Paper No. ___
Filed: December 29, 2015

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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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1002	Prosecution History of the '135 patent
1003	Declaration of Michael H. Weisman, M.D.
1004	Declaration of Dr. William J. Jusko, Ph.D.
1005	L.B.A. van de Putte et al., *A Single Dose Placebo Controlled Phase I Study of the Fully Human Anti-TNF Antibody D2E7 in Patients with Rheumatoid Arthritis*, 41(Supp.) Arthritis & Rheum. S57 (1998) ("van de Putte 1998")
1006	Rolf Rau et al., *Long-term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF-Antibody D2E7 in Patients with Rheumatoid Arthritis*, 41(Supp.) Arthritis & Rheum. S55 (1998) ("Rau 1998")
1007	Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in Patiens [sic] with Rheumatoid Arthritis - Results of a Phase I Study*, 41 (Supp.) Arthritis & Rheum. S57 (1998) ("Schattenkirchner 1998")
1008	L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42(Supp.) Arthritis & Rheum. S400 (1999) ("van de Putte 1999")
1009	Reserved
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1011	Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 (Supp. I) Ann. Rheum. Dis. 58(Suppl I): I70 (1999) ("Kempeni 1999")
1012	Reserved
1013	Reserved
1014	Michael Weisman et al., *A Dose Escalation Study Designed to Demonstrate the Safety, Tolerability and Efficacy of the Fully Human Anti-TNF Antibody, D2E7, Given in Combination with Methotrexate (MTX) in Patients with Active RA*, 43 (Supp.) Arthritis & Rheum. S228 (2000)
1015	REMICADE® Summary Basis of Approval

Exhibit	Reference
1016	U.S. Food and Drug Administration, *AbbVie's Clinical Review of Abbott's Biologic Licensing Application for adalimumab for the Treatment of RA, (Part 5)*, fda.gov, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/TherapeuticBiologicApplications/ucm080610.htm (last visited Dec. 14, 2015)
1017	U.S. Food and Drug Administration, *FDA's Clinical Review of Abbott's Biologic Licensing Application for adalimumab for the Treatment of RA*
1018	European Medicines Agency, *Scientific Discussion* (2004)
1019	U.S. Food and Drug Administration, *Clinical Pharmacology and Biopharmaceutics Review*
1020	L. B.A. van de Putte et al., *Efficacy and Safety of Adalimumab as Monotherapy in Patients with Rheumatoid Arthritis for whom Previous Disease Modifying Antirheumatic Drug Treatment has Failed*, 63 Ann. Rheum. Dis. 508 (2004) ("van de Putte 2004")
1021	Edward C. Keystone et al., *Radiographic, Clinical, and Functional Outcomes of Treatment with Adalimumab (a Human Anti-Tumor Necrosis Factor Monoclonal Antibody) in Patients with Active Rheumatoid Arthritis Receiving Concomitant Methotrexate Therapy*, 50 Arthritis & Rheum. 1400 (2004) ("Keystone 2004")
1022	Guidance for Industry, Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis (1999)
1023	Applicant's Remarks/Arguments in Response to Oppositions to European Patent 1406656B, dated Dec. 22, 2014
1024	U.S. Food and Drug Administration, HUMIRA® Product Label
1025	U.S. Patent No. 6,090,382 to Salfeld at al.
1026	U.S. Provisional Patent Application No. 60/296,961
1027	Shargel & Yu, *Applied Biopharmaceutics & Pharmacokinetics*, McGraw-Hill, 4th ed. 1999
1028	S. B. Hanauer, *Review Article: Safety of Infliximab In Clinical Trials*, 13: Suppl. (4) Aliment Pharmacol. & Ther. 16 (1999)
1029	J. Kempeni, *Update on D2E7: A Fully Human Anit-tumour Necrosis Factor α Monoclonal Antibody*, Ann. Rheum. Dis. 2000; 59 (Suppl I): i44-i45

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 based on two grounds. *First*, the claims would have been obvious over printed publications qualifying as prior art under § 102(b):

van de Putte 1999 (Ex. 1008) and Kempeni 1999 (Ex. 1011). van de Putte 1999 teaches or suggests all but one element recited in the claims. Namely, van de Putte 1999 discloses administering 20, 40, and 80 mg of D2E7 every *week* subcutaneously, while Kempeni 1999 discloses *every-other-week* administration. *Second*, the claims would have been obvious over three printed publications qualifying as prior art under § 102(b): Rau 1998 (Ex. 1006), Schattenkirchner 1998 (Ex. 1007), and van de Putte 1999. Rau 1998 describes a clinical study in which RA patients received every-other-week intravenous administration of D2E7, Schattenkirchner 1998 discloses that plasma concentrations of D2E7 after subcutaneous administration are comparable to those after intravenous administration, and van de Putte 1999 teaches that fixed subcutaneous doses, including the equivalent of a 40 mg every-other-week dose, were effective to treat RA.

This Petitions shows that a person of ordinary skill in the art would have, at a minimum, tried administering the prior art doses, including the claimed 40 mg dose, subcutaneously 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 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 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 1999, *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 under 37 C.F.R. § 42.8

Real Parties-in-Interest: Petitioner identifies Boehringer Ingelheim GmbH;

Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim International GmbH; Boehringer Ingelheim USA Corporation; and Boehringer Ingelheim Pharmaceuticals, Inc.

Related Matters: Coherus BioSciences Inc. ("Coherus") petitioned for *inter partes* review of claims 1-5 of the '135 patent on November 9, 2015. (*See* 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 prior art under 35 U.S.C. § 102(a).

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.

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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 and Identification of Challenge

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.

Petitioner challenges claims 1-5 of the '135 patent and requests that these claims be found unpatentable in view of the following two grounds, based on printed publications qualifying as § 102(b) prior art:[1]

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[1] For purposes of this Petition, Petitioner has assumed that the claims are entitled to a priority date of June 8, 2001. Petitioner reserves its right to challenge

Ground 1: Claims 1-5 are obvious over: (1) L.B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42(Supp.) Arthritis & Rheum. S400 (1999) ("van de Putte 1999") (Ex. 1008); and (2) Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 (Supp. I) Ann. Rheum. Dis. 58(Suppl I): I70 (1999) ("Kempeni 1999") (Ex. 1011). van de Putte 1999 is an abstract published in a September 1999 supplement to *Arthritis & Rheumatism* and later presented at a conference held on November 13-17, 1999, in Boston, Massachusetts. (Ex. 1006 at 1.) Kempeni 1999 is an article published in November 1999. (*See* Ex. 1011 at 1.) These publications are prior art under § 102(b).

Ground 2: Claims 1-5 are obvious over: (1) Rolf Rau et al., *Long-term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF-Antibody D2E7 in Patients with Rheumatoid Arthritis*, 41(Supp.) Arthritis & Rheum. S55 (1998) ("Rau 1998") (Ex. 1008); (2) Manfred Schattenkirchner et al., *Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human*

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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).

Anti-TNF-Antibody D2E7 in Patien[t]s with Rheumatoid Arthritis - Results of a Phase I Study, 41 (Supp.) Arthritis & Rheum. S57 (1998) ("Schattenkirchner 1998") (Ex. 1007); and (3) van de Putte 1999 (Ex. 1008). Rau 1998 and Schattenkirchner 1998 are abstracts published in the same September 1998 supplement to *Arthritis & Rheumatism* and later presented at a conference held on November 8-12, 1998, in San Diego, California. (Ex. 1006 at 1; Ex. 1007 at 1.) These publications, like van de Putte 1999, are prior art under § 102(b).

V. 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 clinical trials reported and commented on in van de Putte 1999, Kempeni 1999, Rau 1998, and Schattenkirchner 1998. The publications relied on in this Petition 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 publicly available clinical trial data.[2]

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[2] Petitioner relies only on the above-mentioned printed publications in its proposed grounds. (*See* Section VIII, *infra*.) Additional clinical studies are discussed simply to place these publications in context.

Petitioner briefly summarizes the pertinent aspects of these trials below for the sake of completeness.

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. 1011 at 3; 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 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." (Ex. 1006 at 5.) 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. (*Id.*) Thereafter, patients were "retreated only

when the DAS value increased to above 2.4 again." (*Id.*) 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 study known as "DE007" was a Phase II clinical trial involving subcutaneous administration of D2E7 as a total body dose. (*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 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.)

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.[3] (Ex. 1008

[3] 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.)

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 V.C, *infra*.)

5. Commentary on D2E7 Clinical Trials

Kempeni 1999, which was authored by one of the inventors listed on the '135 patent, summarizes and analyzes prior art D2E7 clinical trials. (Ex. 1011 at 5 n.13 & 14; Ex. 1003 (Weisman Decl.) ¶ 26.) For example, Kempeni 1999 characterized results from Rau 1998's DE001 study as "very encouraging." (*Id.* at 2.) "[T]herapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." (*Id.*) Based on pharmacokinetic parameters calculated from DE001, Kempeni 1999 reported that D2E7's "estimated mean terminal half life was 11.6 to 13.7 days." (*Id.*) Similarly, Kempeni 1999 explained that "good" DAS responses were achieved with dosing "every two weeks," and that overall "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks." (*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.[4] (*See* Ex. 1003 (Weisman Decl.) ¶¶ 29-30.) 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 prior

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[4] 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.

art clinical trials, as expressly suggested by the prior art. (Ex. 1003 (Weisman Decl.) ¶¶ 29-30, 34, 37-47.)

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, 1534.) 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.*)

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 Kempeni 1999. (*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.)[5] 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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[5] 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.[6]

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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[6] For the reasons explained below, even claims reciting a specific efficacy limitation would have been obvious over the prior art. (*See* Section VIII.A & B, *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.

VI. 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[7]) would have had knowledge regarding the pathophysiology of RA. (Ex. 1003 (Weisman Decl.) ¶¶ 12, 14-28.) 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

[7] 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.

VII. 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.[8]

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[8] 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.

VIII. Detailed Explanation of Grounds for Invalidity

As discussed in detail below, claims 1-5 would have been obvious over (1) van de Putte 1999 in view of Kempeni 1999 and (2) Rau 1998 in view of Schattenkirchner 1998 and van de Putte 1999.

A. Ground 1: van de Putte 1999 and Kempeni 1999 Render Claims 1-5 Obvious

van de Putte 1999 and Kempeni 1999 teach or suggest every element of claims 1-5. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 31-44; Ex. 1004 (Jusko Decl.) ¶¶ 15-23.) van de Putte 1999 expressly teaches each of the claimed features except for the claimed every-other-week dose and administration for 24 weeks (which is a limitation in dependent claims 3 and 4). But an every-other-week subcutaneous dose and administration for 24 weeks (and longer) would have been obvious in view of the teachings of these references, including Kempeni 1999. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 31-44.) The collective teachings of these two references demonstrate that claims 1-5 would have been obvious and should be canceled.

1. Claim 1

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

Both van de Putte 1999 and Kempeni 1999 disclose treating RA in humans. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 26, 27.) van de Putte 1999, 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. 1008

at 7.) Kempeni 1999 similarly explains that early clinical studies "enrolled patients with an established diagnosis of RA who also had active disease . . . ." (Ex. 1011 at 3.)

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

Administering D2E7 subcutaneously to human subjects was well known. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 26, 27.) Kempeni 1999 reported that D2E7 "given subcutaneously was safe and as effective as when administered intravenously[,] demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery" for treatment of RA. (Ex. 1011 at 5.) In the van de Putte 1999 study, 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 three months. (Ex. 1008 at 7.)

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

van de Putte 1999 provides three-month efficacy data from DE007, which involved subcutaneous weekly dosing of 20, 40, and 80 mg D2E7. (Ex. 1008 at 7.) The only claim feature not expressly disclosed in van de Putte 1999 is every-other-week dosing. Kempeni 1999, however, expressly discloses this feature and one of ordinary skill would have arrived at the claimed invention in light of the teachings of van de Putte 1999 and Kempeni 1999. (Ex. 1003 (Weisman Decl.) ¶¶ 31-44;

see also Ex. 1004 (Jusko Decl.) ¶¶ 15-23.) At the time of the alleged invention, one of ordinary skill would have combined the teachings of these references for at least three reasons. *First*, a person of ordinary skill in the art would have been motivated to optimize the van de Putte 1999 subcutaneous dosing regimens because each dosing regimen was determined to be effective for treating RA. (*See* IX.A.1.c.(i), *infra*.) *Second*, Kempeni 1999 would have provided motivation to optimize the van de Putte 1999 doses to a less frequent dosing interval. (*See* IX.A.1.c.(ii), *infra*.) *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* IX.A.1.c.(iii), *infra*.)

(i) One of Ordinary Skill Would Have Been Motivated to Optimize the Effective Van de Putte 1999 Dosing Regimens

The weekly subcutaneous doses described in van de Putte 1999 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.") (quoting *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007)) (internal quotations omitted). 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 1999 discloses weekly subcutaneous doses of D2E7 at 20, 40, and 80 mg total body doses. (Ex. 1008 at 7.) Each dose reported in van de Putte 1999, including the lowest effective dose reported (*i.e.*, 20 mg), was effective in treating RA. (*Id.* at 7 ("[A]ll doses of D2E7 were statistically significantly superior to placebo."); Ex. 1003 (Weisman Decl.) ¶¶ 32-36.) The patients in the van de Putte 1999 study were suffering from severe RA, which is reflected by the placebo group's low 10% ACR20 response. (Ex. 1008 at 7; Ex. 1003 (Weisman Decl.) ¶ 32.) By comparison, 49% of patients receiving the lowest 20 mg dose achieved an ACR20 response, which is a robust response, particularly considering the low placebo response. (Ex. 1008 at 7; Ex. 1003 (Weisman Decl.) ¶ 32.)

The increase in ACR20 responses for each dose reported in van de Putte 1999, 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.) ¶¶ 33-34.) 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.* ¶ 33.) The increase in ACR20 responses achieved with the van de Putte 1999 doses ranged from 39 to 47%, and thus each dose would have been viewed as clinically effective. (*Id.*

¶¶ 33-34.)

The FDA's approval of a 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, 33.) 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.) ¶ 33.) The increase in the number of patients receiving infliximab achieving ACR 20 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.) ¶ 33.)

While each dose in van de Putte 1999 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 1999. (Ex. 1003 (Weisman Decl.) ¶¶ 34-35.) The DE007 study reported by van de Putte 1999 was a parallel "randomised double-blind, placebo-controlled study." (Ex. 1008 at 7.) 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." (Ex. 1008 at 7; Ex. 1003 (Weisman Decl.) ¶ 35.) As with any parallel study, individual patients often exhibit different reactions to treatment. (Ex. 1003 (Weisman Decl.) ¶ 35.) 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 1999 suggests that each dose was superior to placebo, but not that any dose was better or worse than another dose.[9] (*Id.*)

The claimed dosing regimen would have been the result of routine

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[9] 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, $p < 0.0001$) and no dose response relation was apparent at month 3."); *see also* Ex. 1003 (Weisman Decl.) ¶ 34, n.6.)

optimization regardless of whether a person of ordinary skill read van de Putte 1999 as showing, consistent with the authors' conclusion, the 20, 40, and 80 mg dosages to be "nearly 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.) ¶¶ 32-36.) This is because van de Putte 1999'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 1999 would have at least suggested that an analogous, every-other-week 40 mg dose would have been an option worth investigating. (Ex. 1003 (Weisman Decl.) ¶¶ 41-43.) And a person of ordinary skill would have been particularly attracted to pursuing the every-other-week equivalent (*i.e.*, 40 mg) of the lowest weekly dose (*i.e.*, 20 mg) that was shown to be efficacious in the prior art. (Ex. 1003 (Weisman Decl. ¶ 43.)

(ii) Kempeni 1999 Would Have Motivated One of Ordinary Skill to Optimize the Van de Putte 1999 Dosing Regimens to Every-Other-Week Regimens

Kempeni 1999 teaches that every-other-week subcutaneous administration of D2E7 is effective for treating RA. (Ex. 1003 (Weisman Decl.) ¶¶ 37-39.) For example, Kempeni 1999 discloses in connection with the DE001 study that, after a single dose, D2E7's "therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." (Ex. 1011 at 4.) DE001 also demonstrated that D2E7's "estimated mean terminal half life was 11.6 to 13.7 days." (Ex. 1011 at 4.) These statements indicate that D2E7 remains in the body for at least two weeks and is therapeutically active during that time, suggesting that D2E7 would be compatible with every-other-week dosing. (Ex. 1003 (Weisman Decl.) ¶ 37; Ex. 1004 (Jusko Decl.) ¶¶ 17-22.)

Moreover, Kempeni 1999 teaches that every-other-week dosing is not only effective, but in fact a preferred dosing frequency for treating RA at the disclosed doses. (Ex. 1003 (Weisman Decl.) ¶ 38.) According to Kempeni 1999, DE003 demonstrated that every-other-week "intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated" and produced a "good" EULAR response, "defined as an absolute DAS of < 2.4" (Ex. 1011 at 4) — *i.e.*, a robust clinical response. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 20, 38.) Thereafter, "patients

were retreated only upon disease flare up." (Ex. 1011 at 4.) In other words, the DE003 investigators determined how long it would take for RA symptoms to reappear once a "good" EULAR response had been achieved with every-other-week dosing. (Ex. 1003 (Weisman Decl.) ¶ 20, 38.) This treatment protocol resulted in a "mean dosing interval of 2.5 weeks" (Ex. 1011 at 4), indicating that, on average, RA symptoms reappeared 2.5 weeks after the last "good" EULAR response was achieved. (Ex. 1003 (Weisman Decl.) ¶ 20, 38.) This would have suggested not only that every-other-week dosing is effective to treat RA at the disclosed doses, but that slightly longer dosing intervals (*i.e.*, 2.5 weeks) may result in loss of efficacy. (*Id.*; Ex. 1004 (Jusko Decl.) ¶ 23.)

While the DE001 and DE003 studies described in Kempeni 1999 involved *intravenous* administration of D2E7, nothing in Kempeni 1999 indicates that subcutaneous dosing would have produced different results. (Ex. 1003 (Weisman Decl.) ¶ 39.) To the contrary, Kempeni 1999 reports, based on the DE004 study, that "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration" and that "[u]p to 78% of patients achieved a DAS/ACR 20 response after three months of treatment with subcutaneous D2E7." (Ex. 1011 at 5 (crediting the DE004 investigators' conclusion that "D2E7 given subcutaneously was safe and as effective as when administered intravenously[,] demonstrating that subcutaneous self administration

is a promising approach for D2E7 delivery"). A person of ordinary skill in the art would have therefore reasonably expected every-other-week subcutaneous administration to produce clinical results similar to those achieved with every-other-week intravenous administration. (Ex. 1003 (Weisman Decl.) ¶ 39; Ex. 1004 (Jusko Decl.) ¶¶ 19-23.)

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.) ¶¶ 19-22.) 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 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 1999 (Ex. 1003 (Weisman Decl.) ¶¶ 32-34; *see also* Ex. 1004 (Jusko Decl.) ¶¶ 20, 22), a person of ordinary skill would have been motivated to pursue a 40 mg every-other-week subcutaneous dose (Ex. 1003 (Weisman Decl.) ¶¶ 37-39; *see also* Ex. 1004 (Jusko Decl.) ¶¶ 20, 22).[10]

[10] 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.) ¶ 36.)

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.) ¶ 44.) 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. regulatory authorities, the EMA similarly characterized "40 mg every other week [as] . . . equivalent to 20 mg weekly." (Ex. 1018 at 14.)[11]

Even if the level of ordinary skill in the art were considered to have included the understanding of a pharmacokineticist, this conclusion would have been buttressed by D2E7's linear pharmacokinetics. (Ex. 1004 (Jusko Decl.) ¶¶ 19-23.)

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

Analysis from the DE001 study demonstrated that D2E7 systemic drug exposure (referred to as "AUC," *see* Ex. 1004 (Jusko Decl.) ¶ 19 n.4) increased proportionally over a wide (20-fold) dose range, implying linear kinetics (Ex. 1011 at 4). As would have been expected with such a linear system, the half-life varied over this dose range by only roughly two days. (Ex. 1011 at 4; Ex. 1004 (Jusko Decl.) ¶ 20.) 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.) ¶¶ 18-21.)

(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 1999 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.) ¶¶ 41-44.) A person of ordinary

skill in the art would have been further motivated to move from the weekly dosing in van de Putte 1999 to less frequent every-other-week dosing, as taught in Kempeni 1999, in view of clinical considerations. (Ex. 1003 (Weisman Decl.) ¶ 42.) *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.) ¶¶ 29, 42.) 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, particularly in light of Kempeni 1999's teaching that this dosing interval was preferable. (Ex. 1003 (Weisman Decl.) ¶ 42; *see also* pages 27-28, *supra*.)

(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.) ¶¶ 31-58; Ex. 1004 (Jusko Decl.) ¶¶ 15-28.)

For instance, Patent Owner may argue that, even though van de Putte 1999 expressly concludes that "20, 40, and 80 mg/week were nearly 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.) ¶ 36.) Instead, a person of ordinary skill in the art would have been able to conclude based on the van de

Putte 1999 data only that each dose was effective relative to placebo. (Ex. 1003 (Weisman Decl.) ¶¶ 32-36.) 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. (Ex. 1003 (Weisman Decl.) ¶ 36.) This is particularly true given that van de Putte reports that each dose was "nearly equally efficacious." (Ex. 1008 at 7; *see also* Ex. 1003 (Weisman Decl.) ¶ 36.)[12]

Even assuming, *arguendo*, that one of ordinary skill would have concluded that van de Putte 1999 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 Section VIII.A.1 above. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 32-36.) 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 1999. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 19-20, 27-28.) van de Putte 1999 concluded that all doses were

[12] Drs. Weinblatt and Pope made similar arguments during prosecution that, as explained in Section VIII.C.1 below, are equally unavailing.

"statistically significantly superior to placebo," and — based on all of the study-related information available to the van de Putte 1999 authors, as opposed to the data that was made publicly available through that article — that each dose was "nearly equally efficacious" when administered subcutaneously. (Ex. 1008 at 7.) 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").)

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.)[13]

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. The Examiner erred by adopting the flawed arguments of AbbVie's experts.

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[13] 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 1999 and Kempeni 1999 teach this feature. (Ex. 1003 (Weisman Decl.) ¶ 31.) For example, van de Putte 1999's dosing was administered over the course of three months to treat RA. As explained above, each of the D2E7 doses administered "were statistically superior to placebo" in treating RA. (Ex. 1008 at 7.) Kempeni 1999 discusses similar results from other clinical studies, including that "[t]he therapeutic effects became evident within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks." (Ex. 1011 at 4.)

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 1999 and Kempeni 1999 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 1999 and Kempeni 1999 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 VIII.1.e, *supra*.) Because van de Putte 1999 and Kempeni 1999 disclose the use of D2E7, they disclose the features of claim 2.

3. Claims 3 and 4

Claim 3 depends from claim 2 and claim 4 depends from claim 1. They both recite that the anti-TNFα antibody is administered for a period of at least 24 weeks. (Ex. 1001 at 45:31-46:12.) Prolonged treatment with D2E7 was nothing new. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 14-16, 19.) Kempeni 1999, for example, described a continuation study in which, "[a]fter six months, 86% of patients continued to receive treatment with D2E7." (Ex. 1011 at 4.) Because rheumatoid arthritis is a chronic condition with no known cure, the person of ordinary skill in the art would have been motivated to continue treatment as long as necessary, including 24 weeks and beyond. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 14-16, 19.)

4. Claim 5

Claim 5 is similar to claim 1. As such, van de Putte 1999 and Kempeni

1999 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 1999 and Kempeni 1999 disclose treating rheumatoid arthritis in humans, as discussed above with respect to claim 1. (*See* Section VIII.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 1999 and Kempeni 1999 both describe studies in which D2E7 was the only active ingredient administered subcutaneously. (Ex. 1008 at 7; Ex. 1011 at 4.) As such, van de Putte 1999 and Kempeni 1999 disclose this feature of claim 5. (*See* Section VIII.A.1.a, *supra*.)

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

As explained above with respect to claim 1, both van de Putte 1999 and Kempeni 1999 disclose this feature. (*See* Section VIII.A.1.b, *supra*.) They describe studies in which D2E7 was administered subcutaneously, the advantages of which were well-known in the prior art. (*See id*.)

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

van de Putte 1999 discloses this feature. (*See* Ex. 1003 (Weisman Decl.) ¶ 27.) The total body dose of 40 mg of D2E7 described in van de Putte 1999 was

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 the teachings of van de Putte 1999 and Kempeni 1999. (*See* Section VIII.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 1999 and Kempeni 1999 disclose this feature. (*See* Section VIII.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 CDR3 having 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 1999 and Kempeni 1999. (*See* Section VIII.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 1999 and Kempeni 1999 were

necessarily "pharmaceutically acceptable." (*See* Ex. 1003 (Weisman Decl.) ¶¶ 23, 25, 27.) 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. Ground 2: Rau 1998, Schattenkirchner 1998, and van de Putte 1999 Render Claims 1-5 Obvious

The claimed dosing regimen would have been equally obvious over Rau 1998 in view of Schattenkirchner 1998 and van de Putte 1999. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 45-51; *see also* Ex. 1004 (Jusko Decl.) ¶ 28.) A 40 mg subcutaneous dose is the only element that is not expressly disclosed by Rau 1998. This element, however, would have been suggested by Schattenkirchner 1998 and van de Putte 1999. The collective teachings of these references demonstrate that claims 1-5 would have been obvious and should be canceled. (Ex. 1003 (Weisman Decl.) ¶¶ 45-51; *see also* Ex. 1004 (Jusko Decl.) ¶ 28.)

1. Claim 1

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

Rau 1998, Schattenkirchner 1998, and van de Putte 1999 all disclose treating RA in humans. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 23, 25, 27.) Rau 1998 describes a study in which "patients with active arthritis . . . were treated with multiple iv [intravenous] doses of D2E7." (Ex. 1006 at 5.) Similarly, Schattenkirchner 1998 reports a study involving "patients with active rheumatoid

arthritis" in which "injections of D2E7 have been given for up to 6 months." (Ex. 1007 at 5.) van de Putte 1999 also discloses this feature. (*See* Section VIII.A.1.a, *supra*.)

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

Administering D2E7 subcutaneously to humans was well known, as explained above. (*see* Section VIII.A.1.b, *supra.*) In addition to van de Putte 1999 (*see* Section VIII.A.1.a, *supra*), Schattenkirchner 1998 reports that patients received D2E7 subcutaneously, concluding that "[t]he s.c. administration of D2E7 has been shown to be safe and efficacious" (Ex. 1007 at 5).

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

Rau 1998, Schattenkirchner 1998, and van de Putte 1999 collectively teach this feature. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 45-51.) As explained in section VIII.B.1.c(i) below, one of ordinary skill would have optimized the dosing regimen in Rau 1998 based on the teachings of Schattenkirchner and van de Putte 1999. Specifically, Rau 1998 discloses intravenous administration of D2E7 every-other-week, and Schattenkirchner explains that subcutaneous administration is comparable to intravenous administration. Subcutaneous, fixed dosing would have been preferred for clinical reasons (Ex. 1003 (Weisman Decl.) ¶¶ 47-50) and reasonably expected to be effective in view of van de Putte 1999, including at a 40

mg every-other-week dose. (*See* Section VIII.A.1.c(i), *supra*.) In addition, while not necessary to arrive at the claimed dose, the fact that the 0.5 mg/kg weight-based dose in Rau 1998 roughly correlates to the van de Putte 40 mg dose under reasonable patient-weight assumptions further confirms that one of ordinary skill would have pursued the claimed dosing regimen with a reasonable expectation of success. (Ex. 1003 (Weisman Decl.) ¶ 49.) At a minimum, 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. (*See* Section VIII.B.1.c(ii), *infra*.)

(i) One of Ordinary Skill Would Have Been Motivated to Optimize the Rau 1998 Dosing Regimens Based on the Teachings of Schattenkirchner 1998 and van de Putte 1999

The every-other-week intravenous doses described in Rau 1998 were collectively described as effective, and would have been further optimized. *See Biomarin*, IPR 2013-00534, Paper No. 81 at 14 ("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 route of administration would have been a "routine optimization" of the prior art therapy, particularly in view of well-known clinical considerations, and would have yielded predictable results. (*Id*. at 11-18; Ex. 1003 (Weisman Decl.) ¶¶ 41-51.)

As explained above (*see* pages 8-9, *supra*), the DE003 study reported in Rau 1998 demonstrates that every-other-week dosing of D2E7 is both effective and desirable. (Ex. 1003 (Weisman Decl.) ¶¶ 23-24, 45-51.) DE003 patients received D2E7 intravenously every two weeks until they achieved a "good" EULAR response, which would have indicated that every-other-week dosing is effective for treating RA. (*See* Ex. 1006 at 5; Ex. 1003 (Weisman Decl.) ¶ 45.) Once this "good" EULAR response was achieved, the patient received D2E7 only after RA symptoms reappeared. (Ex. 1006 at 5.) This treatment protocol resulted in a mean dosing interval of 2.5 weeks, demonstrating that, on average, RA symptoms reappeared 2.5 weeks after the last dose — *i.e.*, shortly after every-other-week. (*Id.*; Ex. 1003 (Weisman Decl.) ¶ 45.) Every-other-week dosing would have therefore been viewed as a preferred dosing interval that should be further investigated. (Ex. 1003 (Weisman Decl.) ¶ 45.)

While Rau 1998 describes intravenous weight-based doses, subcutaneous fixed dosing would have been suggested by Schattenkirchner 1998 and van de Putte 1999 (Ex. 1003 (Weisman Decl.) ¶¶ 41-42, 44-48, 51), both of which disclose that subcutaneous dosing is effective for treating RA (*see* Ex. 1007 at 5; Ex. 1008 at 7). Further, optimizing an every-other-week intravenous dose to an every-other-week subcutaneous dose would have reasonably been expected to succeed. The DE004 study described in Schattenkirchner 1998 demonstrated 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." (Ex. 1007 at 5; Ex. 1003 (Weisman Decl.) ¶ 46.)

As explained above, one of ordinary skill would have pursued a 40 mg dose in connection with an every-other-week subcutaneous regimen in light of van de Putte 1999. (*See* Section VIII.A.1.c.i, *supra*.) As a result, the combination of Rau 1998, Schattenkirchner 1998, and van de Putte 1999 teach the claimed 40 mg every-other-week subcutaneous total body dose.

Finally, while not necessary to arrive at the claimed dose, the 0.5 mg/kg weight based dose in Rau 1998, which would have correlated to the efficacious 40 mg dose reported in van de Putte 1999, further confirm that one of ordinary skill would have arrived at the claimed dose with a reasonable expectation of success. (Ex. 1003 (Weisman Decl.) ¶ 49.) Under the reasonable assumption of an average RA patient weight of 80 kg (about 176 lbs.), the 0.5 mg/kg weight-based dose disclosed in Rau 1998 would have been understood to correspond roughly to a 40 mg fixed dose. (*See* Ex. 1002 (Office Action dated Sept. 21, 2009) at 366 (Examiner recognizing "about 0.5 mg/kg" encompasses "about 40 mg" "based on an average weight of 80 kg (176 lbs) for the average human subject"); *see also* Ex. 1002 (Office Action dated April 21, 2014) at 1538 (Examiner explaining that

German RA patients have "a body weight in the range of 62-88 kg").) Other weight-based doses described in Rau 1998 could have been similarly converted into approximate fixed doses. (Ex. 1003 (Weisman Decl.) ¶ 49.)

(ii) 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

Administering a 40 mg every-other-week, subcutaneous dose would have at least been obvious to try based on the Rau 1998 every-other-week dosing regimen in view of the finite number of administration routes employed in the D2E7 prior art (subcutaneous and intravenous), the two possible dosing options (fixed and weight-based), and the small number of fixed dosing amounts (20, 40, and 80 mg) disclosed in van de Putte 1999. *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 would have specifically included 40 mg among the doses to be further studied. (Ex. 1003 (Weisman Decl.) ¶ 43.) This would have been particularly true given that an every-other-week 40 mg dose would have corresponded to the lowest effective fixed subcutaneous dose described in prior art clinical trials, *i.e.*, the 20 mg weekly dose described in van de Putte 1999. (*See* Section VIII.A.1.c.(iii), *supra*; Ex. 1003 (Weisman Decl.) ¶ 43.)

Moreover, even if a person of ordinary skill in the art would have been

limited to one route of administration (they would not have), subcutaneous dosing would have been preferred for a number of reasons, including that subcutaneous administration would have been known to avoid complications associated with intravenous administration, such as thrombosis or other problems at the injection site. (Ex. 1003 (Weisman Decl.) ¶¶ 41-44, 47.) Subcutaneous doses would also have increased patient compliance and convenience through at-home administration and decreased both patient and health-care provider costs. (*Id.* at ¶¶ 42, 47.) Fixed doses would likewise have been preferred over variable-amount, weight-based doses for similar reasons. (*Id.* at ¶¶ 46-48.) Moreover, subcutaneous administration was one of only two routes of administration disclosed in the D2E7 art. (*Id.* at ¶ 47.)

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

As discussed above, Patent Owner made several arguments during the original 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 in Section VIII.A.1.c.(iv) above. In addition, Patent Owner argued during prosecution that Rau 1998 does not disclose *only* every-other-week dosing, and thus does not suggest the claimed dosing frequency. (*See, e.g.*, Ex. 1002 (Office Action Response dated June 1, 2010) at 784-85.) As the Examiner

acknowledged, however, Rau 1998 teaches every-other-week dosing during the initial phase of the study, and the overall mean dosing interval described in that reference was 2.5 weeks. (*Id*. (Office Action dated Aug. 3, 2011) at 1001-02.) As explained in Section VIII.B.1.c.(i) above, this teaches that an every-other-week dosing schedule is preferred. (Ex. 1003 (Weisman Decl.) ¶ 45.)

Patent Owner may also argue that converting a "weight-based dose to a flat dosing is a well-known pharmacokinetic fallacy." (*See, e.g.*, Ex. 1002 (Mould Decl.) at 1213 ¶ 34.) Such arguments, however, ignore the fact that van de Putte 1999 discloses effective, fixed doses, and a person of ordinary skill in the art would have been motivated to pursue improved dosing regimens utilizing these fixed dose amounts. The van de Putte 1999 doses would have been understood to correlate roughly to a weight-based dose encompassed within the range of doses studied in Rau 1998 (and the 40 mg dose in particular to Rau 1998's 0.5 mg/kg dose), thus providing a reason to combine Rau 1998 and van de Putte 1999. (*See* Section VIII.B.1.c.(i), *supra*.) A precise conversion of a weight-based dose to a fixed dose would not have been required. (Ex. 1003 (Weisman Decl.) ¶ 49.)

Finally, Patent Owner may argue, as it did during prosecution, that a fixed dose would not have been preferred over a weight-based dose because a person of ordinary skill in the art would have been motivated, first and foremost, to find a regimen that is safe and effective, rather than a dose that is convenient. (*See, e.g.*,

Ex. 1002 (Mould Decl.) at 1216 ¶¶ 42-50.) These arguments ignore that all of the fixed doses described in van de Putte 1999 were in fact found to be safe and effective. No data is reported in prior art D2E7 clinical trials would have suggested otherwise. (Ex. 1003 (Weisman Dec.) ¶¶ 27-28, 50.)

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

Rau 1998 and Schattenkirchner 1998 disclose this feature. (*See* Ex. 1003 (Weisman Dec.) ¶¶ 23-25.) Rau 1998's doses were administered for up to 12 months, after which "[m]ore than 80% of the patients achieved and sustained responder status." (Ex. 1006 at 5.) Schattenkirchner 1998's doses were administered over the course of up to six months, producing "a mean reduction in DAS of about 50%, in SWJC of about 60% and in TJC of about 70% for D2E7 treated patients after 2 months." (Ex. 1007 at 5.) And as discussed in Section VIII.A.1.d above, van de Putte 1999 also discloses this feature.

e. "wherein the anti-TNFα antibody comprises . . . 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. (*See* Section VIII.A.1.e, *supra*.) Rau 1998, Schattenkirchner 1998, and van de Putte 1999 disclose administration of D2E7. (Ex. 1006 at 5; Ex. 1007 at 5.) As a result, these references disclose this claim feature.

2. Claim 2

As discussed in Section VIII.A.2.a, *supra*, claim 2 defines sequences that

AbbVie has admitted encompass D2E7. Because Rau 1998, Schattenkirchner 1998, and van de Putte 1999 disclose the use of D2E7, they disclose the features of claim 2.

3. Claims 3 and 4

Claim 3 depends from claim 2 and claim 4 depends from claim 1. They both recite that the anti-TNFα antibody is administered for a period of at least 24 weeks. (Ex. 1001 at 45:31-46:12.) As discussed in Section VIII.A.3, *supra*, prolonged treatment with D2E7 was nothing new. (*See* Ex. 1003 (Weisman Decl.) ¶¶ 14-16, 19.) Rau 1998 describes treatment with D2E7 for up to six months, and Schattenkirchner 1998 describes a continuation study in which D2E7 was administered for up to 12 months. (Ex. 1006 at 5; Ex. 1007 at 5.)

4. Claim 5

As discussed in Section VIII.A.5, *supra*, claim 5 is similar to claim 1. As such, Rau 1998, Schattenkirchner 1998, and van de Putte 1999 render claim 5 obvious for the same reasons as claim 1 and for the additional reasons below.

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

Rau 1998, Schattenkirchner 1998, and van de Putte 1999 disclose treating rheumatoid arthritis in humans, as discussed above with respect to claim 1. (*See* Section VIII.B.1.a, *supra*.) The only difference in the preamble of claim 1 and 5 is that claim 5 recites the transitional phrase "consisting of." Rau 1998,

Schattenkirchner 1998, and van de Putte 1999 all describe studies in which D2E7 was the only active ingredient administered subcutaneously. (Ex. 1006 at 6; Ex. 1007 at 5; Ex. 1008 at 7.) As such, these references disclose this feature of claim 5.

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

As explained above with respect to claim 1, Schattenkirchner 1998 and van de Putte 1999 disclose this feature. (*See* Section VIII.B.1.b, *supra*.) Both publications describe studies in which D2E7 was administered subcutaneously, the advantages of which were well-known in the prior art. (*See id*.)

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

van de Putte 1999 discloses this feature. (*See* Ex. 1008 at 7; Ex. 1003 (Weisman Decl.) ¶ 27.) The total body doses of 40 mg of D2E7 described in van de Putte 1999 were administered subcutaneously, and necessarily as part of a composition. (*See* Ex. 1008 at 7; Ex. 1003 (Weisman Decl.) ¶ 27.)

d. "once every 13 -15 days"

As explained above with respect to claim 1, Rau 1998 discloses this every-other-week dosing interval. (*See* Ex. 1006 at 5; *see also* Section VIII.B.1.c, *supra*.)

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

As explained above with respect to claim 1, Rau 1998, Schattenkirchner

1998, and van de Putte 1999 disclose this feature. (*See* Section VIII.B.1.d, *supra*.)

f. "wherein the anti-TNFα antibody comprises . . . 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 in Rau 1998, Schattenkirchner 1998, and van de Putte 1999. (*See* Section VIII.B.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 Rau 1998, Schattenkirchner 1998, and van de Putte 1999 were necessarily "pharmaceutically acceptable." (*See* Ex. 1003 (Weisman Decl.) ¶¶ 23, 25, 27.) 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* Ex. 1003 (Weisman Decl.) ¶¶ 23, 25, 27.)

C. 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.) ¶¶ 41-48, 52-58.) 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 1999 demonstrates, however, that a 20 mg weekly dose is clinically effective. (Ex. 1003 (Weisman Decl.) ¶¶ 32-34, 40; *see also* Section VIII.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.) A person of ordinary skill in the art would have disagreed with Dr. Weinblatt's assertions, 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 VIII.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.[14] "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.

AbbVie's admissions are consistent with other post-filing date evidence,

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[14] 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.) ¶¶ 21-28, 32-39, 41-48, 52-56.)

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.) ¶ 56.) 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.) ¶ 55.)

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. 1002 (Weisman Decl.) ¶¶ 52-57.) 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.

IX. 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(b), including a ground that was raised in Coherus's petition, while the other petition raises prior art under § 102(a). 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 1999, Kempeni 1999, Schattenkirchner 1998, and Rau 1998 (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).

X. 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/
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Counsel for Petitioners