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.: 9,067,992
Issue Date: June 30, 2015
Title: Use of TNFα Inhibitor for Treatment of Psoriatic Arthritis

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,067,992 PURSUANT TO 35 U.S.C. §§311-319 AND 37 C.F.R. §42

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EXHIBIT LIST

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1001	United States Patent No. 9,067,992, filed Dec. 8, 2014, issued June 30, 2015	"'992 patent"	n/a	
1002	Declaration of Simon M. Helfgott, M.D.	"Helfgott Decl."	n/a	
1003	E. Keystone et al., *The Fully Human Anti-TNF Monoclonal Antibody, Adalimumab (D2E7), Dose Ranging Study: The 24-Week Clinical Results in Patients with Active RA on Methotrexate Therapy (the Armada Trial)*, 60 ANNALS RHEUMATIC DISEASES A1 (2001) [OP0086][3]	"Keystone"	102(b)	
1004*	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 5 (2002) [OP11]	"Marzo-Ortega"	102(b)	102(a)
1005	Enbrel® (etanercept) Package Insert, (Immunex Corp., issued June 2000), 2001 Physician's Desk Reference, 55th ed.[4]	"2000 Enbrel® Package Insert"	102(b)	

[1] Pincites in the Petition and Declaration to exhibits marked with an asterisk (*) refer to stamped-on page numbers. All other pincites in the Petition and Declaration are to original page numbers.

[2] This column indicates whether an exhibit is prior art under 35 U.S.C. §§102(a), (b) or (e). "n/a" indicates the exhibit is not being relied upon as prior art.

[3] Keystone was published in June 2001. Ex.1013; *see also* ex.1057.

[4] The 2001 Physician's Desk Reference was published in November 2000. *See* ex.1015.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1006	Enbrel® (etanercept) Package Insert (Immunex Corp. Jan. 2002)	"2002 Enbrel® Package Insert"	102(b)	102(a)
1007*	B. A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42 ARTHRITIS & RHEUMATISM S400 [1977] (1999)	"van de Putte"	102(b)	
1008	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766666/	n/a	n/a	
1009	P. J. Mease, *Tumour Necrosis Factor (TNF) in Psoriatic Arthritis: Pathophysiology and Treatment with TNF Inhibitors*, 61 ANNALS RHEUMATIC DISEASES 298 (2002)[5]	"Mease 2002"	102(b)	102(a)
1010	*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"	n/a	
1011	Alan J. Lewis & Anthony M. Manning, *New Targets for Anti-Inflammatory Drugs*, 3 CURRENT OPINION CHEMICAL BIOLOGY 489 (1999)[6]	"Lewis"	102(b)	
1012	C. Antoni et al., *Sucessful [sic] Treatment of Severe Psoriatic Arthritis with Infliximab*, 42 ARTHRITIS & RHEUMATOLOGY S371 (1999)[7]	"Dechant 1999"	102(b)	

[5] Mease 2002 was published in April of 2002. Ex.1024.

[6] See ex.1048 for publication information.

[7] See ex.1036 for publication information.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1013	http://ard.bmj.com/content/60/Suppl_1#Speakerabstracts2001	n/a	n/a	
1014	George Spencer-Green, *Etanercept (Enbrel): Update on Therapeutic Use*, 59 ANNALS RHEUMATIC DISEASES i46 (2000)	"Spencer-Green"	102(b)	
1015	https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752	n/a	n/a	
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"	102(b)	
1017	Philip J. Mease, *Etanercept in the Treatment of Psoriatic Arthritis and Psoriasis: A Randomised Trial*, 356 LANCET 385 (2000)	"Mease 2000"	102(b)	
1018	P. J. Mease, *Cytokine Blockers in Psoriatic Arthritis*, 60 ANNALS RHEUMATIC DISEASES iii37 (2001)[8]	"Mease 2001"	102(b)	102(a)
1019	Joachim R. Kalden, *Emerging Role of Anti-Tumor Necrosis Factor Therapy in Rheumatic Diseases*, 4 ARTHRITIS RES. S34 (May 2002)	"Kalden"	102(b)	102(a)
1020	*Amgen Inc. v. AbbVie Biotech. Ltd.*, No. IPR2015-01517 (Patent Owner's Preliminary Response Oct. 19, 2015)	"Prelim. Response in '158 IPR"	n/a	
1021*	R. Rau et al., *Experience with D2E7*, 25 RHEUMATOLOGY TODAY 83 (2000)	"Rau"	102(b)	
1022	http://onlinelibrary.wiley.com/doi/10.1046/j.1365-2133.2001.04089.x/full	n/a	n/a	

[8] Mease 2001 was published in November 2001. *See* ex.1008.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1023	Christopher G. Jackson, *Immunomodulating Drugs in the Management of Psoriatic Arthritis*, 2 AM. J. CLINICAL DERMATOLOGY 367 (2001)[9]	"Jackson"	102(b)	102(a)
1024	https://www.ncbi.nlm.nih.gov/pubmed/11874829	n/a	n/a	
1025	Kelley's Textbook of Rheumatology vol. 2 (Shaun Ruddy et al. eds., 6th ed.) (2001)[10]	"Kelley's Textbook"	102(b)	
1026	Humira™ (adalimumab) Package Insert (Abbott Labs, Dec. 2002)	"Humira™ Package Insert"	102(a)	not prior art
1027	Remicade® (Infliximab) Package Insert, (Centocor, Inc. 1999) 2001 Physician's Desk Reference, 55th ed.[11]	"Remicade® Package Insert"	102(b)	
1028	Hanns-Martin Lorenz & Joachim R. Kalden, *Perspectives for TNF-α-Targeting Therapies*, 4 ARTHRITIS RES. S17 (May 2002)	"Lorenz"	102(b)	102(a)
1029	Claudia Dechant et al. *One Year Outcome of Patients with Severe Psoriatic Arthritis Treated with Infliximab*, 43 ARTHRITIS & RHEUMATISM S102 [212] (2000)[12]	"Dechant 2000"	102(b)	
1030	K. Eberhardt & E. Fex, *Clinical Course and Remission Rate in*	"Eberhardt"	102(b)	

[9] Jackson was published in December 2001. *See* ex.1041.

[10] Kelley's Textbook was published in June 2001. *See* ex.1055.

[11] *Supra* n.4.

[12] See ex.1032 for publication information.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	Patients with Early Rheumatoid Arthritis: Relationship to Outcome After 5 Years, 37 BRIT. J. RHEUMATOLOGY 1324 (1998)			
1031	Corrected Application Data Sheet (Apr. 7, 2015)	n/a	n/a	
1032	http://onlinelibrary.wiley.com/doi/10.1002/art.v43:9%2B/issuetoc	n/a	n/a	
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)[13]	"Ogilvie"	102(b)	
1034	*TNF-Alpha Inhibitor Projected to Offer Huge Market by 2010*, JAPAN CHEMICAL WEEK (Sept. 2001)	"Japan Chemical Week"	102(b)	102(a)
1035	2001 Physician's Desk Reference, 55th ed.[14] (excerpts)	"2001 PDR"	102(b)	
1036	http://onlinelibrary.wiley.com/doi/10.1002/art.1780422107/full	n/a	n/a	
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"	102(b)	
1038	http://onlinelibrary.wiley.com/doi/10.1046/j.1468-3083.2002.00391.x/full	n/a	n/a	

[13] Ogilvie was published in March 2001. *See* ex.1022.

[14] The 2001 PDR was published in November 2000. *Supra* n.4.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1039*	WO 98/05357, filed Aug. 1, 1997, published Feb. 12, 1998	"Feldmann"	102(b)	
1040	Douglas J. Perkins et al., *Reduction of NOS2 Overexpression in Rheumatoid Arthritis Patients Treated with Anti-Tumor Necrosis Factor α Monoclonal Antibody (cA2)*, 41 ARTHRITIS & RHEUMATISM 2205 (1998)	"Perkins"	102(b)	
1041	https://link.springer.com/journal/40257/2/6/page/1	n/a	n/a	
1042	Joachim Kempeni, *Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7*, 58 ANNALS RHEUMATIC DISEASES I70 (1999)	"Kempeni"	102(b)	
1043*	U.S. Provisional Application No. 60/397,275 filed July 19, 2002	"'275 application"	n/a	
1044*	U.S. Provisional Application No. 60/411,081 filed Sept. 16, 2002	"'081 application"	n/a	
1045*	U.S. Provisional Application No. 60/417,490 filed Oct 10, 2002	"'490 application"	n/a	
1046*	U.S. Provisional Application No. 60/455,777, filed Mar. 18, 2003	"'777 application"	n/a	
1047*	U.S. Application No. 10/622,932 filed July 18, 2003	"'932 application"	n/a	
1048	https://www.ncbi.nlm.nih.gov/pubmed/10419850	n/a	n/a	
1049*	Abbott Laboratories Press Release: Abbott laboratories initiates clinical trials to explore use of Humira™ (adalimumab) in psoriasis and psoriatic arthritis (Mar. 3, 2003), *available at*	"AbbVie Press Release"	102(a)	not prior art

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	https://web.archive.org/web/20030701072200/https:/www.immunetolerance.org/artman/publish/article_148.html			
1050	U. Wollina & H. Konrad, *Treatment of Recalcitrant Psoriatic Arthritis with Anti-Tumor Necrosis Factor-α Antibody*, 16 J. EUR. ACAD. DERMATOLOGY &VENEREOLOGY 127 (2002)[15]	"Wollina"	102(b)	102(a)
1051*	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"	n/a	
1052	Declaration of Victoria L. Reines	"Reines Decl."	n/a	
1053*	U.S. Environmental Protection Agency, *Exposure Factors Handbook* (1997)	"EPA Handbook"	102(b)	
1054	https://academic.oup.com/rheumatology/article/41/suppl_2/3/1788099/Paediatrics-and-Other-Inflammatory-Arthopathies	n/a	n/a	
1055	United States Copyright Office, Public Catalog for Kelley's Textbook of Rheumatology	n/a	n/a	

[15] Wollina was published in March 2002. *See* ex.1038.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
1056	Philip J. Mease et al., *Adalimumab Therapy in Patients with Psoriatic Arthritis: 24-Week Results of a Phase III Study*, 50 ARTHRITIS & RHEUMATISM 4097 (2004)	"Mease 2004"	102(b) for 2006 priority date (n/a for 2002, 2003 dates)	
1057	60 Annals Rheumatic Diseases (July 2001) cover	n/a	n/a	
1058*	U.S. Provisional Application No. 60/681,845 filed May 16, 2005	n/a	n/a	
1059	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 5 (2002) [OP11][16]	n/a	102(b)	102(a)
1060	Cover of Arthritis Research vol. 4, supplement 3 (2002) supplied by the British Library	n/a	n/a	

[16] See ex.1054 for publication information (noting that ex.1059 was published in April 2002).

I. INTRODUCTION

Sandoz Inc. ("Sandoz" or "Petitioner") respectfully requests *Inter Partes* Review ("IPR") pursuant to 35 U.S.C. §§311-319 and 37 C.F.R. §42 of claims 1, 2 and 5-7 of U.S. Patent No. 9,067,992 ("the '992 patent," ex.1001[17]), which is assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner").

The '992 patent claims methods of treating psoriatic arthritis ("PsA") by subcutaneously administering the anti-TNF-α antibody adalimumab, the active ingredient in AbbVie's Humira® product, at a dose of 40mg every other week ("eow").

Claims 1, 5 and 6 are anticipated by AbbVie's prior art publication, Mease 2004 (ex.1056), which explicitly disclosed every element of those claims more than one year before the earliest priority date to which they are entitled, May 16, 2006. It was not until that date that AbbVie filed a CIP application adding the limitations of claims 1, 5 and 6.

Moreover, *all* of the challenged claims are obvious over prior art available more than one year before AbbVie's earliest claimed priority date. AbbVie had placed in the prior art (Keystone, ex.1003) the exact same 40mg eow subcutaneous adalimumab dosing regimen to treat rheumatoid arthritis ("RA"). The prior art

[17] Pincites in the Petition and Declaration to exhibits marked with an asterisk (*) refer to stamped-on page numbers. All other pincites in the Petition and Declaration are to original page numbers.

rendered obvious that the same RA adalimumab dosing regimen could also be used to treat PsA. It was known that RA and PsA are closely related diseases, both mediated by TNF-α, which can be treated using the same drugs, including the TNF-α inhibitors infliximab and etanercept, with the same or similar dosing regimens. The prior art also accurately indicated that adalimumab could treat PsA based on its already-proven ability to treat RA. Accordingly, it would have been obvious to a person of ordinary skill in the art ("POSA") to have used the prior art RA dosing regimen of subcutaneously administering 40mg adalimumab eow, to also treat PsA.

In view of the known relationship between RA and PsA, and the history of using the same drugs and dosing regimens to treat both conditions, a POSA would have been motivated to use the known RA dosing regimen of 40mg adalimumab eow to also treat PsA. The prior art also showed that PsA was successfully treated with RA drugs and dosing regimens, which gave a POSA more than a reasonable expectation of success in achieving the claimed method. Accordingly, the claims of the '992 patent are invalid as obvious over the prior art.

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 '992 patent is related to two of the patents at issue[18] 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-MSG (D. Del. filed Aug. 4, 2016). The '992 patent is not related to any of the patents that have been asserted in the following judicial matter in which Petitioner was not and is not a party: *AbbVie Inc. et al. v. Boehringer Ingelheim Int'l GMBH et al.*, 1:17-cv-01065-MSG (D. Del. filed Aug. 2, 2017). Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '992 patent.

2. Related Proceedings Before the Board

AbbVie owns the patents that are the subjects of the following administrative matters: (1) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00172 (P.T.A.B.), Final Written Decision ("FWD") invalidating U.S. Patent No. 8,889,135 (the "'135 patent"), dated May 16, 2017

[18] U.S. Patent Nos. 8,961,973; 8,986,693 and the '992 patent claim priority to the same application, SN 60/561,139 filed April 9, 2004.

(hereinafter "*Coherus*"); (2) *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00408 (P.T.A.B), FWD invalidating U.S. Patent No. 8,889,135, dated July 6, 2017 (hereinafter "*BI408*"); (3) *Boehringer Ingelheim Int'l GmbH v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00409 (P.T.A.B), FWD invalidating U.S. Patent No. 8,889,135, dated July 6, 2017 (hereinafter "*BI409*"); (4) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00188 (P.T.A.B.), FWD invalidating U.S. Patent No. 9,017,680 (the "'680 patent"), dated June 9, 2017; (5) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00189 (P.T.A.B.), FWD invalidating U.S. Patent No. 9,073,987 (the "'987 patent"), dated June 9, 2017.

All three of the '135, '680 and '987 patents were directed to a method of treating RA by administering 40mg D2E7 subcutaneously eow. In its decisions, the Patent Trial and Appeal Board (the "Board") found the claims of all three patents invalid over the prior art. The patents that are the subjects in the identified administrative matters and the '992 patent however do not claim priority to any of the same applications. The '992 patent was filed later than and has a later priority date than the '135, '680, and '987 patents.

Petitioner has filed the following petitions for IPR: IPR2017-01823 (U.S. Patent No. 8,802,100); IPR2017-01824 (U.S. Patent No. 9,512,216); IPR2017-01987 (U.S Patent No. 8,911,737) and IPR2017-01988 (U.S Patent No. 8,974,790).

AbbVie is the patent owner of these four patents, however only U.S. Patent No. 9,512,216 and the '992 patent claim priority to the same applications, the earliest of which is SN 60/561,139 filed on April 9, 2004. Petitioner is also concurrently filing a petition for *inter partes* review of U.S. Patent No. 9,090,689, which claims priority to the same applications to which the '992 claims priority.

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

Lead Counsel	Back-up Counsel
David K. Barr (Reg. No. 31,940) David.Barr-PTAB@apks.com Arnold & Porter Kaye Scholer LLP 250 W. 55th Street New York, NY 10019 T: 212-836-7560 F: 212-836-6560	Daniel L. Reisner (*pro hac vice* motion filed) Daniel.Reisner@apks.com Arnold & Porter Kaye Scholer LLP 250 West 55th Street New York, NY 10019 T: 212-836-8132 F: 212-836-6432

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-PTAB@apks.com
Daniel.Reisner@apks.com

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 '992 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR on the grounds 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 '992 Patent

The '992 patent issued from SN 14/563,056 filed December 8, 2014. Each claim of the '992 patent is directed to a method of treating PsA by subcutaneously administering 40mg adalimumab eow.

The '992 patent states on its face that it is "[r]elated" to several continuation and CIP applications, with the earliest filed application, SN 10/622,932, filed July 18, 2003. Ex.1001. Because new matter was added to the specification at different times, the challenged claims are entitled to different effective filing dates. For purposes of this petition only, Petitioner asserts the following effective filing dates for the challenged claims:

- **Claims 1, 5 and 6: May 16, 2006** (when the American College of Rheumatology (ACR) response criteria was first added to the disclosure and to the claims, by filing CIP application SN 11/435,844) (*infra* pp.12-13)
- **Claim 2: July 18, 2003** (when the recited 40mg adalimumab eow dosing regimen to treat PsA was first added to the disclosure, by filing SN 10/622,932) (*infra* p.7-8);

- **Claim 7: May 16, 2005** (when the recited reduction/inhibition of progression of structural damage assessed by radiograph was first filed with provisional application SN 60/681,645) (ex.1058 at pp.33-35).

To the extent that AbbVie claims the benefit of any earlier-filed applications for any of the challenged claims, Sandoz disputes such claims.

In filing SN 14/563,056 which led to the issuance of the '992 patent, AbbVie claimed priority to four provisional applications having filing dates before the July 18, 2003 filing of non-provisional application SN 10/622,932 (collectively the "Provisional Applications") (exs.1043-47)[19]:

- Provisional No. 60/397,275 filed July 19, 2002 (ex.1043);
- Provisional No. 60/411,081 filed September 16, 2002 (ex.1044);
- Provisional No. 60/417,490 filed October 10, 2002 (ex.1045); and
- Provisional No. 60/455,777 filed March 18, 2003 (ex.1046).

No claim of the '992 patent is entitled to the priority date of any of these provisional applications because none disclose the "40mg" adalimumab administered "every other week" PsA dosing regimen required by every claim in the '992 patent.[20] *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290,

[19] AbbVie claimed priority to the Provisional Applications by filing an April 7, 2015 Corrected Application Data Sheet. Ex.1031.

[20] AbbVie may argue that the disclosures of the Provisional Applications would render the claimed PsA dosing regimen obvious to a POSA. However, it is well established that a disclosure that renders the claimed subject matter obvious is insufficient to satisfy the disclosure requirement. *Regents of the Univ. of Cal. v.*

1294 (Fed. Cir. 2002) ("[T]he specification of the *provisional* must 'contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms,' 35 U.S.C. §112 ¶1, to enable an ordinarily skilled artisan to practice the invention *claimed* in the *non-provisional* application.") (emphasis in original).

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

Petitioner requests IPR and cancellation of claims 1, 2 and 5-7 of the '992 patent on the grounds set forth in Table 1. 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.

Eli Lilly & Co., 119 F.3d 1559, 1567 (Fed. Cir. 1997) (reiterating that a description which merely "renders obvious a claimed invention is not sufficient to satisfy the written description requirement of that invention.").

Table 1 – Grounds for *Inter Partes* Review

Ground	Claims	Assumed Priority Date	Statutory Basis and Prior Art
1	1, 5 and 6	May 16, 2006	Anticipated under 35 U.S.C. §102(a) by Mease 2004 (ex.1056)
2	1, 2, 5, 6 and 7	July 18, 2003	Obvious under 35 U.S.C. §103(a) over Keystone (ex.1003) combined with Lorenz (ex.1028) and Mease 2000 (ex.1017)
3	Same as Ground 2	July 19, 2002	Obvious under 35 U.S.C. §103(a) over Keystone combined with Mease 2000 and Dechant 2000 (ex. 1029), and, for claim 7, combined with Rau (ex.1021*)

Furthermore, the POSA would understand these prior art references in the context of the wider body of prior art concerning the treatment of PsA and related diseases. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362-63 (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 [POSA],' and 'the inferences and creative steps that a [POSA] would employ.'").[21]

[21] Although AbbVie disclosed to the Patent Office most of the above-listed references and background prior art discussed herein, they were included along with several hundred other references. There is no evidence the Examiner considered the specific portions of the prior art described in this Petition. *Microsoft Corp. v. Parallel Networks Licensing, LLC*, No. IPR2015-00486, Decision Institution of *Inter Partes* Review, Paper No. 10, at 14-15 (P.T.A.B. July 15, 2015) (rejecting argument that the Board 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

Section VI and the Declaration of Simon Helfgott, M.D. (ex.1002) further support the grounds for invalidity of the challenged claims of the '992 patent. Ex.1002 at ¶¶114-57. Helfgott is an expert in rheumatology and the treatment of PsA, and is qualified to opine on what a POSA would have understood and concluded from the prior art (*id.* at ¶¶3-15, 24-26). He is therefore competent to testify in this proceeding.

Many prior art references cited herein were published in medical journals. As Helfgott explains, over the course of his career he has subscribed to many such journals and/or has accessed them in libraries or from online databases. *Id.* at ¶15. In his experience, journal issues are available to the public (either through the mail to subscribers, including libraries, or online when published over the internet), as of approximately the date printed on the face of the reference, if not slightly earlier. *Id.*

V. SUMMARY OF THE '992 PATENT

A. Background of the '992 Patent

According to the '992 patent, "[p]soriatic arthritis refers to chronic inflammatory arthritis which is associated with psoriasis . . . ." Ex.1001 at 24:45-46. The '992 patent acknowledges that the prior art taught that TNF-α "has been

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the expert declaration submitted herewith which places the teachings of the prior art in context. Accordingly, this petition presents invalidity grounds that were not considered during prosecution.

implicated in the pathophysiology of [PsA]" (*id.* at 24:22-24), and explains the known link between PsA and RA. The '992 patent states that both PsA and RA are "disorder[s] in which TNFα activity is detrimental," (*id.* at 3:5-11) and that both PsA and RA patients suffer from "[e]rosive polyarthritis" – *i.e.*, inflammatory arthritis that results in joint destruction and erosion. *Id.* at 1:39-49, 22:42-45. The specification further explains that the same criteria used to assess disease severity in RA (*e.g.*, American College of Rheumatology ("ACR") scores, swollen joint count ("SJC"), tender joint count ("TJC") and progression of structural damage (*e.g.*, Total Modified Sharp Score ("mTSS"))) are also used in PsA. *Id*. at 21:19-56, 37:31-40:33.

The '992 patent issued with two independent claims.

Claim 2 claims a method for reducing or inhibiting symptoms in a patient with PsA, comprising subcutaneously administering to the patient 40mg adalimumab eow.

Claim 1 claims a method of treating "moderate to severe" PsA in adult patients, wherein each patient has ≥3 swollen and ≥3 tender joints prior to the treatment and has failed NSAID therapy, comprising subcutaneously administering 40mg adalimumab eow, wherein 23% of the patients treated achieve ACR70[22] at

[22] As Helfgott explains, a 70% reduction in ACR score is commonly referred to as an "ACR70" response. Ex.1002 at ¶34.

week 24 of treatment. Thus, claim 1 claims the same PsA treatment method as claim 2, but also specifies certain clinical trial patient enrollment criteria and a clinical endpoint.

Claim 5 depends from claim 2 and recites that the patient treated achieves at least a 50% reduction in ACR score at week 24. Claim 6 depends from claim 5 and recites that the patient achieves at least a 70% reduction in ACR score at week 24. Claim 7 depends from claim 2 and recites that the symptoms are progression of structural damage assessed by radiograph.

The ’992 patent includes an example of a 24-week clinical trial treating patients having “moderate to severely active PsA (≥3 swollen and ≥3 tender joints) who had failed NSA[I]D therapy” by subcutaneously administering 40mg adalimumab or placebo eow for 24 weeks. *Id*. at 37:31-50. Patients were assessed by radiographs, and it was found that “[a]dalimumab was more effective compared with placebo in inhibiting radiographic disease progression over a 24-week period.” *Id.* at 37:52–40:33. The example includes Table 1, reproduced below, which provides the clinical results in terms of the percentage of patients achieving reduction in ACR scores.

TABLE 1

ACR response: % of patients			
	ACR20	ACR50	ACR70
Placebo (N = 162)	15	6	1
Adalimumab (N = 151)	57	39	23

Id. at 38:35-43.

Based on this example, AbbVie added claims such that (a) independent claim 1 recites the treatment of adult patients having ≥3 swollen and ≥3 tender joints and that 23% of patients achieve an ACR70 response at week 24 of the treatment; (b) claim 5 (which depends from claim 2) recites that the patient treated achieves a 50% reduction in ACR score at week 24 of treatment; and (c) claim 6 (which depends from claim 5) recites that the patient treated achieves a 70% reduction in ACR score at week 24 of treatment. However the complete example, including ACR response data, was not added to the ’992 specification until the May 16, 2006 filing of CIP application SN 11/435,844. Thus, prior to May 16, 2006, there was no support in the ’992 specification for the subject matter of claim 1 reciting “wherein 23% of said patients achieve 70% reduction in [ACR] score at week 24 of the treatment,” or for the 50% and 70% reduction in ACR scores recited respectively in claims 5 and 6. Therefore, none of claims 1, 5 and 6 is entitled to priority before May 16, 2006.

B. Person of Ordinary Skill in the Art

As explained by Helfgott, a POSA relating to the subject matter of the '992 patent would have an M.D. and at least 3 years' post-residency experience treating patients for PsA and RA, including with TNF-α inhibitors, and would be familiar with dosing regimens for TNF-α inhibitors that had been reported in the literature. Ex.1002 at ¶25.

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

The claim terms in the '992 patent are presumed have 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 preambles to claim 1 ("A method of treatment of moderate to severe active [PsA]" (ex.1001)) and claim 2 ("A method for reducing or inhibiting symptoms in a patient with [PsA]" (*id.*)) are statements of intended use and are not limiting. *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,* 320 F.3d 1339, 1345 (Fed. Cir. 2003). If the Board concludes that the preambles should be construed, the term "treatment" in claim 1 should be given its BRI of "reducing the signs, symptoms and/or progression" of "moderate to severe active [PsA]." If the Board construes claim 2's preamble, it should be given its plain and

ordinary meaning of reducing or inhibiting symptoms of PsA without requiring any specific level of therapeutic effect, as supported by the '992 specification:

> [t]his invention provides a method of treating erosive polyarthritis in which the administration of a TNFα inhibitor e.g., a TNFα antibody . . . is beneficial. . . .[A] disorder in which TNFα activity is detrimental is a disorder in which inhibition of TNFα activity is expected to alleviate the symptoms and/or progression of the disorder.

Ex.1001 at 11:20-23, 22:26-29. Helfgott further supports this interpretation of the preambles of claims 1 and 2. Ex.1002 at ¶¶28-30.

The term "moderate to severe active" PsA is defined in the specification to mean that a patient has ≥3 swollen and ≥3 tender joints ("patients with moderate to severely active PsA (≥3 swollen and ≥3 tender joints)"). Ex.1001 at 37:31-33; Ex.1002 at ¶22. This common definition would have been familiar to the POSA. Ex.1002 at ¶30.

Otherwise, for purposes of this petition only, Sandoz does not assert that any special meanings apply to claim terms in the '992 patent.

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 IPR 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 each 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

1. Ground 1: Claims 1, 5 and 6 are Anticipated by Mease 2004 (May 16, 2006 Priority Date)

Claims 1, 5 and 6 are anticipated by Mease 2004, which discloses each element of those claims and was published more than one year before their May 16, 2006 priority date.

2. Ground 2: Claims 1, 2 and 5-7 are Obvious Over the Prior Art (July 18, 2003 Priority Date)

The ’992 patent claims a PsA dosing regimen of subcutaneously administering 40mg adalimumab eow. AbbVie had already placed in its prior art Keystone reference (ex.1003) the subcutaneous administration of 40mg adalimumab eow to successfully treat RA. Therefore, the only difference between Keystone and the ’992 claims is that in Keystone the dosing regimen was used to treat RA, whereas the ’992 claims recite the same dosing regimen to treat PsA.

More than one year before July 18, 2003, however, the prior art taught that:

- Adalimumab subcutaneously dosed at 40mg eow would successfully treat RA (Keystone, ex.1003);
- Adalimumab would be useful to treat PsA (Lorenz, ex.1028); and
- TNF-α inhibitors, *e.g.*, infliximab and etanercept, could be used to treat PsA using the same dosing regimen used to treat RA

(Lorenz, ex.1028; Dechant 2000, ex.1029; references summarized *infra* Table 2).

The prior art would have motivated a POSA to use the already known 40mg eow adalimumab RA dosing regimen to treat PsA and a POSA would have had a reasonable expectation of success in so doing. The prior art taught that RA and PsA are related conditions, both mediated by TNF-α. The POSA also knew that adalimumab, like infliximab and etanercept, was a TNF-α inhibitor that successfully treated RA. The POSA further knew that infliximab and etanercept had successfully treated PsA using the same dosing regimens that had been successful in treating RA. For example, Lorenz and the prior art summarized *infra* Table 2 demonstrate the successful treatment of PsA with the same infliximab and etanercept doses that had been used to treat RA. A POSA also knew that the prior art accurately predicted that adalimumab would be useful in the treatment of PsA. Therefore, the POSA would have expected that the subcutaneous administration of 40mg adalimumab eow would treat not only RA (shown by Keystone), but would also treat PsA.

The recitation of ACR responses (claims 1, 5 and 6) or of reduction in progression of structural damage (claim 7) as clinical endpoints does not impart a patentable distinction under well-established Federal Circuit authority. *Infra* VI.E.5-VI.E.6. Moreover, a POSA would expect from Keystone that PsA patients receiving 40mg eow adalimumab would likely achieve ACR responses comparable

to those achieved by the RA patients in Keystone, rendering the ACR responses recited in the '992 claims obvious. Ex.1002 at ¶129. A POSA would also know from Mease 2000 and Dechant 2000 that patients in PsA clinical trials receiving etanercept and infliximab achieved ACR responses comparable to those recited in the '992 claims, again rendering the recited ACR responses obvious. A POSA would further know from Lorenz and Rau that treatment with TNF-α inhibitors resulted in the inhibition of progression of structural damage in RA, as assessed by radiograph, and would expect similar results in PsA. Ex.1002 at ¶¶140, 156.

3. Ground 3: Claims 1, 2 and 5-7 are Obvious Over the Prior Art (July 19, 2002 Priority Date)

Even assuming *arguendo* that AbbVie can establish that the '992 patent is entitled to the July 19, 2002 priority date of the earliest filed provisional application, the '992 patent is obvious over Keystone combined with Mease 2000 and Dechant 2000.

Keystone disclosed the 40mg eow adalimumab dosing regimen to treat RA. Mease 2000 and Dechant 2000 provided the POSA with the motivation to use this known RA dosing regimen to treat PsA with a reasonable expectation of success. Mease 2000 and Dechant 2000 described the role of TNF-α in RA and in PsA and the ability of infliximab and etanercept to relieve the signs and symptoms of RA and PsA using the same dosing regimens of those drugs. Therefore, a POSA

would have been motivated to apply Keystone's RA adalimumab dosing regimen to treat PsA and would have reasonably expected it to succeed. Ex.1002 at ¶144.

Accordingly, the prior art renders obvious the '992 patent's claimed PsA dosing regimen of administering 40mg adalimumab eow.

B. Patents and Printed Publications Relied on in this Petition

1. Mease 2004 (Ex.1056)

Mease 2004 described the results of the same clinical study of adalimumab to treat PsA that was added as an example in the '992 specification with the filing of a May 16, 2006 CIP application. The results of Mease 2004 in terms of ACR responses are the same as those recited in claims 1, 5 and 6. The 24-week study evaluated the efficacy and safety of treating PsA patients with 40mg adalimumab administered subcutaneously eow, compared with placebo. Ex.1056 at 4097. "Adult patients were eligible to enroll if they had active PsA ($\geq$3 swollen and $\geq$3 tender joints), and had failed NSAID therapy." *Id*. Patients were assessed using ACR response criteria. At week 24, among adalimumab-treated patients, 57% achieved ACR20, 39% achieved ACR50, and 23% achieved ACR70. *Id.*

2. Keystone (Ex.1003)

Keystone described a clinical trial investigating the use of adalimumab to treat RA. Ex.1003 at A481. Patients with active RA were subcutaneously

administered 20, 40 or 80mg D2E7[23] eow over a 24-week period. *Id.* Keystone concluded: "[t]he efficacy of the fully human anti-TNFα monoclonal antibody, adalimumab (D2E7), in addition to [methotrexate ("MTX")] in patients with longstanding RA is significantly better than placebo when given every other week subcutaneously. The ACR50 and ACR70 responses were impressive in this group of patients with refractory RA."[24] *Id.* A POSA would have understood that Keystone shows that each of the 20, 40 and 80mg eow dosing regimen was effective in treating RA.[25] Ex.1002 at ¶37.

Keystone thus described the exact method claimed by the '992 patent of subcutaneously administering 40mg adalimumab eow, except that the method was used to treat RA instead of PsA.

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[23] The specification of the '992 patent equates adalimumab with "D2E7." Ex.1001 at 20:66-21:1. For the purposes of this Petition only, the claimed antibody will be termed "adalimumab" or "D2E7" without prejudice to Sandoz's ability to challenge the meaning, scope, and indefiniteness of the term in other proceedings.

[24] As described by Helfgott, ACR scores are standardized measures of joint disease activity in inflammatory arthritis. Ex.1002 at ¶34.

[25] In *Coherus*, *BI408*, *BI409*, IPR2016-00188 and IPR2016-00189, the Board's FWDs found the 40mg eow adalimumab RA dosing regimen claimed in the '135, '680, and '987 patents (all of which have an earlier priority date of June 8, 2001), obvious based on prior art that pre-dated Keystone.

3. 2002 Humira® Package Insert (Ex.1026)

When Humira® was approved in December 2002, AbbVie's product label (the "2002 Humira® Package Insert") included 40mg Humira® administered subcutaneously eow as the recommended dosing regimen to treat RA. Ex.1026 at 14. The 2002 Humira® Package Insert therefore confirmed what a POSA would have already known from Keystone – that this 40mg eow dosing regimen effectively blocked TNF-α to treat RA.

4. Lorenz (Ex.1028)

Lorenz summarized the vast body of prior art establishing the role of TNF-α in the related conditions of RA, PsA and psoriasis, and taught that TNF-α inhibitors like adalimumab could be used to treat PsA. Ex.1028 at S17-19. Lorenz reviewed clinical trial results for infliximab, etanercept, and "the fully human monoclonal antibody D2E7" (adalimumab). *Id*. at S17-18.

Lorenz reviewed the use of TNF-α inhibitors, including infliximab and etanercept, in the treatment of RA and Crohn's, stating that "further steps will be taken to establish this therapeutic principle for treatment of other chronic inflammatory diseases." *Id*. at S18. Lorenz accurately predicted that "[t]hese developments may include . . . clinical studies with new TNF-α-targeting immunobiologicals, such as the human D2E7 antibody," citing to a successful RA clinical trial of adalimumab in a publication by van de Putte. *Id*. at reference 1.

Under a heading, "New indications for TNF-α-targeting therapies, [PsA] and psoriasis," Lorenz discussed the use of TNF-α inhibitors to treat PsA, stating "[t]he current therapeutic approaches for PsA are similar to those for RA . . . ." *Id.* Lorenz observed that "the levels of TNF-α are elevated in the synovial fluid, tissue and skin lesions in PsA patients, with TNF-α levels correlating with disease activity." *Id*. "As a logical consequence," Lorenz cited to "studies with TNF-α-blocking biologicals" including "[s]everal open-label studies [that] have investigated the use of anti-TNF-α agents in the treatment of PsA and psoriasis." *Id.* Lorenz reviewed publications describing clinical trials for infliximab and etanercept in treating PsA, demonstrating the successful treatment of both RA and PsA with anti-TNF-α agents. *Id.* at S17-19.

Lorenz described the authors' own clinical trials: "[i]n our open-label experience, infliximab treatment was efficacious and safe in PsA and psoriasis." *Id.* at S18. Infliximab was administered at a dose of $5^{mg}/_{kg}$ at weeks 0, 2 and 6, and all 10 patients in the study achieved ACR20 by week 2. *Id.* At 10 weeks, eight patients achieved ACR70, "six of whom maintained this improvement to week 54." *Id*.

Lorenz also described a study by Mease in which PsA patients were successfully treated with etanercept 25mg subcutaneously twice weekly[26], and reported "[i]n an open-label extension study, etanercept continued to effectively reduce the clinical signs and symptoms of PsA and psoriasis for up to 36 weeks." *Id.* at S19. Lorenz concluded, "[t]he results of these studies suggest that TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis. In addition, anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." *Id*. at S19.

Lorenz also reported that a clinical trial of infliximab "showed, for the first time in any RA trial, that there was no median radiological progression in the groups given infliximab plus methotrexate over a 12-month observation period." *Id*. at S17. As Helfgott explains, a POSA would expect similar results in PsA, since PsA, like RA, was understood to be an inflammatory arthritis, mediated by TNF-α. Ex.1002 at ¶¶72-81.

Lorenz accordingly taught that "anti-TNF-α therapy," including treatment with infliximab, etanercept and D2E7 (adalimumab), provides "option[s] for the

[26] Mease 2000, discussed below, described the RA dosage of 25mg etanercept subcutaneously administered twice weekly. Ex.1017 at 389. A POSA would also know from the Enbrel® label that the FDA-approved etanercept dosage for treating RA and PsA was the same 25mg subcutaneously administered twice weekly. Ex.1006 at 23.

control of" PsA and psoriasis. *Id.* at S18-19. Lorenz's conclusion was an accepted consensus view in the field at the time. *Infra* VI.B.5-VI.B.9.

5. Japan Chemical Week (Ex.1034)

Japan Chemical Week summarized the previously reported use of TNF-α inhibitors in the treatment of RA, PsA and psoriasis. Ex.1034 at 1. Commenting on infliximab and etanercept, Japan Chemical Week also identified "D2E7" as "likely to have wider applications, covering not only RA and IBD but also psoriasis, indicating further development of markets. It has become known that TNF-alpha is a cytokine causing various inflammatory diseases, such as RA . . . psoriasis, [and] [PsA] . . . ." *Id.*

Japan Chemical Week evidences the POSA's understanding of the logical progression of TNF-α inhibitors, including adalimumab, in treating PsA and psoriasis as well as RA. *Id.*

6. AbbVie Press Release (Ex.1049*)

On March 3, 2003, AbbVie's predecessor, Abbott Laboratories, published a press release announcing that it had initiated a clinical trial to explore the use of Humira® to treat PsA. Ex.1049* at 1. AbbVie explained its rationale for the clinical trials: (1) "[p]soriatic arthritis . . . [is an] autoimmune disorder[] in which . . . [TNF-α] . . . has been suggested to play a role;" (2) clinical data "suggest[s] that treatments that inhibit TNF-[α] may be effective in th[is] disease;" and (3)

"HUMIRA . . . works by specifically blocking TNF-[α]." *Id.* Accordingly, AbbVie's development of Humira® for the PsA indication was premised directly on the prior art's teaching that TNF-α inhibition could treat PsA.

7. Marzo-Ortega (Ex.1004*)

Marzo-Ortega described the efficacy of treating PsA with $3^{mg}/_{kg}$ infliximab, noting that "[p]ro-inflammatory cytokines such as TNF alpha have been found in psoriatic skin lesions and in the serum and synovium of patients with PsA." Ex.1004* at 6. Marzo-Ortega further explained that because a dose of $3^{mg}/_{kg}$ infliximab had been proven to treat RA, the researchers decided to use that identical dose to treat patients with PsA and psoriasis. *Id.* ("[I]nfliximab at a dose of $3^{mg}/_{kg}$ with methotrexate has proven effective in [RA]. 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.").

The $3^{mg}/_{kg}$ dose of infliximab was administered to patients with "active" PsA at weeks 0, 2, 6 and 14. *Id.* "Clinical outcomes including TJC [tender joint count], SJC [swollen joint count], PGAS (physician assessment of disease activity) and CRP [C-reactive protein]" were measured to assess PsA improvement. *Id.* "ACR50 (for [RA]) was achieved in four patients." *Id.* Marzo-Ortega concluded that "[t]hese preliminary results suggest a dramatic beneficial effect on skin and joint disease in patients with PsA and skin psoriasis on methotrexate." *Id.*

8. Mease 2000 (Ex.1017)

Mease 2000 described a clinical trial testing the safety and efficacy of treating PsA with 25mg etanercept administered twice-weekly subcutaneously, the same etanercept dosing regimen that had successfully treated RA. Ex.1017 at 385, 389.

Mease 2000 applied to etanercept the well-known prior art premise that drugs known to treat RA are prime candidates for treating PsA: "[e]tanercept, a [TNF] inhibitor, has shown efficacy in the treatment of [RA]. [PsA] and psoriasis are disease states in which [TNF], a proinflammatory cytokine, is present in increased concentrations in joints and in the skin. Therefore, [PsA] and psoriasis may be appropriate therapeutic targets for etanercept." *Id*. at Abstract.

In discussing the etanercept PsA clinical trials, Mease 2000 stated that "[t]umour-necrosis-factor inhibition with etanercept has previously been shown to diminish the activity of [RA]." *Id*. at 385. Mease 2000 further associated using etanercept to treat PsA with the drug's prior success treating RA with the same dosing regimen:

> [t]here is a need for a new therapy to treat both [PsA] and psoriasis. Etanercept has been shown in previous trials to be effective against [RA] with no serious toxic effects. In two randomised controlled trials of etanercept (25 mg subcutaneously twice weekly) in patients with active DMARD-refractory [RA], 59–71% of etanercept patients achieved the ACR20 response at 6 months, compared with 11–23% of placebo patients ($p<0.001$); 39–40% and

> 3–5% of patients, respectively, achieved the ACR50 response ($p<0.01$).

Id. at 389.

Mease 2000 enrolled "adults between 18 and 70 years who had active [PsA] (defined as ≥3 swollen joints and ≥3 tender or painful joints) at the time of study enrolment" and who "had an inadequate response to [NSAID] drugs." *Id.* at 385. Mease 2000's clinical results showed that the same twice weekly subcutaneous dosing of 25mg etanercept that was successful in treating RA was also successful in treating PsA. *Id.* at 387-89; ex.1006 at 5, tbl. 1 (at month 3 of Study I, of the Enbrel®-treated patients, 62% achieved ACR20, 41% achieved ACR50 and 15% achieved ACR70).

Mease 2000 concluded, "[t]he results of this study indicate that blocking [TNF] in both [PsA] and psoriasis may offer a new therapeutic option for patients with both diseases." Ex.1017 at 389.

9. Dechant 2000 (Ex.1029)

Dechant 2000 described a clinical study of infliximab to treat patients having "severe" PsA, based on the proven ability of infliximab to treat RA: "[t]he anti-TNF-alpha antibody infliximab proved to be highly effective in treatment of [RA]. For [PsA] it is known, that TNF-alpha is elevated in the synovial fluid and skin lesions. Therefore we wondered whether an anti-TNF-therapy could be similar[l]y successful in the treatment of [PsA]." Ex.1029 at S102. Dechant 2000 described

an extension of an earlier infliximab clinical trial to treat PsA (Dechant 1999, ex.1012) in which PsA patients were successfully treated with $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6. *Id.*; ex.1029 at S102.

The extension study described in Dechant 2000 used lower infliximab doses to treat PsA. Ex.1029 at S102. Dechant 2000 explained that in the initial trial, 10 patients having "severe [PsA]" were administered $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 and all of them "showed a dramatic[] response to infliximab treatment" at week 10. *Id.* "Thereafter infliximab treatment was adapted to the individual needs of the patients. Patients were followed for up to one year by evaluating the ACR criteria (for RA)." *Id.* Five of the original 10 patients (4 of whom had achieved ACR70, and one who had achieved ACR50 at week 10) were then treated with a lower dose of 3-$4^{mg}/_{kg}$ at an infusion interval of ≥8 weeks. *Id.* "At follow up at year one after start of infliximab therapy all of these 5 patients still had an ACR 70 response." *Id.* Four of the other 5 original patients also received ongoing infliximab treatment at the reduced dose of 3-$4^{mg}/_{kg}$ at intervals of ≥8 weeks. *Id.* "[Three] of these patients with an ACR 70 response at week 10 had an ACR 50 response at the one-year evaluation." *Id.*

Dechant 2000 concluded, "[t]hese data show that infliximab was effective over one year. Therefore infliximab seems to be effective in the treatment of severe [PsA] as well." *Id.*

A POSA would understand from Dechant 2000 that infliximab treated "severe" PsA as well as RA and, moreover, that more than 23% of the patients treated achieved ACR70 after one year of treatment. Ex.1002 at ¶68. In addition, a POSA would understand from Dechant 2000 that infliximab was effective in treating PsA at three dosage levels, $5^{mg}/_{kg}$, $4^{mg}/_{kg}$ and $3^{mg}/_{kg}$. *Id.*

10. Rau (Ex.1021*)

Rau described clinical studies of D2E7 (adalimumab) to treat RA using eow doses of 0.5-$10^{mg}/_{kg}$. Ex.1021***** at 5. For patients in the Rau studies, progression of structural damage was assessed by radiograph prior to and during treatment, and was quantified using standardized scores measuring joint destruction and erosion, and joint space narrowing. *Id.* at 7. "[A]n increase in [joint destruction] scores could be seen in nearly all patients," during the period before treatment with adalimumab began, "but in almost none of the patients during the treatment." *Id.* Similarly, "[i]n the [erosion score], one sees in the pre-treatment phase a strongly significant increase" whereas there was "almost no change during the treatment with D2E7." *Id.* "[T]he same is true for the Joint Space Narrowing Score." *Id.*

A POSA would therefore understand that treatment with D2E7 inhibited progression of structural damage in RA, as assessed by radiograph. As Helfgott explains, a POSA would expect similar results when D2E7 was used to treat PsA. Ex.1002 at ¶70.

C. The Prior Art Taught that RA and PsA Shared Disease Characteristics and Were Treated by the Same Drugs with the Same or Similar Dosing Regimens

1. RA and PsA Are Related Autoimmune, Inflammatory, Chronic Diseases

The prior art taught that RA and PsA are autoimmune inflammatory diseases. *E.g.*, ex.1011 at 489 ("Inflammatory and autoimmune diseases, include[e] [RA], . . . [and] psoriasis . . . ."); ex.1023 at 367 ("[PsA] is a chronic inflammatory arthropathy . . . . The cause of [PsA] remains unknown but appears to be autoimmune in nature . . . ."). The prior art also taught that both RA and PsA are systemic, chronic diseases. *E.g.*, ex.1025 at 1072 ("[PsA] is a systemic inflammatory disease with articular and extra-articular features."); ex.1025 at 921 ("RA has features of a systemic disease that is capable of involving a variety of major organ systems."); ex.1030 at 1325 ("Different patterns of [RA] have been described. The two main patterns are chronic persistent and the relapsing-remitting disease course.").

2. RA and PsA Are TNF-α-Related Disorders

Prior art publications widely reported the connection between TNF-α and both RA and PsA. In 1999, Furst et al. ("Furst") discussed the role of TNF-α in RA and the use of TNF-inhibitors to treat RA. Ex.1016. Mease 2000 explained that "[PsA] and psoriasis are disease states in which tumour necrosis factor, a proinflammatory cytokine, is present in increased concentrations in joints and in

the skin." Ex.1017 at 385. Also in 2000, Spencer-Green explained that "TNF is an important inflammatory disease mediator in a wide spectrum of articular diseases, including RA, JRA, and PsA." Ex.1014 at i48.

Mease 2002 emphasized TNF's role in "inflammatory conditions (for example, RA and other autoimmune diseases)," explaining that "TNF is present at high levels in the joint fluid and tissue of patients with RA and PsA." Ex.1009 at 301. In 2002, Kalden reported, "[i]t 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.1019 at S34-35. In 2002, Lorenz similarly observed that "[c]irculating T lymphocytes and macrophages isolated from PsA patients produce an increased amount of TNF-α compared with macrophages isolated from healthy controls. Furthermore, the levels of TNF-α are elevated in the synovial fluid, tissue and skin lesions in PsA patients, with TNF-α levels correlating with disease activity." Ex.1028 at S18.

Therefore the prior art clearly taught that TNF-α was a causative factor in both RA and PsA.

3. The Prior Art Taught That Adalimumab Was a Prime Candidate To Treat PsA

Lorenz specifically identified D2E7 as one of the new anti-TNF-α therapies for treating chronic inflammatory diseases mediated by TNF-α. Ex.1028 at S17-18. Based on a review of the art establishing the role of TNF-α in chronic inflammatory diseases, including RA and PsA, Lorenz restated the known relationship between TNF-α and PsA: "TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis." *Id.* at S19. Lorenz cited successful PsA clinical trials with infliximab ("[i]n our open-label experience, infliximab treatment was efficacious and safe in PsA and psoriasis") and etanercept ("[i]n an open-label extension study, etanercept continued to effectively reduce clinical signs and symptoms of PsA and psoriasis for up to 36 weeks."). *Id.* at S18-19. Lorenz concluded that "anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." *Id.* at S19. Lorenz specifically identified D2E7 (adalimumab), along with infliximab and etanercept, as an anti-TNF-α therapy available to treat "chronic inflammatory diseases" caused by TNF-α and identified PsA as among the "[n]ew indications for TNF-α-targeting therapies." *Id.* at S17-19.

Japan Chemical Week similarly identified adalimumab, in addition to infliximab and etanercept, as TNF-α inhibitors that would be used to treat not only RA, but also PsA and psoriasis. Ex.1034 at 1.

AbbVie's development of Humira® to treat PsA and psoriasis was premised directly on the prior art's teaching that TNF-α inhibition could treat PsA and psoriasis. On March 3, 2003, AbbVie published a press release announcing that it had initiated clinical trials to explore the use of Humira® to treat PsA and psoriasis. Ex.1049***** at 1. AbbVie explained its rationale for the trials, stating: (1) "[p]soriasis and [PsA] are autoimmune disorders in which . . . tumor necrosis factor-alpha . . . has been suggested to play a role in the disease development. Data from clinical trials suggest that treatments that inhibit TNF-[α] may be effective in these disease states;" and (2) "HUMIRA . . . works by specifically blocking TNF-[α]." *Id.*

4. The Prior Art Taught Using TNF-α Inhibitors To Treat RA and PsA

Based on the role of TNF-α, prior art publications taught the use of TNF-α inhibitors to treat RA and PsA. By 2002, infliximab (Remicade®), etanercept (Enbrel®) and adalimumab (Humira®) had all been approved to treat RA, and their efficacy in RA was well established in the prior art. As described *supra* VI.C.2, in 1999 Furst discussed TNF blockade in treating RA and predicted that "TNF blocking treatment will be used in other diseases where TNF appears to have a pathogenetic role. As evidence supporting the use of these agents in those diseases (for example, . . . psoriatic arthropathy) is accumulated, TNF blocking treatment should be used in those populations." Ex.1016 at 726. Lorenz summarized the

vast body of prior art establishing the role of TNF-α in the related conditions of RA and PsA, and taught that TNF-α inhibitors like adalimumab could be used to treat PsA. Ex.1028 at S17-19. Lorenz further described studies treating PsA with infliximab and etanercept, and explained that these studies "were initiated . . . [a]s a logical consequence" of the known role of TNF-α in PsA. *Id.* at S18.

Mease 2000 described the successful treatment of PsA with etanercept and stated that "blocking tumour necrosis factor in both [PsA] and psoriasis may offer a new therapeutic option for patients with both diseases." Ex.1017 at 389.[27] Similarly, Kalden stated, "anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." Ex.1019 at S36.

5. The Prior Art Demonstrated That TNF-α Inhibitors Treated RA and PsA Using the Same or Similar Dosing Regimens

Prompted by TNF-α's known role in RA and PsA, researchers demonstrated that TNF-α inhibitors were effective in treating both diseases. Ex.1002 at ¶¶82-89. Furthermore, the prior art taught that drugs used to treat RA could also be used to treat PsA using the same or similar dosing regimens. For example, the prior art

[27] 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.

established that infliximab and etanercept were effective in treating both RA and PsA using the same or similar dosing regimens. *Infra* Table 2.

a. The Prior Art Taught That Infliximab at 3 and 5$^{mg}/_{kg}$ Doses Effectively Treated RA and PsA

The prior art taught that 3 and 5$^{mg}/_{kg}$ infliximab effectively treated RA. For example, the Remicade® Package Insert taught that 3$^{mg}/_{kg}$ or 10$^{mg}/_{kg}$ infliximab administered at weeks 0, 2 and 6, then every 4 or 8 weeks thereafter in combination with methotrexate effectively treated RA. Ex.1027 at 1085.

Feldmann and Perkins each taught that a single infusion of 5, 10, or 20$^{mg}/_{kg}$ infliximab in combination with methotrexate effectively treated RA. Ex.1039***** at 65:11 – 68:6; Ex.1040 at 2206, 2208.

The prior art also taught that 3 and 5$^{mg}/_{kg}$ infliximab effectively treated PsA. For example, Marzo-Ortega taught that 3$^{mg}/_{kg}$ administered at weeks 0, 2, 6 and 14, in combination with methotrexate effectively treated RA. Ex.1004* at 6. Marzo-Ortega explained that the decision to use 3$^{mg}/_{kg}$ infliximab to treat PsA was based on infliximab's efficacy in treating RA at that exact dose. *Id.*

Dechant 2000 described clinical trials showing that infliximab effectively treated the signs and symptoms of PsA at doses of 3, 4, and 5$^{mg}/_{kg}$. While the 10 patients in the Dechant 2000 PsA clinical trials were started at 5$^{mg}/_{kg}$, (ex.1012 at S371) all 9 of the patients remaining in the trial were administered reduced infliximab doses of 3 and 4$^{mg}/_{kg}$. Ex.1029 at S102. In one group of 5 patients

receiving the reduced doses, each achieved ACR70 after one year. *Id.* Of the other 4 patients receiving the reduced doses, 3 achieved ACR70 at week 10 and ACR50 at the one-year evaluation, while one patient with an ACR50 response at week 10 experienced an arthritis flare after 9 months of starting infliximab treatment. *Id.*

Wollina described the treatment of two patients having PsA with an infliximab dose of 300mg (corresponding to $3^{mg}/_{kg}$) at weeks 0, 2, 4 and 8 in combination with methotrexate and concluded that it was effective in treating PsA. Ex.1050 at 128.

Ogilvie described administering $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 in combination with methotrexate or sulphasalazine to "patients with progressive joint disease and psoriatic skin lesions" and stated that "[i]mprovement of psoriatic skin lesions was observed in all patients. In addition, a marked improvement of the joint disease was noted." Ex.1033 at 587-89.

Van den Bosch described administering $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 to patients with spondyloarthropathy, including PsA, and concluded that "there was a fast and significant improvement of axial and peripheral articular manifestations" and noted that "in eight patients with [PsA] a significant decrease of the [PASI] was observed." Ex.1037 at 429, 432.

b. The Prior Art Taught That 25mg Etanercept Administered Twice Weekly Effectively Treated RA and PsA

Mease 2000 described a clinical trial in which 25mg etanercept administered subcutaneously twice weekly effectively treated PsA: "[t]his trial shows that etanercept provides clinically significant benefit to patients with active [PsA]. . . . [E]tanercept resulted in significant clinical benefit in the composite measures (PsARC, ARC20, and ARC50) and in each individual factor of disease activity." Ex.1017 at 389. In addition, "[e]tanercept was also effective in improving the skin lesions of psoriasis in the trial." Ex.1017 at 386, 388. Mease 2000 emphasized that the same dosage regimen of etanercept had previously been shown to be effective in treating RA: "[e]tanercept has been shown in previous trials to be effective against [RA] with no serious toxic effects" at a dose of "25 mg subcutaneously twice weekly."[28] *Id.* at 389.

Table 2 – Anti-TNF-α Drugs Used to Treat RA and PsA at the Same or Similar Dosing Regimens

Drug	RA		PsA	
	Reference	**Dosing Regimen**	**Reference**	**Dosing Regimen**
$3^{mg}/_{kg}$ Infliximab	Remicade® Package Insert (ex.1027	$3^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6, then every 8 weeks thereafter	Marzo-Ortega (ex.1004* at 6)	$3^{mg}/_{kg}$ at weeks 0, 2, 6 and 14, in combination with MTX

[28] The 2000 Enbrel® Package Insert set forth the etanercept dosing regimen of 25mg administered subcutaneously twice weekly to treat RA. Ex.1005 at 1554.

Drug	RA		PsA	
	Reference	Dosing Regimen	Reference	Dosing Regimen
	at 1087)	in combination with MTX	Wollina (ex.1050 at 128)	300mg (equivalent to $3^{mg}/_{kg}$[29]) at weeks 0, 2, 4 and 8 in combination with MTX
			Dechant 2000 (10 weeks - 1 year) (ex.1029 at S102)	3-$4^{mg}/_{kg}$ with an infusion interval of ≥8 weeks
$5^{mg}/_{kg}$ Infliximab	Feldmann (ex.1039* at 65:15-17)	patients received single infusion of either 5, 10, or $20^{mg}/_{kg}$ infliximab in combination with MTX	Dechant 1999 (1-10 weeks) (ex.1012 at S371)	$5^{mg}/_{kg}$ on 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 MTX	Van den Bosch (ex.1037 at 429)	$5^{mg}/_{kg}$ at weeks 0, 2 and 6
			Ogilvie (ex.1033 at 587)	$5^{mg}/_{kg}$ at 0, 2, 6 weeks in combination with MTX or sulphasalazine
Etanercept	Mease 2000 (ex.1017 at 389)	25mg twice weekly	Mease 2000 (ex.1017 at 386)	25mg twice weekly
	2002 Enbrel® Package	25mg twice weekly	2002 Enbrel® Package	25mg twice weekly

[29] Although the average adult weight is about 70kg (ex.1053* at 14), it appears that in these case studies the patients each weighed about 100kg. Ex.1050 at 128 ("[A] dose of 300 mg each corresponding to 3 $^{mg}/_{kg}$ body weight.").

Drug	RA		PsA	
	Reference	Dosing Regimen	Reference	Dosing Regimen
	Insert (ex.1006 at 23)		Insert (ex.1006 at 23)	

Therefore, a POSA would have had (1) a motivation to use the known RA adalimumab dosage regimen of subcutaneously administered 40mg eow to treat PsA, and (2) a reasonable expectation of success based upon the knowledge that the prior TNF-α inhibitors were effective in treating both RA and PsA at the same dosage regimens.

6. Prior to TNF-α Inhibitors, Other Drugs With the Same or Similar Dosing Regimens Were Used to Treat Both RA and PsA

Support for the use of the same or similar dosing regimens for TNF-α inhibitors in treating both RA and PsA is also based on the practice of using earlier generations of drugs to treat both diseases with the same or similar dosing regimens prior to the development of TNF-α inhibitors. Lorenz stated that "[t]he current therapeutic approaches for PsA are similar to those for RA and include nonsteroidal anti-inflammatory drugs (NSAIDs), DMARDs and immunosuppressive agents." Ex.1028 at S18. Table 3 demonstrates that hydrocortisone, cortisone, dexamethasone, prednisolone and betamethasone were all approved in the prior art for use in treating RA and PsA at the same or similar maintenance doses and dosing regimens.

Table 3 – Small Molecule Drugs Used to Treat RA and PsA at the Same or Similar Dose

Drug	Reference	RA dosing regimen	PsA dosing regimen
Hydrocortone® (hydrocortisone sodium phosphate)	Ex.1035 at 1938, 1940	The initial dosage varies from 15 to 240 $^{mg}/_{day}$ depending on disease	
Cortone® (cortisone acetate)	Ex.1035 at 1897-98	The initial dosage varies from 25 to 300 $^{mg}/_{day}$ depending on disease	
Decadron® (dexamethasone)	Ex.1035 at 1912-14	The initial dosage varies from 0.75 to 9 $^{mg}/_{day}$ depending on disease	
Prelone® (Prednisolone)	Ex.1035 at 2110-11	The initial dose varies from 5 to 60 $^{mg}/_{day}$ depending on disease	
Solu-medrol® (methylprednisolone sodium succinate)	Ex.1035 at 2641-42	30 $^{mg}/_{kg}$ (can be repeated every 4 to 6 hours for 48 hours)	
Celestone® (betamethasone)	Ex.1035 at 2883	0.6 to 7.2 $^{mg}/_{day}$ depending on disease	

Therefore, the prior art clearly taught that drugs useful to treat RA are also useful to treat PsA at the same dosage regimen.

D. Ground 1: Mease 2004 Anticipates Claims 1, 5 and 6

As described *supra* IV.A, claims 1, 5 and 6 are not entitled to any priority date earlier than May 16, 2006. Mease 2004 anticipates claims 1, 5 and 6 because it described all of the limitations of those claims more than one year before May 16, 2006. Ex.1056 at 4097.

Mease 2004 described the same clinical study that was added as an example of the ’992 patent when a May 16, 2006 CIP was filed. The patients in the Mease

2004 study, who suffered from moderate to severe active PsA (having ≥3 swollen and ≥3 tender joints) and had failed NSAID therapy, were treated with a dosing regimen of 40mg adalimumab administered subcutaneously eow. *Id.* Mease 2004 reported that, after 24 weeks of treatment, 23% of patients achieved ACR70 (*i.e.*, a 70% reduction in ACR score), and 39% of patients achieved ACR50. *Id.*

Accordingly, Mease 2004 explicitly discloses every limitation of claim 1. Mease 2004 further explicitly discloses every limitation of claims 5 and 6, because it discloses the method of claim 2 (reducing or inhibiting symptoms in a patient with PsA by subcutaneously administering 40mg adalimumab eow), and also discloses that the patients achieved the ACR50 score recited in claim 5 and the ACR70 score recited in claim 6.

Claims 1, 5 and 6 are therefore invalid as anticipated by Mease 2004. *See, e.g., Verdegaal Brothers, Inc. v. Un. Oil Co. of Cal.* 814 F.2d 628 (Fed. Cir. 1987).

E. Ground 2: Keystone Combined with Lorenz and Mease 2000 Render Claims 1, 2 and 5-7 Obvious

Independent claims 1 and 2 both recite a method for reducing or inhibiting symptoms in a patient with PsA, comprising subcutaneously administering 40mg adalimumab eow. Claim 1 includes additional limitations reciting the patient enrollment criteria for a 24-week clinical trial for patients having moderate to severe PsA and a clinical endpoint of 23% of the patients achieving a 70% improvement in ACR score at week 24. Claims 5 and 6 depend from claim 2 and

recite that the patient treated in claim 2 achieves, respectively, a 50% reduction and a 70% reduction in ACR score at week 24 of treatment.

All this was obvious from the prior art, assuming a July 18, 2003 priority date for all of the challenged claims of the '992 patent.

Keystone described the 40mg adalimumab eow subcutaneous dosing regimen to treat RA. Lorenz taught that TNF-α inhibitors, including adalimumab, infliximab and etanercept, could be used to treat both RA and PsA, and accurately predicted that adalimumab, like infliximab and etanercept, would also be useful in treating PsA.

Lorenz and the background art described *supra* Tables 2 and 3, taught that the same drugs, including TNF-α inhibitors, used to treat RA could be used to treat PsA with the same dosing regimens, thus providing the motivation to combine those references and the reasonable expectation of success that the claimed dosing regimen would treat PsA.

1. Keystone Described the Claimed Adalimumab Dosing Regimen to Treat RA

Keystone described an RA clinical trial in which 40mg adalimumab was subcutaneously administered eow. Ex.1003 at A481. Keystone established the "efficacy of the fully human anti-TNFα monoclonal antibody, adalimumab (D2E7) . . . in patients with longstanding RA . . . when given every other week subcutaneously." *Id.* All three doses (20, 40, and 80mg) administered eow were

effective as assessed by ACR20, ACR50 and ACR70 responses, and all three doses would therefore have been obvious choices for treating RA. Ex.1002 at ¶130. The 2002 Humira® Package insert confirms that Keystone's 40mg adalimumab eow dosing regimen effectively treated RA.

The only difference between Keystone and the claimed dosing regimen is that the claimed dosing regimen recites the treatment of PsA (ex.1001 at claim 2) instead of the treatment of RA.

2. The Prior Art Taught That Adalimumab Would Effectively Treat PsA

Lorenz taught that TNF-α inhibitors were effective in treating PsA and reviewed the reports of successful clinical trials of infliximab, etanercept, and adalimumab (D2E7) in treating RA. Ex.1028. Lorenz further described studies identifying the elevated levels of TNF-α in the skin lesions of PsA patients and explained that "[a]s a logical consequence, studies with TNF-α-blocking biologicals were initiated . . . . in the treatment of PsA and psoriasis." *Id.* at S18. Lorenz detailed the clinical trial successes with infliximab (including by the authors and others) and etanercept (including Mease 2000) in the treatment of PsA. *Id.* at S18-19. Lorenz specifically mentioned "the fully human monoclonal antibody D2E7 [adalimumab]" as one of the TNF-α inhibitors which may produce "encouraging results" in clinical trials. *Id*. at S17.

Lorenz stated that "[t]he results of these studies suggest that TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis. In addition, anti-TNF-α therapy offers patients with PsA and psoriasis a new therapeutic option for the control of their disease." *Id.* at S19. As Helfgott states, a POSA reading Lorenz would clearly understand that adalimumab was an obvious therapeutic agent for the treatment of PsA. Ex.1002 at ¶90.

Japan Chemical Week confirms that a POSA would understand Lorenz and the art reviewed therein as teaching the use of D2E7 to treat PsA and psoriasis. It reported developments in anti-TNF-α therapies, stating that D2E7 was "likely to have wider applications, covering not only RA and IBD but also psoriasis, indicating further development of markets" and that it was recognized that TNF-α is a cause of "RA, IBD, psoriasis, [and] [PsA]." Ex.1034 at 1. The AbbVie Press Release (ex.1049*) similarly confirms this understanding, and notes that a clinical trial of adalimumab in PsA had in fact been initiated.

Accordingly, the prior art clearly taught that adalimumab would be useful in treating PsA as well as RA.

3. The Known RA Adalimumab Dosing Regimen of 40mg eow by Subcutaneous Injection Was an Obvious Choice to Treat PsA

The prior art established that drugs, including TNF-α inhibitors, known to be effective in treating RA, were also effective in treating PsA at the same or similar dosing regimens as used in RA. *Supra* VI.C.5-VI.C.6.

These prior art teachings are summarized *supra* Tables 2 and 3. For example, Marzo-Ortega demonstrated the efficacy of infliximab in treating PsA and psoriasis at the same $3^{mg}/_{kg}$ dose that had been approved to treat RA. Ex.1004* at 6. In fact, Marzo-Ortega's goal was to determine whether the psoriasis infliximab dose could be lowered from $5^{mg}/_{kg}$, which was successful in a previous psoriasis study, to $3^{mg}/_{kg}$, an effective dose for treating RA. *Id.* ("Recent studies have shown the efficacy of TNF blockade with infliximab . . . in psoriasis at a dose of 5 $^{mg}/_{kg}$. However infliximab at a dose of $3^{mg}/_{kg}$ with methotrexate has proven effective in [RA]. 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.").

Lorenz reported that the subcutaneous administration of 25mg etanercept twice weekly successfully treated PsA. Ex.1028 at S19. A POSA would have known that the same etanercept dosing regimen had successfully been used to treat

RA. Ex.1002 at ¶46; ex.1005 at 1554 (The FDA-approved dose of Enbrel® (etanercept) for treating RA is 25mg administered twice weekly subcutaneously.).

As Helfgott explains, a POSA would have been motivated to use the same adalimumab dosing regimen (40mg eow) shown to be effective in treating RA to also treat PsA, because a POSA would know that other TNF-α inhibitors (*e.g.*, infliximab and etanercept) could be used to treat each of these conditions at the same dosing regimen. Ex.1002 at ¶¶130, 146. Additionally, a POSA would have known that TNF-α was implicated in RA and PsA, and thus a dosing regimen known to effectively block TNF-α to sufficiently relieve the signs and symptoms of RA, would be likely to also block TNF-α to sufficiently relieve the signs and symptoms of PsA. Accordingly, a POSA would have had a reasonable expectation that the RA dosing regimen would effectively treat PsA, and would have found obvious the method of treatment recited in claim 2. Ex.1002 at ¶¶134-35, 151.

4. Mease 2000 Taught the Patient Enrollment Criteria and "Moderate to Severe" Recited in Claim 1 of the '992 Patent

Claim 1 recites a method of treatment of moderate to severe active PsA in adult patients, wherein each patient has ≥3 swollen and ≥3 tender joints prior to the treatment and has failed NSAID therapy, comprising subcutaneously administering to each said patient 40mg adalimumab eow, wherein 23% of said patients achieve 70% reduction in ACR score at week 24 of the treatment. Accordingly, claim 1, like claim 2, recites the known adalimumab RA dosing regimen to treat PsA.

Claim 1 differs from claim 2 only in that it specifies certain patient enrollment criteria and clinical endpoints. Mease 2000 enrolled "adults between 18 and 70 years who had active [PsA] (defined as ≥3 swollen joints and ≥3 tender or painful joints) at the time of study enrolment." Ex.1017 at 385. The '992 specification defines this criteria as "moderate to severely active [PsA]," which is then recited in claim 1 of the '992 patent. Ex.1001 at 37:31-33; *id.* at claim 1 ("moderate to severe active [PsA]"). Moreover, the enrollment criteria in the Mease 2000 study, just as in the study in the '992 example (and as recited in claim 1 of the '992 patent), required that "[p]atients . . . had an inadequate response to non-steroidal anti-inflammatory [(NSAID)] drugs." Ex.1017 at 385.

In addition, under well-established Federal Circuit case law, these patient enrollment criteria, which are recited in the first "wherein" clause of claim 1 of the '992 cannot impart patentability. *Minton v. Nat'l Ass'n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."). However, even if those criteria are deemed limitations of the claim, Mease 2000 taught the same patient enrollment criteria, rendering them obvious.

5. Keystone Combined with Lorenz and Mease 2000 Taught the Claimed ACR Responses (Claims 1, 5 and 6)

Claim 1 additionally recites in its second "wherein" clause that "23% of said patients achieve 70% reduction in [ACR] score at week 24 of the treatment." Ex.1001 at claim 1. Claim 5 depends from claim 2 and recites that the patient treated "achieves at least a 50% reduction in ACR score at week 24 of the treatment" (*id.* at claim 5) and claim 6, which depends from claim 5, recites that the patient treated "achieves at least a 70% reduction in ACR score at week 24 of the treatment." *Id.* at claim 6. These are, however, merely statements of intended result that cannot impart patentability. *Minton*, 336 F.3d at 1381.

Even if such statements of intended result could be deemed claim limitations, they cannot render patentable the obvious method of treating PsA by subcutaneously administering 40mg adalimumab eow.

First, the claims merely recite the endpoints of a clinical trial AbbVie described in the example of the '992 patent in which after 24 weeks of 40mg eow adalimumab treatment, 57% of patients achieved ACR20, 39% achieved ACR50 and 23% achieved ACR70. Ex.1001 at 37:45-47, tbl. 1. Such results are simply the natural consequence of an obvious method of treatment and, accordingly, the addition of these limitations specifying the clinical endpoints inherent in this method of treatment cannot save claims 1, 5 and 6 from invalidation. *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."). Because the "wherein" clauses of claims 1, 5 and 6 merely "characteriz[e] the result" of the claimed method while failing to inform "how" the method is performed, the clauses do not limit the scope of the claims.

Second, the prior art discloses TNF-α inhibitors having such clinical efficacy in treating PsA, creating an expectation that the use of TNF-α inhibitors in treating PsA should be as effective as was proven in RA. The prior art makes clear that, in addition to the method of treatment being obvious, the recited resulting improvements in ACR scores are also the obvious result of TNF-α inhibition in PsA patients. Reductions in ACR scores measure improvement in the signs and symptoms of arthritis patients and are used with both RA and PsA patients. Ex.1002 at ¶34. Keystone described a 24-week clinical trial for RA patients in which 40mg eow subcutaneous dosing of adalimumab resulted in 65.7% of patients achieving ACR20, 53.7% achieving ACR50 and 26.9% achieving ACR70. As Helfgott explains, a POSA reading Keystone would reasonably expect that PsA patients would achieve comparable ACR responses to those achieved by the RA patients in Keystone. *Id.* at ¶129.

The prior art describing clinical trial results in the treatment of PsA with infliximab and etanercept only confirms that expectation. Lorenz described the authors' own infliximab clinical trial where ten patients with PsA were

administered $5^{mg}/_{kg}$ at weeks 0, 2 and 6 and reported that "all 10 patients [*i.e.*, 100%] in our study achieved [ACR20] by week 2." Ex.1028 at S18. "After 10 weeks of treatment, eight patients [*i.e.*, 80%] achieved [ACR70], six of whom maintained this improvement to week 54." *Id.* Mease 2000 reported that after 12 weeks, of the 30 patients with PsA who received etanercept, 73% achieved ACR20, 50% achieved ACR50 and 13% achieved ACR70. Ex.1017 at tbl.2. As Helfgott explains, the prior art clinical trials treating PsA patients with infliximab and etanercept clearly taught a POSA that inhibiting TNF-α in PsA patients would result in a significant improvement in the signs and symptoms of PsA as reflected in ACR20, 50, and 70 responses. Based on this prior art, in combination with Keystone and Lorenz, a POSA would reasonably expect, and find obvious, that PsA patients would achieve the ACR responses recited in claims 1, 5 and 6 of the '992 patent when treated with 40mg adalimumab eow. Ex.1002 at ¶¶128-30.

6. Keystone Combined with Lorenz Taught That TNF-α Inhibitors Reduce/Inhibit Progression of Structural Damage in a PsA Patient as Assessed by Radiograph (Claim 7)

Claim 7, which depends from claim 2, requires that the "symptoms [of PsA] are progression of structural damage assessed by radiograph." Ex.1001 at claim 7.

Like the clinical endpoints of claims 1, 5 and 6, the reduction/inhibition of "progression of structural damage" is a natural consequence of an obvious method of treatment. *Par Pharm.*, 773 F.3d at 1194–95. Accordingly, for the reasons

discussed with respect to claims 1, 5 and 6 (*supra* VI.E.5) the recited inherent result of claim 7 does not impart patentability.

Moreover, the prior art taught that treatment with TNF-α inhibitors reduced the progression of structural damage in RA patients, as assessed by radiograph. Ex.1002 at ¶140. Lorenz reported that an earlier clinical trial "showed, for the first time in any RA trial, that there was no median radiological progression in the groups given infliximab plus methotrexate over a 12-month . . . period." Ex.1028 at S17. As Helfgott explains, based on these reported radiographic results in RA patients, a POSA would expect that treatment with TNF-α inhibitors would similarly inhibit the progression of structural damage in PsA patients. Ex.1002 at ¶140. Accordingly, a POSA would have found it obvious that treatment with adalimumab, a TNF-α inhibitor, would reduce/inhibit the progression of structural damage, as assessed by radiograph, in PsA patients.

7. A POSA Would Have Been Motivated to Combine Keystone with Lorenz and Mease 2000 to Achieve the Claimed Methods with a Reasonable Expectation of Success

The well-documented history of (1) TNF-α's role in both RA and PsA; (2) the use of TNF-α inhibitors to treat both RA and PsA using the same or similar dosing regimens; and (3) adalimumab's known potential for treating PsA provide an overwhelming motivation for a POSA to combine Keystone with Lorenz, with a

reasonable expectation that 40mg subcutaneously-administered adalimumab eow would effectively treat PsA.

The background prior art provided a POSA with a wealth of information about how to select drugs and dosing regimens to treat PsA based on known treatments for RA, thus providing further motivation for using the RA dosing regimen in the treatment of PsA:

- TNF-α played a major role in the development of RA and PsA (*supra* VI.C.2);
- TNF-α inhibitors such as etanercept and infliximab were used successfully to treat RA and PsA using the same or similar dosing regimens (*supra* VI.C.5);
- non-TNF-α inhibitors had been used to treat RA and PsA using the same or similar dosing regimens (*supra* VI.C.6); and
- adalimumab was identified as a TNF-α inhibitor that had been proven to treat RA and was expected to be used to treat PsA (*supra* VI.C.3).

A POSA would know this "background information" when reading Lorenz. *Randall Mfg.*, 733 F.3d at 1362-63 (vacating 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 . . . cited to demonstrate the knowledge and perspective of one of ordinary skill in the art. . . .").

The success of TNF-α inhibitors (Table 2) as well as other drugs (Table 3) in treating RA and PsA using the same or similar dosing regimens, would have

motivated a POSA to combine the teachings of Lorenz with Keystone. Lorenz and Table 2, which summarizes numerous prior art references, including Marzo-Ortega, Mease 2000, Ogilvie, Van den Bosch, Wollina, Perkins, Feldmann, Dechant 1999, Dechant 2000, the 2002 Enbrel® Package Insert and the Remicade® Package Insert, demonstrate the successful treatment of PsA with the same infliximab and etanercept doses that had been used to treat RA and provide a reasonable expectation of success, which is also supported by the background art (*e.g.*, Table 3), that Keystone's method of administering 40mg adalimumab subcutaneously eow would be effective in treating PsA as claimed by the '992 patent, as they taught the same dosing regimen was effective in both PsA and RA. A POSA would have additionally had a reasonable expectation, based on these prior art references, that this method of treatment would result in the inhibition of progression of structural damage, measured by radiograph, as recited in claim 7. Mease 2000 further discloses the patient enrollment criteria recited in claim 1, and, along with Keystone, provides a reasonable expectation that the recited ACR responses recited in claims 1, 5 and 6 would be achieved. *Supra* VI.B.8, VI.E.4-VI.E.5.

Accordingly, a POSA would have been motivated to combine the teachings of Keystone, Lorenz and Mease 2000 to arrive at the methods of the challenged claims and would have had a reasonable expectation of success in so doing.

F. Ground 3: Keystone Combined with Mease 2000 and Dechant 2000 Render Claims 1, 2 and 5-7 Obvious

In the event that AbbVie successfully asserts the benefit of the July 19, 2002 filing date of its earliest-filed provisional application, claims 1, 2, 5-7 of the '992 patent are nevertheless obvious over the prior art.

Keystone taught that 40mg adalimumab subcutaneously administered eow successfully blocked TNF-α and treated the signs and symptoms of RA. Ex.1003 at A481. As discussed *supra* VI.B.8–VI.B.9, VI.C.5, Mease 2000 and Dechant 2000 described the use of etanercept and infliximab, respectively, to successfully treat PsA with the same dosing regimens that had been used with those TNF-α inhibitors to successfully treat RA.

Mease 2000 and Dechant 2000 additionally taught that TNF-α is associated with RA and PsA and both described the success, respectively, of etanercept and infliximab, in the treatment of RA as a basis for the use of those drugs to also treat PsA. Ex.1017 at 385-89; Ex.1029 at S102. Both Mease 2000 and Dechant 2000 concluded that blocking TNF-α would be useful in the treatment of PsA. Ex.1017 at 389 ("[B]locking tumour necrosis factor in both [PsA] and psoriasis may offer a new therapeutic option for patients with both diseases."); Ex.1029 at S102 ("These data show that infliximab was effective [in treating PsA] over one year. Therefore infliximab seems to be effective in the treatment of severe [PsA] as well.").

Accordingly, a POSA would know that the TNF-α inhibitor adalimumab was a prime candidate for treating PsA based on (1) Keystone's description of adalimumab's success in treating RA and (2) the teachings of Mease 2000 and Dechant 2000 that the TNF-α inhibitors etanercept and infliximab were successful in treating RA and PsA. Ex.1002 at ¶146.

Moreover, a POSA would have been motivated by Mease 2000 or Dechant 2000 to use adalimumab at the 40mg eow RA dosing regimen disclosed in Keystone to treat PsA because etanercept and infliximab were shown in the prior art to treat both RA and PsA with the same dosing regimens. Mease 2000 used the same subcutaneous 25mg twice weekly dose to successfully treat PsA that had been approved to treat RA and PsA. Dechant 2000 showed that a range of infliximab doses of 3, 4 and $5^{mg}/_{kg}$ could treat PsA, which included doses that had been shown to be effective in treating RA. *Supra* Table 2. For the above reasons, a POSA would also have had a reasonable expectation that adalimumab subcutaneously administered at a 40mg eow dosing regimen would succeed in treating the signs and symptoms of PsA just as it had in treating RA. Ex.1002 at ¶146.

As discussed *supra* VI.E.4, the patient enrollment criteria of the first "wherein" clause of claim 1 of the '992 patent (≥3 swollen and ≥3 tender joints, and having failed NSAID therapy) cannot impart patentability. However, even if

these enrollment criteria are deemed claim limitations, they are rendered obvious by Mease 2000, which described the treatment with etanercept of PsA patients having ≥3 swollen and ≥3 tender joints (*i.e.*, moderate to severe active PsA) who had previously failed NSAID therapy. *Supra* VI.E.4.

Nor can the ACR responses recited in claims 1 and 5-7 impart patentability to an obvious method. *Supra* VI.E.5-VI.E.6. Even if such statements of intended result are deemed claim limitations, they cannot render patentable the obvious method of treating PsA by subcutaneously administering 40mg adalimumab eow. Keystone gave a POSA a reasonable expectation that 40mg eow subcutaneous adalimumab treatment would achieve comparable ACR responses in PsA patients as had been achieved by Keystone in RA patients. Ex.1002 at ¶147. Mease 2000 and Dechant 2000 provided further support, based on the ACR70 and ACR50 responses achieved in etanercept and infliximab trials, for a POSA to conclude that TNF-α inhibition by adalimumab would achieve ACR responses comparable to the responses reported in Keystone. *Id.*

Finally, that adalimumab therapy reduced/inhibited progression of structural damage in RA patients was known in the prior art. Rau, for example, reported that adalimumab treatment inhibited progression of structural damage (joint destruction, erosion, and joint space narrowing) in RA patients. Ex.1021***** at 7. A

POSA would have expected similar inhibition of the progression of structural damage in PsA patients treated with adalimumab. Ex.1002 at ¶156.

Accordingly, for all of the reasons stated above, Keystone combined with Mease 2000 and Dechant 2000 render obvious claims 1, 2, 5 and 6 and with the addition of Rau, render obvious claim 7 of the ’992 patent.

G. No Secondary Considerations Demonstrate Nonobviousness

1. No Proof of Commercial Success

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 ’992 patent because at different times AbbVie has attributed the commercial success of Humira® to entirely different patents. The Federal Circuit, however, has held that where one patent blocks market entry, any commercial success enjoyed by the product cannot be convincingly attributed to other patents. *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 32 (P.T.A.B. 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 '992 patent that drives Humira®'s sales. For example, in defending the alleged patentability of a patent claiming an adalimumab formulation (U.S. Patent No. 8,916,158 (the "'158 patent") against a petition for IPR, AbbVie argued that the commercial success of Humira® was "driven in large part by" its formulation. Ex.1020 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 . . . ."). If the commercial success of Humira® was "driven in large part" by the formulation, as AbbVie asserted, then there is no basis for it to argue now that it was largely driven by a 40mg eow dosing regimen for PsA. Moreover, in defending the alleged patentability of the '158 patent, AbbVie argued that the commercial success of Humira® was due to its initial patent on the 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.1051***** at 5 (cited as ex.2003 in the '158 IPR).

When trying to defend its RA dosing patent (the '135 patent), AbbVie attributed Humira®'s commercial success, not to its PsA 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.1010 at 58. In one FWD 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* at 40. The Board continued: "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 '992 patent from invalidity by asserting that the commercial success of Humira® is due to the methods claimed in the '992 patent, particularly when the teachings of the prior art

so clearly render those methods 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. . . . Here, where the inventions represented no more than 'the predictable use of prior art elements according to their established functions,' the secondary considerations . . . are inadequate to establish nonobviousness as a matter of law.") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 417 (2007).

2. No Proof of Long-Felt Need and Failure of Others

In the '135 IPRs, AbbVie argued that "[t]here was a long-felt but unmet need for new RA therapies" with convenient dosing. Ex.1010 at 55; *BI408* at 41 ("Patent Owner contends there was a long-felt need for new RA therapies supporting the nonobviousness of the challenged claims."). AbbVie argued that two anti-TNF-α agents used to treat RA (Enbrel® and Remicade®) were both inconvenient for patients. Ex.1010 at 55-56 (noting that Enbrel® requires two doses per week and Remicade® is administered intravenously instead of subcutaneously); *BI408* at 41. However, biweekly dosing of D2E7 and subcutaneous administration of D2E7 were already disclosed by Keystone. Ex.1003 at A481; *see Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 838 (Fed. Cir. 2015) ("If commercial success is due to an element in the prior art, no nexus exists.").

Additionally, AbbVie previously argued that "[o]thers [sic] companies tried and failed to satisfy" a need for "additional biologics with more advantageous dosing regimens" and asserted that two drugs Roche and Celltech attempted to develop failed because they produced anti-drug antibodies. Ex.1010 at 56. AbbVie did not offer any proof that the prior art actually recognized any such need. Moreover, AbbVie's argument fails because even if it could demonstrate such a recognized need, its alleged satisfaction of that need would be attributable to an inherent property of the prior art D2E7 antibody (ex.1042 at I70) which had been protected by the now expired U.S. Patent No. 6,090,382. *Coal. for Affordable Drugs II LLC*, IPR2015-01093, at 33 (holding that where the "Patent Owner does not provide evidence sufficient to permit a determination as to whether the long-felt need was met by the [patented invention] . . . the record . . . does not sufficiently indicate that the claimed subject matter itself satisfied a long-felt need.").

For similar reasons in *Coherus*, *BI409* and *BI408* the Board rejected AbbVie's "long-felt need" arguments. *Coherus* at 41-43; *BI409* at 43-45, *BI408* at 41-43.

H. Summary of Invalidity Grounds

As discussed above, Mease 2004 discloses every limitation of claims 1, 5 and 6, and therefore anticipates these claims for Ground 1. The claim charts below

provide a summary of the prior art disclosures that render obvious each limitation of claims 1, 2 and 5-7 for Grounds 2 and 3. The charts for the dependent claims hereby incorporate all of the grounds in the independent and any other dependent claims from which they depend.

Claims 1, 2, 5-7 Are Obvious Over Keystone (ex.1003) Combined with Lorenz (ex.1028) and Mease 2000 (ex.1017) [GROUND 2]
OR
Over Keystone (ex.1003) Combined with Mease 2000 (ex.1017) and Dechant 2000 (ex.1029) [GROUND 3]

'992 Patent Claim Language	**Prior Art Disclosures**
Claim 1	
A method of treatment of moderate to severe active [PsA]	
in adult patients, wherein each said patient has ≥3 swollen and ≥3 tender joints prior to the treatment	"Eligible patients were adults between 18 and 70 years who had active [PsA] (defined as ≥3 swollen joints and ≥3 tender or painful joints) at the time of study enrolment." Ex.1017 at 385.
and has failed NSAID therapy,	"Patients must have had an inadequate response to non-steroidal anti-inflammatory drugs . . . ." Ex.1017 at 385.
comprising subcutaneously administering to each said patient	"[G]iven every other week subcutaneously." Ex.1003 at A481.

<table>
<tr><th>’992 Patent Claim Language</th><th colspan="2">Prior Art Disclosures</th></tr>
<tr><td>40 mg of adalimumab</td><td colspan="2">“The patients were randomised to receive placebo or the fully human anti TNF monoclonal antibody, adalimumab (D2E7), at one of 3 doses (20, 40 and 80 mg every other week).” Ex.1003 at A481.</td></tr>
<tr><td>every other week,</td><td colspan="2">“[G]iven every other week subcutaneously.” Ex.1003 at A481.</td></tr>
<tr><td rowspan="2">wherein 23% of said patients achieve 70% reduction in American College of Rheumatology (ACR) score at week 24 of the treatment.</td><td>Inherency argument</td><td>Obviousness argument</td></tr>
<tr><td>Ex.1001 at tbl.1[30] (reporting that 23% of adalimumab-treated patients achieved ACR70 at week 24 when they were administered 40mg adalimumab subcutaneously eow).</td><td>“After 10 weeks of [infliximab] treatment, eight [PsA] patients [i.e., 80%] achieved [ACR70], six of whom maintained this improvement to week 54.” Ex.1028 at S18 (Ground 2 only).

Ex.1029 at S102 (describing a study of 10 patients, where 8 patients achieved ACR70 at week 10); supra VI.B.9 (Ground 3 only)

Ex.1017 at tbl. 2</td></tr>
</table>

[30] The ’992 patent is not prior art, but its disclosure demonstrates the result is inherent for some portion of treated patients. *Supra* VI.E.5.

’992 Patent Claim Language	Prior Art Disclosures	
		(reporting that 13% of etanercept-treated patients with PsA achieved ACR70 at week 12) (Grounds 2 and 3).

’992 Patent Claim Language	Prior Art Disclosures
Claim 2	
A method for reducing or inhibiting symptoms in a patient with [PsA],	*See* claim 1.
comprising subcutaneously administering to said patient	
40 mg of adalimumab	
every other week.	

Dependent Claims 5-7

’992 Patent Claim Language	Prior Art Disclosures	
	Inherency argument	**Obviousness argument**
Claim 5	Ex.1001 at tbl.1[31] (reporting that at week 24, 57% of patients with PsA achieved a 20% reduction in ACR score (ACR20), 39% of adalimumab-treated patients achieved a 50% reduction in ACR score	“[T]reatment was efficacious and safe in PsA and psoriasis. With infliximab treatment ($5^{mg}/_{kg}$ at weeks 0, 2, and 6) . . . . After 10 weeks of treatment, eight [of 10] patients achieved
The method of claim **2**, wherein the patient achieves at least a 50% reduction in ACR score at week 24 of the treatment.		
Claim 6		
The method of claim **5**,		

[31] *Supra* n.30.

'992 Patent Claim Language	Prior Art Disclosures	
	Inherency argument	**Obviousness argument**
wherein the patient achieves at least a 70% reduction in ACR score at week 24 of the treatment.	(ACR50) and 23% of adalimumab-treated patients achieved a 70% reduction in ACR score (ACR70) when treated with 40mg adalimumab subcutaneously eow).	[ACR70]. . . ." Ex.1028 at S18 (Ground 2 only). Ex.1017 at tbl. 2 (reporting that at week 12, 73%, 50% and 13% of PsA patients treated with etanercept achieved ACR20, ACR50 and ACR70, respectively) (Grounds 2 and 3) Ex.1003 at A481 (reporting ACR20, ACR50 and ACR70 data for 20mg, 40mg and 80mg eow adalimumab dosing at 24 weeks. In the 40mg eow adalimumab group, 65.7% achieved ACR20, 53.7% achieved ACR50 and 26.9% achieved ACR70 at week 24) (Grounds 2 and 3).
Claim 7	Ex.1001 at tbl. 3, 40:23-25[32] (reporting that "[a]dalimumab was more	"[F]or the first time in any RA trial . . . there was no median
The method of claim **2**,		

[32] *Supra* n.30; *supra* VI.E.6.

’992 Patent Claim Language	Prior Art Disclosures	
	Inherency argument	**Obviousness argument**
wherein said symptoms are progression of structural damage assessed by radiograph.	effective compared with placebo in inhibiting radiographic disease progression over a 24-week period” in PsA patients receiving 40mg adalimumab eow.	radiological progression in the groups given infliximab plus methotrexate over a 12-month observation period.” Ex.1028 at S17 (Ground 2 only). or *Supra* VI.F (Ground 3 only).

VII. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that claims 1, 2 and 5-7 of the ’992 patent are unpatentable as anticipated and/or obvious in view of the prior art identified herein. Petitioner therefore requests that the Board institute *inter partes* review for each of those claims.

Dated: September 14, 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 C.F.R. 42.24(a), this Petition contains 13,987 words as counted by the word processing program used for its preparation (Microsoft Word 2010), including figure labels and annotations, which were manually counted.

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. 9,067,992 and Exhibits 1001 – 1060 were served on September 14, 2017 via Federal Express to the correspondence address for the attorney of record for AbbVie Biotechnology Ltd., the assignee of the '992 patent.

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