivan 2001 in View of Bickel 1998
1.A method for treating a hypoxic or ischemic disorder or condition in a subject the method comprising	<p><u>Ivan 2001</u></p> <p>"In the presence of oxygen, HIF is targeted for destruction Because proline hydroxylation requires molecular oxygen and FE^{2+}, this protein modification may play a key role in mammalian oxygen sensing." Ex. 1025, at 464 (abstract)</p> <p>"hypoxia leads to the stabilization of a sequence-specific DNA binding transcription factor called HIF, which transcriptionally activates a variety of genes linked to processes such as angiogenesis and glucose metabolism</p>

Claim	Ivan 2001 in View of Bickel 1998
	<p>(1-4). HIF binds to DNA as a heterodimer consisting of an α subunit and a β subunit" Ex. 1025 at 464, col. 1.</p> <p>"The results . . . suggest that HIF hydroxylation is carried out by an enzyme. The same conclusion is reached by Jaakkola et al." Ex. 1025 at 467, col. 1.</p> <p>"The requirement of molecular oxygen and iron for proline hydroxylase activity would potentially explain the stabilization of HIF observed under hypoxic conditions or after treatment with agents that eliminate or compete with iron." Ex. 1025 at 467, col. 2.</p> <p>"In principle, drugs that stabilize HIF may augment angiogenesis and the adaption to chronic hypoxia. Several small-molecule proline hydroxylase inhibitors have been developed as antifibrotic agents and can now be tested in ischemia models (22, 32-34)." Ex. 1025 at 467, col. 2.</p> <p><u>Bickel 1998</u> Experimental Liver Fibrosis; Ex. 1027 at 405, col. 2.</p>
administering to the subject an effective amount of a heterocyclic carboxamide compound	<p><u>Bickel 1998</u></p> <p>"S4682 was given concomitantly with CCl₄ twice daily at a dose of 60 mg/ intraperitoneally dissolved in saline and administered in a volume of 2 mL/kg." Ex. 1027 at 405, col. 2.</p>

Claim	Ivan 2001 in View of Bickel 1998
	<p>S 4682 is "a heterocyclic carbonyl-glycine derivative (Fig 1)." This compound is a heterocyclic carboxamide.</p> <div data-bbox="820 462 1421 756">  </div>
<p>that stabilizes the alpha subunit of hypoxia inducible factor (HIFα).</p>	<p><u>Ivan 2001</u></p> <p>"The requirement of molecular oxygen and iron for proline hydroxylase activity would potentially explain the stabilization of HIF observed under hypoxic conditions or after treatment with agents that eliminate or compete with iron." Ex. 1025 at 467, col. 2.</p>
<p>2. The method of claim 1, wherein the heterocyclic carboxamide compound inhibits HIF prolyl hydroxylase enzyme activity.</p>	<p><u>Ivan 2001</u></p> <p>"The results . . . suggest that HIF hydroxylation is carried out by an enzyme. The same conclusion is reached by Jaakkola et al." Ex. 1025 at 467, col. 1.</p> <p>"The requirement of molecular oxygen and iron for proline hydroxylase activity would potentially explain the stabilization of HIF observed under hypoxic conditions or after treatment with agents that eliminate or compete with iron." Ex. 1025 at 467, col. 2.</p>
<p>3. The method of claim 1, wherein the hypoxic or ischemic disorder or</p>	<p><u>Ivan 2001</u></p>

Claim	Ivan 2001 in View of Bickel 1998
condition is associated with an ischemic event.	"In principle, drugs that stabilize HIF may augment angiogenesis and the adaption to chronic hypoxia. Several small-molecule proline hydroxylase inhibitors have been developed as antifibrotic agents and can now be tested in ischemia models (22, 32-34)." Ex. 1025 at 467, col. 2. <u>Bickel 1998</u> Experimental Liver Fibrosis; Ex. 1027 at 405, col. 2.
5. The method of claim 3, wherein the ischemic event is associated with surgery, organ transplantation, infarction, trauma, or injury.	<u>Bickel 1998</u> Experimental Liver Fibrosis; Ex. 1027 at 405, col. 2.
6. The method of claim 1, wherein the ischemic disorder or condition is chronic.	<u>Bickel 1998</u> Experimental Liver Fibrosis; Ex. 1027 at 405, col. 2.

C. Explanation of Ground 3 for Unpatentability – Claim 8 is Obvious Over Ivan 2001 in View of Bickel 1998 and Weidmann

Claim 8 depends from claim 1 and requires oral administration of the heterocyclic carboxamide compound. Although a person of ordinary skill in the art would understand that oral administration of a compound is preferable even without a prior art reference that shows oral administration of a heterocyclic carboxamide, Weidmann teaches such administration. *See* Ex. 1002, Schumacker Decl. ¶ 113; Ex. 1019, Weidmann, col. 10, lns. 16-34 (oral administration of the test substance from Example 9, Table II). As shown above, the limitations of claim 1 are obvious in view of Ivan 2001 and Bickel 1998. *See* B.1 *supra*. A

person of ordinary skill in the art would be motivated to combine Weidmann with Ivan 2001 and Bickel 1998 because Ivan 2001 suggests administering known prolyl hydroxylase inhibitors in ischemia models. Ex. 1025, Ivan 2001 at 467; Ex. 1002, Schumacker Decl. ¶ 113. Weidmann discloses such compounds. Ex. 1019, Weidmann, col. 9, ln. 36-col. 10, ln. 39; col. 17, lns. 11-50. The disclosure of an oral administration of a heterocyclic prolyl hydroxylase inhibitor coupled with the analysis for claim 1 discussed *supra* shows that claim 8 is invalid as obvious.

The chart below shows how claim 8 is obvious over Ivan 2001 in view of Bickel 1998 and Weidmann.

Claim	Ivan 2001 in View of Bickel 1998 and Weidmann																												
8. The method of claim 1, wherein the administering is oral administration.	<p>See Claim Chart for Claim 1 in Ground 2.</p> <p><u>Weidmann</u></p> <p style="text-align: center;">TABLE II</p> <table><tr><td>25</td><td>Test substance from Example</td><td>Dose [mg/kg] (number of animals)</td><td>Inhibition of hydroxyproline formation</td></tr><tr><td></td><td>1</td><td>20 (15)</td><td>-55%</td></tr><tr><td></td><td>9</td><td>20 (15)</td><td>-67%</td></tr><tr><td>30</td><td></td><td>40 (15)</td><td>-65%</td></tr><tr><td></td><td></td><td>100 (24)</td><td>-58%</td></tr><tr><td></td><td></td><td>100* (14)</td><td>-71%</td></tr><tr><td></td><td>19</td><td>40 (13)</td><td>-39%</td></tr></table> <p>*oral administration</p> <p>Ex. 1019, Weidmann, col. 9, ln. 62 – col. 10, ln. 51.</p>	25	Test substance from Example	Dose [mg/kg] (number of animals)	Inhibition of hydroxyproline formation		1	20 (15)	-55%		9	20 (15)	-67%	30		40 (15)	-65%			100 (24)	-58%			100* (14)	-71%		19	40 (13)	-39%
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D. Explanation of Ground 4 for Unpatentability – Claims 4 and 7 are Obvious Over Ivan 2001 in View of Bickel 1998 and Semenza 2000

Claims 4 and 7 depend from claims 3 and 1, respectively. Ex. 1001, col. 63, ln. 42 to col. 64, ln. 39. As shown above, Ivan 2001 combined with Bickel 1998 renders claims 1 and 3 obvious. *See B supra*. Claim 4 adds the requirement that the disorder or condition be an acute ischemic event, while claim 7 adds the requirement that the disorder or condition be associated with ischemic reperfusion injury. Ex. 1001, col. 63, ln. 42-col. 64, ln. 39. Semenza 2000 teaches that HIF stabilization benefits both of these conditions.

Semenza 2000 describes that an increase in HIF-1 α and protein expression are induced during an acute ischemic event such as a myocardial infarction.²⁹ Ex. 1009, Semenza 2000 at 1984 ("HIF-1 α mRNA and protein expression are induced and precede VEGF expression during acute ischemia and early infarction in the human heart.") Semenza 2000 then states that "therapeutic strategies designed to increase HIF-1 α expression may promote angiogenesis with ischemic myocardium." *Id.* In light of this teaching, a person of ordinary skill in the art would understand that one could treat acute ischemic events through the administration of a compound that can modulate HIF-1 α . Ex. 1002, Schumacker

²⁹ The '172 patent defines "acute ischemic conditions" as including myocardial infarction. Ex. 1001, col. 21, lns. 29-31.

Decl. ¶ 114. Thus, the teaching of Semenza 2000 combined with (i) the Ivan 2001 disclosure that teaches inhibitors of prolyl hydroxylase can stabilize HIF-1 α and (ii) the Bickel 1998 disclosure of heterocyclic carboxamide compounds as prolyl hydroxylase inhibitors renders claim 4 obvious. Ex. 1002, Schumacker Decl. ¶ 115. A person of ordinary skill in the art would have been motivated to combine these references because Ivan 2001 directs a person of ordinary skill in the art to test the HIF stabilizing, heterocyclic carboxamide, prolyl hydroxylase inhibitors disclosed in Bickel 1998 against ischemic conditions, and Semenza 2000 delineates acute ischemic events. Ex. 1002, Schumacker Decl. ¶ 115. Ivan 2001 actually cites similar articles by Semenza that discuss HIF- α . *See* Ex. 1025, Ivan 2001 at 467, n. 1, 3. Furthermore, the data of Bickel 1998 provides the person of ordinary skill in the art with a reasonable expectation of successful treatment.

Semenza 2000 discusses the benefits of preconditioning a subject before experiencing an ischemic event. Ex. 1009, Semenza 2000 at 1984. The preconditioning model discussed exposes a subject to a sublethal reduction of blood flow followed by a lethal reduction of blood flow.³⁰ *Id.* These experiments

³⁰ Semenza 2000 references several articles that describe preconditioning studies. Ex. 1009, Semenza 2000 at 1984. These articles describe protocols for establishing preconditioning that are models for understanding protection against reperfusion injury. *See* Ex. 1002, Schumacker Decl. ¶¶ 43, 83.

show that the up-regulation of HIF-1 α that results from the exposure to the non-lethal ischemic event provides protection against a subsequent lethal ischemic event. *Id.* ("Thus, NO production in response to the preconditioning stimulus may induce HIF-1 mediated NOS2 expression that is protective against a subsequent lethal ischemic challenge.") The protection afforded by the HIF-1 mediated response includes protection of surviving cells that may experience reperfusion injury once the ischemic condition is alleviated, i.e., once sufficient blood flow is restored. Ex. 1002, Schumacker Decl. ¶ 116. Based upon the results described by Semenza 2000, a person of ordinary skill in the art would understand that conditions that induce HIF-1 α expression under non-hypoxic conditions, such as preconditioning, may result in protection against reperfusion injury associated with an ischemic event. Ex. 1002, Schumacker Decl. ¶ 117; Ex. 1009, Semenza 2000 ("Furthermore, NO has shown to induce HIF-1 α expression under non-hypoxic conditions."). This understanding coupled with the disclosure of Ivan 2001 and Bickel 1998 would render claim 7 obvious to a person of ordinary skill in the art. Ex. 1002, Schumacker Decl. ¶ 117.

The chart below shows how claims 4 and 7 are obvious over Ivan 2001 in view of Bickel 1998 and Semenza 2000.

Claim	Ivan 2001 in View of Bickel 1998 and Semenza 2000
4. The method of claim 3, wherein the	See Claim Chart for Claim 3 in Ground

Claim	Ivan 2001 in View of Bickel 1998 and Semenza 2000
ischemic event is acute	<p>2.</p> <p><u>Semenza 2000</u></p> <p>"Ischemic cardiovascular disorders Myocardial ischemia Atherosclerosis leads to arterial stenosis, impaired perfusion of the downstream vascular bed, and ischemia. When oxygen and glucose deprivation irreversibly affect myocardial viability, the end result is an infarction (heart attack). . . [I]schemia induces the development of collateral blood vessels that allow perfusion of myocardium downstream of coronary artery stenosis and that influence the incidence and severity of myocardial infarction."</p> <p>Ex. 1009 at 1984, col. 1.</p>
7. The method of claim 1, wherein the hypoxic or ischemic disorder or condition is associated with ischemic reperfusion injury in a subject	<p>See Claim Chart for Claim 1 in Ground 2.</p> <p><u>Semenza 2000</u></p> <p>"Ischemic preconditioning is an experimental phenomenon in which subjecting an animal to a sublethal ischemic challenge results in protection against a subsequent lethal challenge. . . . Thus, NO production in response to the preconditioning stimulus may induce HIF-1 mediated NOS2 expression that is protective against a subsequent lethal ischemic challenge."</p> <p>Ex. 1009 at 1984, col. 2.</p>

VI. MANDATORY NOTICES UNDER 37 C.F.R. § 42.8(a)(1)

As set forth below and pursuant to 37 C.F.R. § 42.8(a)(1), the following mandatory notices are provided as part of this Petition:

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

GlaxoSmithKline LLC and GlaxoSmithKline PLC are the real parties-in-interest for Petitioner GlaxoSmithKline LLC. GlaxoSmithKline PLC is a publicly traded entity and is the ultimate parent of GlaxoSmithKline LLC.

GlaxoSmithKline PLC's shares are traded on the London Stock Exchange, and its American depository receipts (ADR) are traded on the New York Stock Exchange.

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

There are no related matters at this time. But concurrently with the filing of this IPR, Petitioner has filed five IPRs on other FibroGen patents. See IPR2016-01318; IPR2016-01319; IPR2016-01320; IPR2016-1322; and IPR2016-01323.

C. Lead and Back-up Counsel Under 37 C.F.R. § 42.8(b)(3)

Pursuant to 37 C.F.R. § 42.8(b)(3) and § 42.10(a), GSK provides the following designation of counsel:

Lead Counsel	Back-up Counsel
Brian W. Nolan (Reg. No. 45,821) BNolan@mayerbrown.com <u>Postal and hand Delivery Address</u> Mayer Brown LLP 1221 Avenue of the Americas	Lisa M. Ferri (<i>pro hac vice</i> to be filed) LFerri@mayerbrown.com <u>Postal and hand Delivery Address</u> Mayer Brown LLP 1221 Avenue of the Americas

New York, NY 10020 Tel: (212) 506-2500 Fax: (212) 262-1910 <i>Petitioner consents to email service at: MB-Fibrogen-IPR@mayerbrown.com</i>	New York, NY 10020 Tel: (212) 506-2500 Fax: (212) 262-1910 Jonathan H. Kim (Reg. No. 65,439) <u>Postal and hand Delivery Address</u> Mayer Brown LLP 71 South Wacker Drive Chicago, IL 60606 Tel: (312) 782-0600 Fax: (312) 701-7711
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Petitioner will request authorization to file a motion for Lisa M. Ferri to appear *pro hac vice*. Ms. Ferri is an experienced litigation attorney and has an established familiarity with the subject matter at issue in this proceeding. In addition, she has appeared as Back-up Counsel previously, e.g., IPR2013-00024, IPR2016-00558, IPR2015-01624, IPR2015-00405 and IPR2016-00383. Petitioner intends to file a motion seeking the admission of Lisa M. Ferri to appear *pro hac vice* when authorized to do so.

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

Please address all correspondence to the lead counsel at the address shown above. GSK also consents to electronic service by email to: MB-Fibrogen-IPR@mayerbrown.com.

VII. CONCLUSION

For the foregoing reasons, there is a reasonable likelihood that Petitioner will prevail as to each of the challenged claims. Thus, Petitioner respectfully

requests that the Board grant *inter partes* review of claims 1-8 of the '172 patent, and that claims 1-8 be cancelled as unpatentable under 35 U.S.C. §318(b).

Please charge any fees or credit overpayment to Deposit Account 130019.

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned attorney for the Petitioner declares that the argument section of this Petition (Sections I–V) has a total of 9,643 words, according to the word count tool in Microsoft Word™.

Dated: June 30, 2016

Respectfully submitted,

By: /s/ Brian W. Nolan

Brian W. Nolan (Reg. No. 45,821)

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Attorneys for Petitioner GlaxoSmithKline LLC

CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Petition for *Inter Partes* Review of U.S. Pat. No. 8,466,172 and Exhibits 1001-1047 were served on June 30, 2016 via UPS Overnight service to the correspondence address for FibroGen, Inc, Address and Attorney of Agent listed for the '172 patent as evidenced in Public PAIR on June 28, 2016 at the address listed below

General Counsel
FibroGen, Inc.
409 Illinois Street
San Francisco, CA 94158

Dated: June 30, 2016

/s/ Brian W. Nolan
Brian W. Nolan, Reg. No. 45,821
Attorney for Petitioner GlaxoSmithKline LLC