UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner

v.

ABBVIE BIOTECHNOLOGY LTD.,
Patent Owner

U.S. Patent No.: 9,512,216
Issue Date: December 6, 2016
Title: Use of TNFα Inhibitor

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,512,216 PURSUANT TO 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42

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1002	Declaration of Simon M. Helfgott, M.D.	"Helfgott Decl."
1003	THERAPY OF MODERATE-TO-SEVERE-PSORIASIS (Gerald D. Weinstein & Alice B. Gottlieb eds., 2nd ed. Mar. 19, 2003)	"Weinstein"
1004	Letter from Jay P. Siegel, Center for Biologics Evaluation and Research, to Abbott Laboratories, Approval Letter(s) Application Number 125057/0 (Dec. 31, 2002)	"HUMIRA® approval letter"
1005	WOLFGANG A. RITSCHEL & GREGORY L. KEARNS, HANDBOOK OF BASIC PHARMACOKINETICS . . . INCLUDING CLINICAL APPLICATIONS (5th ed. 1999)	"Ritschel & Kearns"
1006	Enbrel® (etanercept) Package Insert (Immunex Corp. issued Jan. 2002)	"Enbrel® 2002 Package Insert"
1007	B. A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM (1999) (ACR Abstract Concurrent Session, RA: TNF-Blockade, Wednesday, Nov. 17, 1999 S400)	"van de Putte"
1008	TEXTBOOK OF PSORIASIS (Paul D. Mier & Peter C. M. van de Kerkhof eds., 1986)	"Mier"
1009	P. J. Mease, *Tumour Necrosis Factor (TNF) in Psoriatic Arthritis: Pathophysiology and Treatment with TNF Inhibitors*, 61 ANNALS RHEUMATIC DISEASES 298 (2002)	"Mease 2002"
1010	Marjorie Ridley & Margaret Safranek, *Common Skin Conditions*, 58 *OCCASIONAL PAPER ROYAL C. GEN. PRACTITIONERS* 50 (1992)	"Ridley"

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1011	Alan J. Lewis & Anthony M. Manning, *New Targets for Anti-Inflammatory Drugs*, 3 CURRENT OPINION CHEMICAL BIOLOGY 489 (1999)	"Lewis"
1012	Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug That Toppled Lipitor as No. 1*, XCONOMY (Apr. 16, 2012), *available at* http://www.xconomy.com/national/2012/04/16/abbotts-humira-the-3rd-in-class-drug-that-toppled-lipitor-as-no-1/#	"Timmerman"
1013	P. Ettehadi et al., *Elevated Tumour Necrosis Factor-Alpha (TNF-α) Biological Activity in Psoriatic Skin Lesions*, 96 CLINICAL & EXPERIMENTAL IMMUNOLOGY 146 (1994)	"Ettehadi"
1014	George Spencer-Green, *Etanercept (Enbrel): Update on Therapeutic Use*, 59 ANNALS RHEUMATIC DISEASES i46 (2000)	"Spencer-Green"
1015	Petra D. Cravens & Peter E. Lipsky, *Dendritic Cells, Chemokine Receptors and Autoimmune Inflammatory Diseases*, 80 IMMUNOLOGY & CELL BIOLOGY 497 (2002)	"Cravens"
1016	D. E. Furst et al., *Building Towards A Consensus for the Use of Tumour Necrosis Factor Blocking Agents*, 58 ANNALS RHEUMATIC DISEASES 725 (1999)	"Furst"
1017	Philip J. Mease et al., *Etanercept in the Treatment of Psoriatic Arthritis and Psoriasis: A Randomised Trial*, 356 LANCET 385 (2000)	"Mease 2000"
1018	P. J. Mease, *Cytokine Blockers in Psoriatic Arthritis*, 60 ANNALS RHEUMATIC DISEASES iii37 (2001)	"Mease 2001"
1019	Joachim R. Kalden, *Emerging Role of Anti-Tumor Necrosis Factor Therapy in Rheumatic Diseases*, 4 ARTHRITIS RES. S34 (2002)	"Kalden"
1020	B. Everts et al., *Morphine Use and Pharmacokinetics in Patients with Chest Pain*	"Everts"

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1021	WO 99/65867, filed June 17, 1999, published Dec. 23, 1999	"WO '867"
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1026	Humira™ (adalimumab) Package Insert (Abbott Laboratories issued Dec. 20, 2002)	"Humira® 2002 Package Insert"
1027	Remicade® (infliximab) Package Insert (Centocor, Inc. revised June 2002)	"Remicade® 2002 Package Insert"
1028	Hanns-Martin Lorenz & Joachim R. Kalden, *Perspectives for TNF-α-Targeting Therapies*, 4 ARTHRITIS RES. S17 (2002)	"Lorenz"
1029	Claudia Dechant et al., *One Year Outcome of Patients with Severe Psoriatic Arthritis Treated with Infliximab*, 43 ARTHRITIS & RHEUMATISM [212] (2000)	"Dechant"
1030	K. Eberhardt & E. Fex, *Clinical Course and Remission Rate in Patients with Early Rheumatoid Arthritis: Relationship to Outcome After 5 Years*, 37 BRIT. J. RHEUMATOLOGY 1324 (1998)	"Eberhardt"
1031	HARRY L. ARNOLD ET AL., ANDREWS' DISEASES	"Diseases of

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1032	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172 (Patent Owner's Response, Paper No. 37, Sept. 13, 2016)	"Patent Owner's Response in '135 IPR"
1033	A. L. J. Ogilvie et al., *Treatment of Psoriatic Arthritis with Antitumour Necrosis Factor-α Antibody Clears Skin Lesions of Psoriasis Resistant to Treatment with Methotrexate*, 144 BRIT. J. DERMATOLOGY 587 (2001)	"Ogilvie"
1034	Humira® (adalimumab) Package Insert (AbbVie Inc. revised April 2017), 2017 Physician's Desk Reference	"2017 Humira® Package Insert"
1035	2001 Physician's Desk Reference (55th ed. published Nov. 2000[1]) excerpts	"2001 PDR"
1036	U. Chaudhari et al., *Efficacy and Safety of Infliximab Monotherapy for Plaque-Type Psoriasis: A Randomised Trial*, 357 LANCET 1842 (2001)	"Chaudhari"
1037	Filip Van den Bosch et al., *Effects of a Loading Dose Regimen of Three Infusions of Chimeric Monoclonal Antibody to Tumour Necrosis Factor α (Infliximab) in Spondyloarthropathy: An Open Pilot Study*, 59 ANNALS RHEUMATIC DISEASES 428 (2000)	"Van den Bosch"
1038	U.S. Environmental Protection Agency, Office of Research and Development, EXPOSURE FACTORS HANDBOOK (Aug. 1997)	"EPA Handbook"
1039	WO 98/05357, filed Aug. 1, 1997, published Feb. 12, 1998	"Feldmann"
1040	Douglas J. Perkins et al., *Reduction of NOS2*	"Perkins"

[1] According to Amazon the 2001 PDR was published in November 2000. *See* https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752.

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	Overexpression in Rheumatoid Arthritis Patients Treated with Anti-Tumor Necrosis Factor α Monoclonal Antibody (cA2), 41 ARTHRITIS & RHEUMATISM 2205 (1998)	
1041	Chaity Chaudhury et al., *The Major Histocompatibility Complex-Related Fc Receptor for IgG (FcRn) Binds Albumin and Prolongs Its Lifespan*, 197 J. EXPERIMENTAL MED. 315 (Feb. 2003)	"Chaudhury"
1042	Frank M. Balis et al., *Pharmacokinetics of Subcutaneous Methotrexate*, 6 J. CLINICAL ONCOLOGY 1882 (1988)	"Balis"
1043	Roelien H. Enting et al., *A Prospective Study Evaluating the Response of Patients with Unrelieved Cancer Pain to Parenteral Opioids*, 94 CANCER 3049 (2002)	"Enting"
1044	Application No. 11/104,117, Declaration of Diane R. Mould (dated Mar. 17, 2014)	"Mould Decl."
1045	Application No. 11/104,117, Declaration of John Collett (dated Mar. 17, 2014)	"Collett Decl."
1046	Alfons den Broeder et al., *A Single Dose, Placebo Controlled Study of the Fully Human Anti-Tumor Necrosis Factor-α Antibody Adalimumab (D2E7) in Patients with Rheumatoid Arthritis*, 29 J. RHEUMATOLOGY 2288 (2002)	"den Broeder"
1047	Center for Drug Evaluation and Research, Medical Review(s) for Application No. sBLA 125057/110 (Mar. 2007)	"FDA Medical Doc"
1048	Enbrel® (etanercept) Package Insert (Immunex Corp. revised November 2016), 2016 Physician's Desk Reference	"Enbrel® 2016 Package Insert"
1049	Center for Drug Evaluation and Research, Clinical Pharmacology and Biopharmaceutics Review(s) for Application No. sBLA	"FDA Pharmacology Doc."

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1051	PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN (M. E. Aulton ed., 2nd ed. 2002)	"Aulton"
1052	Press Release, Abbott Laboratories, Abbott Laboratories Initiates Clinical Trials to Explore Use of Humira(™) (Adalimumab) in Psoriasis and Psoriatic Arthritis (Mar. 3, 2003), *available at* https://web.archive.org/web/20030701072200/https:/www.immunetolerance.org/artman/publish/article_148.html	"AbbVie Press Release"
1053	Madhulika A. Gupta & Aditya K. Gupta, *Age and Gender Differences in the Impact of Psoriasis on Quality of Life*, 34 INT'L J. DERMATOLOGY 700 (1995)	"Gupta"
1054	DEREK WALLER & ANDREW RENWICK, PRINCIPALS OF MEDICAL PHARMACOLOGY (1994)	"Waller"
1055	M. Schattenkirchner et al. *Long-Term Use of the Fully Human Anti-TNF Antibody D2E7 in Combination with Methotrexate in Active Rheumatoid Arthritis*, 43 ARTHRITIS & RHEUMATISM. S228 [968] (2000)	"Schattenkirchener"
1056	GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Joel G. Hardman & Lee E. Limbird eds., 10th ed. 2001)	"Goodman & Gilman's"
1057	United States Patent No. 8,889,136, filed April 11, 2005, issued Nov. 18, 2014	"'136 patent"
1058	*TNF-Alpha Inhibitor Projected to Offer Huge Market by 2010*, JAPAN CHEMICAL WEEK (Sept. 2001)	"Japan Chemical Week"
1059	Humira® (adalimumab) Package Insert (Abbott Laboratories July 30, 2004)	"Humira® 2004

Exhibit No.	Description	Referred To In The Petition As
		Package Insert"
1060	H. Marzo-Ortega et al., *Infliximab is Effective in the Treatment of Resistant Psoriatic Arthritis and Skin Psoriasis: A Clinical and MRI Study*, 41 RHEUMATOLOGY [OP11] (2002)	"Marzo-Ortega"
1061	U. Wollina & H. Konrad, *Treatment of Recalcitrant Psoriatic Arthritis with Anti-Tumor Necrosis Factor-α Antibody*, 16 EURO. ACAD. DERMATOLOGY &VENEREOLOGY 127 (2002)	"Wollina"
1062	Joachim Kempeni, *Update on D2E7: A Fully Human Anti-Tumour Necrosis Factor α Monoclonal Antibody*, 59 ANNALS RHEUMATIC DISEASES i44 (2000)	"Kempeni"
1063	SN 11/104,117, Applicant Amendment and Response to December 16, 2013 Non-Final Office Action and accompanying Declarations (Mar. 18, 2014)	"Applicant Amendment and Response"
1064	Ronald D. Schoenwald, Basic Principles, *in* PHARMACOKINETICS IN DRUG DISCOVERY AND DEVELOPMENT (Ronald D. Schoenwald ed., 2002)	"Schoenwald"
1065	United States Copyright Office, Public Catalog Record *for* THERAPY OF MODERATE-TO-SEVERE-PSORIASIS (Gerald D. Weinstein & Alice B. Gottlieb eds., 2nd ed., *available at,* http://cocatalog.loc.gov/cgi-bin/Pwebrecon.cgi?v1=1&ti=1,1&Search_Arg=therapy%20of%20moderate-to-severe%20psoriasis&Search_Code=TALL&CNT=25&PID=0J1PXsO32tjweyYIbh-mYPU3kOT2zkE&SEQ=20170705164824&SID=1	"Weinstein Copyright"
1066	US National Library of Medicine, National Institutes of Health, Website Printout of	"Ridley Copyright"

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1067	ResearchGate Website for H. Marzo-Ortega et al., *Infliximab is Effective in the Treatment of Resistant Psoriatic Arthritis and Skin Psoriasis: A Clinical and MRI Study*, 41 RHEUMATOLOGY [OP11] (2002), *available at* https://www.researchgate.net/publication/295374875_INFLIXIMAB_IS_EFFECTIVE_IN_THE_TREATMENT_OF_RESISTANT_PSORIATIC_ARTHRITIS_AND_SKIN_PSORIASIS_A_CLINICAL_AND_MRI_STUDY	"Marzo-Ortega Copyright"
1068	Declaration of Victoria Reines	"Reines Decl."

I. INTRODUCTION

U.S. Patent No. 9,512,216 (the "'216 patent," ex. 1001) claims a subcutaneously administered dosing regimen for the anti-TNF-α antibody adalimumab, the active ingredient in AbbVie's Humira® product, to treat moderate to severe chronic plaque psoriasis ("PsO"). The patient is administered an initial dose of 80 mg, followed by 40 mg every other week ("eow") starting one week after the initial 80 mg dose, wherein the treated patient achieves a Psoriasis Area and Severity Index ("PASI") 75 response after 12 weeks of treatment. The '216 patent explains that the 40 mg eow dose is a "treatment" dose and the initial, one-time 80 mg dose is an "induction" dose.

The prior art rendered the claimed PsO dosing regimen obvious to a person of ordinary skill in the art ("POSA"). It taught all of these elements and provided the motivation to combine them with a reasonable expectation of success.

First, the PsO treatment dose of 40 mg adalimumab subcutaneously administered eow was obvious because the prior art taught that (i) the FDA had already approved this exact same dosing regimen to treat rheumatoid arthritis ("RA"); (ii) adalimumab would be useful in treating PsO, and (iii) RA and PsO are closely related conditions, mediated by TNF-α, that could be treated with the same drugs using the same dosing regimens.

Second, it was obvious to administer an 80 mg induction dose of adalimumab one week before beginning the PsO adalimumab treatment dose because a POSA would have known that (i) an induction dose would provide more rapid relief to patients suffering severe physical and psychological symptoms associated with diseases like PsO; (ii) the first-in-class TNF-α inhibitor infliximab was administered with an induction dose to treat PsO; (iii) an appropriate induction dose for a drug like adalimumab, which has linear (*i.e.*, "first order") pharmacokinetics and is dosed approximately on its two-week half-life, would be double the 40 mg treatment dose; (iv) 80 mg was shown to be effective in treating RA when dosed weekly;(v) an interval of one week instead of two weeks between administering an induction dose and beginning treatment dosing would have achieved the goal of more rapid relief; and (v) it would be most convenient to use an induction dose (such as 80 mg) that was a multiple of AbbVie's already approved 40 mg pre-filled syringe.

Given the clear teachings of the prior art, the claimed induction dosing regimen was one of a finite number of obvious options that a POSA would have considered.

Under well-established Federal Circuit authority, the recited PASI 75 response score is not entitled to patentable weight since it simply expresses an intended result of the claimed method. Even if the recited PASI 75 response score

is considered a claim limitation, the ’216 patent specification makes plain that it is simply a natural result for a certain percentage of patients from receiving adalimumab according to an obvious dosing regimen.

As explained below, a POSA would have been motivated by the prior art to treat PsO patients with an induction dose of 80 mg of adalimumab followed one week later by the same 40 mg adalimumab subcutaneously administered eow dosing regimen already proven in the prior art to be effective in treating RA, and would have had a reasonable expectation that the dosing regimen would be successful in treating PsO.

Accordingly, pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Sandoz Inc. (“Sandoz” or “Petitioner”) respectfully requests *Inter Partes* Review (“IPR”) of claims 1-16 of the ’216 patent, which is currently assigned to AbbVie Biotechnology Ltd. (“AbbVie” or “Patent Owner”).

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

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

Sandoz is the real party-in-interest.

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

1. Related Litigations

The ’216 patent is related to two of the patents at issue[2] in the following judicial matter in which Petitioner was not and is not a party, which may affect, or be affected by, a decision in this proceeding: *AbbVie Inc. et al. v. Amgen Inc. et. Al.*, No. 1:16-cv-00666-SLR-SRF (D. Del. Filed Aug. 4, 2016). Petitioner is not aware of any reexamination certificates or pending prosecution concerning the ’216 patent.

2. Related Board Proceedings

AbbVie owns the patents that are the subjects of the following administrative matters: (1) *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2016-00172 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated November 9, 2015; (2) *Boehringer Ingelheim GmbH v. AbbVie Biotech. Ltd.*, Case No. IPR2016-00408 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (3) *Boehringer Ingelheim GmbH v. AbbVie Biotech. Ltd.*, Case No. IPR2016-00409 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (4) *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, Case No. IPR2016-00188 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,017,680, dated December 7, 2015; (5) *Coherus BioSciences Inc. v. AbbVie*

[2] U.S. Patent Nos. 8,961,973 ; 8,986,693 and the ’216 patent claim priority to the same application, SN 60/561,139 filed April 9, 2004.

Biotech. Ltd., Case No. IPR2016-00189 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,073,987, dated December 7, 2015. On May 17, 2016, the Board issued a decision instituting *inter partes* review for Case No. IPR2016-00172. On June 13, 2016, the Board issued decisions instituting *inter partes* review for Case Nos. IPR2016-00188 and IPR2016-00189. On July 7, 2016, the Board issued decisions instituting *inter partes* review for Case Nos. IPR2016-00408 and IPR2016-00409.

On May 16, 2017, the Board issued a Final Written Decision in IPR No. 2016-00172 on the '135 patent. On June 9, 2017, the Board issued Final Written Decisions in IPR Nos. 2016-00188 and 2016-00189 on the '680 and '987 patents, respectively. All three patents were directed to a method of treating RA by administering 40 mg D2E7 subcutaneously eow. *Coherus BioSciences, Inc v. AbbVie Biotech. Ltd.*, IPR Nos. 2016-00172, 2016-00408, 2016-00409 (P.T.A.B). In its decisions, the Board found the claims of all three patents invalid over van de Putte (ex. 1007) and Kempeni 1999. *Id.* The patents that are the subjects in the identified administrative matters and the '216 patent however do not claim priority to any of the same applications. On July 6, 2017, the Board issued Final Written Decisions in Nos. IPR2016-00408 and IPR2016-00409. In IPR2016-00408, the Board found the claims of the '135 patent unpatentable over van de Putte 2000 and Rau 2000. In IPR2016-00409, the Board found the claims of the '135 patent over

van de Putte 1999 and Kempeni 1999, and alternatively over Rau 1998, Schattenkirchner 1998, and van de Putte 1999.

The following list includes U.S. applications and patents that claim the benefit of the priority of the filing of the '216 patent or that the '216 patent claims priority from: U.S. Patent Nos. 9,067,992; 8,906,373; 8,808,700; 8,715,664; 8,889,136; 9,090,689; 9,187,559; 9,061,005; 9,499,615; 9,085,620; 8,961,973; 8,961,974; 8,986,693 and U.S. Application Nos. 60/681,645; 60/569,100; 60/561,710; 60/561,139; 14/809,828; 11/804,587; 12/008,064; 14/229,703; 14/229,709; 14/326,061; 14/745,092; 14/229,602 and 15/288,750.

C. Lead and Backup Counsel (37 C.F.R. § 42.8(b)(3))

Lead Counsel	**Back-up Counsel**
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D. Service Information (37 C.F.R. § 42.8(b)(4))

Please address all correspondence to the lead and backup counsel at the contact information above. Petitioner also consents to service by email to:

David.Barr@apks.com
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E. Fee Payment Authorization (37 C.F.R. § 42.103(a))

The Petitioner authorizes the Patent and Trademark Office to charge Deposit Account No. 502387 for the fees set in 37 C.F.R. § 42.15(a) for this Petition for IPR, and further authorizes payment of any additional fees to be charged to this Deposit Account.

III. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '216 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR on the ground identified herein.

IV. IDENTIFICATION OF CHALLENGE AND STATEMENT OF THE PRECISE RELIEF REQUESTED (37 C.F.R. § 42.104(b))

A. Effective Filing Date of the '216 Patent

For purposes of this Petition only, the effective filing date of the challenged claims is assumed to be the filing date of the earliest application to which the '216 patent claims priority, April 9, 2004. Sandoz reserves the right to challenge the effective filing date of the '216 patent in any other proceeding.

B. The Prior Art and Statutory Grounds of the Challenge (37 CFR § 42.104(b)(2))

Petitioner requests *inter partes* review and cancellation of claims 1-16 of the '216 patent on one ground pursuant to 35 U.S.C. § 103 as set forth herein. Petitioner's detailed statement of the reasons for the relief requested is set forth below in Section VI. In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits

are filed herewith. In addition, the Petition is accompanied by the declaration of Simon Helfgott, M.D. (ex. 1002) and John Posner, Ph. D. (ex. 1050).

The Petition contains one ground for invalidating the claims of the ’216 patent which includes the following publications that are pre-AIA Section 102(b) prior art based on the assumed April 9, 2004 priority date:

Table 1. Prior Art Publications Relied Upon by Petitioner

Reference	Publication Date	Type of Prior Art
Humira® 2002 Package Insert	Dec. 2002	102(b)
AbbVie Press Release	March 3, 2003	102(b)
Aulton	2002	102(b)
Weinstein	March 19, 2003[3]	102(b)
Marzo-Ortega	April 2002[4]	102(b)

These prior art references and the knowledge of a POSA are supported and informed by the wider body of prior art concerning the treatment of PsO and related diseases. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (explaining that *KSR* "required an analysis that reads the prior art in context, taking account of 'demands known to the design community,' 'the background knowledge possessed by a person having ordinary skill in the art,' and 'the inferences and creative steps that a person of ordinary skill in the art would

[3] Weinstein was published on March 19, 2003. *See* exs. 1065, 1068.

[4] Marzo-Ortega was published in April 2002. *See* exs. 1067, 1068.

employ.'"). The additional publications discussed in Section VI, each of which is Section 102(b) prior art, illustrate this wider body of prior art.[56]

The challenged claims are unpatentable based upon the following ground:

Table 2. Ground for Inter Partes Review

Claims	Priority Date	Statutory Basis and Prior Art
1-16	April 9, 2004	Obvious under 35 U.S.C. § 103(a) over the Humira® 2002 Package Insert, the AbbVie Press Release, Aulton and Weinstein, in view of Marzo-Ortega.

[5] Although AbbVie disclosed to the Patent Office most of the above-listed references and the background prior art listed below, they were included along with several hundred other references. With the exception of Aulton, which was considered in an earlier application (SN 11/104,117) in the chain that lead to the '216 patent that claims a different dosing regimen for a different disease, there is no evidence the Examiner ever considered the specific portions of the prior art described in this Petition. *See generally* 1063; *see also Microsoft Corp. v. Parallel Networks Licensing, LLC*, No. IPR2015-00486, Decision Institution of *Inter Partes* Review, at 14-15 (July 15, 2015) (rejecting the argument that the PTAB should not institute an IPR because the Petition relied on a reference that "was previously presented to the [PTO]"; explaining that the reference was "not applied against the claims and there is no evidence that the Examiner considered the particular disclosures cited by [the Petitioner] in the Petition.") Moreover, the Examiner did not have the benefit of the expert declarations submitted here by Sandoz which places the teachings of the prior art in context. Accordingly, the instant petition presents a ground of invalidity that was not considered during the original prosecution.

[6] Section VI of the Petition and the accompanying declarations also cite to the following exhibits for purposes other than assessing the state of the prior art: exs. 1012, 1022, 1032, 1034, 1044, 1045, 1047, 1048, 1049, 1057, 1059, 1063.

Section VI and the Declarations of Simon Helfgott, M.D. (ex. 1002) and John Posner, Ph. D. (ex. 1050) further describe the grounds for the invalidation of the '216 patent. Ex. 1002 at ¶¶ 105-113; Ex. 1050 at ¶¶ 87-91.

Dr. Helfgott is an expert in the field of rheumatology. Ex. 1002 at ¶¶ 3-18. He is an Associate Professor of Medicine in the Division of Rheumatology, Immunology and Allergy at Harvard Medical School. *Id.* at ¶ 3, Appx. A. He has been treating patients with psoriasis for over 20 years, using a variety of therapeutics, including monoclonal antibodies. *Id.* at ¶ 14.

Dr. Posner is an expert in the field of pharmacology. Ex. 1050 at ¶¶ 3-18. He has over 30 years of experience in clinical pharmacology. *Id.* He has considerable experience devising and executing plans for evaluating the human pharmacology of many novel compounds, including developing dosing regimens. Ex. 1050 at ¶ 3.

Drs. Helfgott and Posner are qualified to provide opinions as to what a POSA would have understood, known, or concluded as of April 9, 2004 and are therefore competent to testify in this proceeding.[7]

[7] Some references have been stamped with page numbers. Pincites for references that have such stamped-on page numbers refer to those page numbers, otherwise they refer to the document's original page numbering.

V. SUMMARY OF THE ’216 PATENT

A. Background of the ’216 Patent

The ’216 patent has two independent claims, both directed to methods of administering adalimumab “for treating moderate to severe chronic plaque psoriasis” by subcutaneously administering an initial dose of 80 mg adalimumab followed by 40 mg of adalimumab eow starting one week after the 80 mg dose. Ex. 1001 at claims 1 and 9. Claim 1 further requires that the patient achieve at least a PASI 75 response at week 12 of treatment. *Id.* at claim 1. In the ’216 specification, the “initial dose of 80 mg of adalimumab” (*id.*) is referred to as an “induction” dose (*id.* at 41:18) and the “40 mg of adalimumab every other week” dose (*id.* at claim 1) is referred to as a “treatment” dose. *Id.* at 41:19-20.[8]

The dependent claims of the ’216 patent add various limitations, including that: at least 5% of the body surface area (“BSA”) of the patient is affected by PsO (claims 2 and 10); the adalimumab is in pre-filled syringes for subcutaneous injections (claims 3, 6, 11, and 14); and the adalimumab is formulated at a concentration of 50 $^{mg}/_{ml}$ (claims 4, 5, 7, 8, 12, 13, 15, and 16).

[8] The specification of U.S. Patent No. 8,889,136 (the “’136 patent”) (ex. 1057), the first patent in the priority chain leading to the ’216 patent, explains that “induction dose” and “loading dose” may be “used interchangeably” (*id.* at 11:47-50) and that “treatment dose” and “maintenance dose” may be used interchangeably. *Id.* at 12:1-15.

The ’216 patent explains that PsO is “a skin inflammation (irritation and redness) characterized by frequent episodes of redness, itching, and thick, dry, silvery scales on the skin.” Ex. 1001 at 26:23-26. The ’216 specification also describes the well-known connection between PsO and RA and their common connection to TNF-α: “[p]soriasis is often associated with other inflammatory disorders, for example arthritis, including rheumatoid arthritis, inflammatory bowel disease (IBD), and Crohn's disease.” *Id.* at 26:37-40. TNF “has been implicated in the pathophysiology of psoriasis (Takematsu et al. (1989) *Arch Dermatol Res.* 281:398; Victor and Gottlieb (2002) *J Drugs Dermatol*. 1(3):264),” (*id.* at 26:20-23) RA, Crohn’s disease, and several other inflammatory diseases. *Id.* at 22:48-56. As explained in this Petition, the well-known prior art association between RA and PsO would motivate a POSA to apply the teachings regarding the use of TNF-α inhibitors to treat RA to the treatment of PsO.

The ’216 patent describes two PsO clinical trials using various dosing regimens of adalimumab which, according to the patent, show that adalimumab is more effective than placebo.[9]

[9] The ’216 patent discloses two ways to evaluate a patient’s “psoriatic skin lesions”: “Psoriasis Area and Severity Index (PASO [sic] (Fredriksson and Petterson (1978) *Dermatologica* 157:238-44) and the Physician’s Global Assessment [(PGA)].” *Id*. at 40:52-57.

The first study involved the treatment of patients "with moderate to severely active [psoriatic arthritis ("PsA")]" and compared 40 mg adalimumab eow with placebo eow for 24 weeks. *Id*. at 37:56-57, 38:4-6. Patients in this first study did not receive an induction dose (the "non-induction study"). Some of the patients had both PsA and PsO. *Id.* at 37:59-61. The specification states that the resulting PASI scores "for adalimumab-treated patients at week 24 were significantly better than placebo." *Id*. at 38:54-56. The results showed that 59% of the adalimumab-treated patients had a PASI 75 score after 24 weeks compared with only 1% of the patients receiving placebo. *Id.* at 39:1-10 (tbl. 2).

The second study involved a "multiple-variable dose"[10] treatment of patients with moderate to severe chronic plaque psoriasis. *Id*. 41:3-10 (the "induction study"). The patients were divided into three groups:

- **80/40/40 eow**: The first group "received an induction dose of 80 mg of D2E7," followed by a 40 mg dose the next week and then 40 mg eow. *Id*. at 41:17-21.[11]

[10] The '216 patent defines "multiple-variable dose" to mean "different doses of a TNFα inhibitor which are administered to a subject for therapeutic treatment." Ex. 1001 at 10:33-35. The specification further explains that "[m]ultiple-variable dose regimen . . . describe[s] a treatment schedule which is based on administering different amounts of TNFα inhibitor at various time points throughout the course of treatment." *Id.* at 10:35-39. The specification states that "[i]n one embodiment, the invention describes a multiple-variable dose method of treatment of erosive polyarthritis comprising an induction phase and a treatment phase, wherein a TNFα inhibitor is administered at a higher dose during the induction phase than the treatment phase." *Id.* at 10:39-44.

- **80/80/40 weekly**: The second group also "received an induction dose of 80 mg of D2E7" followed by another 80 mg dose the next week and then 40 mg every week thereafter. *Id.* at 41:21-26.

- **Placebo**: The third group received placebo. *Id*. at 41:25-26.

While the regimens that provided higher or more frequent doses of adalimumab apparently yielded better results (*id.* at 42:5-32), the '216 patent fails to provide data sufficient to determine any benefit from using either of the induction doses over a non-induction dose of only a 40 mg eow treatment dose. The two induction groups were only compared to placebo: both induction groups did "better on D2E7 than those on a placebo treatment." *Id*. at 42:7. The patients in the second induction group (80/80/40 weekly), who received more adalimumab than the first induction group (80/40/40 eow), achieved better PASI scores. *Id*. at 42:8-12 ("For patients receiving 40 mg treatment dose of D2E7 eow [starting one week after receiving an 80 mg induction dose], 53% demonstrated a PASI of 75 or higher. In addition, 80% of patients receiving a 40 mg treatment dose of D2E7 weekly [starting one week after receiving 80mg/80mg induction doses one week apart] showed a PASI 75 or higher, compared to only 4% of the placebo treatment group. . . ."); *see also* tbl. 5, fig. 5. A comparison of the data, however, from the two treatment groups in the induction study does not demonstrate which induction

[11] The '216 specification equates adalimumab with "D2E7" "a human anti-TNF mAb, described in U.S. Pat. No. 6,090,382." *Id*. at 11:64-66.

dose (80/80 vs. 80), if any, was superior because the two induction groups had different induction doses ***and*** different treatment doses: the effect of an induction dose of a single 80 mg dose, combined with a treatment dose of 40 mg eow, cannot be compared with the effect of an induction dose of two 80 mg doses one week apart, combined with a treatment dose of 40 mg weekly. Ex. 1002 at ¶¶ 99-101. Therefore, a POSA cannot determine whether the differences in PASI scores shown in Figure 5 of the '216 patent were due to differences in the induction doses, or treatment doses, or both.

Furthermore, the data in the specification does not demonstrate a benefit from either induction dose regimen compared with the non-induction dose regimen of 40 mg eow. As shown in Figure 7, of those patients in the induction study with PsO and PsA who received adalimumab 80/40/40 eow, 47% achieved a PASI 75 score at week 12 and 53% achieved a PASI 75 score at week 24, and of those patients who received adalimumab 80/80/40 weekly, 58% achieved a PASI 75 score at both weeks 12 and 24. Ex. 1001 at fig. 7. As shown in Table 2, of those patients with PsO and PsA in the non-induction study only receiving 40 mg adalimumab eow, 59% achieved a PASI 75 score at week 24. *Id*. at 39:1-10. Therefore, if anything, the data in the '216 patent demonstrates that patients (in this case patients with PsO and PsA) who did not receive an induction dose had a greater clinical response than those patients who did receive an induction dose.

Accordingly, the ’216 patent simply demonstrates that both induction and non-induction adalimumab dosing regimens are effective in treating PsO, not that the claimed induction dosing regimen is superior in treating PsO in accordance with any other dosing regimen. The patent does not offer any explanation for why an induction dose would be preferred over the non-induction dosing regimen, nor does it even say an induction dose is preferred. Moreover, the ’216 patent does not claim the 80/80/40 weekly dosing regimen that yielded greater efficacy than the 80/40/40 eow regimen.

Therefore, the ’216 patent does not demonstrate any advantages for the claimed induction dosing regimen and cannot support any unexpected results.

B. Person of Ordinary Skill in the Art

As explained by Dr. Helfgott in his declaration, a POSA developing a treatment for plaque psoriasis would have an M.D. with at least 3 years’ experience post-residency treating patients for psoriasis.[12] Ex. 1002 at ¶ 27.

As explained by Dr. Posner in his declaration, a POSA developing a dosing regimen for plaque psoriasis would have a Ph.D. in pharmacology,

[12] Plaque psoriasis is “the major form of psoriasis.” Ex. 1009 at 298; *see also* ex. 1008 at 21 (“Chronic plaque psoriasis . . . is the most common manifestation” of psoriasis.) The term “plaque” is used to denote “coin-sized (nummular) or palm-sized plaques.” *Id.* at 13.

pharmacokinetics, or a related field and at least 3 years of experience working on the pharmacokinetics/pharmacodynamics of biologic drugs. Ex. 1050 at ¶ 27.

C. Challenged Claims and Claim Construction (37 C.F.R. § 42.104(b)(1) and (b)(3))

The claim terms in the '216 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation ("BRI") of the claim language. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278-79 (Fed. Cir. 2015). The terms in the challenged claims of the '216 patent should therefore be given their BRI. For purposes of this petition only, Sandoz does not assert that any special meanings apply to claim terms in the '216 patent. In addition, because the "wherein" clause of claim 1 merely "characteriz[es] the result" of the claimed method while failing to inform "how" the method is performed, the clause does not limit the scope of the claim. *See Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003).

VI. STATEMENT OF REASONS FOR THE RELIEF REQUESTED (37 C.F.R. § 42.104(b)(4) and (b)(5))

This petition meets the threshold requirement for *inter partes* review because it establishes "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). As explained below, for the ground of unpatentability proposed, there is a

reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

A. SUMMARY OF THE ARGUMENT

The ’216 patent claims a dosing regimen for treating PsO requiring 40 mg treatment dosing eow of adalimumab preceded by an 80 mg induction dose one week earlier. All of this was known.

Adalimumab (D2E7) was a prior art drug known to treat TNF-α mediated disorders, including PsO and RA. Adalimumab was known in the prior art to be safe and effective in treating RA over a range of doses, including both 40 mg weekly and eow and 80 mg weekly; the FDA approved it, and the prior art described it, for use in treating RA with 40 mg eow dosing.[13] Because the prior art repeatedly taught that drugs known to treat RA, including TNF-α inhibitors, could be administered according to the same dosing regimen used to treat PsO, a POSA would have been motivated to administer 40 mg adalimumab eow to treat PsO and would have expected success in doing so because RA drugs had previously been successful in treating PsO.

In particular, a POSA knew that:

[13] *See* ex. 1026; *see also* ex. 1007 (disclosing a phase II study which found that 40 mg and 80 mg weekly doses of D2E7 were effective at treating RA).

(1) the FDA had approved adalimumab to treat RA by subcutaneous administration at 40 mg eow (ex. 1026 – the Humira® 2002 Package Insert);

(2) AbbVie's own press release announcing its PsO clinical trials acknowledged and demonstrated the rationale for using adalimumab to treat "moderate to severe" PsO (ex. 1052 – March 3, 2002 AbbVie Press Release); and

(3) the same dosages and dosing regimens of the TNF-α inhibitors infliximab and etanercept had been used to treat both RA and PsO (*e.g.*, ex. 1060 – Marzo-Ortega (infliximab); ex. 1006 – Enbrel® 2002 Package Insert; ex. 1009 – Mease 2002 (etanercept)).

Therefore, it would have been obvious to a POSA that the subcutaneous injection of 40 mg adalimumab eow already approved and described in the prior art to treat RA would also likely be effective in treating PsO.

Not only was the subcutaneous administration of 40 mg adalimumab eow obvious for treating PsO, it was also obvious that it could be preceded by an induction dose, that 80 mg could be safely and effectively used as the induction dose, and that the 40 mg eow treatment dosing could begin one week after the induction dose. The use of induction doses was known, as was the specific use of an induction dose of a TNF-α inhibitor to treat PsO. Furthermore, a POSA would be motivated for several reasons to use 80 mg as one of a finite number of possible induction doses for adalimumab, and would expect it to provide efficacy in treating PsO if followed one week later by 40 mg eow dosing.

In particular, a POSA knew that:

(1) administering a higher induction dose of a drug preceding treatment dosing was a well-established way to more rapidly achieve a full therapeutic response and would therefore be useful for diseases (like PsO) which cause patients significant physical and psychological suffering (ex. 1051 at 284-85 – Aulton; ex. 1002 at Section VIII);

(2) the first-in-class TNF-α inhibitor infliximab was administered with an "induction regimen" to treat PsO resulting in a "rapid" and "substantial" response (ex. 1003 at 251, 316 – Weinstein);

(3) an 80 mg adalimumab induction dose would likely be effective because:

a. 80 mg was known to be safe for RA (ex. 1026 at 14 –Humira® 2002 Package Insert); and

b. an induction dose (80 mg) could be set at twice the treatment dose (40 mg) for drugs (like adalimumab) that possess linear or first order pharmacokinetics and treatment dosing regimens corresponding to their half-life (ex. 1026 at 2 ("The pharmacokinetics of adalimumab were linear . . . ."); ex. 1051 at 285 – Aulton); *see also* ex. 1056 at 27; ex. 1050 at ¶¶ 53-70.

(4) 80 mg adalimumab was a most convenient induction dose because it could be administered using two injections of AbbVie's already-approved 40 mg syringe, eliminating the need to develop a new pre-loaded syringe for the one-time induction dose (ex. 1026 at 1 –Humira® 2002 Package Insert; ex. 1059 at 1 – Humira® 2004 Package Insert); and

(5) a one week interval between the 80 mg induction dose and the 40 mg eow treatment dosing was an obvious choice that would reasonably be expected to rapidly achieve therapeutically effective blood levels and had already been demonstrated to be safe (ex. 1051 at 284-85

– Aulton; ex. 1050 at Sections VII.C – VII.D; ex. 1026 at 14).

Accordingly, it would have been obvious to a POSA to treat PsO by subcutaneously administering an 80 mg adalimumab induction dose one week before commencing 40 mg eow adalimumab treatment dosing. At minimum, the claimed induction dosing regimen was one of a limited number of obvious options that a POSA would have considered. In addition, under well-established Federal Circuit authority, the PASI 75 response score recited in claim 1 is not entitled to patentable weight since it simply expresses an intended result of the claimed method. However, even if the PASI 75 response score is deemed to be a claim limitation, it is merely a natural result of an obvious dosing regimen.

B. STATE OF THE PRIOR ART

As described in detail below, it would have been obvious to a POSA in view of the prior art that 40 mg adalimumab injected subcutaneously eow would be effective at treating PsO and that using an 80 mg adalimumab induction dose one week before the start of treatment dosing would provide PsO patients with the added benefits of more quickly attaining blood levels comparable to steady state and obtaining more rapid relief from their symptoms.

1. The Prior Art Taught that Subcutaneous Administration of 40 mg Adalimumab Every Other Week Was Effective in Treating RA

Humira® was approved in December 2002 to treat RA. Ex. 1004 at 2; *see also* ex. 1026. The prior art FDA approved label stated that the recommended dose was 40 mg of adalimumab eow as a subcutaneous injection. Ex. 1026 at 14. Accordingly, 40 mg subcutaneously administered adalimumab eow was known to be effective at treating RA.

2. The Prior Art Predicted the Use of Adalimumab To Treat PsO

In September 2001, Japan Chemical Week predicted that adalimumab would be used to treat PsO. Ex. 1058 at 1 ("[D2E7 is] likely to have wider applications, covering not only RA and IBD but also psoriasis, indicating further development of markets.").

On March 3, 2003, AbbVie's predecessor, Abbott Laboratories (hereinafter "AbbVie"), issued a press release announcing that it had initiated clinical trials on the use of Humira® to treat PsO. Ex. 1052 at 2. AbbVie explained its rationale for the clinical trials: "[p]soriasis . . . [is an] autoimmune disorder[] in which . . . tumor necrosis factor-alpha . . . has been suggested to play a role;" clinical data "suggest[s] that treatments that inhibit TNF-alpha may be effective in these disease states . . . . [and that] "HUMIRA . . . works by specifically blocking TNF-alpha." *Id.* at 2. Therefore, a POSA was motivated, and had a reasonable expectation of success, in using adalimumab to treat PsO.

3. The Prior Art Taught that RA and PsO Were Often Treated by the Same Drugs at the Same or Similar Doses and Dosing Regimens

As described in detailed below, RA and PsO are both chronic autoimmune diseases that were often treated by the same drugs administered at the same or similar doses and dosing regimens. It was also known in the prior art that TNF-α was implicated in both conditions and therefore drugs that inhibited TNF-α could effectively treat both diseases when administered at the same or similar doses and dosing regimens. Thus, a POSA would have been motivated to use a TNF-α inhibitor that was effective in treating RA to also treat PsO at the same or similar doses and dosing regimens, and would have had a reasonable expectation that it would be effective in treating PsO. This was the precise rationale for the clinical studies that led to the Humira® PsO indication. Ex. 1052 at 2.

a. RA and PsO Are Both Known To Be Chronic TNF-α-Related Disorders Treatable Using TNF-α Inhibitors with the Same Doses and Dosing Regimens

Prior art publications widely reported the discovery of a connection between the proinflammatory cytokine TNF-α and both RA and PsO, including identifying D2E7 as one of the potential anti-TNF-α therapies for PsO.[14] In 1994, Ettehadi

[14] The prior art taught that PsO and RA are "autoimmune inflammatory" diseases. *See, e.g.*, ex. 1015 at 500 ("Psoriasis is an autoimmune inflammatory skin disease . . . ."; ex. 1011 at 489 ("Inflammatory and autoimmune diseases, including rheumatoid arthritis, . . . psoriasis . . . ."). The prior art also taught that both RA and PsO are chronic remitting and relapsing diseases. Ex. 1002 at ¶¶ 64-67; *see*

reported finding elevated TNF-α activity in psoriatic skin lesions. *See generally* ex. 1013. Many others in the prior art similarly reported TNF-α's close association with RA and PsO. *See, e.g.*, ex. 1019 at S34-35 ("It is thought that TNF-α resides at the apex of an inflammatory cytokine cascade that is responsible for the pathophysiology of RA. . . . TNF-α has been linked to the pathogenesis of PsA and psoriasis because of its ability to upregulate adhesion molecules and to trigger an inflammatory cytokine cascade."); ex. 1009 at 301; ex. 1017 at 385 ("Psoriatic arthritis and psoriasis are disease states in which tumour necrosis factor, a proinflammatory cytokine, is present in increased concentrations in joints and in the skin."). Based on the finding of "elevated TNF-α in psoriatic lesions," Ettehadi concluded "that anti-TNF-α strategies, such as the use of TNF-α and TNF receptor antibodies and recombinant soluble TNF receptors, may be of value in the treatment of inflammatory dermatoses." Ex. 1013 at 150. Thus in 1994, Ettehadi accurately concluded that TNF-α antibodies would be useful in treating PsO. *Id.*

Many others followed suit. Mease stated in 2000 "that blocking tumour necrosis factor in both psoriatic arthritis and psoriasis may offer a new therapeutic

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also ex. 1008 at 21 (describing "[c]hronic plaque psoriasis" as "the most common manifestation" of psoriasis); ex. 1030 at 1325 ("Different patterns of [RA] have been described. The two main patterns are chronic persistent and the relapsing-remitting disease course."); ex. 1031 at 198 (PsO is a recurrent relapsing/remitting disease and "Psoriasis is a common, chronic, recurrent, inflammatory disease of the skin . . . .").

option for patients with both diseases." Ex. 1017 at 389.[15] Similarly, Kalden stated: "[A]nti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." Ex. 1019 at S36. Lorenz in May 2002, based on a review of clinical evidence, stated that "TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis." Ex. 1028 at S19. Lorenz concluded that "anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease" and observed that D2E7 (adalimumab) is one of these potential anti-TNF-α therapies. *Id*. at S18-S19.

Prompted by TNF-α's known role in triggering RA and PsO, researchers soon demonstrated that TNF-α inhibitors, including infliximab and etanercept, were effective in treating both RA and PsO. Ex. 1002 at Section VII.D.

Furthermore, the prior art taught that PsO drugs could be administered using the same or similar doses and dosing regimens as used for RA. For example, the prior art taught that the TNF-α inhibitors infliximab and etanercept were effective in treating both RA and PsO using the same or similar doses and dosing regimens. *See infra* Table 3. Marzo-Ortega (ex. 1060), an April 2002 abstract, described clinical trials to assess the efficacy of using the proven RA dose of infliximab to

[15] In 2001 Mease further stated that "[i]nhibitors of TNF thus seem to have excellent potential for treating PsA and psoriasis." Ex. 1018 at iii39. And again in 2002 Mease stated that "[i]nhibitors of TNF thus appear to have excellent potential for treating PsA and psoriasis." Ex. 1009 at 303.

treat PsO and PsA. Ex. 1060 at 1 (reporting that "infliximab at a dose of $3^{mg}/_{kg}$ with methotrexate has proven effective in rheumatoid arthritis. We therefore aimed to assess the efficacy of infliximab at a dose of $3^{mg}/_{kg}$ in combination with methotrexate in the treatment of patients with PsA and skin psoriasis.")

For all of these reasons, a POSA would have a reasonable expectation of success that TNF-α inhibitors could be used to treat both RA and PsO at the same dose, and an even higher expectation of success that a TNF-α inhibitor like D2E7 that had already been shown to be effective in treating RA would also be effective in treating PsO at the same dose.

Table 3. Anti-TNF-α Drugs Used to Treat RA and PsO at the Same or Similar Doses and Dosing Regimens

Drug	RA		PsO	
	Reference	**Dosing Regimen**	**Reference**	**Dosing Regimen**
3 $^{mg}/_{kg}$ Infliximab	Remicade® 2002 Package Insert (Ex. 1027 at 21)	3 $^{mg}/_{kg}$ at weeks 0, 2 and 6, then every 8 weeks thereafter in combination with methotrexate	Marzo-Ortega (Ex. 1060 at 1)	3 $^{mg}/_{kg}$ at weeks 0, 2, 6 and 14, in combination with methotrexate
			Wollina (Ex. 1061 at 128)	300 mg (equivalent to 3 $^{mg}/_{kg}$[16]) at weeks 0, 2, 4 and 8 in combination with methotrexate
5, 10, or 20 $^{mg}/_{kg}$ Infliximab	Feldmann (Ex. 1039 at 66)	patients received single infusion of either 5, 10, or 20 $^{mg}/_{kg}$ infliximab in combination with methotrexate	Chaudhari (Ex. 1036 at 1843)	5 or 10 $^{mg}/_{kg}$ at weeks 0, 2 and 6
			Van den Bosch (Ex. 1037 at 429)	5 $^{mg}/_{kg}$ at weeks 0, 2 and 6
	Perkins (Ex. 1040 at 2206)	patients received single infusion of either 5, 10, or 20 $^{mg}/_{kg}$ infliximab in combination with methotrexate	Ogilvie (Ex. 1033)	5 $^{mg}/_{kg}$ at 0, 2 and 6 weeks in combination with MTX
Etanercept	Enbrel® 2002 Package Insert (Ex. 1006 at 23)	25 mg twice weekly	Mease 2002 (Ex. 1009 at 301)	25 mg twice weekly

[16] Although the average adult weighs about 70 kg (ex. 1038 at 22), it appears that in Wollina, the patients each weighed about 100 kg. Ex. 1061 at 128 ("a dose of 300 mg each corresponding to 3 $^{mg}/_{kg}$ body weight").

b. Prior to TNF-α Inhibitors, the Same Drugs With the Same or Similar Doses and Dosing Regimens Were Often Used to Treat Both RA and PsO

The impetus that prompted researchers to use the same or similar doses and dosing regimens when using TNF-α inhibitors to treat RA and PsO came from the prior practice of using other types of drugs to treat both diseases with the same doses and dosing regimens. As explained by Dr. Helfgott in his declaration, prior to the development of TNF-α inhibitors, drugs used to treat RA were frequently used for the treatment of PsO at the same or similar treatment doses and dosing regimens. Ex. 1002 at Section VII.D.2. The drugs methotrexate, cyclosporine, hydrocortisone, cortisone, dexamethasone, prednisolone and betamethasone were all approved in the prior art for use in treating RA and shown to have efficacy in treating PsO at the same or similar treatment doses and dosing regimens. *Id.* at tbl. 2.

Numerous patents and patent applications apply and supplement the teachings of the prior art described by Dr. Helfgott that the same therapeutic agents are frequently used to treat RA and PsO using the same treatment dosing ranges. *Id.* at tbl. 3.

Therefore, the prior art clearly taught that drugs useful to treat RA are also useful to treat PsO at the same dose.

4. Induction Doses Were a Well-Known Technique to Achieve a Rapid, Therapeutic Response

a. The Prior Art Taught the Use of, and How to Determine, Induction Doses to Achieve Rapid, Therapeutic Responses

The use of "induction doses," or higher initial doses followed by lower treatment doses, as required by the claims of the '216 patent, was well-known in the prior art. Waller (1994) taught that "[a] therapeutic problem may arise when a rapid effect is required for a drug which has a long or very long half-life," and that this "delay between the initiation of treatment and the attainment of steady state may be avoided by the administration of a loading dose."[17] Ex. 1054 at 36. Similarly, Goodman & Gillman, a leading prior art pharmacology text explained: "[a] loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated." Ex. 1056 at 27. It generally takes approximately five half-lives to reach steady state, irrespective of the size or frequency of dosing. Ex. 1050 at ¶ 37. Aulton explains that it takes approximately "4.3 biological half-lives . . . to reach 95% of the average steady-state plasma concentration." Ex. 1051 at 284.[18] With dosing at regular intervals,

[17] *See supra* n.8 (noting that AbbVie's '136 patent uses "loading dose" and "induction dose" interchangeably).

[18] "Steady state" is when "the amount of drug eliminated from the body over each dosing time interval is equal to the amount that was absorbed into the body

50% of steady state concentrations will have been reached after one half-life has elapsed, 75% after two half-lives, 87.5% after 3 half-lives and 93.75% after 4 half-lives. Ex. 1050 at ¶ 37. For adalimumab, it would take almost 10 weeks using 40 mg eow without an induction dose to reach full therapeutic effect. *Id.*

Accordingly, for drugs like adalimumab with long half-lives relative to the desired time for reaching full therapeutic effect, it will take a substantial amount of time for a patient to experience the full therapeutic benefit of the drug. *Id.* Thus, "[t]o reduce the time required for onset of the full therapeutic effect, a large single dose of the drug may be administered initially in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug and is approximately equal to the value of C^{ss}_{max} required." Ex. 1051 at 284-85; *see also* ex. 1056 at 27 ("The 'loading dose' is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly."). "Thereafter smaller, equal doses are administered respectively at suitable fixed intervals so as to maintain the plasma concentrations of the drug" and these doses "are known as maintenance doses." Ex. 1051 at 285.

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compartment following administration of the previous dose." Ex. 1051 at 280; Ex. 1050 at ¶ 36. At steady state, with constant dosing intervals and the same dose, a patient's blood concentrations will stay between consistent C_{max} and C_{min} values. Ex. 1051 at 280 (fig. 19.4); Ex. 1050 at ¶ 36.

Aulton also disclosed how to determine an appropriate induction dose. "As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug." Ex. 1051 at 285; *see also* ex. 1005 at 353 (tbl. 28-1) ("If the dosing interval τ is equal to or somewhat shorter than the elimination half-life $t_{1/2}$, then the dose Ratio R [of Induction Dose/Treatment Dose] should be 2:1."). This allows a patient to achieve blood levels close to steady-state blood levels from the induction dose alone. Ex. 1051 at 285 (fig. 19.8); *see* ex. 1050 at ¶¶ 37-38, 59.

Goodman & Gilman provides the following standard equation to determine an induction dose "with the aim of achieving the target concentration rapidly":

$$\text{loading dose} = \text{target } C_p \times (V_{ss}/F)$$[19]

An induction regimen may also be designed by dosing a constant dose amount more frequently than treatment dosing. For example, dosing a drug, such as infliximab, at 0, 2 and 6 weeks, is an induction dosing regimen because the increased dosing frequency achieves the goals of achieving an early steady state blood level and more rapid therapeutic effect. Ex. 1050 at ¶ 40. Van den Bosch, for example, described the "three infusions of 5 $^{mg}/_{kg}$ infliximab (at weeks 0, 2, and 6)" used to treat patients with spondyloarthropathy, which includes PsA, as "a

[19] Ex. 1056 at 27. "V_{ss}" refers to distribution volume at steady state, "F" refers to bioavailability and target C_p refers to target plasma concentration. *Id.* at 22, 23, 27.

loading dose regimen." Ex. 1037 at 428. Similarly, in describing the clinical trials evaluated by Chaudhari, Weinstein states that "patients with moderate to severe plaque psoriasis received a three-dose induction regimen of infliximab 5 or 10 $^{mg}/_{kg}$ at weeks 0, 2, and 6." Ex. 1003 at 251; *see also* Ex. 1027 at 21 (treating IBD with "an induction regimen at 0, 2 and 6 weeks"). Goodman & Gillman also explained that it can be "advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time," particularly if there are toxicity concerns. Ex. 1056 at 27.

Accordingly, the prior art taught that induction doses in the form of a higher or more frequent initial dose(s) can be used to more rapidly reach steady state blood levels for drugs with a long half-life to more rapidly achieve full therapeutic effect.

b. The Prior Art Taught Administration of TNF-α Inhibitors with Induction Doses Followed by Treatment Doses

The prior art demonstrated that a POSA understood that TNF-α inhibitors could be used to effectively treat PsO. *See supra* VI.B.2 – VI.B.3; *see also* ex. 1052 at 2. A POSA was also aware that, because PsO is a skin disease that causes the appearance of lesions which can be "psychologically and physically disabling,"

patients needed rapid therapeutic benefits.[20] Ex. 1036 at 1842; Ex. 1002 at ¶¶ 90-94; *see* also ex. 1010 at 51.[21] Accordingly, researchers identified the need to use induction doses of TNF-α inhibitors to induce a rapid therapeutic response to PsO. Weinstein and Chaudhari both disclosed that an induction dose regimen for TNF-α inhibitor infliximab was effective in inducing rapid therapeutic benefits for PsO patients. Ex. 1003 at 317; Ex. 1036 at 1844.

Chaudhari described a 33 patient, 10-week double-blind infliximab study which used a 0, 2 and 6 week induction regimen of 5 or 10 $^{mg}/_{kg}$ to treat PsO. Ex. 1036 at 1842.[22] Chaudhari found that the infliximab-treated patients experienced clinically significant benefits from this dosing regimen. *Id.* at 1845.

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[20] PsO is characterized itchy, dry, red patches on a patient's skin that may be painful. Ex. 1002 at ¶ 90. The unsightly red plaques may occur anywhere on a patient's body, and are often visible to other people. *Id.* Therefore, as stated in AbbVie's prior art press release, "[p]soriasis can have a significant emotional and psychological impact on a patient's quality of life . . . ." Ex. 1052 at 2 (internal quotation marks omitted); Ex. 1002 at ¶¶ 91-92. Accordingly, a treatment goal for PsO is to quickly reduce the plaques. *Id.* at ¶¶ 93-94. Drugs available to treat PsO, such as methotrexate, were criticized for taking "4-8 weeks to produce significant improvement." Ex. 1036 at 1842.

[21] Ridley (ex. 1010) was published in 1992. *See* exs. 1066, 1068.

[22] Chaudhari and Weinstein describe a two-step induction dose regimen for infliximab (i.e., the 0, 2 and 6 week induction regimen includes a two-week and four-week period between doses, prior to beginning less frequent treatment dosing). Although the claims of the '216 patent are directed to an induction dose regimen having one step before beginning treatment dosing, a two-step PsO induction dose regimen based on these references would have also been an obvious choice. Both one-step and two-step induction dose regimens achieve the goal of

Weinstein, in reviewing and commenting on the Chaudhari study, as well as on results from a subsequent open-label period, reiterated that "patients with moderate to severe plaque psoriasis received a three-dose induction regimen of infliximab 5 or 10 $^{mg}/_{kg}$ at weeks 0, 2, and 6." Ex. 1003 at 251. Weinstein noted that "the magnitude and rapid onset of response to infliximab therapy in these initial studies have been substantial." Ex. 1003 at 317.

Weinstein expressly suggested that an effective dosing regimen for PsO with a TNF-α inhibitor would include both an induction dose regimen followed by a treatment dose regimen: "[a]n appropriate regimen to consider may be an induction regimen followed by infrequent maintenance infusions, which offer the advantage of continual suppression of [PsO] and may be preferable to episodic treatment based of [sic] recurrence." *Id.* at 321.

Thus, a POSA knew than an induction dose of a TNF-α inhibitor prior to treatment dosing was an appropriate and effective dosing regimen for PsO.

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any induction dose, reaching therapeutic blood levels more quickly than by treatment dosing alone. Ex. 1050 at ¶ 43 n.5.

C. THE HUMIRA® 2002 PACKAGE INSERT (EX. 1026) COMBINED WITH THE ABBVIE PRESS RELEASE (EX. 1052), AULTON (EX. 1051) AND WEINSTEIN (EX. 1003) IN VIEW OF MARZO-ORTEGA (EX. 1060), RENDER CLAIMS 1-16 OBVIOUS

The Humira® 2002 Package Insert combined with the AbbVie Press Release, Aulton and Weinstein together disclose each element of claims 1 and 9 of the '216 patent.

The Humira® 2002 Package Insert disclosed that 40 mg adalimumab eow, administered subcutaneously in pre-filled syringes formulated at a concentration of 50 $^{mg}/_{ml}$, is effective at treating RA. It does not disclose the (1) use of adalimumab to treat PsO, (2) whether RA dosing regimens are effective in treating PsO, or (3) an induction regimen.

The prior art, however, disclosed each of these elements: (1) the AbbVie Press Release disclosed the use of adalimumab to treat PsO; (2) Marzo-Ortega taught that the same doses of TNF inhibitors can be used to treat both RA and PsO; and (3) Weinstein taught the use of induction doses of TNF inhibitors to treat PsO, while Aulton made the specifically claimed 80 mg induction dose of adalimumab one week before treatment dosing an appropriate and obvious induction dose based on the 40 mg adalimumab eow treatment dosing.

Further, for the reasons discussed *infra* VI.C.1-VI.C.7, a POSA would have been motivated to combine the Humira® 2002 Package Insert with the AbbVie

Press Release, Aulton and Weinstein in view of Marzo-Ortega to arrive at an adalimumab induction dosing regimen for PsO with a reasonable expectation of success. *Infra* VI.D provides a claim-by-claim and element-by-element identification of the portions of the references that disclose these claim limitations.

1. The Humira® 2002 Package Insert Combined with the AbbVie Press Release and Weinstein in View of Marzo-Ortega Taught Subcutaneous Administration of 40 mg Adalimumab EOW To Treat Moderate to Severe PsO in Adults (All Claims)

The prior art Humira® 2002 Package Insert disclosed administration of Humira® using syringes pre-filled with 40 mg of adalimumab in an 0.8 ml solution (i.e., a 50 $^{mg}/_{ml}$ concentration) to treat RA by subcutaneous injection eow. Ex. 1026 at 1-2, 14. A POSA had more than sufficient knowledge to conclude that adalimumab could be administered to treat PsO with this same dosing regimen. *See supra* VI.B.2 – VI.B.3.

Because TNF-α was known to play a role in both RA and PsO, researchers believed TNF-α inhibitors administered using similar dosing regimens could be used to treat both diseases. The AbbVie Press Release explained that TNF-α's role in PsO was the very basis for AbbVie's conducting clinical trials to study the treatment of PsO with adalimumab. Ex. 1052 at 2. As the AbbVie Press Release acknowledged, a POSA knew exactly how to select drugs, doses and dosing regimens to treat PsO based on known treatments for RA because the art taught:

- TNF-α played a major role in the development of RA and PsO (*supra* VI.B.3.a);
- TNF-α inhibitors such as etanercept and infliximab were used successfully to treat both RA and PsO using the same doses and dosing regimens (*supra* VI.B.3.a); and
- many other drugs had been used to treat both RA and PsO using the same doses and dosing regimens (*supra* VI.B.3.b)

Lorenz recounted much of this history before concluding that "anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." Ex. 1028 at S19. This conclusion was an accepted consensus view in the field at the time. *See supra* VI.B.3.a. Lorenz further observed that D2E7 is a potential anti-TNF-α therapy. Ex. 1028 at S18.[23]

Marzo-Ortega explained that they selected the proven RA dose of infliximab to treat PsO and that the RA dose was successful in treating PsO. *See supra* VI.B.3.a. Marzo-Ortega's teaching to use the RA dose of infliximab to treat PsO, and the more general success of TNF-α inhibitors (*supra* VI.B.3.a) and other drugs (*supra* VI.B.3.b) in treating both RA and PsO using the same or similar doses and dosing regimens, motivated a POSA to combine the teachings of the AbbVie Press Release regarding the use of adalimumab to treat PsO with the Humira® 2002

[23] Lorenz provides relevant background art that a POSA would have known. *See Randall Mfg.*, 733 F.3d at 1362-63 (reversing Board's nonobviousness determination because it "narrowly focus[ed] on the four prior-art references cited by the Examiner and ignor[ed] the additional record evidence [the requester] cited to demonstrate the knowledge and perspective of one of ordinary skill in the art.").

Package Insert's disclosure of the RA dose and dosing regimen for adalimumab. The success in treating PsO using doses and dosing regimens of drugs that had been successful in treating RA, such as infliximab, etanercept, methotrexate, cyclosporine, hydrocortisone, cortisone, dexamethasone, prednisolone and betamethasone, clearly supported a reasonable expectation of success that administering 40 mg adalimumab subcutaneously eow would be effective in treating PsO.

2. Weinstein Taught the Treatment of Moderate to Severe Chronic Plaque Psoriasis with the TNF Inhibitor Infliximab

The claims require treating "moderate to severe chronic plaque psoriasis." Ex. 1001 at claims 1, 9. The prior art taught this using TNF-α inhibitors.

Weinstein discloses the results from the 33-patient Chaudhari infliximab clinical trial, as well as an open-label extension. Ex. 1003 at 250-51, 316-21; *see also id.* at 254 fn. 11 (citing Chaudhari), 328 fn. 33 (same). Weinstein explains that the clinical trial evaluated "33 patients with moderate to severe plaque psoriasis" (*id.* at 250) and that these patients "had at least a 6 month history of plaque-type psoriasis that had been insensitive to treatment with topical corticosteroids, and whose psoriasis covered at least 5% of the body." *Id.* at 316; *see also* ex. 1036 at 1843 ("Adult patients . . . had moderate to severe plaque psoriasis involving at least 5% of the body surface area . . . . Patients had a history of plaque psoriasis for a minimum of 6 months and a history of topical

corticosteroid failure."). The patients in the study received 5 $^{mg}/_{kg}$ or 10 $^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6. Ex. 1003 at 250. Weinstein found that "the magnitude and rapid onset of response to infliximab therapy in these initial studies have been substantial." Ex. 1003 at 317.

Accordingly, a POSA would have known from Weinstein that a TNF-α inhibitor could be used in the treatment of moderate to severe chronic plaque psoriasis covering at least 5% BSA.

3. Aulton, Weinstein and the Humira® 2002 Package Insert Would Have Made It Obvious to Administer an 80 mg Induction Dose of Adalimumab One Week Prior to 40 mg EOW Dosing

It would have been obvious to administer an 80 mg adalimumab induction dose one week before 40 mg eow treatment dosing. A POSA would have known that an induction dose of adalimumab would more rapidly achieve blood levels comparable to steady state, providing PsO patients with quicker therapeutic benefits compared to treatment dosing alone. Ex. 1050 at ¶¶ 59-70. A POSA would have been motivated to include an induction dose in the adalimumab PsO dosing regimen because the prior art identified a need to provide rapid relief to PsO patients, taught the use of induction doses in treating PsO and demonstrated that adalimumab was safe at much higher doses. *See id.* at ¶¶ 71-75.

a. 80 mg One Week Before 40 mg eow Treatment Dosing Was an Obvious Induction Dose

Given the art-acknowledged benefits of induction dosing to treat PsO discussed *supra* VI.B.4, the Humira® 2002 Package Insert provided all of the information needed for a POSA for determining that adalimumab had suitable pharmacokinetics for induction dosing and for determining an appropriate size for that induction dose.

Adalimumab, according to the Humira® 2002 Package Insert, had a known half-life of "approximately [two] weeks." Ex. 1026 at 2. While a POSA would reasonably expect that 40 mg eow would be effective to treat PsO, a POSA would also know it would take approximately 5 such biweekly doses, or 10 weeks, for a patient to reach steady-state blood levels. Ex. 1050 at ¶ 37. Therefore, a POSA would expect that treatment dosing alone might not provide the rapid therapeutic benefits PsO patients require.[24] *Id.* Accordingly, a POSA would be motivated to provide PsO patients with a higher induction dose prior to beginning 40 mg eow dosing to reach steady state blood levels earlier and thereby provide more rapid relief of PsO symptoms. *Id.* at ¶¶ 55-56.

[24] As Dr. Posner demonstrates, a POSA would know based on the approximately two week half-life of adalimumab that a patient administered adalimumab 40 mg eow does not reach steady-state until approximately ten weeks after initiating treatment. Ex. 1050 at ¶ 53.

To determine a desirable induction dose for adalimumab, a POSA would use the 40 mg eow treatment dose as a starting point. *Id.* at ¶ 60; Ex. 1051 at 284-285. As Dr. Posner explains, the prior art taught that for drugs whose treatment dosage interval corresponds to the half-life, a POSA would understand that the induction dose should be twice the treatment dose. Ex. 1051 at 285 ("As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug"); *see also* ex. 1005 at 352-53 ("If the dosing interval τ is equal to or somewhat shorter than the elimination half-life $t_{1/2}$, then the dose Ratio R [of induction dose/treatment dose] should be 2:1."). This is precisely the case for adalimumab based on the FDA-approved 40 mg eow treatment and adalimumab's approximately two-week half-life. Ex. 1026 at 2. Therefore, a POSA would understand that one appropriate adalimumab induction dosing regimen is 80 mg (twice the 40 mg treatment dose) two weeks prior to beginning 40 mg eow treatment dosing. As shown in Aulton's Figure 19.8, this regimen allows a patient to achieve blood levels close to steady-state from the induction dose alone. *See* ex. 1051 at 285; ex. 1050 at ¶¶ 37-38, 59.

The determination of an 80 mg adalimumab induction dose using the principle set forth in Aulton and Ritschel & Kearns is confirmed by established pharmacokinetic calculations. Goodman & Gilman provides the following

standard equation to determine an induction or loading dose "with the aim of achieving the target concentration rapidly" (ex. 1056 at 27):

$$\text{loading dose} = \text{target } C_p \times (V_{ss}/F)$$ [25]

A POSA would know the target plasma concentration (C_p) would be at or near the C_{max} achieved at steady state because that is the amount eventually achieved by practicing the FDA-approved dosing regimen for RA. Ex. 1050 at ¶ 62. As shown by Dr. Posner, using the steady state C_{min} of 5 µg/mL provided in the Humira® 2002 Package Insert (ex. 1026 at 2), the fact that adalimumab exhibits first order pharmacokinetics and that it is administered with a frequency near its half-life, a POSA would know that the target plasma concentration (C_{max} at steady state) is 10 µg/ml (because the steady state C_{min} occurs 1 half-life from the C_{max} by virtue of dosing on the half-life). Ex. 1050 at ¶¶ 62-63. The Humira® 2002 Package Insert states that V_{ss} ranged from 4.7 to 6.0 L and bioavailability (F) was 64%. Ex. 1026 at 2. Using those values a POSA could calculate that an appropriate induction or loading dose of adalimumab would be between 73.43 mg and 93.75 mg, depending on whether 4.7 L or 6.0 L is used for distribution volume. Ex. 1050 at ¶¶ 65-66. Accordingly, an 80 mg adalimumab induction dose would have been an obvious choice (within a limited range of obvious loading

[25] *Supra* n.19.

doses) for a POSA to select and to have reasonably expected would succeed in achieving a more rapid therapeutic benefit in PsO patients.[26]

A POSA would also have known that a range of induction dosing regimens, both in amount and in interval before commencement of treatment dosing, would be efficacious and result in more rapid patient relief of symptoms. Ex. 1050 at ¶ 68. Thus, in general, induction doses that are greater than the treatment dose and which are known to be safe, would reasonably be expected to be effective. *Id.* at Section VII.C – VII.D. Dr. Posner explains that it would have been obvious that an 80 mg induction dose could be administered either one week or two weeks before commencing treatment dosing to achieve higher blood levels, with the one-week interval achieving higher initial blood concentrations. *Id.* at ¶¶ 68-70. A POSA would have reasonably expected that either a one week or a two week interval would provide a PsO patient with therapeutic benefits more rapidly than treatment dosing alone. *Id.* at ¶ 69. Accordingly, both a one week and a two week interval between an 80 mg induction dose and the commencement of 40 mg eow treatment dosing would have been obvious choices for an adalimumab dosing regimen for PsO. *Id.* at ¶¶ 68-70; Ex. 1051 at 284-85 (induction doses "reduce the

[26] Although induction doses for some drugs can impose added risks necessitating dividing the dose into several smaller doses administered over a relatively brief period of time, adalimumab's substantial safety margin (demonstrated by the Humira® 2002 Package Insert), would likely render this unnecessary for adalimumab.

time required for onset of the full therapeutic effect"). The claimed induction dose of 80 mg one week before treatment dosing was, at a minimum, one of a finite number of obvious choices a POSA would have considered.

Moreover, a POSA would also have a reasonable expectation that an adalimumab induction dose would increase blood levels predictably because the prior art Humira® 2002 Package Insert stated that adalimumab exhibits linear pharmacokinetics and thus, "steady state [blood levels] increased approximately proportionally with dose following . . . 40 and 80 mg . . . subcutaneous dosing."[27] Ex. 1026 at 2; *see* ex. 1050 at ¶¶ 52-56. Thus, it would have been obvious that combining an initial 80 mg induction dose before beginning a 40 mg eow treatment dosing regimen would be efficacious and could result in more rapid relief.

A POSA would also have known that an 80 mg induction dose was well within the range of adalimumab doses that the prior art had established were safe and well tolerated based on published clinical trial results. The prior art described a Phase II study where patients received either 20, 40 or 80 mg weekly doses of

[27] The prior art Humira® 2002 Package Insert disclosed that both intravenous and subcutaneously administered adalimumab exhibited "linear" pharmacokinetics. Ex. 1050 at ¶ 55; Ex. 1026 at 2. For drugs with linear, or first order, pharmacokinetics, drug plasma concentrations are predictable because they are proportional to the dose. Ex. 1050 at ¶¶ 55-56; *see also* ex. 1064 at 18 ("In a linear pharmacokinetic model, plasma concentrations are additive, which is a useful principle for predicting multiple dosing profiles and for estimating dosing regimens in chronic conditions. This principle is referred to as the superposition principle, which states that the concentration of drug remaining in the body at any time is added to the concentration remaining from previous doses.").

adalimumab by subcutaneous self-injection for three months. Ex. 1007.[28] In addition, the Humira® 2002 Package Insert explained that "[m]ultiple doses up to 10 $^{mg}/_{kg}$ have been administered to patients in clinical trials without evidence of dose-limiting toxicities." Ex. 1026 at 14. Using an average human weight of 70 kg, 10 $^{mg}/_{kg}$ corresponds to an average dose of 700 mg, far beyond the claimed 80 mg induction dose. Thus, even without considering the well-known pharmacokinetic principles discussed above, a POSA would reasonably expect that a single induction dose of 80 mg could be safely administered to patients and, by virtue of it being a larger dose, would provide more rapid relief. Ex. 1050 at ¶¶ 70-76. It was obvious that any initial dose (including 80 mg) appreciably larger than 40 mg and known to be safe based on the Humira® 2002 Package Insert would be effective in more rapidly raising adalimumab blood levels, which in turn would be likely to provide a more rapid therapeutic response to patients.

PsO was known to be a disease for which more rapidly acting treatments would be desirable. Ex. 1002 at ¶¶ 90-94. The prior art identified a need for a quick acting and "highly efficacious [PsO] treatments that are safe to use in a long-term regimen." Ex. 1036 at 1842; Ex. 1050 at ¶¶ 49-50. Weinstein taught that PsO patients suffer significantly and would benefit from rapid therapeutic

[28] In addition, a 1 $^{mg}/_{kg}$ (approximately 70 mg) subcutaneous dose of adalimumab had been described in the prior art disclosure of AbbVie's clinical trials for RA and was stated to be "very well tolerated." Ex. 1055 at 4.

treatments. *See* ex. 1003 at 1, 250. Weinstein explicitly stated that an appropriate dosing regimen would include both an induction dose and treatment dosing. Ex. 1003 at 321. Therefore, a POSA would have been motivated to precede a known, safe and effective 40 mg eow treatment dose for PsO with a safe, 80 mg induction dose to induce a more rapid therapeutic benefit and to begin the eow treatment dosing one week after the administration of the induction dose. A POSA would also have had an expectation, at a minimum, that the treatment dose would be effective in treating PsO for the reasons stated *supra* VI.B.3 and would further reasonably expect that inclusion of the induction dose would raise blood levels of adalimumab more quickly to effectuate a more rapid clinical response.

b. AbbVie's Commercially Available Prior Art 40 mg Adalimumab RA Dose Provided a Further Reason for Choosing an 80 mg Induction Dose

As of April 2004, AbbVie had a single commercial embodiment for its Humira® product, a 40 mg pre-filled syringe. Ex. 1026 at 1; Ex. 1059 at 1. Accordingly, both AbbVie, and a POSA trying to make a biosimilar form of Humira®, had every incentive to select an induction dose that was a whole number multiple of the then-existing 40 mg pre-filled syringe (*i.e.*, 80, 120, 160 mg) to avoid the burden of developing a new dosing format. Thus, a POSA, like AbbVie, would have been motivated to use an induction dose that was a whole number multiple of 40 mg. Ex. 1050 at ¶ 76. Unsurprisingly, the '216 patent discloses

only a single example of an induction dose combined with a 40 mg eow regimen: 80 mg one week before treatment dosing. Ex. 1001 at tbl. 5.[29]

4. The Humira® 2002 Package Insert Combined with the AbbVie Press Release and Weinstein in View of Marzo-Ortega Taught the Recited Clinical Endpoints (Claims 1-8)

Claims 1-8 recite "achiev[ing] at least [PASI] 75 response at week 12 of the treatment." Ex. 1001 at claim 1. By merely reciting the intended result of the method, these clauses do not limit the scope of claims 1-8. *Minton*, 336 F.3d at 1381 ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."); *see supra* V.C. Furthermore, even if these clauses limited the scope of the claims, the recited results, according to the '216 patent itself, are a natural result inherently achieved by at least some PsO patients receiving adalimumab in accordance with the obvious dosing regimen recited in the '216 patent claims. Ex. 1001 at 41:4 – 42:58. In other words, these results are achieved in at least certain patients by administering an 80 mg initial adalimumab dose and 40 mg adalimumab eow

[29] While Humira® is currently available in 10 mg and 20 mg injections, those forms were not commercially available in 2004. Moreover, the 10 mg and 20 mg doses are only used for pediatric conditions. The current dosage for all adult conditions is 40 mg, or a multiple thereof including 80 and 160, all administered by one or more pre-filled 40 mg syringes or self-injectors. Ex. 1034 at 1-2.

without the need for any additional steps.[30] Accordingly, the addition of these limitations specifying the clinical endpoints inherent in this method of treatment cannot save the claims from invalidation. *See Par Pharm., Inc. v. Twi Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) ("We have recognized that inherency may supply a missing claim limitation in an obviousness analysis.").

5. The Humira® 2002 Package Insert Taught "pre-filled syringes for subcutaneous injection" (Claims 3, 6, 11, 14)

The prior art Humira® 2002 Package Insert disclosed "pre-filled syringes for subcutaneous injection," (ex. 1001 at claims 3, 6, 11, 14) stating that "Humira is supplied in single-use, 1 mL pre-filled glass syringes . . . for subcutaneous administration." Ex. 1026 at 1. The prior art thus taught the limitation "pre-filled syringes for subcutaneous injection" as required by claims 3, 6, 11 and 14.

6. The Humira® 2002 Package Insert Taught the Claimed "Concentration of 50 $^{mg}/_{ml}$" (Claims 4, 5, 7, 8, 12, 13, 15 and 16)

The Humira® 2002 Package Insert disclosed a syringe with "0.8 mL (40 mg) of drug product," which is equal to 50 $^{mg}/_{ml}$, and the corresponding formulation with all of its ingredients and their amounts. Ex. 1026 at 1. Thus, the Humira® 2002 Package Insert disclosed the recited 50 $^{mg}/_{ml}$ adalimumab concentration in claims 4, 5, 7, 8, 12, 13, 15 and 16.

[30] In fact, the '216 specification does not state that the 80 mg induction dose was necessary to achieve at least a 75% reduction in PASI at week 12 (ex. 1001 at 41:4 – 42:58). The PASI reduction was simply achieved by 40 mg eow. *Id.* at tbl. 2.

7. The Humira® 2002 Package Insert Combined with the AbbVie Press Release and Weinstein in View of Marzo-Ortega Taught Treating Patients Having "at least 5% body surface area . . . affected by the [psoriasis]" (Claims 2, 10)

Claims 2 and 10 require that the treated patient has "at least 5% body surface area (BSA) . . . affected by the [psoriasis]." Ex. 1001 at claims 2, 10. A POSA, however, understood that patients having 5% or more body surface area affected by PsO could be treated using TNF-α inhibitors. Weinstein reported Chaudhari's treatment of patients having "moderate to severe plaque psoriasis" "whose psoriasis covered at least 5% of the body" with infliximab, a TNF-α inhibitor. Ex. 1003 at 251, 316; *see also* ex. 1036 at 1843 ("Adult patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area" participated in the study.).

8. AbbVie Did Not Offer Any Credible Contrary Arguments During Prosecution

During the prosecution of application no. 11/104,117 (the "'117 application" which issued as U.S. Patent No. 8,889,136), to which the application for the '216 patent claims priority, AbbVie argued that a POSA would not apply the induction dose teachings of Aulton to a subcutaneously administered large molecule, such as an antibody. *See* ex. 1063 at 17. AbbVie submitted the declarations of Dr. John Collett, Ph.D. (ex. 1045) and Dr. Diane Mould, Ph.D. (ex. 1044) in support of its argument. The '117 application contained claims directed to an induction dose

regimen of adalimumab for the treatment of a different condition (Crohn's disease). Ex. 1063 at 3-8. As explained by Dr. Posner, none of AbbVie's criticisms are correct or undermine the applicability of Aulton to determining the appropriate range of induction doses for adalimumab. Ex. 1050 at ¶¶ 77-86. As Dr. Posner explains, there is no basis for limiting Aulton to "small" molecules or for excluding subcutaneous administration. *Id.* at ¶¶ 81-82. The same principles apply to biologics and small molecules. *Id.* Indeed, Ritschel & Kearns provides the same induction dose guidance as Aulton without any specific reference to route of administration or molecule. *See* ex. 1005 at 352-53. Similarly, the standard loading dose equation provided by Goodman & Gillman is not limited to small molecules or oral dosing, and confirms that 80 mg is an appropriate loading dose. *See supra* VI.C.3.a. Both small molecules and large molecules, however administered, with long half-lives relative to the desired time to reach full therapeutic effect that are administered with a larger initial dose will necessarily produce higher blood levels of the drug more rapidly—so long as they, like adalimumab, exhibit first order pharmacokinetics. Ex. 1050 at ¶ 81.

Further, although Dr. Mould admits that Aulton applies to drugs with linear pharmacokinetics (ex. 1044 at 8), neither of the prior declarations AbbVie submitted during prosecution of the '117 application addressed the fact that the Humira® 2002 Package Insert explicitly disclosed that subcutaneously

administered adalimumab exhibits linear pharmacokinetics. Ex. 1026 at 2; Ex. 1050 at ¶¶ 54-55. This data confirms that a POSA would have understood that Aulton's teachings were in fact applicable to subcutaneously administered adalimumab. Thus, as Dr. Posner explains, based on the known pharmacokinetics for adalimumab, a POSA would reasonably expect that a subcutaneously administered adalimumab induction dose would proportionally increase a patient's blood levels relative to the treatment dose. *Id.* at ¶¶ 54-58.

9. No Secondary Considerations, Such As Commercial Success or Unexpected Results, Demonstrate Nonobviousness

AbbVie has repeatedly made contradictory arguments of commercial success attempting to support the patentability of its varied portfolio of secondary D2E7-related patents. There can be no nexus between Humira®'s commercial success and the claims of the '216 patent because at different times AbbVie has attributed the commercial success of Humira® to entirely different patents. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005) (where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak."); *Coal. for Affordable Drugs II LLC v. NPS Pharm., Inc.*, No. IPR2015-01093, Final Written Decision, Paper 67, at 30-32 (Oct. 21, 2016) (holding there was no showing of commercial success where the Board could not "conclude from the evidence before [it] whether the sales are due to the

merits of the invention of the [patent at issue] and not, for example, [a different patent].").

Because AbbVie's own evidence and inconsistent assertions point to different patents as the driver of Humira®'s commercial success, it has no basis for now arguing that it is the '216 patent that drives Humira®'s sales. For example, in defending the alleged patentability of a patent claiming an adalimumab formulation against a petition for inter partes review, AbbVie argued that the commercial success of Humira® was "driven in large part by" its formulation. Ex. 1022 at 28 (arguing that the commercial "success was driven in large part by (i) the ability of patients to self-administer a liquid antibody formulation via s.c. administration without lyophilization and the accompanying need for reconstitution, and (ii) the fact that it is stable enough to be commercially viable . . . .") (citation omitted). If Humira®'s commercial success was "driven in large part" by the formulation, as AbbVie previously asserted, then there is no basis for AbbVie to argue now that Humira®'s commercial success was largely driven by the '216 patent's claimed induction dosing regimen for treating PsO. Moreover, the very evidence that AbbVie submitted, supposedly in support of its response to the '158 formulation patent petition, acknowledged that the commercial success of Humira® was due to its initial patent on D2E7 antibody itself: "Abbott loses its key patent on the composition of matter for Humira in 2016, meaning it could face

competition from cheaper 'biosimilar' knock-offs." Ex. 1012 at 5 (cited as Ex. 2003 in the '158 IPR).

When trying to defend its RA dosing patent (U.S. Patent No. 8,889,135), AbbVie attributed Humira®'s commercial success, not to its PsO induction dosing regimen, not to its formulation, and not (more plausibly) to D2E7 itself, but (more conveniently) to the RA dosing regimen. It argued that Humira®'s dosing "regimen . . . specifies the biological agent (D2E7), the method of administration (subcutaneous), the dose (40mg fixed dose) and the dosing interval (13-15 days)." Ex. 1032 at 58. In the Final Written Decision for the '135 IPR, the Board recognized that AbbVie has inconsistently argued that different attributes of Humira® have led to its commercial success in different proceedings: "[t]hus, Patent Owner has relied on features other than the dosing regimen recited in the '135 patent claims as driving the commercial success of HUMIRA®." *Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172, Final Written Decision, Paper No. 60, at 40 (May 16, 2017). The Board stated: "it is not clear whether the sales of HUMIRA® are due to the dosing regimen recited in the '135 patent, or the formulation that Patent Owner argued was the driver of commercial success in another *inter partes* review, or the known and patented fully human D2E7 antibody." *Id.* at 41.

Accordingly, AbbVie cannot save the claims of the ’216 patent from invalidity by asserting that the commercial success of Humira® is due to the PsO induction dosing regimen claimed in U.S. Patent No. 8,802,100, particularly when the teachings of the prior art so clearly render that method obvious. *See, e.g.*, *W. Union Co. v. MoneyGram Payment Sys., Inc.*, 626 F.3d 1361, 1373 (Fed. Cir. 2010) (“[W]eak secondary considerations generally do not overcome a strong prima facie case of obviousness.”) (quoting *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007)).

Additionally, there are no unexpected results from the claimed dosing regimen. As explained *supra* V.A, the data in the ’216 specification for the induction study does not show any unexpected benefits of the claimed dosing regimen. Additionally, although there are reasons a POSA would not compare the data in the induction and non-induction studies, even if a POSA did, the data in the ’216 specification demonstrates that PsO patients *without* an induction dose had a greater clinical response at week 24. Ex. 1002 at ¶¶ 101-02.

Petitioner reserves the right to respond to any assertions of secondary considerations that Patent Owner alleges during this proceeding.

D. SUMMARY OF GROUNDS FOR INVALIDITY

The claim charts below provide a summary of the prior art disclosures that render obvious each claim in the ’216 patent. The charts for the dependent claims

hereby incorporate all of the grounds in the independent and any other dependent claims from which they depend.

Independent Claims 1 and 9 Are Obvious

'216 Claim Language	Prior Art Disclosures
Claims 1 and 9	
A method for treating moderate to severe chronic plaque psoriasis,	See below.
comprising subcutaneously administering	"HUMIRA is supplied in single-use, 1 mL pre-filled syringes, and also 2 mL glass vials as a sterile, preservative-free solution for subcutaneous injection." Ex. 1026 at 1. "The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection." Ex. 1026 at 14.
to an adult patient having moderate to severe chronic plaque psoriasis	"[T]reatment was efficacious and safe in PsA and psoriasis." Ex. 1028 at S18. "Adult patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area and who were in good general health were referred to us . . . or were identified through general advertisements" to participate in the study. Ex. 1036 at 1843; *see also* Ex. 1003 at 250, 316. "Psoriasis . . . [is an] autoimmune disorder[] in which . . . tumor necrosis factor-alpha . . . has been suggested to play a role." Clinical data "suggest[s] . . . treatments that inhibit TNF-alpha may be effective in these disease states." "HUMIRA . . . works by specifically blocking TNF-alpha." Abbott sought to "assess safety and efficacy [of

’216 Claim Language	Prior Art Disclosures
	adalimumab] in adult patients with moderate to severe chronic-plaque psoriasis.” Ex. 1052 at 2. “[I]nfliximab at a dose of 3 $^{mg}/_{kg}$ with methotrexate has proven effective in rheumatoid arthritis. We therefore aimed to assess the efficacy of infliximab at a dose of 3 $^{mg}/_{kg}$ in combination with methotrexate in the treatment of patients with PsA and skin psoriasis.” Ex. 1060 at 1.
an initial dose of 80 mg of adalimumab,	An induction dose “may be administered initially in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug” and “[t]o reduce the time required for onset of the full therapeutic effect.” Ex. 1051 at 284-285. “As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug.” Ex. 1051 at 285
followed by 40 mg of adalimumab	“Each syringe delivers 0.8 mL (40 mg) of drug product. . . . Each 0.8 mL HUMIRA contains 40 mg adalimumab . . .” Ex. 1026 at 1.
every other week	“The recommended dose of HUMIRA for adult patients with rheumatoid arthritis is 40 mg administered every other week as a subcutaneous injection.” Ex. 1026 at 14.
starting one week after said first dosing,	An induction dose “may be administered initially in order to achieve

’216 Claim Language	Prior Art Disclosures
	a peak plasma concentration that lies within the therapeutic range of the drug” and “[t]o reduce the time required for onset of the full therapeutic effect.” Ex. 1051 at 284-285.
[claim 1 only:] wherein the patient achieves at least Psoriasis Area and Severity Index (PASI) 75 response at week 12 of the treatment.	“[A]t Week 12, statistically significantly greater percentages of patients achieved a PASI 75 response or better on D2E7 than those on a placebo treatment.” Ex. 1001 at 42:5-8.[31]

Dependent Claims 2 and 10 (psoriasis affects at least 5% BSA) Are Obvious

’216 Claim Language	Prior Art Disclosures
Claim 2: The method of claim **1**, wherein at least 5% body surface area (BSA) of the patient is affected by the moderate to severe chronic plaque psoriasis.	“Adult patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area . . . . participated in the study.” Ex. 1036 at 1843; *see also* ex. 1003 at 250, 316.
Claim 10: The method of claim **9**, wherein at least 5% body surface area (BSA) of the patient is affected by the moderate to severe chronic plaque psoriasis.	

Dependent Claims 3, 6, 11, and 14 (pre-filled syringes for subcutaneous injection) Are Obvious

’216 Claim Language	Prior Art Disclosures
Claim 3: The method of claim **1**, wherein adalimumab is comprised in pre-filled syringes for subcutaneous	“HUMIRA is supplied in single-use, 1 mL pre-filled syringes, and also 2 mL glass vials as a sterile, preservative-free

[31] The ’216 patent is not prior art but its disclosure demonstrates the result is inherent for some portion of treated patients. *See supra* V.A.

'216 Claim Language	**Prior Art Disclosures**
injection.	solution for subcutaneous injection. . . . Each syringe delivers 0.8 mL (40 mg) of drug product. . . . Each 0.8 mL HUMIRA contains 40 mg adalimumab . . . ." Ex. 1026 at 1.
Claim 6: The method of claim **2**, wherein adalimumab is comprised in pre-filled syringes for subcutaneous injection.	
Claim 11: The method of claim **9**, wherein adalimumab is comprised in pre-filled syringes for subcutaneous injection.	
Claim 14: The method of claim **10**, wherein adalimumab is comprised in pre-filled syringes for subcutaneous injection.	

Dependent Claims 4, 5, 7, 8, 12, 13, 15 and 16 (pharmaceutical composition of 50 $^{mg}/_{ml}$) Are Obvious

'216 Claim Language	**Prior Art Disclosures**
Claim 4: The method of claim **1**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	"HUMIRA is supplied in single-use, 1 mL pre-filled syringes, and also 2 mL glass vials as a sterile, preservative-free solution for subcutaneous injection. . . . Each syringe delivers 0.8 mL (40 mg) of drug product." Ex. 1026 at 1. "Each 0.8 mL HUMIRA contains 40 mg adalimumab, 4.93 mg sodium chloride, 0.69 mg monobasic sodium phosphate dihydrate, 1.22 mg dibasic sodium phosphate dihydrate, 0.24 mg sodium citrate, 1.04 mg citric acid monohydrate, 9.6 mg mannitol, 0.8 mg polysorbate 80 and Water for Injection, USP. Sodium hydroxide added as necessary to adjust pH." Ex. 1026 at 1.
Claim 5: The method of claim **3**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 7: The method of claim **2**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 8: The method of claim **6**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 12: The method of claim **9**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 13: The method of claim **11**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 15: The method of claim **10**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	
Claim 16: The method of claim **15**, wherein adalimumab is formulated in a pharmaceutical composition and at a concentration of 50 $^{mg}/_{ml}$.	

VII. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that all claims of the '216 patent are unpatentable as obvious in view of the prior art identified herein and therefore requests that the Board institute *inter partes* review for all claims.

Dated: July 20, 2017

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 CFR 42.24(a), this Petition contains 13,620 words as counted by the word processing program used for its preparation (Microsoft Word 2010).

The undersigned further certifies that this brief complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and typestyle requirements of 37 C.F.R. § 42.6(a)(2)(iii). This brief has been prepared in a proportionally spaced typeface using Microsoft Word 2010 in Times New Roman 14 point font.

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Sandoz Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 9,512,216 and Exhibits 1001 – 1068 were served on July 20, 2017 via Federal Express to the correspondence address for the attorney of record for AbbVie Biotechnology Ltd., the assignee of the '216 patent.

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