IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent of:	Fischkoff et al.	
U.S. Patent No.:	9,017,680	Attorney Docket No.: 40299-0013IP1
Issue Date:	April 28, 2015	
Appl. Serial No.:	14/542,529	
Filing Date:	November 14, 2014	
Title:	METHODS OF ADMINISTERING ANTI-TNFα ANTIBODIES	

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PETITION FOR *INTER PARTES* REVIEW OF UNITED STATES PATENT NO. 9,017,680 PURSUANT TO 35 U.S.C. §§ 311–319 AND 37 C.F.R. § 42

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1005	Rau et al., "Effective Combination of the Fully Human Anti-TNF Antibody D2E7 and Methotrexate in Active Rheumatoid Arthritis," *Ann. Rheum. Dis.,* 217, No. 907 (1999) ("Rau #907").
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1009	Rau et al., "Long-term treatment with the fully human anti TNF alpha-antibody D2E7 slows radio-graphic disease progression in rheumatoid arthritis," *Arthritis & Rheum.,* 42 (S9):S400, No. 1978, Sept. 1999 ("Rau #1978").
1010	Dorland's Illustrated Medical Dictionary, p. 4-5 (1988).
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1015	"Updated consensus statement on tumour necrosis factor blocking agents for the treatment of rheumatoid arthritis and other rheumatic diseases." (April 2001).
1016	Guidance for Industry, Clinical Development Programs for Drugs, Devices and Biological Products for the Treatment of Rheumatoid Arthritis (1999).
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I. INTRODUCTION

Coherus BioSciences Inc. ("Petitioner" or "Coherus") petitions for *inter partes* review ("IPR") under 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 of claims 1-4 of U.S. Patent No. 9,017,680 ("the '680 patent"). As explained in this petition, review should be instituted because there is a reasonable likelihood that Coherus will prevail with respect to at least one claim challenged in this petition.

The '680 patent claims a method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis ("RA") by subcutaneously administering a total body dose of 40 mg of a certain human anti-TNFα antibody every 13-15 days in combination with methotrexate. The antibodies recited in the '680 claims include antibodies known as "D2E7." *See* EX. 1001, 3:32-42.

The '680 claims would have been obvious over van de Putte 1999 (EX. 1004) in view of Kempeni (EX. 1003). van de Putte 1999 discloses administering a total body dose of 20, 40, and 80 mg of D2E7 subcutaneously on a weekly basis to treat RA, and that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)." van de Putte 1999 (EX. 1004), p. 1. In other words, each dose successfully treated RA. Kempeni teaches that the estimated mean terminal half-life of D2E7 was 11.6 to 13.7 days.

Kempeni (EX. 1003), p. 2. Kempeni further teaches treating RA by administering D2E7 intravenously on a biweekly basis, and that subcutaneous administration was "as effective as when administered intravenously." *Id.*, pp. 2-3. Kempeni also teaches that D2E7 was "safe and effective as monotherapy or in combination with methotrexate." *Id.,* p. 3.

Based on the teachings of van de Putte 1999 and Kempeni, a person of ordinary skill would have been motivated to dose 40 mg of D2E7 in combination with methotrexate biweekly, and would have expected this dose to be safe and effective in treating RA. Indeed, when viewed in the context of the advanced state of the art at the time of filing, the '680 patent claims represent no more than "a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures." *Biomarin Pharms. Inc. v. Genzyme Therapeutic Products Ltd. P'ship*, IPR2013-00534, Paper No. 81, pp. 12-14 (PTAB Feb. 23, 2015). Accordingly, claims 1-4 are unpatentable under 35 U.S.C. § 103 as obvious. Petitioner therefore respectfully solicits institution of *inter partes* review of claims 1-4, and their cancelation as unpatentable.

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

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

Coherus BioSciences Inc. is the real party-in-interest.

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

The following pending U.S. applications and issued U.S. patents are related via priority to the '680 patent: U.S.S.N. 14/175,993; U.S.S.N. 14/292,759; U.S.S.N. 14/634,478; U.S.S.N. 14/634,530; U.S.S.N. 14/715,310; U.S. 8,889,135; U.S. 9,073,987; U.S. 8,911,737; U.S. 8,984,790; and U.S. 8,992,926.

U.S. 8,889,135 is the subject of an *inter partes* review petition filed on November 9, 2015 (IPR2016-00172). U.S. 9,073,987 is the subject of a concurrently filed *inter partes* review petition (IPR2016-00189).

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

Petitioner provides the following designation of counsel.

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D. Service Information

Please address all correspondence and service to counsel at the address provided in Section I(C). Petitioner also consents to electronic service by email at IPR40299-00013IP1@fr.com.

III. PAYMENT OF FEES – 37 C.F.R. § 42.103

Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 06-1050 for the fee set in 37 C.F.R. § 42.15(a) for this petition and further authorizes any additional fees to be charged to this Deposit Account.

IV. REQUIREMENTS FOR IPR UNDER 37 C.F.R. § 42.104

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

Petitioner certifies that the '680 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR.

B. Challenge under 37 C.F.R. § 42.104(b); Relief Requested

Petitioner requests *inter partes* review of claims 1-4 on the ground set forth in the following table and requests that each claim be found unpatentable.

Ground	'680 Patent Claims	Basis for Unpatentability
Ground 1	**1-4**	Obvious under 35 U.S.C. § 103 in light of van de Putte 1999 (EX. 1004) in combination with Kempeni (EX. 1003)

V. BACKGROUND

Tumor necrosis factor α ("TNFα") is a cytokine that has been implicated in a number of autoimmune diseases, including RA. Kempeni (EX. 1003), p. 1; Salfeld (EX. 1008), 1:6-22; Baughman Decl'n (EX. 1006), ¶ 20. Prior to the effective filing date of the '680 patent, there were at least three types of recombinant proteins developed as potential therapeutics and known to bind specifically to human TNFα ("anti-TNFα proteins"). Kempeni (EX. 1003), p. 1.

The first type, exemplified by etanercept, is a dimeric fusion protein consisting of the extracellular ligand-binding portion of the human TNF receptor linked to the Fc portion of human IgG1 antibody. Kempeni (EX. 1003), p. 1. Etanercept was developed and is marketed by Amgen under the tradename "ENBREL®." FDA approved ENBREL® in 1998 for treating RA in a fixed dose via subcutaneous injection. Baughman Decl'n (EX. 1006), ¶ 23; EX. 1011.

The second type, exemplified by infliximab, is a chimeric (part mouse, part human) monoclonal antibody that specifically binds TNFα. Infliximab is marketed

by Janssen under the tradename "REMICADE®." Kempeni (EX. 1003), p. 1; Baughman Decl'n (EX. 1006), ¶ 24. REMICADE® consists of the variable region of a murine antibody coupled to the constant region of a human IgG1 antibody, resulting in a construct that is approximately two thirds human. Kempeni (EX. 1003), p. 1. FDA approved REMICADE® in 1999 for treating RA via intravenous infusion. Baughman Decl'n (EX. 1006), ¶ 24; EX. 1012.

The third type is a fully human anti-TNFα antibody. One advantage of fully human antibodies, relative to chimeric antibodies, is that because they have no non-human components, they are less likely to cause an immune response in a patient. Kempeni (EX. 1003), p. 1; Baughman Decl'n (EX. 1006), ¶ 27.

Salfeld (EX. 1008) describes recombinant fully human anti-TNFα antibodies that specifically bind to human TNFα. *Id.,* 2:50-52. According to Salfeld, the antibodies can be "full-length (e.g., an IgG1 or IgG4 antibody)," *id.,* 2:56-57, and preferably are a genus that Salfeld describes as "D2E7" (*id.,* 2:59-67):

> The most preferred recombinant antibody of the invention, termed D2E7, has a light chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 3 and a heavy chain CDR3 domain comprising the amino acid sequence of SEQ ID NO: 4. Preferably, the D2E7 antibody has a light chain variable region (LCVR) comprising the amino acid sequence of SEQ ID NO: 1 and a heavy chain variable region (HCVR) comprising the amino acid sequence of SEQ ID NO: 2.

In a table appearing at col. 36, Salfeld describes D2E7 antibodies as including a number of amino acid sequences. *Id.,* 36:1-35. These are the same amino acid sequences listed in the claims of the '680 patent. Salfeld teaches that D2E7 antibodies can be administered to patients "suffering from a disorder in which TNFα activity is detrimental," such as RA. *Id.,* 24:21-22 and 25:22-55. Salfeld further teaches that D2E7 antibodies can be administered intravenously or subcutaneously, and as a fixed dose (*i.e.* total body dose) "for ease of administration." *Id.,* 21:21-27 and 22:65 to 23:6.

A number of clinical studies beginning in the late 1990's investigated the use of D2E7 to treat RA. Baughman Decl'n (EX. 1006), ¶¶ 30-47. For example, van de Putte 1999 administered 20, 40, and 80 mg doses of D2E7 subcutaneously to RA patients on a weekly basis and concluded that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)." van de Putte 1999 (EX. 1004), p. 1. Others, summarized in Kempeni, investigated administering D2E7 intravenously on a biweekly basis over a range of dosages. *See, e.g.,* Kempeni (EX. 1003), p. 2. Kempeni also describes studies in which D2E7 was dosed alone or in combination with methotrexate. *Id.,* p. 2 (Table 2).

Prior to the effective filing date of the '680 patent, therefore, clinicians had already successfully used D2E7, a class of fully human anti-TNFα antibodies, in combination with methotrexate to treat RA.

VI. THE '680 PATENT AND ITS PROSECUTION HISTORY

A. The '680 Patent

The '680 patent is entitled "Methods of Administering Anti-TNFα Antibodies." It is a continuation of U.S.S.N. 10/163,657, which issued as U.S. Patent No. 8,889,135 ("the '135 patent"). The '680 patent contains four claims, each of which covers a method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis by subcutaneously administering 40 mg of a certain human anti-TNFα antibody in combination with methotrexate every 13-15 days. Claim 1 is representative and reads as follows (paragraph structure added for clarity):

> 1. A method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising:
>
> administering to said patient, in combination with methotrexate, a human anti-TNFα antibody,
>
> wherein the human anti-TNFα antibody is administered subcutaneously in a total body dose of 40 mg once every 13-15 days, and
>
> 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.

Claim 3 depends on claim 1, and states that the dosage is administered "from a 40 mg dosage unit form." The '680 patent defines a "dosage unit form" as follows (EX. 1001, 23:6-14):

> It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

Claim 2 also depends on claim 1, and claim 4 depends on claim 3. Each states that the V_L chain of the antibody has the amino acid sequence of SEQ ID NO:1 and V_H chain region of the antibody has the amino acid sequence of SEQ ID NO:2. According to the '680 patent specification, the "most preferred recombinant antibody of the invention" is D2E7, a genus described in the Salfeld patent (EX. 1008), which the '680 patent incorporates by reference. '680 patent (EX. 1001),

10:3-5. In particular, the amino acid sequences of the V_L and V_H chains set forth in claims 2 and 4 are the same as the amino acid sequences Salfeld ascribes to D2E7. *Compare* claims 2 and 4 *with* Salfeld (EX. 1008), 36:1-35 and SEQ ID NOS 1-8 of the '680 patent *with* SEQ ID NOS 1-8 of Salfeld (EX. 1008).

Example 2 of the '680 patent is entitled "Total Body Dose of a Subcutaneously Administered Anti-TNFα Antibody." '680 patent (EX. 1001), 28:60-61. This example describes a clinical study that is virtually identical to the Phase II clinical study described in van de Putte 1999. The '680 patent states the purpose of the study as determining "the ***optimal*** total body dose of subcutaneously administered D2E7." *Id.,* 28:66-67 (emphasis added). Patients were dosed weekly with 20, 40, or 80 mg D2E7, or placebo. *Id.,* 28:67 to 29:3.

Example 2 reports the ACR 20 response for each dosing protocol. *Id.*, 29:4-7 and FIG. 1A. The "ACR 20 response" is shorthand for the American Academy of Rheumatology improvement criteria. Baughman Decl'n (EX. 1006), ¶ 31. It is defined as follows:

> [T]o be classified as a responder according to ACR 20 criteria, patients must demonstrate (1) greater than or equal to 20% improvement in swollen joint count; (2) greater than or equal to 20% improvement in tender joint count; and (3) at least 20% improvement in three of five other measures (patient global assessment of disease activity, physician global assessment of disease activity, patient assessment of pain, an acute phase reactant (for example, erythrocyte

> sedimentation rate (ESR) or C reactive protein), and a measure of disability (for example, the Health Assessment Questionnaire).

Kempeni (EX. 1003), p. 2; Baughman Decl'n (EX. 1006), ¶ 32.

From the standpoint of a clinician treating RA patients, the ACR 20 is the accepted measure of clinical response because it represents a composite of all other test scores. Indeed, rheumatologists regard it as the "gold standard" with respect to efficacy for FDA approval of new RA medications. O'Dell Decl'n (EX. 1007), ¶ 28. Example 2 characterizes the ACR 20 responses, which are virtually identical to the results disclosed in van de Putte 1999, as follows ('680 patent, 29:11-12 and FIG. 1A):

> These data illustrate that subcutaneous D2E7, particularly at a dose of 40 mg/week, generates a good response.

In other words, Example 2 concludes that each of the doses tested (20, 40, and 80 mg) produced a clinically significant response relative to placebo, as measured by the ACR 20 score, and thus that all 3 doses treated RA. This statement in Example 2 is critical because it contradicts statements that AbbVie made to the Examiner during prosecution of the '135 parent patent in order to convince the Examiner to allow the claims.

B. The '680 Patent U.S. Prosecution History

The '680 patent is a continuation of U.S.S.N. 10/163,657, which issued as U.S. Patent No. 8,889,135 ("the '135 patent").

1. The '135 parent patent prosecution history

During prosecution of U.S.S.N. 10/163,657, the Examiner rejected the claims over van de Putte 1999 (EX. 1004) in combination with a number of secondary references, including Kempeni (EX. 1003), Rau #907 (EX. 1005), van de Putte 2000 (EX. 1024), and Weisman 2000 (EX. 1023). EX. 1002, pp. 1091-1106 and 1529-1549 (Office Actions mailed 6/10/13 and 4/21/14). In response, AbbVie attempted to distinguish van de Putte 1999's statement that "20, 40 and 80 mg/week [doses of D2E7] were nearly equally efficacious when given s.c. in patients with active RA." van de Putte 1999 (EX. 1004), p. 1.

With the aid of declarations from Drs. Pope, Mould, and Weinblatt, AbbVie made two arguments. EX. 1002, pp. 1138-1330 ((Office Action Response dated 2/7/14 (pp. 1260-1330); Pope Decl'n (pp. 1140-1171); Mould Decl'n (pp. 1200-1233); Weinblatt Decl'n (pp. 1172-1199)) and pp. 1562-1574 (Office Action Response dated 5/1/14). First, AbbVie argued that van de Putte 1999 was designed to compare only the efficacy of doses versus placebo, rather than to each other. *Id.,* p. 1305 (Office Action Response dated 2/7/14). Second, AbbVie argued that

despite van de Putte 1999's statement regarding the equal efficacy of the 3 doses, a person of ordinary skill would have recognized that the 20 mg dose was not as effective as either the 40 or 80 mg doses. *Id.* As noted above, however, AbbVie described virtually identical data in Example 2 of the '680 patent as demonstrating that all 3 doses generated a "good response." '680 patent (EX. 1001), 29:11-13.

The Examiner ultimately allowed the '135 patent claims. EX. 1002, pp. 1579-1587 (Notice of Allowance dated 7/8/14). After characterizing van de Putte 1999, van de Putte 2000, and Weisman 2000 as the references of "primary importance," the Examiner relied on testimony from Drs. Mould, Pope, and Weinblatt to conclude that, contrary to what van de Putte 1999 said about the results of his study, persons of ordinary skill would have recognized that the 20, 40, and 80 mg doses were not "equally effective." *Id.,* pp. 1584-1585. The Examiner credited their testimony that van de Putte 1999's study was not designed to compare the three doses to each other, but rather to compare each to placebo. *Id.,* p. 1585. However, after acknowledging that one could not draw comparisons among doses based upon van de Putte 1999's data, the Examiner then concluded, again based upon testimony from Drs. Mould, Pope, and Weinblatt, that a person of ordinary skill would have recognized that the 20 mg dose was "clearly inferior" to 40 or 80 mg doses (*id.;* emphasis in original):

> More particularly, applicant's argument that (i) one of ordinary skill in the art would have understood that Van de Putte is not drawing their conclusions based on a comparison *between* the dosing groups and that (ii) even knowing that between group comparisons have no validity, one of ordinary skill in the art would nonetheless interpret the data of Van de Putte to demonstrate that 20 mg D2E7 administered subcutaneously weekly is clearly inferior to the 40 or 80 mg D2E7 dose is found convincing.

The Examiner's conclusion is inherently contradictory. If it is not valid to compare the doses to each other, then it is not valid to draw conclusions regarding the relative efficacy of the three doses to each other. It also misses a critical point, which is that van de Putte 1999 indisputably teaches that ***all three doses were statistically significantly superior to placebo***, as measured by the ACR 20 responses. In other words, all three doses were effective in treating RA.

The Examiner also distinguished Weisman 2000 on the ground that one of ordinary skill would have recognized that Weisman 2000 taught "treatment with less than 1.0 mg/kg/biweek D2E7 + methotrexate to be insufficient for a substantial number of patients." *Id.* The Examiner reached this conclusion despite the fact that Weisman 2000 itself reports ACR 20 data for doses ranging from 0.25 mg/kg to 5.0 mg/kg, and states that all of these doses were "well-tolerated, safe,

and efficacious." Weisman 2000 (EX. 1024), p. 1. Finally, the Examiner credited AbbVie's evidence of commercial success. *Id.*

2. The '680 patent prosecution history

AbbVie filed the '680 patent as a continuation of the '135 patent on November 14, 2014. The Examiner did not issue any prior art-based rejections during prosecution. *See* EX. 1035, pp. 212-18, 372. AbbVie filed terminal disclaimers over the '135 patent and pending application 14/292,759 (now U.S. 9,073,987), and made minor amendments to address § 112-based issues. *Id.*, p. 354. The '680 patent issued on April 28, 2015, a mere four and a half months after its filing date.

The Examiner erred in allowing claims 1-4 of the '680 patent. For the reasons discussed in detail below, the Examiner's decision to credit the testimony of AbbVie's declarants submitted during the '135 parent patent's prosecution history, rather than what the references themselves teach, is based upon a critical misunderstanding of the ACR 20 responses reported in the references and their significance with respect to designing a dosing protocol for treating RA. The ACR 20 responses are the "gold standard" for clinicians when measuring treatment efficacy. When the ACR 20 responses reported in van de Putte 1999 are properly understood, it is evident that 20, 40, and 80 mg weekly doses of D2E7 all treated RA when measured relative to placebo.

VII. CLAIM CONSTRUCTION UNDER 37 C.F.R. § 42.104(B)(3)

Claims are interpreted using the "broadest reasonable construction in light of the specification of the patent in which [they] appear[]." 37 C.F.R. § 42.100(b); *see also In re Cuozzo Speed Techs., LLC*, No. 2014-1301, slip op. at 10–19 (Fed. Cir. 2015). Under the broadest reasonable construction standard, claim terms are given their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *In re Translogic Tech., Inc*., 504 F.3d 1249, 1257 (Fed. Cir. 2007).

Petitioner submits that except as set forth below, the terms in claims 1-4 should be given their plain meaning. To Petitioner's knowledge, no court has construed any term of the '680 patent.

A. "Method of reducing signs and symptoms"

Each of claims 1-4 recites, in the preamble, "a method of reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis." Based upon the ordinary meaning of the claim language, the broadest reasonable interpretation of the phrase "method of reducing signs and symptoms" does not require a particular level of efficacy. On the contrary, the claims merely require that the "signs and symptoms" the patient exhibits are reduced relative to their level prior to administration of the antibody plus methotrexate. Thus, for example, the claims do not require a level of efficacy required for regulatory approval.

B. "Every 13-15 days"

Claims 1-4 recite administering the human anti-TNFα antibody "once every 13-15 days." Under the broadest reasonable interpretation standard, a dosage regimen of every 13-15 days would encompass a dosing regimen of every 14 days, i.e., a biweekly dosing regimen.

C. "Dosage unit form"

Claim 3 recites administering the dosage "from a 40 mg dosage unit form." The '680 patent defines "dosage unit form" as follows (EX. 1001, 23:6-14):

> It is especially advantageous to formulate parenteral compositions in dosage unit form for ease of administration and uniformity of dosage. Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier.

Based upon this definition, a "40 mg dosage unit" form would encompass a syringe filled with 40 mg of D2E7.

VIII. THERE IS A REASONABLE LIKELIHOOD THAT AT LEAST ONE CLAIM OF THE '680 PATENT IS UNPATENTABLE

The question of obviousness requires analyzing (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of skill in the art; and (4) objective evidence of nonobviousness.

Graham v. John Deere Co., 383 U.S. 1, 17-18 (1966). "The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR Int'l Co. v. Teleflex, Inc.,* 550 U.S. 398, 416 (2007).

Claims covering a process are not patentable where "'the prior art would have suggested to one of ordinary skill in the art that this process should be carried out and would have a reasonable likelihood of success, viewed in light of the prior art.'" *Merck & Co., Inc. v. Biocraft Labs*, Inc., 874 F.2d 804, 809 (Fed. Cir. 1989), quoting *In re Dow Chemical*, 837 F.2d 469, 473 (Fed. Cir. 1988). Absolute predictability is not required. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[O]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success."). On the contrary, a claim can be unpatentable despite requiring some level of trial and error. *Biomarin Pharms. Inc. v. Genzyme Therapeutic Products Ltd. P'ship*, IPR2013-00534, Paper No. 81 (PTAB Feb. 23, 2015).

The *Biomarin* decision provides a useful framework for analyzing the obviousness of claims directed toward dosing protocols. The claims at issue in *Biomarin* covered a method of treating Pompe's disease by intravenously administering a therapeutically effective amount of human acid alpha glucosidase biweekly to a patient. *Id*. at 4. The only limitation in claim 1 not expressly

disclosed in the prior art was the biweekly administration limitation. *Id*. at 11. While recognizing that "a person of ordinary skill in the art could not have predicted with absolute certainty … a safe and effective dosing regimen," the Board concluded that "that the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [a prior art reference teaching use of the claimed enzyme to treat Pompe's disease], which would have been achievable through the use of standard clinical trial procedures." *Id*. at 12-14. "[T]he experimentation needed to achieve biweekly administration," the Board found, was "'nothing more than the routine' application of a well-known problem-solving strategy . . . 'the work of a skilled [artisan], not of an inventor.'" *Id*. at 14 (quoting *Pfizer*, 480 F.3d at 1368). And, furthermore, that 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." *Id*.

In *Boehringer Ingelheim Int'l Gmbh et al. v. Genentech, Inc.,* IPR2015-00417, Paper No. 11 (PTAB Jul. 14, 2015), the Board applied this analysis in the context of claims covering methods of treating rheumatoid arthritis. The claims at issue required treating a patient with an anti-CD20 antibody (e.g., rituximab) administered as two intravenous doses of 1000 mg. *Id.* at 4-5. The prior art disclosed dosing regimens involving four infusions of rituximab totaling 1500 mg or 2100 mg. *Id.* at 20-21. In deciding to grant the petition, the Board rejected the

patent owner's argument that even though there were only a finite number of number of possible treatment choices, there was no reasonable expectation that one of them would work (*id.* at 21-22) (emphasis added):

> [T]he prior art shows that a patient who had not responded to TNFα therapy achieved an ACR 20 response in month +5 after receiving 4 intravenous infusions per week of 375 mg/m^2 rituximab each. EX. 1006. The fact that a suggested dose of two intravenous doses of 1000 mg had not been established yet does not demand a conclusion of nonobviousness. ***All that is required to show obviousness is a reasonable expectation of success, not conclusive proof of efficac***y.

The Board further noted that the need to solve the problem of patient compliance provided a motivation to optimize the existing four infusion protocol by increasing the individual dosage while reducing the dosing frequency (*id.* at 22):

> The motivation to optimize the therapy disclosed in the combined references in order to improve patient compliance "flows from the 'normal desire of scientists or artisans to improve upon what is already known.'" *Pfizer*, 480 F.3d at 1348 (quoting *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003)).

The claims of the '680 patent cover a biweekly dosing regimen for administering 40 mg of a certain anti-TNFα antibody subcutaneously, in combination with methotrexate, to treat rheumatoid arthritis. For the reasons

discussed below, they are unpatentable over van de Putte 1999 (EX. 1004) in combination with Kempeni (EX. 1003). Just like the dosing claims in *Biomarin* and *Boehringer Ingelheim*, the selection of the dosing protocol set forth in the '680 patent claims merely represents no more than the "routine optimization" of the therapy outlined in the van de Putte 1999 and Kempeni references.

A. Scope and Content of the Prior Art

1. van de Putte 1999 (EX. 1004)

van de Putte 1999 qualifies as prior art under 35 U.S.C. § 102(b) because it published in November, 1999, and thus more than 1 year before the earliest filing date to which the '680 patent claims are entitled (June 8, 2001). van de Putte 1999 describes treating RA in patients by administering subcutaneous injections of D2E7 at 20, 40, and 80 mg doses once a week over the course of 3 months. van de Putte 1999, p. 1. van de Putte 1999 reports the percentage of patients achieving ACR 20 response, as well as the median improvement in tender joint count (TJC), swollen joint count (SWJC), and C reactive protein (CRP) for the 20, 40, and 80 mg doses versus placebo (*id.*):

	Placebo	D2E7	D2E7	D2E7
	(n=70)	20 mg (n=71)	40 mg (n=70)	80 mg (n=72)
% of pts achieving ACR 20 response	10	49	57	56
Median % improvement in TJC	5	57	61	55
Median % improvement in SWJC	16	42	59	61
Median % improvement in CRP	1	55	67	65

On the basis of these results, van de Putte 1999 concludes that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$). 20, 40, and 80 mg/week were nearly equally efficacious when given s.c. in patients with active RA." *Id.; see also* Baughman Decl'n (EX. 1006), ¶ 45; O'Dell Decl'n (EX. 1007), ¶¶ 26-27.

Of all the values reported by van de Putte 1999, the most important is the ACR 20 response because it represents a composite of all the other scores. O'Dell Decl'n (EX. 1007), ¶ 28. Thus, from the perspective of a clinician treating RA patients, it is the accepted measure of clinical response. *Id.*

A person of ordinary skill, reading van de Putte 1999's ACR 20 results, would recognize, consistent with van de Putte 1999's conclusion, that there was a statistically significant difference between each of the three doses and placebo (where only 10% of patients reported achieving an ACR 20 response). O'Dell Decl'n (EX. 1007), ¶ 30; Baughman Decl'n (EX. 1006), ¶ 59. In other words, a person of ordinary skill would recognize that each dose successfully treated RA.

To put these results in perspective, it is useful to compare them to the ACR 20 responses reported for REMICADE® (infliximab) at the time of its FDA approval for treating RA in 1999. Baughman Decl'n (EX. 1006), ¶¶ 60-61. In the pivotal RA trial for REMICADE®, 50-58% of patients dosed with infliximab either at 3 mg/kg or 10 mg/kg achieved an ACR 20 response, compared to 20.5% of patients dosed with placebo. *Id.,* ¶ 60; Ex. 1021, p. 20, tbl. 3.8. Based on these data, FDA concluded in October 1999 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. 1021, p. 26; Baughman Decl'n (EX. 1006), ¶ 60. Significantly, the percentage of patients at each D2E7 dose tested in van de Putte 1999's trials who achieved an ACR 20 response (49-57%) is similar to the percentage of patients who achieved an ACR 20 response in the infliximab pivotal clinical trial (50-58%). Baughman Decl'n (EX. 1006), ¶ 60.

Accordingly, a person of ordinary skill would conclude from van de Putte 1999 that 20, 40, and 80 mg doses of D2E7 administered once a week via subcutaneous injection could successfully treat RA (i.e. reduce the signs, symptoms, and/or progression of RA). O'Dell Decl'n (EX. 1007), ¶ 28; Baughman Decl'n (EX. 1006), ¶ 61.

2. Kempeni (EX. 1003)

Kempeni is a review article that describes the results from several early trials investigating the use of D2E7 to treat RA. Baughman Decl'n (EX. 1006), ¶¶ 38-44. It qualifies as prior art under 35 U.S.C. § 102(b) because it published in 1999, and thus more than 1 year before the earliest filing date to which the '680 patent claims could be entitled (June 8, 2001).

Kempeni notes that based upon data generated during one clinical trial, the estimated mean terminal half-life of D2E7 was 11.6 to 13.7 days. Kempeni (EX. 1003), p. 2. The half-life of a drug is the time required for the concentration of the drug to reach half of its original value. Baughman Decl'n (EX. 1006), ¶ 39. Pharmacokineticists frequently use half-life data to develop an appropriate dosing frequency and, in particular, to determine which dosing intervals would likely be efficacious. *Id.,* ¶ 66. In the case of D2E7, the estimated half-life of 11.6 to 13.7 days would have supported dosing less frequently than once a week because a substantial amount of the antibody would still be circulating in the blood one week after the initial injection. *Id.,* ¶ 68.

Kempeni describes another early clinical trial in which D2E7 was administered intravenously on a biweekly basis at doses ranging from 0.5 to 10 mg/kg for a total of 6 months (24 weeks). Kempeni, p. 2. Kempeni observes that "[t]reatment lasting several years is intended" and that the results "demonstrated

sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7." *Id.*

Kempeni also describes a third early clinical trial in which D2E7 was administered once a week via subcutaneous injection at a dose of 0.5 mg/kg over a period of 3 months (12 weeks). *Id.,* pp. 2-3. Kempeni states (*id.,* p. 3) (emphasis added):

> Based on preliminary data, plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration …. With the exception of mild and transient injection site reactions, adverse events occurred with the same frequency and distribution in the D2E7 and placebo groups. The investigators concluded 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***.

Kempeni further describes a fourth trial in which D2E7 was dosed intravenously or subcutaneously in combination with methotrexate. *Id.,* pp. 2-3 (Table 2). An ACR 20 response was seen in 67% of patients receiving D2E7 by subcutaneous injection and 72% of patients receiving D2E7 by intravenous injection. *Id.,* p. 3.

On the basis of these studies, Kempeni concludes that subcutaneous delivery of D2E7 is safe and effective whether administered alone or in combination with

methotrexate, paving the way for further studies aimed at optimizing treatment (*id.,* emphasis added):

> Collectively, these early data suggest that the fully human anti-TNF α antibody D2E7 is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections. ***Additional studies are underway to further define optimal use of this novel treatment.***

In summary, van de Putte 1999 and Kempeni teach the following regarding D2E7:

- Subcutaneous 20, 40, and 80 mg weekly doses are statistically superior to placebo for treating RA (van de Putte 1999);
- D2E7 has a half-life of 11.6-13.7 days (Kempeni);
- Biweekly dosing of D2E7 is efficacious (Kempeni);
- Subcutaneous and intravenous dosing of D2E7 are equally effective (Kempeni);
- D2E7 is safe and efficacious over a wide range of doses (Kempeni);
- D2E7 is safe and efficacious when administered in combination with methotrexate. (Kempeni).

B. Differences between the Claimed Subject Matter and the Prior Art

The only differences between van de Putte 1999 and the '680 claims are that (a) van de Putte 1999 describes dosing 40 mg of D2E7 weekly, rather than every 13-15 days (*i.e.* biweekly), as recited in the claims and (b) van de Putte 1999 does not describe administering D2E7 in combination with methotrexate. However, Kempeni teaches (1) the estimated mean terminal half-life of D2E7 was 11.6 to 13.7 days, (2) biweekly intravenous infusions of D2E7, and (3) administration of D2E7 with methotrexate. Kempeni, p. 2. Kempeni further notes that "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration." Kempeni, p. 3. Kempeni also states that "D2E7 is safe and effective as monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections." *Id*., p. 3.

The following table compares van de Putte 1999 and Kempeni to claim 1 of the '680 patent:

	Route of administration	**Amount D2E7**	**Frequency of administration**	**Drug Combination**
Claim 1 of '680 patent	**subcutaneous**	**40 mg**	**13-15 days**	**methotrexate**
Van de Putte 1999	**subcutaneous**	**40 mg**	Weekly	None
Kempeni 1999	intravenous	0.5 mg/kg (~40 mg in an 80 kg patient)	**Bi-weekly**	**methotrexate**

C. Level of Skill in the Art

A person of skill in the art would have the skill sets of both a physician treating RA patients and a pharmacokineticist with experience related to monoclonal antibodies. Baughman Decl'n (EX. 1006), ¶ 15; O'Dell Decl'n (EX. 1007), ¶ 12. The physician would have an MD and at least three years of experience treating RA patients, including with one or more of the then-available anti-TNFα biologic agents. *Id.* The pharmacokineticist would have a PhD in pharmacokinetics or a related field, and at least three years of experience working in industry or academia on pharmacokinetics/pharmacodynamics of biologic agents. *Id.*

This definition is consistent with the definition that AbbVie proposed during prosecution of the '135 parent patent. *See* EX. 1002, p. 1152 (Pope Decl'n, ¶ 15); p. 1184 (Weinblatt Decl'n, ¶ 14); and pp. 1207-1208 (Mould Decl'n, ¶¶ 17-18). It is also consistent with the definition that the Examiner applied. *See id.,* p. 1008 (Office Action mailed 8/3/11) (skilled artisan is "anyone qualified to administer a drug to a rheumatoid arthritis patient, e.g., a medical doctor, who has a well-informed, one-one-on [sic] relationship with a given rheumatoid arthritis patient that will be treated with the human anti-TNFα antibody") and p. 1546 (Office Action mailed 4/21/14) (recognizing that the art of pharmacokinetics is relevant to the claimed subject matter).

D. No Objective Evidence of Nonobviousness

Objective evidence of nonobviousness, even when available, cannot defeat a strong case of obviousness based upon the prior art references themselves. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1364-65 (Fed. Cir. 2012). Here, there is no credible objective evidence of nonobviousness. The fact that 40 mg of D2E7 administered biweekly via subcutaneous injection was safe and effective for treating RA was entirely expected based upon van de Putte 1999 and Kempeni. Although AbbVie submitted alleged evidence of unexpected results during prosecution, Petitioner agrees with the Examiner's rejection of this evidence

on grounds that it was not commensurate with the scope of the claims. EX. 1002, p. 1586 (Notice of Allowance) and pp. 1541-1545 (Office Action mailed 4/21/14).

The Examiner, in his reasons for allowance, credited AbbVie's evidence of commercial success related to sales of its HUMIRA® product. *Id.* However, sales volumes alone, unrelated to the claimed invention, do not prove commercial success. *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC,* 683 F.3d 1356, 1363 (Fed. Cir. 2012) (stating that "for commercial success to be probative evidence of nonobviousness, a nexus must be shown between the claimed invention and the evidence of commercial success."); *Tokai Corp. v. Easton Enterprises, Inc.,* 632 F.3d 1358, 1370 (Fed. Cir. 2011) (finding no nexus between commercial success and the claimed feature of the invention.) Here, HUMIRA®'s commercial success is not due to the dosing regimen claimed in the '680 patent. Reisetter Decl'n (EX. 1025), ¶ 9. Rather, it is due in part to the antibody itself, and in large part to AbbVie's marketing and sales strategies. *Id.*

AbbVie's marketing and contracting strategies have contributed to HUMIRA®'s commercial success. *Id.,* ¶ 14. The HUMIRA® marketing team was named 2014 Marketing Team of the Year by Medical Marketing & Media, earning praise for growing market share even though HUMIRA® was nearing "the end of its product lifecycle." *Id.*; EX. 1029. Moreover, in 2013, AbbVie spent $132.4 million on direct-to-consumer advertising for HUMIRA®, the fourth

highest amount among pharmaceutical brands. Reisetter Decl'n (EX. 1025), ¶ 14; EX. 1030.

AbbVie's success in contracting with insurance companies has contributed to HUMIRA®'s commercial success as well. Reisetter Decl'n (EX. 1025), ¶ 15. HUMIRA® is frequently on prescription benefit preferred drug lists. *Id.*; EX. 1031-33. Because drugs are given preferred status by contracting with insurance companies, a process that includes offering rebates, HUMIRA®'s consistently preferred status relative to other TNFα inhibitors reflects AbbVie's greater ability to contract with payers. *Id.,* ¶ 16.

During prosecution, AbbVie's declarants touted HUMIRA®'s ease of use as related to HUMIRA®'s commercial success. Even if true, the ease of use, to which AbbVie's declarants refer, was related to its subcutaneous injection syringe design, not the dosing regimen claimed in the '680 patent. *Id.* at ¶¶ 9 and 13; EX. 1026 (HUMIRA®'s syringe is "easier for arthritic hands to hold and use than traditional syringes").

Finally, AbbVie had other patents covering HUMIRA® that existed prior to the effective filing date of the '680 patent, e.g., the Salfeld patent (EX. 1008). "Where market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the claims], from evidence of commercial success, is weak." *Galderma Labs., L.P. v. Tolmar, Inc.,* 737 F.3d 731, 740 (Fed.

Cir. 2013); *see also Merck Co. Inc. v. Teva Pharm. USA Inc.,* 395 F.3d 1364, 1377 (Fed. Cir. 2005).

For at least these reasons, there is no credible objective evidence of nonobviousness.

E. Claims 1-4 Would Have Been Obvious over van de Putte 1999 in view of Kempeni

The claims of the '680 patent would have been obvious over van de Putte 1999 (EX. 1004) in view of Kempeni (EX. 1003). van de Putte 1999 describes treating RA by administering subcutaneous injections of D2E7 at 20 and 40 mg doses once a week over the course of 3 months, and that each dose was "statistically significantly superior to placebo." van de Putte 1999, p. 1. Based upon the known half-life of 11.6 to 13.7 days for D2E7 and clinical trials being conducted with biweekly dosing, as disclosed in Kempeni, a person of ordinary skill would have been motivated to dose 40 mg of D2E7 biweekly, via subcutaneous administration, and would have expected this dose to be safe and effective in treating RA. Baughman Decl'n (EX. 1006), ¶ 73; O'Dell Decl'n (EX. 1007), ¶ 33. Moreover, a person of ordinary skill would have known, based upon the clinical studies described in Kempeni, that D2E7 could be co-administered with methotrexate. *See* Kempeni (EX. 1003), pp. 2-3.

1. Fixed dose, subcutaneous administration had well-known advantages

van de Putte 1999's selection of fixed dose, subcutaneous administration reflects well-known advantages of this type of administration for treating chronic conditions such as RA. *See* Baughman Decl'n (EX. 1006), ¶ 53 (fixed dose, subcutaneous administration approved in 1998 for the anti-TNF α antibody, ENBREL®); Salfeld (EX. 1008), 22:65 to 23:1 ("it is especially advantageous to formulate parenteral compositions in dosage unit form [i.e. fixed dose form] for ease of administration and uniformity of dosage.").

Prior to the effective filing date of the '680 patent, persons of skill in the art recognized that subcutaneous injection was preferable to intravenous infusion for treating chronic conditions such as RA. *See, e.g.,* WO98/004281 (EX. 1022), p. 9 ("subcutaneous administration is more desirable for doctors and patients than intravenous administration"). For example, unlike intravenous infusions, patients can self-administer subcutaneous injections, thereby eliminating the need to go to a doctor's office for every treatment. *Id.* ("[subcutaneous] administration can be performed practically anywhere without catheterization"); Baughman Decl'n (EX. 1006), ¶ 51. Subcutaneous injections, therefore, are more convenient and less costly for the patient. *See* Baughman Decl'n (EX. 1006), ¶ 51.

van de Putte 1999's selection of a fixed dose likewise reflects well-known advantages of fixed dosing versus per-body weight dosing. For example, it is

easier for a patient to self-administer a fixed dose because it requires no patient action beyond injection. Baughman Decl'n (EX. 1006), ¶ 52. In contrast, per-body weight-based dosing requires the patient to prepare each injection (i.e., draw the correct volume of the composition into a syringe from an ampule) before administration, a time-consuming process that is prone to error and difficult for RA patients, who have tender and swollen joints, to carry out. *Id.* Per-body weight-based dosing is also more costly and wasteful than fixed dosing because once a patient removes the needed dose from the ampule, the remaining contents of the ampule must be discarded. *Id.* During prosecution of the '135 parent patent, the Examiner agreed and rejected AbbVie's arguments that persons of ordinary skill would not have turned to fixed dosing. EX. 1002, p. 1546 (Office Action dated 4/21/14).

2. <u>van de Putte 1999 taught that 20, 40, and 80 mg weekly doses of D2E7 could treat RA</u>

van de Putte 1999 reports the percentage of patients achieving ACR 20 response, as well as the median improvement in tender joint count (TJC), swollen joint count (SWJC), and C reactive protein (CRP) for the 20, 40, and 80 mg doses versus placebo. van de Putte 1999, p. 1. On the basis of these results, van de Putte concludes that "[f]or all efficacy parameters studied, all doses of D2E7 were statistically significantly superior to placebo ($p < 0.001$)." *Id.* The percentage of patients achieving ACR 20 for all three doses (49-57%) is similar to the percentage

of patients who achieved an ACR 20 response in the clinical trial involving use of REMICADE® to treat RA. Baughman Decl'n (EX. 1006), ¶ 60.

The '680 patent includes a study virtually identical to van de Putte 1999's study as Example 2. '680 patent (EX. 1001), 28:57 to 29:13. The '680 patent states that "[t]hese data illustrate that subcutaneous D2E7, particularly at a dose of 40 mg/week, generates a good response." *Id.,* 29:12-13. In other words, the '680 patent concludes that each of the doses tested (20, 40, and 80 mg) produced a clinically significant response relative to placebo, as measured by the ACR 20 score.

A person of ordinary skill, reading van de Putte 1999, therefore, would have known that 20, 40, and 80 mg weekly subcutaneous doses of D2E7 could treat RA (i.e. reduce the signs, symptoms, and/or progression of RA). Baughman Decl'n (EX. 1006), ¶ 58; O'Dell Decl'n (EX. 1007), ¶¶ 25-33.

3. Biweekly dosing was a logical choice based on D2E7's reported half-life of 11.6 to 13.7 days

Based upon the 11.6 to 13.7 day half-life of D2E7 reported in Kempeni, a person of ordinary skill in the art would have been motivated to modify van de Putte 1999's dosing protocol to administer subcutaneous doses biweekly, rather than weekly. Baughman Decl'n (EX. 1006), ¶¶ 48, 56-57, 63-68; O'Dell Decl'n, ¶ 32. Pharmacokineticists frequently use half-life data to develop an appropriate dosing frequency and, in particular, to determine which dosing intervals would

likely be efficacious. Baughman Decl'n (EX. 1006), ¶ 66. In the case of D2E7, the estimated half-life of 11.6 to 13.7 days reported in Kempeni would have suggested dosing less frequently than once a week because a substantial amount of the antibody would still be circulating in the blood one week after the initial injection. *Id.,* ¶ 67.

Kempeni (EX. 1003) also described studies investigating biweekly dosing of D2E7, proving not only that persons of ordinary skill ***would*** have tried biweekly dosing but ***did*** in fact try it and demonstrated that it was a viable treatment protocol. *Id.,* ¶ 72. Kempeni reported biweekly intravenous dosing of D2E7 and noted that this regimen "demonstrated sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7." Kempeni (EX. 1003), p. 2.

During prosecution, the Examiner agreed that a person of ordinary skill would have been motivated to pursue biweekly dosing of D2E7. EX. 1002, pp. 1548-1549 (Office Action dated 4/21/14). By reducing the frequency of injections required, biweekly dosing offered the recognized advantage of optimizing patient convenience, increasing patient compliance, and limiting pain and side effects such as injection site inflammation. Baughman Decl'n (EX. 1006), ¶ 64. O'Dell Decl'n (EX. 1007), ¶ 43. Biweekly dosing, therefore, was a logical choice.

4. A person of ordinary skill would have chosen 40 mg as the biweekly dosage

The logical dosage choice for treating RA with subcutaneous biweekly injections of D2E7 would have been 40 mg. Baughman Decl'n, ¶¶ 69-71; O'Dell Decl'n, ¶ 32. A central principle of drug development is the desirability of administering the lowest effective drug dose. The goal is to treat the patient with as little drug as possible in order to reduce potential side effects, while at the same time attaining a therapeutic response. Baughman Decl'n, ¶ 69. Here, based upon available data, a person of ordinary skill would have recognized that 40 mg biweekly represented the lowest effective dosage. *Id.*

van de Putte 1999 taught that 20, 40, and 80 mg doses of D2E7, when administered once a week via subcutaneous injection, "were statistically significantly superior to placebo," based upon ACR 20 responses achieved with each dose. van de Putte 1999 (EX. 1004), p. 1. Example 2 of the '680 patent likewise characterized ACR 20 results virtually identical to van de Putte 1999's results as generating a "good response." '680 patent (EX. 1001), 29:12-13. Based upon the half-life data disclosed in Kempeni (EX. 1003), a person of ordinary skill reading van de Putte 1999 would have recognized that one week after administration of a 40 mg dose of D2E7, the amount circulating in the patient's blood would have been at least 30 mg, which is greater than the 20 mg dose that van de Putte 1999 already taught was efficacious relative to placebo when

administered on a weekly basis. Baughman Decl'n (EX. 1006), ¶ 68. With respect to the 20 mg dose, van de Putte 1999 discloses that it resulted in 49% of patients achieving an ACR 20 response. Importantly, this was a response rate high enough to result in FDA approval of REMICADE® and a statistically significant difference relative to placebo. *Id.*

van de Putte 1999's ACR 20 data also suggests that even 20 mg administered biweekly could treat RA. *Id.* However, persons of ordinary skill would have reasonably expected 40 mg to be effective and would have selected it as the most conservative choice for biweekly subcutaneous administration. *Id.* Moreover, in view of Kempeni's teaching that D2E7 could be administered safely over a broad range of dosages, a person of ordinary skill likewise would have reasonably expected biweekly dosing of 40 mg to be safe. *See* Kempeni (EX. 1003), p. 2; Baughman Decl'n (EX. 1006), ¶ 57.

5. Combining D2E7 with methotrexate was a logical choice

Prior to the effective filing date of the '680 patent, it was known to co-administer anti-TNFα antibodies such as ENBREL® and REMICADE® with methotrexate. EX. 1011 (ENBREL® label); EX. 1012 (REMICADE® label); O'Dell Decl'n (EX. 1007), ¶¶ 18-19. Indeed, during appeal proceedings related to an opposition concerning a third party European patent (EX. 1036) covering the

combination of anti-TNFα antibodies with methotrexate, AbbVie stated (EX. 1037):

> [T]here can be absolutely no doubt that by the priority date of the [EP] patent [August 1, 1996], the combined use of anti-TNF antibodies with methotrexate for the treatment of rheumatoid arthritis had already been taught within the state of the art."

Even more significantly, prior to the effective filing date of the '680 patent, Kempeni disclosed treating patients with D2E7 both with and without methotrexate. Kempeni (EX. 1003), pp. 2-3. Kempeni concluded that "D2E7 is safe and effective as monotherapy or in combination with methotrexate." *Id.,* p. 3; O'Dell Decl'n (EX. 1007), ¶ 24. Therefore, a person of ordinary skill would have been motivated to combine methotrexate, a well-known therapeutic agent, with D2E7 with every expectation that the combination would effectively treat RA, as measured by ACR 20 score. O'Dell Decl'n (EX. 1007), ¶ 33.

The '680 claims represent, at best, routine optimization of RA treatments using D2E7 already disclosed in the prior art. Accordingly, they are unpatentable as obvious. *See Biomarin,* Paper No. 81, pp. 12-14 (dosing protocol claims not patentable where they represented "a routine optimization of the therapy outlined in [the prior art], which would have been achievable through the use of standard clinical trial procedures.").

The following claim charts compare claims 1-4 with van de Putte 1999 and Kempeni.

The '680 Patent Claims	**van de Putte 1999 (EX. 1004), Kempeni (EX. 1003)**
1. A method for reducing signs and symptoms in a patient with moderately to severely active rheumatoid arthritis, comprising:	van de Putte 1999 discloses treating patients with "long standing active" RA. Kempeni discloses studies in which D2E7 was administered to "patients with an established diagnosis of RA who also had active disease, as evidenced by having a combination of swollen and tender joints, increased concentrations of acute phase reactants, and prolonged early morning stiffness. In addition, all trials involved RA patients with long disease duration and a history of failure of several DMARDs." Kempeni, p. 1.
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administering to said patient, in combination with methotrexate, a human anti-TNFα antibody,	Kempeni discloses studies in which D2E7 was administered alone or in combination with methotrexate. Kempeni, p. 2 (Table 2). Kempeni further discloses that D2E7 is safe and effective when administered as monotherapy or in combination with methotrexate. Kempeni, p. 3.
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wherein the anti-TNFα antibody is administered subcutaneously in a total body dose of 40 mg	van de Putte 1999 discloses administration of an anti-TNFα antibody (D2E7) at 20, 40, and 80 mg doses.
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once every 13-15 days, and	van de Putte 1999 reports that efficacy for all three of the weekly doses (20 mg, 40 mg, and 80 mg) was statistically

	superior to placebo. Kempeni reports an 11.6 to 13.7 day half-life of D2E7, and biweekly intravenous dosing of D2E7, noting that the biweekly regimen "demonstrated sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7." Kempeni, p. 2.
---------- 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.	--------- This is a description of D2E7 antibodies, which the '680 patent states are the preferred anti-TNFα antibodies. '680 patent, 3:32-42; Salfeld (EX. 1008), 2:56-57 and 36:1-35. *Compare* SEQ ID Nos: 3-8 of the '680 patent *with* SEQ ID Nos: 3-8 of Salfeld.
2. The method of claim 1, wherein the VL chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:1 and the VH chain region of the anti-TNFα antibody has the amino acid sequence of SEQ ID NO:2.	This is a description of D2E7 antibodies, which the '680 patent states are the preferred anti-TNFα antibodies. '680 patent, 3:32-42; Salfeld (EX. 1008), 2:56-57 and 36:1-35. *Compare* SEQ ID Nos: 1-2 of the '680 patent *with* SEQ ID Nos: 1-2 of Salfeld.
3. The method of claim 1, wherein the dosage is administered from a 40 mg dosage unit form.	van de Putte 1999 describes administering D2E7 via subcutaneous "self injection." van de Putte 1999, p. 1.
4. The method of claim 3, wherein the V_L chain region of the anti-TNFα	This is a description of D2E7 antibodies, which the '680 patent states

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.	are the preferred anti-TNFα antibodies. '680 patent, 3:32-42; Salfeld (EX. 1008), 2:56-57 and 36:1-35. *Compare* SEQ ID Nos: 1-2 of the '680 patent *with* SEQ ID Nos: 1-2 of Salfeld.

6. Nothing in the prior art counseled against a 40 mg biweekly dosage in combination with methotrexate

During prosecution of the '135 parent patent, the Examiner, relying on testimony from AbbVie's declarants, concluded that a person of ordinary skill, reading van de Putte 1999's results, would recognize that a weekly 20 mg dose of D2E7 was less effective in treating RA than either a weekly 40 mg or weekly 80 mg dose. EX. 1002, pp. 1584-1586 ('135 Patent Notice of Allowance). From this, the Examiner agreed with AbbVie that a person of ordinary skill would not have tried 40 mg biweekly dosing. *Id.* This conclusion was incorrect for a number of reasons.

First, as even the Examiner acknowledged, van de Putte 1999's study was not designed to compare the three doses to each other, but rather to compare each to placebo. *See id.,* p. 1585. Thus, there is no basis for conclusions regarding the relative merits of the 20, 40, and 80 mg doses tested. *See* Baughman Decl'n (EX. 1006), ¶ 61 (beyond van de Putte 1999's general conclusion, the data "are not useful in comparing each dose to one another, as no statistics are presented comparing the three dosing groups. Thus, no conclusion can be made about the

superiority or inferiority (statistically) of the 20, 40 or 80 mg dose groups based on the data reported in van de Putte 1999.").

Second, and more importantly, it is based on a misunderstanding of the significance of the ACR 20 data that van de Putte 1999 reports. As noted above, the ACR 20 response is the data on which a clinician would rely to determine whether a particular RA treatment was effective. O'Dell Decl'n (EX. 2007), ¶ 28. van de Putte 1999 clearly teaches that each dose performed statistically significantly better than placebo based upon the ACR 20 results. *Id.,* ¶¶ 35-37; Baughman Decl'n (EX. 2006), ¶¶ 58-59. In particular, the data show that 49% of patients receiving the 20 mg dose, 57% of patients receiving the 40 mg dose, and 56% of patients receiving the 80 mg dose of D2E7 achieved an ACR 20 response. This is in contrast to just 10% of patients receiving placebo. Baughman Decl'n (EX. 1006), ¶ 59.

van de Putte 1999's ACR 20 data are comparable to ACR 20 data associated with REMICADE®, which FDA approved for treating RA. A pivotal clinical trial for REMICADE® resulted in 50-58% of patients achieving an ACR 20 response, compared to 20.5% of patients dosed with placebo. *Id.,* ¶ 60.

The REMICADE® results provide a useful baseline for determining whether a protocol successfully treats RA. *Id.,* ¶ 61. Based on the percentage of ACR 20 responses achieved by REMICADE® and the comparable percentage of ACR 20

responses for the 20, 40 and 80 mg D2E7 dosing groups reported by van de Putte 1999, a person of ordinary skill would have regarded all dose levels for D2E7 as reducing the signs, symptoms and/or progression of RA. *Id.,* O'Dell Decl'n (EX. 1007), ¶¶ 35-37. This is consistent with both van de Putte 1999's conclusion that the three doses of D2E7 were "statistically significantly superior to placebo ($p < 0.001$)" for treating RA, and the '680 patent's characterization of the 3 doses as each achieving a "good response."

A person of ordinary skill, reading van de Putte 1999's data, would have agreed with van de Putte 1999's characterization of the results. Based upon the known half-life of 11.6 to 13.7 days for D2E7 and clinical trials being conducted with biweekly dosing, as disclosed in Kempeni, a person of ordinary skill would have been motivated to dose 40 mg of D2E7 biweekly, via subcutaneous administration, in combination with methotrexate and would have expected this dose to be safe and effective in treating RA. Baughman Decl'n (EX. 1006), ¶ 73; O'Dell Decl'n (EX. 1007), ¶ 37. Claims 1-4, therefore, would have been obvious.

IX. CONCLUSION

This petition identifies relevant prior art references and provides a detailed analysis demonstrating why each claim of the '680 patent is unpatentable as obvious. Accordingly, Petitioner respectfully requests institution of an IPR for claims 1-4 of the '680 patent on the grounds presented herein, and cancelation of claims 1-4.

Respectfully submitted,

Dated: December 7, 2015

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CERTIFICATE OF SERVICE

Pursuant to 37 CFR §§ 42.6(e)(4) and 42.205(b), the undersigned certifies that on December 7, 2015, a complete and entire copy of Petitioner Coherus BioSciences Inc.'s Petition for Inter Partes Review of U.S. Patent No. 9,017,680 with supporting exhibits were provided via express mail, costs prepaid, to the Patent Owner by serving the correspondence address of record as follows:

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