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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.
Petitioner

v.

AbbVie Biotechnology Ltd.
Patent Owner

U.S. Patent No. 8,889,135

PETITION FOR *INTER PARTES* REVIEW

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I. Introduction

Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Boehringer" or "Petitioner") request *inter partes* review of all claims (*i.e.*, claims 1-5) of U.S. Patent No. 8,889,135 ("the '135 patent") (Ex. 1001), which is assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner"). This Petition shows that there is a reasonable likelihood that Petitioner will prevail on all claims of the '135 patent and that the prior art renders the claims obvious by a preponderance of the evidence.

The '135 patent claims methods of treating rheumatoid arthritis ("RA") in a human by subcutaneously administering 40 mg of a human anti-tumor necrosis factor alpha ("TNFα") antibody, such as an antibody referred to as "D2E7" in the prior art, once every 13-15 days (referred to as "every other week" in this Petition). The claimed subcutaneous every-other-week 40 mg dose is the only alleged improvement over the prior art. As demonstrated below, however, the prior art teaches each and every feature of the claims, including the every-other-week subcutaneous 40 mg dose, and the claims would have been obvious over the art.

Specifically, this Petition shows that all five claims are unpatentable as obvious under 35 U.S.C. § 103 in view of printed publications qualifying as prior

art under § 102(a), van de Putte 2000 (Ex. 1009) and Rau 2000 (Ex. 1012).[1] Indeed, the '135 patent claims recite nothing more than the result of routine optimization. van de Putte 2000 discloses all but one element recited in the claims. Namely, van de Putte 2000 discloses administering 20, 40, and 80 mg of D2E7 every *week* subcutaneously, while the claims recite *every-other-week* administration. Rau 2000 expressly teaches that every-other-week dosing is effective given D2E7's roughly two-week half-life. Even without Rau 2000's express teaching, a person of ordinary skill in the art would have tried administering the van de Putte 2000 doses on an every-other-week basis. "A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance." *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014), *cert. denied*, 135 S. Ct. 878 (2014).

Supported by declarations from Dr. Michael H. Weisman (Ex. 1003), a renowned rheumatologist, and Dr. William J. Jusko (Ex. 1004), a leading pharmacokinetics expert, this Petition presents analysis and evidence that was not before the Examiner during prosecution. This Petition shows that AbbVie, through

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[1] Petitioner concurrently submits a second Petition requesting *inter partes* review of the '135 patent claims based on printed publications that are prior art under § 102(b).

contradictory factual assumptions and other errors, led the Examiner to conclude that a person of ordinary skill in the art would not have arrived at a 40 mg every-other-week dose from the prior art's *weekly* 20, 40, or 80 mg subcutaneous doses because the 20 mg dose would have allegedly been viewed as inferior to the 40 and 80 mg weekly doses. In doing so, AbbVie caused the Examiner to disregard the "plain teachings" of van de Putte 2000, *i.e.*, that 20, 40, and 80 mg doses were all *effective* at treating RA, which — as opposed to the "best" or "optimum" RA treatment — is all that claims 1-5 require. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1375 (Fed. Cir. 2005).

Contrary to the Examiner's conclusion, the prior art need only provide a "suggestion or motivation to modify the dosages from [the prior art] to those in the claims." *Id*. "Conclusive proof of efficacy is not necessary to show obviousness. All that is required is a reasonable expectation of success." *Hoffmann-La Roche*, 748 F.3d at 1331. Petitioner therefore requests that this Petition be granted and that claims 1-5 be found unpatentable and canceled.

II. Mandatory Notices

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

The real parties-in-interest are: Boehringer Ingelheim GmbH; Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim International GmbH;

Boehringer Ingelheim USA Corporation; and Boehringer Ingelheim Pharmaceuticals, Inc.

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

Coherus BioSciences Inc. ("Coherus") petitioned for *inter partes* review of claims 1-5 of the '135 patent on November 9, 2015. (Case No. IPR2016-00172.) Coherus also petitioned for *inter partes* review of U.S. Patent Nos. 9,017,680 and 9,073,987, which, as noted below, claim the benefit of the priority of the filing date of the '135 patent. (*See* Case Nos. IPR2016-00188 and IPR2016-00189.) Petitioner is also concurrently filing a second petition for *inter partes* review of the '135 patent based on § 102(b) prior art.

The following patents and patent applications claim the benefit of the priority of the filing date of the '135 patent: U.S. Patent Nos. 8,911,737, 8,974,790, 8,992,926, 9,017,680, and 9,073,987, and U.S. Application Nos. 14/175,993, 14/634,478, 14/634,530, and 14/715,310.

C. Lead and Back-Up Counsel and Service Information (37 C.F.R. § 42.8(b)(3)-(4))

Lead counsel is Naveen Modi (Reg. No. 46,224), Paul Hastings LLP, 875 15th Street, N.W., Washington, D.C. 20005, Telephone: 202-551-1990, Facsimile: 202-551-0490, and E-mail: Boehringer-IPR-PH@paulhastings.com. Back-up counsel are: Eric W. Dittmann (Reg. No. 51,188), Paul Hastings LLP, 75 E 55th St, New York, NY 10022, Telephone: 212-318-6689, Facsimile: 212-230-7829,

and Email: Boehringer-IPR-PH@paulhastings.com; Siegmund Y. Gutman (Reg. No. 46,304), Proskauer Rose LLP, 2049 Century Park East, Suite 3200, Los Angeles, CA 90067-3206, Telephone: 310-284-4533, Facsimile: 310-557-2193, and Email: BI-USPTO-Comm@proskauer.com; and Colin G. Cabral (Reg. No. 73,952), Proskauer Rose LLP, 2049 Century Park East, Suite 3200, Los Angeles, CA 90067, Telephone: 310-284-5611, Facsimile: 310-557-2193, and E-mail: BI-USPTO-Comm@proskauer.com. Petitioner consents to electronic service.

III. Payment of Fees (37 C.F.R. §§ 42.15(a) and 42.103)

Petitioner submits the required fees with this Petition. Please charge any additional fees required during this proceeding to Deposit Account No. 50-2613.

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

Petitioner certifies that the '135 patent is available for *inter partes* review, and that Petitioner is not barred or estopped from requesting review on the grounds identified.

V. Identification of Challenge

Petitioner challenges claims 1-5 of the '135 patent and requests that these claims be found unpatentable in view of the following two references, which

qualify as § 102(a) prior art based on the earliest possible priority date for the '135 patent of June 8, 2001:[2]

(1) L. B.A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 (Supp.) Ann. Rheum. Dis. OP.056 (2000) ("van de Putte 2000") (Ex. 1009). The van de Putte 2000 abstract was distributed at a conference in Nice, France held on June 21-24, 2000. (Ex. 1009 at 1.) The abstract was later published in a July 2000 supplement to *Annals of the Rheumatic Diseases*. (*Id.*) van de Putte 2000 is prior art at least under § 102(a).

(2) R. Rau et al., *Experience with D2E7*, 25 Akt. Rheumatol. 83 (2000) (English Translation) ("Rau 2000") (Ex. 1012.)[3] Rau 2000 published in June 2000 and is prior art at least under § 102(a). (*See* Ex. 1012 at 1.)

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[2] For purposes of this Petition, Petitioner has assumed that the claims are entitled to the June 8, 2001 date. Petitioner reserves its right to challenge whether the claims are entitled to this date. The statutory provisions relevant to this Petition are the pre-America Invents Act versions of 35 U.S.C. §§ 102 and 103. *See* Pub. L. 112-29 § 3(n)(1).

[3] Rau 2000 is a certified English translation of the original German publication (Ex. 1013).

Petitioner requests that claims 1-5 be found unpatentable as obvious under § 103(a) over van de Putte 2000 and Rau 2000 and be canceled. An explanation of how claims 1-5 of the '135 patent are unpatentable based on this ground, including the identification of where each element of the claim is found in the prior art, is provided in Section IX, *infra*. In support of this ground, this Petition is accompanied by the Declaration of Dr. Michael H. Weisman ("Weisman Decl.") (Ex. 1003), a renowned rheumatologist, and the Declaration of Dr. William Jusko ("Jusko Decl.") (Ex. 1004), a leading pharmacokinetics expert.

VI. Background

By June 8, 2001, the '135 patent's earliest possible priority date, results from clinical trials suggested that D2E7 was safe and effective for treating RA when administered in every-other-week subcutaneous doses. This Petition is based on a phase II clinical trial known as "DE007," the results of which are published in van de Putte 2000, along with a review of DE007 and other clinical trials in a publication coauthored by Dr. van de Putte, titled Rau 2000. van de Putte 2000 and Rau 2000 fit within a larger context of clinical trials involving D2E7, a context that illustrates how the '135 patent claims are directed to nothing more than routine

optimization, or the next obvious step from the prior art.[4] Petitioner briefly summarizes the pertinent aspects of these trials below for the sake of completeness. (*See also* Ex. 1003 (Weisman Decl.) ¶¶ 21-31.)

A. Clinical Trials Involving D2E7

1. DE001: Intravenous Weight-Based Dosing

The first human clinical trial for D2E7, the "DE001" study, showed "encouraging results." (*See* Ex 1005 at 5; Ex. 1012 at 5; Ex. 1003 (Weisman Decl.) ¶ 22.) Patients enrolled in DE001 received a single dose of D2E7 intravenously at 0.5, 1.0, 3.0, 5.0, or 10.0 mg/ kg body weight. (Ex. 1005 at 5.) The results showed that D2E7 elicited a therapeutic response within 24 hours of administration that peaked after 1-2 weeks. (*Id.*) Preliminary pharmacokinetics indicated D2E7's half-life to be about 10 days. (*Id*.)

2. DE003: A Continuation of DE001

A study known as "DE003," the results of which were reported by Rau 1998 (Ex. 1006), was a long-term continuation study following the DE001 initial study. (*See* Ex. 1006 at 5; Ex. 1003 (Weisman Decl.) ¶¶ 23-24.) The same patients from DE001 were given multiple intravenous administrations of D2E7 at the same dose

[4] Petitioner relies only on van de Putte 2000 and Rau 2000 in its proposed ground. Additional clinical studies are discussed simply to place van de Putte 2000 and Rau 2000 in context.

as that given in DE001, and "[t]he possibility for a dose escalation was offered to patients treated with 0.5 and 1 mg D2E7/kg body weight." (*Id.*) Patients received D2E7 *every other week* until they achieved a "good" European League against Rheumatism ("EULAR") response, defined as a Disease Activity Score ("DAS") of less than 2.4. (*See* Ex. 1006 at 5; Ex. 1003 (Weisman Decl.) ¶¶ 19-20, 23-24.) Thereafter, patients were "retreated only when the DAS value increased to above 2.4 again." (Ex. 1006 at 5.) With this treatment protocol, patients were administered D2E7 (1) every other week until a "good" EULAR response was achieved, and then (2) only again when symptoms reappeared, which resulted in an overall "mean dosing interval" of 2.5 weeks after D2E7 administration. (*Id.*) This study demonstrated that "D2E7 was generally well tolerated." (*Id.*) "More than 80% of the patients achieved and sustained responder status as defined by a drop of at least 1.2 (compared with baseline) in the DAS value," and "[t]he reduction in SWJC and TJC was about 60%." (*Id.*)

3. DE004: Subcutaneous Dosing

"DE004" was the first study to test subcutaneous administration of D2E7 in patients suffering from RA, the results of which were published in Schattenkirchner 1998 (Ex. 1007). (*See* Ex. 1003 (Weisman Decl.) ¶ 25.) Patients participating in the study received either a 0.5 mg per kg dose of D2E7, or placebo, administered in weekly subcutaneous doses for three months. (Ex. 1007 at 5.)

After three months, the patients receiving placebo began receiving D2E7. (*Id.*) The possibility of increasing the dose to 1 mg/kg for any patients that did not respond to treatment was noted. (*Id.*) Based upon data collected for "up to 6 months," Schattenkirchner 1998 concluded that subcutaneous D2E7 administration was comparable to intravenous administration, explaining that "plasma concentrations of D2E7 after multiple s.c. [subcutaneous] injections are comparable with those after i.v. [intravenous] injections of D2E7," and that "[t]he s.c. administration of D2E7 has been shown to be safe and efficacious." (*Id.*)

4. DE007: Total Body, or Fixed, Dosing

a. First Three Months (van de Putte 1999)

A study known as "DE007" was a Phase II clinical trial involving subcutaneous administration of D2E7 as a total body dose.[5] (*See* Ex. 1003 (Weisman Decl.) ¶¶ 27-28.) Patients enrolled in DE007 "receive[d] weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months." (Ex. 1008 at 7.) Clinical efficacy was determined through American College of Rheumatology ("ACR") criteria, which were reported as percent

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[5] The results from the first three months of this study are published in van de Putte 1999 (Ex. 1006), one of the references relied on in Petitioner's concurrently filed petition for *inter partes* review.

improvement. (*Id.*) An "ACR20" response means that a patient achieved a 20% improvement in tender joint count ("TJC"), swollen joint count ("SJC" or "SWJC"), and three of five other indicators, including C-reactive protein level ("CRP"). (Ex. 1003 (Weisman Decl.) ¶¶ 19-20.) "ACR50" and "ACR70" responses mean that a patient achieved corresponding 50 and 70% improvements, respectively. (*Id.*)

The 20, 40, and 80 mg doses of D2E7 produced ACR20 responses in 49%, 57%, and 56% of patients, respectively, compared to 10% for placebo.[6] (Ex. 1008 at 7.) van de Putte 1999 concluded that, "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)," and that "20, 40, and 80 mg/week were nearly equally efficacious when given [subcutaneously] in patients with active RA." (*Id.*) van de Putte 1999's conclusion was one of several consistent prior art teachings disregarded during prosecution of the '135 patent. (*See* Section VI.C, *infra*.)

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[6] The ACR20 data reported in van de Putte 1999 are consistent with data set forth in Example 2 of the '135 patent, which reported that 49%, 55%, and 54% of patients reached ACR20 after weekly administration of 20, 40, and 80 mg D2E7, respectively. (Ex. 1001 at 28:56-29:10.)

b. Next Three Months (van de Putte 2000)

DE007 was continued for an additional three months, the results of which are published in van de Putte 2000 (Ex. 1009). (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-30.) The extended study showed that subcutaneous administration of D2E7 at 20, 40, and 80 mg weekly doses remained effective. (Ex. 1009 at 2.) Weekly doses of 20, 40, and 80 mg of D2E7 produced ACR20 responses in 56%, 64%, and 63% of patients, respectively, after six months of total treatment. (*Id.*) van de Putte 2000 concluded that "all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)," and that "20, 40, and 80 mg/week were statistically equally efficacious when given s.c. in patients with active RA." (*Id.*) The same conclusion held after 12 months of D2E7 treatment. (Ex. 1010 at 5.)

5. Rau 2000's Commentary on D2E7 Clinical Trials

Rau 2000, which was co-authored by Dr. van de Putte, summarizes and analyzes D2E7 clinical trials, including the DE007 study published in the van de Putte articles. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 31.) Rau 2000 confirms that "D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years." (Ex. 1012 at 8.) As for dosing frequency, Rau 2000 concludes that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." (*Id*.)

B. The '135 Patent

Against this backdrop, the '135 patent claims an allegedly novel and nonobvious method of treating RA involving every-other-week subcutaneous 40 mg dosing of an anti-TNFα antibody such as D2E7.[7] (*See* Ex. 1003 (Weisman Decl.) ¶¶ 32-33.) The '135 patent acknowledges the "many advantages" of every-other-week subcutaneous dosing relative to other dosing regimens, including "a lower number of total injections, decreased number of injection site reactions . . . , increased patient compliance . . . , and less cost to the patient as well as the health care provider." (Ex. 1001 at 2:60-66.) Likewise, "[s]ubcutaneous dosing is advantageous because the patient may self-administer a therapeutic substance, . . . which is convenient for both the patient and the health care provider." (*Id.* at 2:66-3:2.) All of these advantages of less frequent, subcutaneous dosing, however, were well known to a person of ordinary skill in the art and would have provided motivation to optimize the dosing regimens described in van

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[7] The '135 patent issued on November 18, 2014, from U.S. Application No. 10/163,657 ("the '657 application") filed on June 5, 2002. (Ex. 1001 at 1.) The '657 application claims priority to U.S. Provisional Application No. 60/296,961 (Ex. 1026) filed on June 8, 2001, (Ex. 1001 at 1:7-8), the earliest possible priority date of the '135 patent.

de Putte 2000, as Rau 2000 would have suggested. (Ex. 1003 (Weisman Decl.) ¶¶ 42-47.)

C. Summary of the Prosecution History of the '135 Patent

The Examiner repeatedly rejected the '135 patent claims over publications reporting clinical studies, including the study described in van de Putte 1999 in combination with a number of secondary references suggesting every-other-week dosing. (*See* Ex. 1002 (Office Actions dated Dec. 1, 2009, June 10, 2013, and April 21, 2014) at 760, 1093, 1531.) The Examiner explained that "[v]an de Putte teaches that for all efficacy parameters studied . . . *each of the antibody doses, i.e., 20, 40, or 80 mg of the anti-TNFα antibody D2E7 were of nearly equal efficacy*." (Ex. 1002 (Office Action dated Dec. 1, 2009) at 761 (emphasis in original).) It would have been obvious to administer an every-other-week 40 mg dose, the Examiner concluded, because "it was known in the art that the D2E7 antibody has a half-life of about 12 days." (*Id.* (citing Rau 2000).)

Applicants responded that drug half-life and dosing frequency were not necessarily correlated, contrary to the teachings and suggestions of the prior art, such as Rau 2000. (*Id.* (Office Action Response dated July 20, 2010) at 800.) Applicants submitted a declaration by Dr. Hartmut Kupper, which contended that "there is no established correlation between optimal dosing frequency and drug half-life, particularly for biologics, including monoclonal antibodies." (*Id.* at 800

(citing Kupper Decl. ¶ 5).) Applicants also relied on publications from 2010, well after the earliest possible '135 patent filing date, suggesting that in some cases dosage frequencies do not correlate with half-life. (*Id.* at 800-01.)

The Examiner rejected this "straw man argument," explaining that half-life would have at least been used "as a guidepost to reasonably suggest dosage regimens other than the one disclosed in [v]an de Putte." (*Id.* (Office Action dated Aug. 3, 2011) at 1002, 1005.)[8] The Examiner reasoned that, "no matter the starting concentration of D2E7 in the body, one half [of D2E7] is eliminated every 12 days." (*Id.* at 1002-03.) The Examiner maintained these and similar rejections through the applicants' Request for Continued Examination filed on February 3, 2012.

After yet another Request for Continued Examination on February 7, 2014, filed along with a Track One Request, applicants first began criticizing van de Putte 1999's dose comparisons. Applicants' criticisms were supported by declarations from Dr. Janet Pope (Ex. 1002 at 1140), Dr. Diane Mould (Ex. 1002 at

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[8] The Examiner's conclusion is consistent with a later declaration submitted by the applicants, the declaration of Dr. Diane Mould, in which Dr. Mould admitted that half-life "is of course a necessary parameter in any model." (Ex. 1002 at 1227 ¶ 78.)

1200), and Dr. Michael Weinblatt (Ex. 1002 at 1172). These declarations attempted to support two conflicting arguments. *First*, applicants suggested that the van de Putte 1999 study was designed to compare only the efficacy of doses versus placebo, and not the efficacy of each dose relative to the other doses. (Ex. 1002 (Office Action Response dated February 7, 2014) at 1304-07). *Second* — and in express contradiction of their first argument — applicants contended that a person of ordinary skill would have concluded that van de Putte 1999's 20 mg weekly dose (corresponding to the claimed 40 mg every-other-week dose over time) was "not as effective as either the 40 or 80 mg [weekly] dose." (*Id*. at 1307-10, 1305.) In other words, applicants made an argument based on a hypothetical claim requiring "the *most effective* dose" — a claim that was not pending before the Examiner and is not present in the '135 patent.[9]

The Examiner nevertheless allowed the claims. (Ex. 1002 (July 8, 2014 Notice of Allowance) at 1579.) The Examiner's explanation for allowing the claims was based solely on the declarations submitted by the applicants. These declarations, according to the Examiner, established that a person of ordinary skill

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[9] For the reasons explained below, even claims reciting a specific efficacy limitation would have been obvious over van de Putte 2000 and Rau 2000. (*See* Section IX.A, *infra*.)

in the art would not have made dose-to-dose comparisons from van de Putte 1999, yet at the same time would not have optimized van de Putte 1999's weekly 20 mg dose based precisely on such a comparison; *i.e.*, because the 20 mg dose was allegedly "clearly inferior to the 40 or 80 mg D2E7 dose." (*Id.* at 1585.)

The claims should have never been allowed. Applicants caused the Examiner to demand too much of the prior art, and to ignore van de Putte 1999's "plain teachings." *See Merck*, 395 F.3d at 1375 (explaining that all that is required of the prior art is a "suggestion or motivation to modify the dosages from [the prior art] to those in the claims").

Aside from this error, the Examiner's factual findings contradict one another. On the one hand, the Examiner suggested that dose-to-dose comparisons cannot be made from van de Putte 1999. On the other, the Examiner *did compare* the 20 mg dose to the 40 and 80 mg doses, ultimately concluding that a person of ordinary skill in the art would have disregarded the allegedly inferior 20 mg dose.

VII. Level of Ordinary Skill in the Art

The claims of the '135 patent relate to methods of treating RA with a human anti-TNFα antibody. A person of ordinary skill in the field of rheumatology at the time of the alleged invention (which is assumed to be June 8, 2001, for purposes of

this petition[10]) would have had knowledge regarding the pathophysiology of RA. (Ex. 1003 (Weisman Decl.) ¶ 12.) One of ordinary skill would also have been knowledgeable about methods for treating RA patients, including treatments involving the use of anti-TNFα antibodies. (*Id*.) Such a person would also have been aware of relevant literature describing clinical studies and would have attended conferences in which clinical trial results were presented. (*Id.*) Accordingly, a person of ordinary skill would have been a practicing rheumatologist with a medical degree, roughly 3 years of experience treating RA patients, and some familiarity or experience with anti-TNFα antibodies and clinical trial procedures and design, including familiarity with basic pharmacokinetic concepts such as half-life. (*Id*.)

Coherus's Petition proposes that a person of ordinary skill in the art would have the understanding of both a rheumatologist and a pharmacokineticist. (*See* Coherus Petition at 27-28.) To the extent that the level of ordinary skill would have included the skills of a pharmacokineticist, this Petition provides that perspective through the Declaration of Dr. Jusko (Ex. 1004), a world-renowned

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[10] The obviousness analysis presented in this Petition would not be affected even if Patent Owner alleges an earlier invention date. (*See* Ex. 1003 (Weisman Decl.) ¶ 12, n.3; Ex. 1004 (Jusko Decl.) ¶ 14, n.3.)

expert in this field. In short, claims 1-5 would have been obvious even if the Board adopts the level of skill proposed by Coherus.

VIII. Claim Construction

For purposes of this Petition, each claim term recited in the '135 patent should be construed according to its ordinary and customary meaning, *see Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (en banc), consistent with the "broadest reasonable construction in light of the specification" of the '135 patent, *see* 37 C.F.R. § 42.100(b). Coherus's Petition explains what Petitioner understands to be the ordinary meaning of three claims terms: "method for treating rheumatoid arthritis," "every 13-15 days," and "pharmaceutically acceptable composition." (*See* Coherus Petition at 14-17.) While Petitioner agrees that the Board should apply the ordinary and customary meaning of these and other terms consistent with the broadest reasonable construction standard, Petitioner does not believe that the Board needs to construe any term explicitly for purposes of this proceeding.[11]

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[11] Petitioner has not necessarily raised all challenges to the '135 patent, including challenges to the claims under § 112, given the limitations placed by the Rules. Petitioner reserves all rights and defenses.

IX. Detailed Explanation of Ground for Invalidity

As discussed in detail below, claims 1-5 would have been obvious over van de Putte 2000 in view of Rau 2000.

A. van de Putte 2000 and Rau 2000 Render Claims 1-5 Obvious

van de Putte 2000 and Rau 2000 teach or suggest every element of claims 1-5. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 34-51; *see also* Ex. 1004 (Jusko Decl.) ¶¶ 15-24.) Specifically, as explained below, van de Putte 2000 expressly teaches each of the claimed features except for the every-other-week dose. Such a dose would have been obvious in view of Rau 2000.

1. Claim 1

a. "A method for treating rheumatoid arthritis in a human subject, comprising"

Both van de Putte 2000 and Rau 2000 disclose treating RA in humans. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-31.) van de Putte 2000, for example, reports a "[d]ose-finding phase II study comparing 3 dose levels of D2E7 and placebo . . . in patients with long standing active rheumatoid arthritis." (Ex. 1009 at 2.) Rau 2000 similarly explains that clinicians had been administering D2E7 to humans to treat RA since at least 1997. (*See* Ex. 1012 at 5.)

b. "administering subcutaneously to a human subject having rheumatoid arthritis"

Administering D2E7 subcutaneously to human subjects was well known. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-31.) Even in early phase I clinical studies,

D2E7 was reported in Rau 2000 to be "effective subcutaneously." (Ex. 1012 at 7.) In the DE007 study reported in van de Putte 2000, patients suffering from "long standing active rheumatoid arthritis" were given doses of "either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection" for six months. (Ex. 1009 at 2.)

c. "a total body dose of 40 mg of a human anti-TNFα antibody once every 13-15 days"

As described above, van de Putte 2000 provides six-month efficacy data from DE007, which involved subcutaneous weekly dosing of 20, 40, and 80 mg D2E7. (Ex. 1009 at 2.) The only claim feature not expressly disclosed in van de Putte 2000 is every-other-week dosing. Rau 2000, however, expressly teaches this feature, and one of ordinary skill would have arrived at the claimed invention in light of the teachings of van de Putte 2000 and Rau 2000. (Ex. 1003 (Weisman Decl.) ¶¶ 34-51; *see also* Ex. 1004 (Jusko Decl.) ¶¶ 15-24.) At the time of the alleged invention, one of ordinary skill would have combined the teachings of van de Putte 2000 and Rau 2000 for at least three reasons. *First*, a person of ordinary skill in the art would have been motivated to optimize the van de Putte 2000 subcutaneous dosing regimens because each dosing regimen was determined to be effective in treating RA. (*See* IX.A.1.c.(i), *infra*.) *Second*, Rau 2000 would have provided motivation to optimize the van de Putte 2000 doses to a less frequent every-other-week dosing interval. (*See* IX.A.1.c.(ii), *infra*.) Specifically, Rau

2000 explains that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." (Ex. 1012 at 8.) *Third*, the claimed dosing regimen was at a minimum one of a finite number of options that a person of ordinary skill in the art would have considered pursuing, and therefore would have been obvious to try. (*See* Section IX.A.1.c.(iii), *infra*.)

(i) One of Ordinary Skill Would Have Been Motivated to Optimize the Effective Van de Putte 2000 Dosing Regimens

The weekly subcutaneous doses described in van de Putte 2000 were all reported as effective and would have been further optimized. *See Biomarin Pharm. Inc. v. Genzyme Therapeutic Prods. Ltd. P'ship*, Final Written Decision, Paper No. 81, IPR 2013-00534, at 14 (PTAB 2015) ("The motivation to optimize the therapy disclosed in [the prior art] flows from the normal desire of scientists or artisans to improve upon what is already generally known."). The selection of the dose and dosing schedule would have been a "routine optimization" of the prior art therapy and yielded predictable results. *Id*. at 11-18.

van de Putte 2000 discloses weekly subcutaneous doses of D2E7 at 20, 40, and 80 mg total body doses administered over six months. (Ex. 1009 at 2.) Each dose reported in van de Putte 2000, including the lowest effective dose reported (*i.e.*, 20 mg), was effective in treating RA. (Ex. 1009 at 2 ("[A]ll doses of D2E7

were statistically significantly superior to placebo."); Ex. 1003 (Weisman Decl.) ¶¶ 35-41.) Patients enrolled in this study suffered from RA for a median duration of eight years, exhibited high median TJC, SJC, and CRP responses, and had been treated with a median of four previous DMARDS. (Ex. 1009 at 2.) These clinical data indicate that DE007 patients were suffering from severe RA, which is reflected in the placebo group's low 10% ACR20 response over the first three months of the study. (Ex. 1009 at 2; Ex. 1003 (Weisman Decl.) ¶ 35.) By comparison, the lowest reported dose of 20 mg resulted in an ACR20 response of 49% over this same three-month time period, which is a robust response, particularly considering the low placebo response. (Ex. 1009 at 2; Ex. 1003 (Weisman Decl.) ¶ 35.)

The increase in ACR20 responses for each dose reported in van de Putte 2000 during the first three months of the study, relative to ACR20 placebo responses, would have demonstrated the clinical effectiveness of each dose to a person of ordinary skill in the art. (Ex. 1003 (Weisman Decl.) ¶¶ 36-37.) In general, a roughly 30-40% increase in the number of patients achieving an ACR20 response with a TNFα agent over placebo would have been viewed as demonstrating clinical effectiveness. (*Id.*) The increase in ACR20 responses achieved with the van de Putte 2000 doses ranged from 39 to 47%, and thus each

dose would have been viewed as clinically effective. (*Id.*) These results were maintained over the next three months of the study. (*Id.* ¶ 35-37.)

The FDA's approval of different TNFα agent for treating RA confirms that this increase in patients achieving an ACR20 response would have been understood to demonstrate efficacy. (*Id.* ¶¶ 17-18, 36.) In an infliximab (REMICADE®) clinical trial (referred to as "C0168T22"), for example, 50-58% of patients receiving 3 mg/kg or 10 mg/kg achieved an ACR20 response, compared to 20.5% of patients receiving placebo. (Ex. 1015 (REMICADE® Summary Basis for Approval) at 20, tbl. 3.8; Ex. 1003 (Weisman Decl.) ¶¶ 17-18,36.) The increase in the number of patients achieving an ACR20 response therefore ranged from about 30 to 38%. Based on this data, the FDA concluded in approving infliximab that "[a]ll of the dosing regimens evaluated in the pivotal trial, T22, showed benefit as adjunctive therapy to MTX in the treatment of patients with rheumatoid arthritis." (Ex. 1015 (REMICADE® Summary Basis for Approval) at 26; Ex. 1003 (Weisman Decl.) ¶ 36.)

While each dose in van de Putte 2000 would have been viewed as effective, a person of ordinary skill in the art could not have compared the effectiveness of one dose to another based on the data reported in van de Putte 2000. (Ex. 1003 (Weisman Decl.) ¶ 38.) The DE007 study reported by van de Putte 2000 was a parallel "randomised double-blind, placebo-controlled study." (Ex. 1009 at 2.)

Patients enrolled in this study were randomized equally into "four arms to receive weekly doses of either D2E7 at 20, 40, 80 mg or placebo by subcutaneous (s.c.) self injection for 3 months," followed by an additional three months for only the three dose groups. (Ex. 1009 at 2; Ex. 1003 (Weisman Decl.) ¶ 38.) As with any parallel study, individual patients often exhibit different reactions to treatment. (Ex. 1003 (Weisman Decl.) ¶ 38.) As a result, statistical information regarding clinical responses would have been essential in attempting to ascertain whether any meaningful difference existed between each dose. (*Id.*) In other words, statistical information would have been necessary for making dose-to-dose comparisons to ensure that any numerical differences did not result from chance. (*Id.*) In sum, van de Putte 2000 suggests that each dose was superior to placebo, but not that any dose was better or worse than another dose.[12] (*Id.*)

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[12] Indeed, one of the co-inventors of the '135 patent confirmed this understanding of the data from the DE007 study in a contemporaneous publication. (*See, e.g.*, Ex.1029 (J. Kempeni, *Update on D2E7: A Fully Human Anit-tumour Necrosis Factor α Monoclonal Antibody*, Ann. Rheum. Dis. 2000 Nov; 59 (Suppl I): i44-i45) at 4 ("All three doses of D2E7 were efficacious (49% to 57% of patients achieved ARC20 responder status compared with 10% with placebo, p <

The claimed dosing regimen would have been the result of routine optimization regardless of whether a person of ordinary skill read van de Putte 2000 as showing, consistent with the authors' conclusion, the 20, 40, and 80 mg dosages to be "statistically equally efficacious," or read the data to show that the 20 mg dose may be less efficacious in some respect for certain patients. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 35-41.) This is because van de Putte 2000's recognition of the effectiveness of the 20 mg dose cannot be ignored, even if one of skill would have understood that dose to be less effective than the 40 or 80 mg doses. *See Dome Patent L.P. v. Lee*, 799 F.3d 1372, 1381 (Fed. Cir. 2015) ("A known or obvious composition does not become patentable simply because it has been described as somewhat inferior to some other product for the same use.") (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)); *see also PAR Pharm., Inc. v. TWI Pharm., Inc*., 773 F.3d 1186, 1197-98 (Fed. Cir. 2014) ("Our precedent . . . does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away."). The efficacy of the weekly 20 mg dose reported in van de Putte 2000 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth

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0.0001) and no dose response relation was apparent at month 3."); *see also* Ex. 1003 (Weisman Decl.) ¶ 35, n.6.)

investigating in light of Rau 2000. (Ex. 1003 (Weisman Decl.) ¶¶ 50-51.) And a person of ordinary skill would have been particularly attracted to pursuing an every-other-week equivalent (*i.e.*, 40 mg) of the lowest weekly dose (*i.e.*, 20 mg) that had been shown to be efficacious in the prior art. (*Id.*)

(ii) Rau 2000 Would Have Motivated One of Ordinary Skill to Optimize the Van de Putte 2000 Dosing Regimens to Every-Other-Week Regimens

Rau 2000 expressly suggests pursuing every-other-week equivalents of the van de Putte 2000 weekly doses for treating RA. (Ex. 1003 (Weisman Decl.) ¶¶ 42-48.) Rau 2000 describes the DE003 study, in which patients initially received every-other-week intravenous administration of D2E7. (*See* Ex. 1012 at 5; Ex. 1003 (Weisman Decl.) ¶ 42.) Patients subsequently received D2E7 through a treatment protocol in which patients were administered D2E7 only after symptoms reappeared, with a minimum two-week interval. (Ex. 1012 at 5.) After reporting efficacy for every-other-week doses (*see, e.g.*, *id.* at 6-7 Figs. 4-5), Rau 2000 concludes that D2E7 can be administered every other week intravenously or subcutaneously. (*Id.* at 8; Ex. 1003 (Weisman Decl.) ¶ 42.)

Nothing in Rau 2000 indicates that subcutaneous dosing would have produced different results when administered every other week. (Ex. 1003 (Weisman Dec.) ¶ 43-47.) To the contrary, Rau 2000 explains that D2E7 can be administered every other week because D2E7 has a "half-life of 12 days"

(Ex. 1012 at 8), which would have suggested to a person of ordinary skill in the art that D2E7 concentrations would have remained high enough to achieve clinical results over two weeks. (Ex. 1003 (Weisman Decl.) ¶ 43.) This is consistent with Rau 2000's conclusion: "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously." (Ex. 1012 at 8; Ex. 1003 (Weisman Decl.) ¶¶ 43-45.)

Based on a half-life of roughly two weeks, a person of ordinary skill in the art would have understood that the every-other-week equivalent of the lowest 20 mg van de Putte 2000 dose was 40 mg. (Ex. 1004 (Jusko Decl.) ¶¶ 17-20.) This is because the approximate amount of D2E7 circulating in the body two weeks after administering a 40 mg dose would have been roughly one half of that dose (*i.e.*, approximately 20 mg). (*Id.*) Because this amount of D2E7 remaining after two weeks would have been considered clinically effective in light of van de Putte 2000 (Ex. 1003 (Weisman Decl.) ¶¶ 35-41; *see also* Ex. 1004 (Jusko Decl.) ¶ 15), a person of ordinary skill would have been motivated to pursue a 40 mg

every-other-week subcutaneous dose. (Ex. 1003 (Weisman Decl.) ¶¶ 35-42; *see also* Ex. 1004 (Jusko Decl.) ¶¶ 15-20.)[13]

That it would have been obvious to move from a 20 mg weekly dose to 40 mg every other week is confirmed by Patent Owner's admissions, as well as findings by the FDA and its European counterpart, the European Medicines Agency ("EMA"). (*See* Ex. 1003 (Weisman Decl.) ¶ 51.) For example, in European opposition proceedings involving a counterpart to the '135 patent, Patent Owner admitted that, "[o]ver time, patients treated . . . with [a] 40 mg flat dose, subcutaneously biweekly, receive the same amount of D2E7 as those treated in the DE007 trial with [a] 20 mg flat dose weekly." (Ex. 1023 at 45.) Patent Owner also admitted in a regulatory submission to the FDA that "every other week doses are assumed to be similar to one-half the same dose given weekly" (Ex. 1016 at 2, tbl. 75), and the FDA made a similar statement in its clinical review report (Ex. 1017 at 109, tbl. 75). Consistent with Patent Owner's prior representations to U.S.

[13] The same would have been thought to be true of the every-other-week equivalents of the 40 and 80 mg van de Putte 2000 doses. (Ex. 1003 (Weisman Decl.) ¶ 39.)

regulatory authorities, the EMA similarly characterized "40 mg every other week [as] . . . equivalent to 20 mg weekly." (Ex. 1018 at 14.)[14]

Even if the level of ordinary skill in the art were considered to have included the understanding of a pharmacokineticist, and while unnecessary to consider in light of Rau 2000's express directive to pursue every-other-week subcutaneous dosing, this conclusion would have been buttressed by D2E7's linear pharmacokinetics. (Ex. 1004 (Jusko Decl.) ¶¶ 23-25.) Analysis from the DE001 study demonstrated that D2E7 systemic drug exposure (referred to as "AUC," *see* Ex. 1004 (Jusko Decl.) ¶ 23 n.5) increased proportionally over a wide (20-fold) dose range, implying linear kinetics (Ex. 1011 at 4;[15] Ex. 1004 (Jusko Decl.) ¶ 24 n.6; *see also* Ex. 1003 (Weisman Decl.) ¶ 26). As would have been expected with such a linear system, the half-life varied over this dose range by only roughly two

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[14] Though not being relied on as prior art, AbbVie's factual admissions are relevant at least because they contradict statements made during prosecution.

[15] Petitioner wishes to emphasize that this Petition does not rely on any references other than van de Putte 2000 and Rau 2000, but merely identifies this information that was available to a person of ordinary skill in the art as further confirmation that these references would have taught a subcutaneous every-other-week 40 mg dosing regimen.

days. (Ex. 1011 at 4; Ex. 1004 (Jusko Decl.) ¶ 24 n.6; *see also* Ex. 1003 (Weisman Decl.) ¶ 26.) This would have provided increased confidence that D2E7's half-life would not appreciably change across 20, 40, and 80 mg doses and, accordingly, that enough D2E7 would remain in the body between every-other-week versions of those doses, including 40 mg. (Ex. 1004 (Jusko Decl.) ¶¶ 20, 24.)

(iii) One of Ordinary Skill Would Have Arrived at the Claimed Dosing Regimen Given the Finite Number of Options and Known Benefits of an Extended Dosing Interval

At a minimum, administering 40 mg every 13-15 days to treat RA would have been obvious to try in view of the finite number of fixed dosing options (20, 40, and 80 mg) employed in van de Putte 2000 and a reasonable expectation of success based on one of ordinary skill's understanding of D2E7's properties, including its long half-life. *See Hoffman-La Roche*, 748 F.3d at 1332 (finding claims directed to a total dose equivalent "obvious to try"). The skilled artisan would have desired a low effective dose, and thus included 40 mg among the dosage amounts to be investigated in connection with efforts to develop improved dosing regimens. (Ex. 1003 (Weisman Decl.) ¶¶ 50-51.) A person of ordinary skill in the art would have been further motivated to administer this dose on a less frequent, every-other-week basis, as described in Rau 2000, in view of clinical considerations. (Ex. 1003 (Weisman Decl.) ¶¶ 48-49.) *See also Hoffman-La*

Roche, 748 F.3d at 1329 (noting that "[a] relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance").

For example, as with any dosing regimen, patient compliance tends to increase as doses become less frequent. (Ex. 1003 (Weisman Decl.) ¶ 49.) A patient generally prefers to self-administer an even moderately painful injection less frequently. (*Id.*) Even the '135 patent acknowledges, consistent with the knowledge of a person of ordinary skill in the art, that every-other-week dosing has "many advantages" over weekly dosing, including "a lower number of total injections, decreased number of injection site reactions (*e.g.*, local pain and swelling), increased patient compliance (*i.e.*, due to less frequent injections), and less cost to the patient as well as the health care provider." (Ex. 1001 at 2:60-66.) Thus, clinical considerations would have motivated a person of ordinary skill in the art to investigate a less frequent every-other-week dosing regimen. (Ex. 1003 (Weisman Decl.) ¶¶ 48-49.)

Moreover, a person of ordinary skill in the art would have been motivated to administer D2E7 subcutaneously as claimed. Rau 2000 teaches that D2E7 has a roughly two-week half-life, and can thus be administered every other week, whether through subcutaneous or intravenous routes. (Ex. 1012 at 8.) And a person of ordinary skill in the art would have appreciated the benefits of subcutaneous administration over intravenous administration. (Ex. 1003

(Weisman Decl.) ¶ 41.) Complications can occur with intravenous administration (*e.g.*, thrombosis and extravasation of injections or infusions at the site of administration) that are not present with subcutaneous administration. (*Id.*) In addition, patients typically prefer the convenience and lower cost of in-home, subcutaneous administration. (*Id.*) Moreover, subcutaneous administration was one of only two routes of administration disclosed in the D2E7 art. (*Id.* at ¶ 46.)

(iv) Patent Owner's Arguments to the Contrary Should Be Rejected

Patent Owner made several arguments during prosecution, and may raise similar arguments in response to this Petition. These arguments should be rejected at least because the Office did not have the benefit of the expert testimony submitted with this Petition, and for the reasons provided herein. (*See, e.g.*, Ex. 1003 (Weisman Decl.) ¶¶ 34-58; Ex. 1004 (Jusko Decl.) ¶¶ 15-25.)

For instance, Patent Owner may argue that, even though van de Putte 2000 expressly concludes that "20, 40, and 80 mg/week were statistically equally efficacious," that is somehow not the case. Specifically, Patent Owner may assert, as it did during prosecution, that 20 mg was not as efficacious as 40 or 80 mg and, as a result, one of ordinary skill would not have selected a 40 mg every-other-week dose. Dr. Mould, for example, stated that, based on van de Putte 1999, a person of ordinary skill in the art would have understood a 7-8% difference in ACR20 response for 20 mg D2E7 compared to 40 and 80 mg D2E7 to indicate a

meaningful difference in efficacy between doses. (*See* Ex. 1002 (Mould Decl.) at 1209-10 ¶¶ 21-23.)

Dr. Mould had no sound basis to draw this conclusion because, among other things, reliable dose-to-dose comparisons cannot be drawn from the data presented in van de Putte 1999. (Ex. 1003 (Weisman Decl.) ¶ 39.) Instead, a person of ordinary skill in the art would have been able to conclude based on the van de Putte 2000 data only that each dose was effective relative to placebo. (Ex. 1003 (Weisman Decl.) ¶¶ 35-41.) As a result, a person of ordinary skill in the art would not have attributed clinical significance to the small numerical differences in the ACR20 responses reported for the 20, 40, and 80 mg doses. (*Id*.) This is particularly true given that van de Putte reports that each dose was "nearly equally efficacious" (Ex. 1008 at 7) or "statistically equally efficacious." (Ex. 1009 at 2; *see also* Ex. 1003 (Weisman Decl.) ¶¶ 28, 39.)[16]

Even assuming, *arguendo*, that one of ordinary skill would have concluded that van de Putte 2000 teaches that 20 mg was somewhat less efficacious than the 40 mg and 80 mg doses, that person would have still pursued a 40 mg every-other-week dosing regimen at the time of the invention for the reasons discussed in

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[16] Drs. Weinblatt and Pope made similar arguments during prosecution that, as explained in Section IX.B.1 below, are equally unavailing.

Section IX.A.1 above. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 50-51.) This is because claim 1 does not require the "most effective dose"; instead, it requires only administering a dose for a time period "sufficient to treat [RA]." (Ex. 1001 at 45:15.) As discussed above, RA treatment is measured using several symptom criteria, including the criteria listed in van de Putte 2000. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-30, 35-38.) van de Putte 2000 concluded that all doses were "statistically significantly superior to placebo," and — based on all of the study related information available to the van de Putte 2000 authors, as opposed to the data that was made publicly available through that article — that each dose was "statistically equally efficacious" when administered subcutaneously. (Ex. 1009 at 2.) As a result, any argument by Patent Owner based on the "most effective dose" or a desire to achieve the "maximum benefit" should be rejected. (*See, e.g.*, Ex. 1002 (Pope Decl.) at 1153-54 ¶¶ 20, 22 (Dr. Pope arguing that a "person of ordinary skill in the art would have concluded that 20 mg s.c. weekly is too low a dose in these patients to provide maximal benefit" and that "the 40 mg and 80 mg doses are clearly better than [the] 20 mg dose"); Ex. 1002 (Weinblatt Decl.) at 1192 ¶ 52 (Dr. Weinblatt alleging that "van de Putte clearly shows that 20 mg weekly is clinically inferior").)[17]

[17] Dr. Pope also erroneously contended that "one of ordinary skill in the art

Patent Owner may also argue that Rau 2000 does not suggest, or even teaches away from, administering D2E7 in every-other-week *subcutaneous* doses. Specifically, Patent Owner argued during prosecution that a comparable English translation of the penultimate (which Patent owner referred to as the last) sentence in Rau 2000 suggests only that "D2E7 can be administered every two weeks as *an intravenous injection* over 3-5 minutes OR subcutaneously." (Ex. 1002 (Office Action Response dated Mar. 25, 2009) at 680 (emphasis in original).) Patent Owner further argued that Rau 2000 teaches away from subcutaneous administration because Rau 2000 discusses "[t]he somewhat better effectiveness of intravenous injection" over subcutaneous injection in a clinical study evaluating D2E7 and methotrexate ("MTX") combination therapy. (*Id.* (quoting English translation of Rau 2000); *Cf.* Ex. 1012 at 8.)

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would have inferred that the authors [of Rau 2000] considered the improvement in CRP and in swollen joint count [SJC] suboptimal." (Ex. 1002 (Pope Decl.) at 1154-55 ¶ 24.) Even if interdose comparisons could be made based on the publicly available data (and they could not), van de Putte 2000 reported a greater numerical value for the 20 mg dose versus the 40 mg dose with respect to both CRP and SJC. (Ex. 1009 at 2; Ex. 1003 (Weisman Decl.) ¶ 40.)

Neither argument has any merit. (Ex. 1003 (Weisman Decl.) ¶¶ 45-47.) As a preliminary matter, the efficacy data focused on by Patent Owner were based on single doses of D2E7, and Rau 2000 expressly states that D2E7 is "effective subcutaneously." (Ex. 1012 at 7; *see also* Ex. 1003 (Weisman Decl.) at ¶ 46.) In any event, Rau 2000 does not come close to "'criticiz[ing], discredit[ing], or otherwise discourag[ing]' investigation into the invention claimed." *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314, 1327 (Fed. Cir. 2009) (quoting *In re Fulton*, 391 F.3d 1195, 1201 (Fed.Cir.2004)). Instead, it states that "D2E7 is . . . effective subcutaneously," (Ex. 1012 at 7; Ex. 1003 (Weisman Decl.) ¶ 46), which is consistent with the efficacy data reported in van de Putte 2000 (*id.* at ¶¶ 35-37). Patent Owner's argument again assumes a hypothetical claim requiring "the most effective dose" — a claim that was neither before the Examiner nor present in the '135 patent as issued. (*See* Section VI.C, *supra*.)

Moreover, the penultimate sentence of Rau 2000 emphasizes D2E7's roughly *two-week half-life*, which explains *why* D2E7 can be administered every other week, whether through intravenous or subcutaneous dosing. (*See* Ex. 1012 at 8.) Every-other-week dosing is the *only* dosing interval mentioned in the penultimate sentence of Rau 2000 — immediately after mentioning D2E7's roughly two week half-life (*see id.*; Ex. 1003 (Weisman Decl.) ¶ 45) — indicating

that this dosing interval may be used for both intravenous and subcutaneous administration. (Ex. 1003 (Weisman Decl.) ¶¶ 45-47.)

At a minimum, Rau 2000 would have provided a person of ordinary skill in the art with motivation to investigate every-other-week subcutaneous dosing, particularly given the known advantages of subcutaneous administration over intravenous administration and the fact that this route of administration was one of only two utilized in the prior art D2E7 clinical trials. (*See, e.g.*, Section IX.A.1.b, *supra*; Ex. 1003 (Weisman Decl.) ¶ 46.) "It is well settled that, even where references do not explicitly convey a motivation to combine, 'any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.'" *ABT Sys., LLC v. Emerson Elec. Co.*, 797 F.3d 1350, 1360 (Fed. Cir. 2015) (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007)).

Dr. Mould also contends that a person of ordinary skill in the art would not have been motivated to pursue a 40 mg every-other-week dose based on D2E7's half-life. (Ex. 1002 (Mould Decl.) at 1227 ¶ 78; *see also* Ex. 1002 (Pope Decl.) at 1166 ¶ 70; Ex. 1002 (Weinblatt Decl.) at 1193 ¶ 57.) But even Dr. Mould admitted that half-life "is of course a necessary parameter in any model." (*Id.*; *see also* Ex.

1003 (Jusko Decl.) ¶ 18.)[18]

In sum, the claimed invention would have been obvious to a skilled artisan in view of the prior art because "the experimentation needed to achieve biweekly administration . . . was 'nothing more than the routine application of a well-known problem-solving strategy . . . [and] the work of a skilled [artisan], not of an inventor.'" *Biomarin*, IPR 2013-00534, Paper No. 81 at 14 (quoting *Pfizer*, 480 F.3d at 1368). The Examiner erred by adopting the flawed arguments of AbbVie's experts.

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[18] AbbVie's experts also contended that a person of ordinary skill would have been concerned that lower serum levels of D2E7 could result in the production of anti-drug antibodies. (Ex. 1002 (Weinblatt Decl.) at 1189-90 ¶¶ 36-40; *see also* Ex. 1002 (Pope Decl.) at 1159-60 ¶¶ 46-47; Ex. 1002 (Mould Decl.) at 1219-1222 ¶¶ 51-60.) As Dr. Weinblatt acknowledges, however, when anti-drug antibodies develop, they are typically reported in the literature. (Ex. 1002 (Weinblatt Decl.) at 1189 ¶ 37; *see also* Ex. 1022 at 14.) No reports of anti-drug antibodies associated with D2E7 administration appeared in the publicly available literature as of June 2001, including with respect to D2E7 doses producing serum levels similar to that produced by a 40 mg every-other-week dose. (Ex. 1003 (Weisman Decl.) ¶ 40, n.7; Ex. 1004 (Jusko Decl.) ¶ 25.)

d. "for a time period sufficient to treat the rheumatoid arthritis"

van de Putte 2000 and Rau 2000 disclose this feature. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-31; Ex. 1004 (Jusko Decl.) ¶¶ 17-20.) For example, van de Putte 2000's dosing was administered over the course of six months to treat RA. As explained above, each of the D2E7 doses administered "were statistically superior to placebo" and "[t]he treatment benefit was stable for all parameters over time." (Ex. 1009 at 2.) Rau 2000 discusses similar results from other clinical studies, concluding that "D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment over, up to now, two and one-half years." (Ex. 1012 at 8.) Rau 2000 also describes one study in which "there was, starting already after 24 hours, a distinct improvement, which amounted to about 40% after one week." (*Id.* at 6.)

e. "wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("V_L") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("V_H") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4"

van de Putte 2000 and Rau 2000 disclose the use of D2E7. Patent Owner admitted that the anti-TNFα antibody recited in claim 1 encompasses the term

"D2E7" recited in the prior art. (*See, e.g.*, Ex. 1001 at 3:28-38; Ex. 1002 (Office Action Response dated March 21, 2007) at 404 (admitting that "D2E7" was "known to those in the art"); Ex. 1002 (Office Action Response dated March 7, 2006) at 223 (representing that "D2E7" is encompassed by the claims); Ex. 1002 (Office Action Response dated February 7, 2014) at 1268 (same).) As a result, van de Putte 2000 and Rau 2000 disclose this claim feature.

2. Claim 2

a. "The method of claim 1, wherein the V_L chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:1 and the V_H chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:2"

Claim 2 defines sequences that AbbVie has admitted encompass D2E7. (*See* Section IX.A.1.e, *supra*.) Because van de Putte 2000 and Rau 2000 disclose the use of D2E7, they disclose the features of claim 2.

3. Claims 3 and 4

a. "The method of claim 2, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks"

b. "The method of claim 1, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks"

Because rheumatoid arthritis is a chronic condition with no known cure, prolonged treatment with D2E7 was nothing new. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 14-16, 19.) The doses studied in van de Putte 2000 were administered "over 3

months in patients with long standing active rheumatoid arthritis followed by 3 months blinded D2E7 treatment," *i.e.*, for 24 weeks. (Ex. 1009 at 2.) Rau 2000 described a continuation study in which "all the patients have completed two years of treatment." (Ex. 1012 at 6.)

4. Claim 5

Claim 5 is similar to claim 1. As such, van de Putte 2000 and Rau 2000 render obvious claim 5 for the same reasons as claim 1 and for the additional reasons set forth below.

a. "A method for treating rheumatoid arthritis in a human subject, consisting of"

Both van de Putte 2000 and Rau 2000 disclose treating RA in humans, as discussed above with respect to claim 1. (*See* Section IX.A.1.a, *supra*.) The only difference in the preamble of claim 1 and 5 is that claim 5 recites the transitional phrase "consisting of." van de Putte 2000 and Rau 2000 both describe studies in which D2E7 was the only active ingredient administered subcutaneously. (*See* Ex. 1009 at 2; Ex. 1012 at 8.) As such, van de Putte 2000 and Rau 2000 disclose this feature of claim 5.

b. "administering subcutaneously to a human subject having rheumatoid arthritis"

As explained above with respect to claim 1, both van de Putte 2000 and Rau 2000 disclose this feature. (*See* Section IX.A.1.b, *supra*.) They describe studies in

which D2E7 was administered subcutaneously, the advantages of which were well-known in the prior art. (*Id*.)

c. "a composition comprising 40 mg of a human anti-TNFα antibody"

van de Putte 2000 and Rau 2000 disclose this feature. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29, 31.) The total body dose of 40 mg of D2E7 described in van de Putte 2000 and Rau 2000 were administered subcutaneously, necessarily as part of a composition. (*See id*.)

d. "once every 13 -15 days"

As explained above with respect to claim 1, administering a composition comprising 40 mg of D2E7 once every 13-15 days would have been obvious in view of van de Putte 2000 and Rau 2000. (*See* Section IX.A.1.c, *supra*.)

e. "for a time period sufficient to treat the rheumatoid arthritis,"

As explained above with respect to claim 1, van de Putte 2000 and Rau 2000 disclose this feature. (*See* Section IX.A.1.d, *supra*.)

f. "wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("VL") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("VH") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of

SEQ ID NO:6 and a CDR3having the amino acid sequence of SEQ ID NO:4"

As discussed above, Patent Owner admitted during prosecution that the anti-TNFα antibody recited in claim 1 encompasses the term "D2E7" recited in the prior art, including van de Putte 2000 and Rau 2000. (*See* Section IX.A.1.e, *supra*.)

g. "and wherein the human anti-TNFα antibody is administered in the form of a pharmaceutically acceptable composition"

The doses administered in van de Putte 2000 and Rau 2000 were necessarily "pharmaceutically acceptable." (*See* Ex. 1003 (Weisman Decl.) ¶ 29, 31.) The compositions were used to treat rheumatoid arthritis as part of human clinical trials, and thus must have complied with regulations defining pharmaceutically acceptable compositions. (*See id*.)

B. Alleged Evidence of Secondary Considerations Does Not Support Nonobviousness

Objective evidence of nonobviousness cannot overcome a strong case of obviousness based on the prior art, such as the case of obviousness presented by this Petition. *See Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364–65 (Fed. Cir. 2012); *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008); *Leapfrog Enterprises, Inc. v. Fisher-Price, Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007). AbbVie's alleged objective evidence of nonobviousness submitted during prosecution — most of which was based on

allegedly "surprising" results — undoubtedly falls short of the mark, particularly in light of the prior art's "reason[s] to select the route that produced the claimed invention." *Bristol-Myers Squibb Co. v. Teva Pharm. USA, Inc.*, 752 F.3d 967, 976 (Fed. Cir. 2014) (quoting *In re Cyclobenzaprine Hydrochloride Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) *cert. denied*, 135 S. Ct. 2050 (2015)).

AbbVie submitted three declarations during prosecution seeking to establish secondary evidence of nonobviousness. Dr. Weinblatt's (Ex. 1002 at 1172) and Dr. Pope's declarations (Ex. 1002 at 1140), for example, alleged that the claimed 40 mg every-other-week dose performed surprisingly better than other doses. AbbVie also submitted a declaration by Medgar Williams (Ex. 1002 at 1239), AbbVie's National Director of Sales for immunology, alleging commercial success of the claimed formulation. As explained below, AbbVie's evidence fails to establish nonobviousness, particularly in light of the strong case of *prima facie* obviousness set forth above.

1. The 40 mg Every-Other-Week Dose Was Not Unexpected or Surprising

AbbVie failed to establish during prosecution that an every-other-week 40 mg dose performed unexpectedly better than prior art dosing regimens, including prior art regimens involving every-other-week administration. A 40 mg every-other-week subcutaneous dose would have been expected to perform as it did because this dose represented the equivalent of the lowest effective subcutaneous

dose tested in the prior art (*i.e.*, 20 mg weekly) with the known added benefit of increased convenience and compliance. (Ex. 1003 (Weisman Decl.) ¶¶ 41, 50-51) AbbVie's prosecution declaration from Dr. Weinblatt does not establish otherwise. Dr. Weinblatt contended, among other things, that "[t]he person of ordinary skill in the art would . . . have had concerns that modifying the weekly dosing schedule of van de Putte to biweekly would compromise efficacy" (Ex. 1002 (Weinblatt Decl.) at 1190 ¶ 41), and that a dose below 40 mg weekly would reduce efficacy (Ex. 1002 (Weinblatt Decl.) at 1190 ¶ 42). van de Putte 2000 demonstrates, however, that a 20 mg weekly dose is clinically effective. (Ex. 1003 (Weisman Decl.) ¶ 47; *see also* Section IX.A.1.c(i), *supra*.)

Dr. Weinblatt also suggested that, because van de Putte 1999 does not disclose D2E7 serum levels, a person of ordinary skill in the art would not have been able assess whether serum levels would have remained high enough with an every-other-week dose. (Ex. 1002 (Weinblatt Decl.) at 1190 ¶ 42.) Rau 2000, however, demonstrates that an every-other week dose achieved favorable clinical results. (Ex. 1003 (Weisman Decl.) ¶ 47.) A person of ordinary skill in the art would have disagreed with Dr. Weinblatt's assertions in any event, however, given D2E7's roughly two-week half-life and demonstrated effectiveness at 20 mg, i.e., a dose comparable to the 40 mg every-other-week dose. (*See* Section IX.A.1.c, *supra*.)

In any event, the evidence submitted by AbbVie during prosecution does not establish any unexpected results *relative to the closest prior art*. AbbVie admitted that, "[o]ver time, patients treated . . . with [a] 40 mg flat dose, subcutaneously biweekly, receive the same amount of D2E7 as those treated in the DE007 trial with [a] 20 mg flat dose weekly." (Ex. 1023 at 45.) Patent Owner similarly admitted in a regulatory submission to the FDA that "every other week doses are assumed to be similar to one-half the same dose given weekly." (Ex. 1016 at 2, tbl. 75.) In other words, Patent Owner has admitted that there is no difference between the claimed dose and what it alleges to be the closest prior art, *i.e.*, a 20 mg weekly dose.[19] "To be particularly probative, evidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art, and that the difference would not have been expected by one of ordinary skill in the art at the time of the invention." *Bristol-Myers*, 752 F.3d at 977.

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[19] To the extent a 40 mg weekly dose is considered to be the closest prior art, Patent Owner did not even attempt to show during prosecution that the claimed 40 mg every-other-week dosing regimen is unexpectedly better than that prior art treatment. Nor could it in light of the available clinical data. (Ex. 1002 (Weisman Decl.) ¶¶ 35-41, 52-58.)

AbbVie's admissions are consistent with other post-filing date evidence, which establish that — consistent with what a person of ordinary skill in the art would have reasonably expected — a 40 mg every-other-week dose and a 20 mg weekly dose perform similarly. (Ex. 1003 (Weisman Decl.) ¶¶ 52-55.) For example, the FDA's Clinical Pharmacology and Biopharmaceutics Review of HUMIRA® (Ex. 1019), a commercial product allegedly embodying the claimed invention, confirms that patients receiving 20 mg D2E7 weekly and 40 mg D2E7 every-other-week had nearly identical D2E7 serum levels. (Ex. 1003 (Weisman Decl.) ¶ 52.)

The declarations submitted by AbbVie during prosecution do not establish otherwise. Dr. Pope's declaration (Ex. 1002 at 1140), for example, alleged that a person of ordinary skill would not have expected an every-other-week 40 mg dose to "work so well, in so many RA patients." (Ex. 1002 (Pope Decl.) at 1166 ¶ 71.) Dr. Pope relied on "van de Putte 2004" (Ex. 1020), which allegedly established that "40 mg administered s.c. on an every other week schedule provided better efficacy than 20 mg s.c. weekly as measured by ACR20, ACR50, and ACR70 scores." (Ex. 1002 (Pope Decl.) at 1166-67 ¶ 73.)

Contrary to Dr. Pope's assertion, a person of ordinary skill in the art would have drawn the opposite conclusion from van de Putte 2004, namely, that a 20 mg weekly dose and 40 mg every-other-week dose provided similar effectiveness.

(Ex. 1003 (Weisman Decl.) ¶¶ 52-56.) And such similar effectiveness would not have been surprising based on what was known at the time because a 20 mg weekly dose and 40 mg every-other-week dose deliver the same steady state serum concentrations of D2E7 over time, and because the half-life of D2E7 is roughly two weeks. (*Id.*)

Dr. Pope also relied on Keystone 2004 (Ex. 1021), another publication describing a clinical trial in which RA patients taking MTX were concurrently treated with D2E7 at 20 mg weekly or 40 mg every-other-week doses. Dr. Pope cited Figure 2C of Keystone 2004 (Ex. 1021 at 5) as alleged evidence of unexpected results for a 40 mg every-other-week dose compared to a 20 mg every-other-week dose. (Ex. 1002 (Pope Decl.) 1168-70 ¶¶ 76-78.) According to Dr. Pope, "[o]nly the 40 mg every other week regimen provided results that reached statistical significance in reducing joint space narrowing." (*Id.* at 1169 ¶ 76.)

Dr. Pope's conclusions are not supported by Keystone 2004. (Ex. 1003 (Weisman Decl.) ¶ 57-58.) The data Dr. Pope cited relate to a combination therapy including MTX, the effect of which Dr. Pope did not address. (*Id.*) Setting this flaw aside, other data in Keystone 2004 show similar clinical responses in patients given 20 mg weekly doses of D2E7 compared to those given 40 mg every-other-week doses. (*Id.*)

2. There Is No Nexus to AbbVie's Alleged Commercial Success

AbbVie also argued during prosecution that HUMIRA® was financially successful based in part on a declaration by Medgar Williams (Ex. 1002 at 1239), AbbVie's National Director of Sales for immunology (*id.* at 1240 ¶ 1). Mr. Williams did not attribute commercial success to any feature of HUMIRA®, much less any feature claimed in the '135 patent. (*Id.* at 1247 ¶ 28 ("In short, it is the combined features of HUMIRA® that makes HUMIRA® a success, not any single, isolated feature.").) Commercial success is not an indication of nonobviousness absent "some causal relation or 'nexus' between an invention and commercial success of a product embodying that invention." *Merck*, 395 F.3d at 1376.

Even if AbbVie attempted to identify such a causal relation, "[f]inancial success is not significantly probative . . . in this case" at least "because others were legally barred from commercially testing [the claimed formulation]" at the '135 patent's earliest possible filing date. *Id.* The question "is whether the claimed invention is non-obvious in relation to the ideas set forth in [*the prior art*]." *Id.* D2E7 formulations described in the prior art could not have been *commercially* used before the earliest possible priority date of the '135 patent, *i.e.*, June 8, 2001, because D2E7 was not commercially approved by the FDA until 2002 (*see* Ex. 1024 (HUMIRA® Product Label) at 1) and D2E7 was covered by U.S. Patent No.

6,090,382 (Ex. 1025) assigned to Patent Owner, which issued on July 18, 2000, and is not scheduled to expire until 2016. Financial success of the claimed invention is therefore irrelevant because such success cannot be compared to commercial success of the prior art. In sum, AbbVie's alleged evidence of nonobviousness cannot overcome Petitioner's strong case of obviousness based on the prior art.

X. The Board Should Adopt All Proposed Grounds

As noted above, Petitioner is filing another petition concurrent with the filing of this Petition. This Petition raises prior art under § 102(a), while the other petition raises prior art under § 102(b), including a ground that was raised in Coherus's petition. Petitioner requests that the Board adopt all grounds at least because they rely on prior art under different subsections of the statute and because Petitioner is not a party to the Coherus petition.

Moreover, the evidence identified in this Petition was not before the Examiner during prosecution. For example, a person of ordinary skill in the art's understanding of van de Putte 2000 and Rau 2000 (explained by Drs. Weisman and Jusko) was not before the Examiner during prosecution. This Petition further highlights legal and factual flaws in the Examiner's analysis. Aside from the Examiner's contradictory factual conclusions regarding dose-to-dose comparisons (*see* Section VI.C, *supra*), AbbVie's experts prompted the Examiner to lose sight

of the effectiveness of van de Putte's doses through allegations that van de Putte's 20 mg dose was somehow inferior to the other doses studied. Claims 1-5 simply do not require a dose with any particular — much less maximum, or superior — level of effectiveness. The Examiner was led to demand too much of the prior art, and to ignore "plain teachings" that equated the effectiveness of each dose, *see Merck*, 395 F.3d at 1375, and at a minimum did not come close to pointing away from the 20 mg dose, *see Dome Patent*, 799 F.3d at 1381; *PAR Pharm.*, 773 F.3d at 1197-98.

In sum, Petitioner requests full adoption of the proposed grounds and notes that such adoption will not hinder the "just, speedy and inexpensive resolution" of this matter in the spirit of 37 C.F.R. § 42.1(b) and 35 U.S.C. § 316(b).

XI. Conclusion

Petitioner has established a reasonable likelihood that it will prevail on claims 1-5 of the '135 patent. This Petition should be granted, *inter partes* review should be instituted, and claims 1-5 of the '135 patent should be found unpatentable and canceled.

Respectfully submitted,

Dated: December 29, 2015

By: /Naveen Modi/
Naveen Modi
Reg. No. 46,224
Counsel for Boehringer

CERTIFICATE OF SERVICE

The undersigned hereby certifies that, pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a), a copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, along with all exhibits and other supporting documents, was served on December 29, 2015, by FedEx overnight delivery at the following address:

Dechert LLP
2440 W. El Camino Real
Suite 700
Mountain View, CA 94040-1499

which is the correspondence address of record (37 C.F.R. § 42.105(a)) indicated in the Patent Office's public PAIR system for U.S. Patent No. 8,889,135.

Respectfully submitted,

Dated: December 29, 2015

By: /Naveen Modi/
Naveen Modi
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Counsel for Petitioners