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.: 9,090,689
Issue Date: July 28, 2015
Title: Use of TNFα Inhibitor for Treatment of Psoriasis

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,090,689 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. 9,090,689, filed Apr. 8, 2015, issued July 28, 2015	"'689 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 Declarations to exhibits marked with an asterisk (*) refer to stamped-on page numbers. All other pincites in the Petition and Declarations 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. *See* ex.1063; *see also* ex.1067.

[4] The 2001 Physician's Desk Reference was published in November 2000. *See* ex.1062.

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	TEXTBOOK OF PSORIASIS (Paul D. Mier & Peter C. M. van de Kerkhof, eds. 1986)	"Mier"	102(b)	
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	Marjorie Ridley & Margaret Safranek, *Common Skin Conditions*, 58 OCCASIONAL PAPER (ROYAL C. GEN. PRACTITIONERS) 50 (1992)[6]	"Ridley"	102(b)	
1011	Alan J. Lewis & Anthony M. Manning, *New Targets for Anti-Inflammatory Drugs*, 3 CURRENT OPINION CHEMICAL BIOLOGY 489 (1999)[7]	"Lewis"	102(b)	
1012	Declaration of R. Todd Plott, M.D.	"Plott Decl."	n/a	
1013	P. Ettehadi et al., *Elevated Tumour*	"Ettehadi"	102(b)	

[5] Mease 2002 was published in April of 2002. *See* ex.1056.

[6] See ex.1058 for publication information.

[7] See ex.1059 for publication information.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	Necrosis Factor-Alpha (TNF-α) Biological Activity in Psoriatic Skin Lesions, 96 CLINICAL & EXPERIMENTAL IMMUNOLOGY 146 (1994)			
1014	George Spencer-Green, *Etanercept (Enbrel): Update on Therapeutic Use*, 59 ANNALS RHEUMATIC DISEASES i46 (2000)	"Spencer-Green"	102(b)	
1015	Petra D. Cravens & Peter E. Lipsky, *Dendritic Cells, Chemokine Receptors and Autoimmune Inflammatory Diseases*, 80 IMMUNOLOGY & CELL BIOLOGY 497 (2002)[8]	"Cravens"	102(a)	not prior art
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)[9]	"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)

[8] Cravens was published in October 2002. *See* ex.1065.

[9] Mease 2001 was published in November 2001. *See* ex.1066.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
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	
1023	Christopher G. Jackson, *Immunomodulating Drugs in the Management of Psoriatic Arthritis*, 2 AM. J. CLINICAL DERMATOLOGY 367 (2001)[10]	"Jackson"	102(b)	102(a)
1024*	Center for Drug Evaluation and Research, Approval Package for ANDA 40-385 (Mar. 21, 2001)	"Trexall Label"	102(b)	
1025	Kelley's Textbook of Rheumatology vol. 2 (Shaun Ruddy et al. eds., 6th ed.) (2001)[11]	"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.[12]	"Remicade® Package Insert"	102(b)	
1028	Hanns-Martin Lorenz & Joachim R. Kalden, *Perspectives for TNF-α-Targeting Therapies*, 4 ARTHRITIS	"Lorenz"	102(b)	102(a)

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

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

[12] *Supra* n.4.

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	RES. S17 (May 2002)			
1029	Claudia Dechant et al. *One Year Outcome of Patients with Severe Psoriatic Arthritis Treated with Infliximab*, 43 ARTHRITIS & RHEUMATISM S102 [212] (2000)[13]	"Dechant"	102(b)	
1030	K. Eberhardt & E. Fex, *Clinical Course and Remission Rate in Patients with Early Rheumatoid Arthritis: Relationship to Outcome After 5 Years*, 37 BRIT. J. RHEUMATOLOGY 1324 (1998)	"Eberhardt"	102(b)	
1031	ANDREWS' DISEASES OF THE SKIN: CLINICAL DERMATOLOGY (Harry L. Arnold et al. eds., 8th ed.1990)	"Diseases of Skin"	102(b)	
1032	C. Pitzalis & N. Pipitone, *Psoriatic Arthritis*, 93 J. ROYAL SOC'Y MED. 412 (2000)	"Pitzalis"	102(b)	
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)[14]	"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.[15] (excerpts)	"2001 PDR"	102(b)	

[13] See ex.1060 for publication information.

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

[15] 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
1036	U. Chaudhari et al., *Efficacy and Safety of Infliximab Monotherapy for Plaque-Type Psoriasis: A Randomised Trial*, 357 LANCET 1842 (June 2001)	"Chaud-hari"	102(b)	
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	
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.	"'081	n/a	

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	60/411,081 filed Sept. 16, 2002	application"		
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	Enbrel® (etanercept) Package Insert (Immunex Corp. Nov. 2016), 2016 Physician's Desk Reference	"2016 Enbrel® Package Insert"	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* https://web.archive.org/web/20030701072200/https:/www.immunetolerance.org/artman/publish/article_148.html	"AbbVie Press Release"	102(a)	not prior art
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)[16]	"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-	"Timmer-man"	n/a	

[16] 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
	in-class-drug-that-toppled-lipitor-as-no-1/			
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*	J. Salfeld et al., *Generation of Fully Human Anti-TNF Antibody D2E7*, 41 ARTHRITIS & RHEUMATISM S57 [147] (1998)	"Salfeld"	102(b)	
1055	United States Copyright Office, Public Catalog for Kelley's Textbook of Rheumatology	n/a	n/a	
1056	https://www.ncbi.nlm.nih.gov/pubmed/11874829	n/a	n/a	
1057	https://academic.oup.com/rheumatology/article/41/suppl_2/3/1788099/Paediatrics-and-Other-Inflammatory-Arthopathies	n/a	n/a	
1058	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2560222/	n/a	n/a	
1059	https://www.ncbi.nlm.nih.gov/pubmed/10419850	n/a	n/a	
1060	http://onlinelibrary.wiley.com/doi/10.1002/art.v43:9%2B/issuetoc	n/a	n/a	
1061	Corrected Application Data Sheet (Apr. 22, 2015)	n/a	n/a	
1062	https://www.amazon.com/Physicians-Desk-Reference-2001-Pdr/dp/1563633752	n/a	n/a	
1063	http://ard.bmj.com/content/60/Suppl_1#Speakerabstracts2001	n/a	n/a	
1064	*Coherus BioSciences Inc. v. AbbVie Biotech. Ltd.*, No. IPR2016-00172,	"Patent Owner's	n/a	

Ex. No.[1]	Description	Referred To As	Reference Type[2]	
			2003 priority date	2002 priority date
	Patent Owner's Response, Paper No. 37 (Sept. 13, 2016)	Response in '135 IPR"		
1065	http://www.nature.com/icb/journal/v80/n5/index.html?foxtrotcallback=true	n/a	n/a	
1066	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1766666/	n/a	n/a	
1067	60 ANNALS RHEUMATIC DISEASES (July 2001) cover	n/a	n/a	
1068	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][17]	"Marzo-Ortega"	102(b)	102(a)
1069	Cover of ARTHRITIS RESEARCH vol. 4, supplement 3 (2002) supplied by the British Library	n/a	n/a	

[17] See ex.1057 for publication information.

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, 4, 7, 10, 13, 16 and 19 of U.S. Patent No. 9,090,689 ("the '689 patent," ex.1001[18]), which is assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner").

The '689 patent claims a method of 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") to treat moderate to severe chronic plaque psoriasis ("PsO").

AbbVie, however, had already placed in the prior art the exact same adalimumab dosing regimen to treat rheumatoid arthritis ("RA"). The prior art also taught that RA and PsO were closely related diseases, both mediated by TNF-α and both treated using the anti-TNF-α drugs infliximab and etanercept with the same or similar dosing regimens. Moreover, the prior art accurately stated that the newer TNF-α drug adalimumab would follow infliximab and etanercept as a PsO treatment 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

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

the prior art adalimumab RA dosing regimen of subcutaneously administering 40mg eow to also treat PsO.

In view of the known relationship between RA and PsO, and the history of using the same drugs and dosing regimens, including TNF-α inhibitors, to treat both conditions, a POSA would have been motivated to use the known RA adalimumab 40mg eow dosing regimen to also treat PsO. The prior art also showed that PsO was successfully treated with RA drugs and dosing regimens and gave a POSA more than a reasonable expectation of success.

Accordingly, the claims of the '689 patent are therefore 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 '689 patent is related to two of the patents at issue[19] 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 '689 patent is not

[19] U.S. Patent Nos. 8,961,973; 8,986,693 and the '689 patent claim priority to the same application, SN 60/561,139 filed April 9, 2004.

related to any of the patents that have been asserted in the following litigation 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 '689 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 (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 ’689 patent however do not claim priority to any of the same applications. The ’689 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 ’689 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. 9,067,992, which claims priority to the same applications to which the ’689 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 '689 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 ’689 Patent

The ’689 patent issued from U.S. patent application No. 14/681,704 filed on April 8, 2015. Each of the claims of the ’689 patent is directed to a method of “treating moderate to severe chronic plaque psoriasis” with adalimumab by “subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week.” Ex.1001 at claim 7.

The ’689 patent states that it is “[r]elated” to several continuation and continuation-in-part applications, with the earliest filed application, SN 10/622,932, having a filing date of July 18, 2003. Ex.1001. For purposes of this petition only, Petitioner asserts that the effective filing date of the challenged claims is July 18, 2003. To the extent that the Patent Owner attempts to claim the benefit of any earlier filing dates for any of the claims, Sandoz disputes its entitlement to any such date(s) associated with earlier-filed provisional applications.

In filing the application (SN 14/681,704) which led to the issuance of the ’689 patent, AbbVie claimed priority to four provisional applications that were filed before the filing of the first non-provisional application, SN 10/622,932

(ex.1047), on July 18, 2003 (collectively the "Provisional Applications") (exs.1043-46)[20]:

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

The '689 patent is not entitled to the priority date of any of these provisional applications because none of them disclose the "40 mg" adalimumab administered "every other week" dosing regimen required by every claim in the '689 patent. *See New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 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).

The Provisional Applications all have the same disclosure with respect to dosing regimen:

[20] AbbVie confirmed this claim to priority to the Provisional Applications when it filed a Corrected Application Data Sheet on April 22, 2015. Ex.1061.

> [d]osage regimens may be adjusted to provide the optimum desired response (*e.g.*, a therapeutic or prophylactic response). For example, a single bolus may be administered, several divided doses may be administered over time or the dose may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation. . . .
>
> An exemplary, non-limiting range for a therapeutically or prophylactically effective amount of an antibody, antibody portion, or other TNFα inhibitor of the invention is 0.1-20 $^{mg}/_{kg}$, more preferably 1-10 $^{mg}/_{kg}$. It is to be noted that dosage values may vary with the type and severity of the condition to be alleviated.

Ex.1043* at 23:9-26; Ex.1044* at 30:7-24; Ex.1045* at 30:17-34; Ex.1046* at 33:7-24.

Because the Provisional Applications do not disclose the '689 patent's claimed PsO dosing regimen of "40 mg of . . . adalimumab . . . every other week," they do not provide the 35 U.S.C. § 112¶1 written description required to support a claim of priority. Accordingly, the '689 patent is not entitled to any priority date before July 18, 2003.[21]

[21] AbbVie may argue that the disclosure of the Provisional Applications would render the claimed PsO dosing regimen (40mg adalimumab subcutaneously administered eow) 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. *See Regents of the Univ. of Cal. v. 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.").

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, 4, 7, 10, 13, 16 and 19 of the '689 patent on two grounds pursuant to pre-AIA 35 U.S.C. § 103. 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.

The Petition contains two grounds for invalidating the '689 patent:

- Ground 1 includes only publications that are 102(b) prior art assuming a July 18, 2003 priority date;
- Ground 2 includes only publications that are 102(b) prior art assuming a July 19, 2002 priority date.

The challenged claims are unpatentable based upon the following grounds:

Table 1 – Grounds for *Inter Partes* Review

Ground	Claims	Assumed Priority Date	Statutory Basis and Prior Art
1	1, 4, 7, 10, 13, 16 and 19	July 18, 2003	Obvious under 35 U.S.C. § 103(a) over Keystone (ex.1003) combined with Lorenz (ex.1028) and Chaudhari (ex.1036)
2	Same as Ground 1	July 19, 2002	Obvious under 35 U.S.C. § 103(a) over Keystone combined with Mease 2000 (ex.1017) and Chaudhari

Furthermore, the skilled artisan would understand these prior art references in the context of the wider body of prior art concerning the treatment of psoriasis 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 person having ordinary skill in the art,' and 'the inferences and creative steps that a person of ordinary skill in the art would employ.'").[22]

Section VI and the Declarations of Simon Helfgott, M.D. (ex.1002) and R. Todd Plott, M.D. (ex.1012) further support the grounds for invalidity of the challenged claims of the '689 patent. Ex.1002 at ¶¶95-135; Ex.1012 at ¶¶71-106. Dr. Helfgott is an expert in the field of rheumatology and has been treating patients with psoriasis and psoriatic arthritis for over 20 years. Ex.1002 at ¶¶3-15. Dr. Plott is an expert in the field of dermatology and has been treating patients with psoriasis and psoriatic arthritis, including with TNF-α inhibitors, for over 20 years.

[22] Although AbbVie disclosed to the Patent Office most of the above-listed references and the background prior art discussed herein, they were included along with several hundred other references. There is no evidence the Examiner ever considered the specific portions of the prior art described in this Petition. *See 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 the expert declarations submitted here by Sandoz which place the teachings of the prior art in context. Accordingly, the instant petition presents grounds of invalidity that were not considered during the original prosecution.

Ex.1012 at ¶¶3-13. Dr. Plott has also designed and tested dosing regimens in the context of clinical trials, including a trial of the antibody infliximab for the treatment of psoriasis. *Id.* at ¶¶5-7.

Dr. Helfgott and Dr. Plott are qualified to provide opinions as to what a POSA would have understood, known, or concluded based on the prior art (*id.* at ¶¶3-13, ¶¶25-27; ex.1002 at ¶¶3-15, 25-27) and are therefore competent to testify in this proceeding. Many of the prior art references cited herein are articles and abstracts that were published in medical journals. As Dr. 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. Ex.1002 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 '689 PATENT

A. Background of the '689 Patent

The '689 patent issued with two independent claims directed to the use of adalimumab to treat "moderate to severe chronic plaque psoriasis." Ex.1001 at claim 1.

Claim 1 is directed to a "method of administering adalimumab for treatment of moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week." *Id.*

Claim 7 is directed to a "method of preparing adalimumab for treating moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and providing said adalimumab for treatment, wherein said treatment comprises subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week." *Id.* at claim 7.

The challenged dependent claims add various limitations, including that the vessels are syringes (claims 4 and 10), the patient treated has at least 5% body surface area affected by psoriasis (claim 13), the patient treated "has both psoriasis and psoriatic arthritis and achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment" (claim 16), and the patient treated "has both psoriasis and psoriatic arthritis and achieves a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment" (claim 19).[23]

[23] Support for the limitation of claim 19 was not added to the '689 specification until continuation-in-part application SN 11/104,117 was filed on April 11, 2005. This limitation was first disclosed when application SN 60/561,710 was filed on

PsO, the '689 patent explains, is "a skin inflammation (irritation and redness) characterized by frequent episodes of redness, itching, and thick, dry, silvery scales on the skin." *Id.* at 25:64-67. This disorder "is often associated with other inflammatory disorders," such as RA (*id.* at 26:11-13) and psoriatic arthritis ("PsA"), which "refers to chronic inflammatory arthritis which is associated with psoriasis." *Id.* at 24:61-63. The '689 patent acknowledges that the prior art taught that TNF-α "has been implicated in the pathophysiology of psoriasis." *Id.* at 25:61-62, 22:26-30.

The '689 patent does not provide any data on the treatment of PsO with the claimed dosing regimen of the subcutaneous administration of 40mg adalimumab eow. Under a heading, "D2E7[24] in Human Subjects with Psoriasis," the specification sets forth a prophetic example of treating "[p]atients with moderate to

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April 12, 2004, to which the '689 patent claims priority. Therefore, claim 19 is not entitled to a priority date before April 12, 2004. Nevertheless, as demonstrated herein, claim 19 is obvious based on the prior art relied on for the assumed July 18, 2003 priority date for Ground 1, and the assumed July 19, 2002 priority date for Ground 2.

[24] The specification of the '689 patent equates adalimumab with "D2E7." Ex.1001 at 31:29. 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.

severe chronic plaque psoriasis" and "[d]oses of D2E7 begin at 40 mg weekly or 40 mg every other week administered by subcutaneous injection."[25] *Id.* at 40:1-7.

The only data on the treatment of PsO with adalimumab reported in the '689 patent involved a clinical trial studying "multiple-variable" dosing regimens. Ex.1001 at 40:25-42:31.

B. Person of Ordinary Skill in the Art

As explained by Drs. Helfgott and Plott, a person of ordinary skill in the art relating to the subject matter of the '689 patent would have an M.D. and at least 3 years' post-residency experience treating patients for psoriasis, 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 ¶26; Ex.1012 at ¶26.

[25] The language of the example uses the future tense, identifying it as a "prophetic" example. Ex.1001 at 40:1-7.

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

The claim terms in the ’689 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation (“BRI”) of the claim language. 37 C.F.R. § 42.100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278-79 (Fed. Cir. 2015). The terms in the challenged claims of the ’689 patent should therefore be given their broadest reasonable interpretation.

The preamble to claims 1 and 7, “[a] method of administering [or preparing] adalimumab for treatment of moderate to severe chronic plaque psoriasis,” is a statement of intended use and is not limiting. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (statements of intended use do not usually limit claim scope because they “usually do no more than define a context in which the invention operates.”). If the Board concludes that the preamble should be construed, the term “treatment” should be given its broadest reasonable interpretation of “reducing the signs and symptoms of moderate to severe chronic plaque psoriasis,” without requiring any specific level of therapeutic effect. The specification of the ’689 patent supports this interpretation:

> [i]n one embodiment, the subject has a disorder in which TNFα activity is detrimental. . . . [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 3:4-5, 22:41-44, *see also* ex.1001 at 25:40-50, 26:43-45. The declarations of Drs. Helfgott and Plott further support this interpretation.

Otherwise, for purposes of this petition only, Sandoz does not assert that any special meanings apply to claim terms in the '689 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 of the grounds of unpatentability proposed, there is a reasonable likelihood that Petitioner will prevail with respect to at least one of the challenged claims.

A. Summary of the Argument

The '689 patent claims a PsO dosing regimen (subcutaneously administering 40mg adalimumab eow) that AbbVie had already placed in the prior art to treat RA more than one year before it filed the earliest of the Provisional Applications to which the '689 patent claims priority. Keystone, published by AbbVie researchers in June 2001, described the subcutaneous administration of 40mg of adalimumab eow to successfully treat RA.

The only difference between Keystone and the '689 claims is that in Keystone the 40mg eow adalimumab dosing regimen was used to treat RA, whereas the '689 claims use the same dosing regimen for the treatment of PsO. However, the prior art taught that RA and PsO are related conditions, both mediated by TNF-α, which can be treated by the same drugs, including TNF-α inhibitors, using the same doses and dosing regimens.

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

- Adalimumab subcutaneously dosed at 40mg eow would successfully treat the signs and symptoms of RA (Keystone, ex.1003);
- Adalimumab would be useful in the treatment of PsO (Lorenz, ex.1028); and
- TNF-α inhibitors, such as infliximab and etanercept, could be used to treat moderate to severe PsO using the same dosing regimen as used to treat RA (Chaudhari, ex.1036; Lorenz, ex.1028; references summarized *infra* Table 2).

A POSA would have been motivated by the prior art to use the already known 40mg eow adalimumab RA dosing regimen to treat PsO and would have had a reasonable expectation of success in so doing. The POSA knew that adalimumab, like infliximab and etanercept, was a TNF-α inhibitor that was successful in treating the signs and symptoms of RA. The POSA further knew that the TNF-α blockers infliximab and etanercept had successfully treated the signs and symptoms of PsO using the same dosing regimens for those drugs that had

been used to treat RA. For example, the background art summarized *infra* Table 2, which taught that the doses of TNF-α inhibitors effective in treating RA also effectively treated PsO provides a reasonable expectation of success that the claimed method of administering 40mg adalimumab subcutaneously eow would be effective in treating moderate to severe chronic plaque psoriasis as claimed by the '689 patent. A POSA also knew from the prior art that adalimumab would be useful in the treatment of PsO. Therefore, the POSA would have expected that the subcutaneous administration of 40mg of adalimumab eow would relieve not only the signs and symptoms of RA (as Keystone had shown), but would also relieve the signs and symptoms of PsO.

Even if AbbVie can establish that the '689 patent is entitled to the July 19, 2002 priority date of the earliest of the Provisional Applications, the '689 patent is still obvious over Keystone combined with Mease 2000 and Chaudhari.

As stated above, Keystone disclosed the 40mg eow adalimumab dosing regimen in the treatment of RA. The only issue is whether the POSA had a motivation to use this RA dosing regimen to treat PsO with a reasonable expectation of success. Mease 2000 and Chaudhari provide both. They described the role of TNF-α in PsO and the ability of the TNF-α inhibitors etanercept and infliximab to relieve the signs and symptoms of RA and PsO. Accordingly, a POSA knew that the same RA dosing regimens of infliximab and etanercept could

be used to treat PsO. A POSA would have been motivated by Chaudhari and Mease 2000 to apply the RA adalimumab dosing regimen disclosed in Keystone to treat PsO. Ex.1002 at ¶117; Ex.1012 at ¶95.

Accordingly, the prior art renders obvious the claimed PsO dosing regimen of administering 40mg of adalimumab eow.

B. Patents and Printed Publications Relied on in this Petition

1. 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 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."[26] *Id.* A POSA would therefore find all three eow doses obvious dosing regimens for treating RA, including the 40mg eow D2E7 dose.[27] Ex.1002 at ¶¶35, 96; Ex.1012 at ¶30 n.2. In addition, because Keystone

[26] As described by Dr. Helfgott, the American College of Rheumatology ("ACR") scores are standardized measures of joint disease activity in inflammatory arthritis. Ex.1002 at ¶32.

[27] When Humira® was approved in December 2002, AbbVie's product label included the 40mg eow adalimumab RA dosing regimen. Ex.1026 at 14. In

described the subcutaneous administration of adalimumab, a POSA would understand that the adalimumab had been "fill[ed] . . . into vessels" as required by the '689 patent claims.

Keystone described the exact method claimed by the '689 patent of subcutaneously administering 40mg adalimumab eow, except that the method was used to treat RA instead of PsO.

2. Lorenz (Ex.1028)

Lorenz summarized the vast body of prior art literature establishing the role of TNF-α in the related conditions of RA, Crohn's disease, PsO and PsA, and taught that TNF-α inhibitors such as adalimumab could be used to treat PsO. 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 first reviewed the use of TNF-α inhibitors, including the then approved TNF-α inhibitors 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.

Coherus, *BI408*, *BI409*, IPR2016-00188 and IPR2016-00189, the Board's FWDs found the 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.

Lorenz accurately predicted that "[t]hese developments may include . . . clinical studies with new TNF-α-targeting immunobiologicals, such as the human D2E7 antibody," citing a 1999 clinical study by van de Putte (ex.1007) on the successful use of subcutaneously administered D2E7 to treat RA. Ex.1028 at S18.

Lorenz next discussed the use of TNF-α inhibitors in the treatment of PsA[28] and PsO, noting that "[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.* (citations omitted). "As a logical consequence," Lorenz reported that researchers initiated "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.* (citations omitted). Lorenz reviewed publications describing clinical trial results for infliximab and etanercept in the treatment of PsA and PsO, demonstrating the successful treatment of both conditions with anti-TNF-α agents: "[i]n our open-label experience, infliximab treatment was efficacious and safe in PsA and psoriasis . . . . [and] [i]n an open-label extension study, etanercept

[28] "Psoriatic arthritis refers to chronic inflammatory arthritis which is associated with psoriasis . . . . About 1 in 20 individuals with psoriasis will develop arthritis along with the skin condition, and in about 75% of cases, psoriasis precedes the arthritis." Ex.1001 at 24:61-66.

continued to effectively reduce clinical signs and symptoms of PsA and psoriasis for up to 36 weeks." *Id.* at S18-19 (citations omitted). The etanercept trials reported by Lorenz used a dose of 25mg twice weekly to treat PsO and PsA. *Id.* A POSA reading Lorenz would already know that Enbrel® (etanercept) was already approved at this exact dose to treat RA. *See* ex.1005 at 1554.

Among the studies discussed by Lorenz was Chaudhari, which described a clinical trial in which psoriasis patients were successfully treated with infliximab (5 or $10^{mg}/_{kg}$). Ex.1028 at S19; *see also* ex.1036. As described by Chaudhari, the patients enrolled in the trial had "moderate to severe plaque psoriasis." Ex.1036 at 1843. Thus the POSA reading Lorenz would understand that the treatment of "psoriasis" included treating patients with "moderate to severe chronic plaque psoriasis" (ex.1001 at claim 1).

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." Ex.1028 at S19.

Lorenz accordingly taught that "anti-TNF-α therapy," including treatment with therapeutic agents such as infliximab, etanercept and D2E7, provides "option[s] for the control of" PsO and PsA. *Id.* at S18-19. This conclusion was an accepted consensus view in the field at the time. *See infra* VI.B.3–VI.B.6.

3. Japan Chemical Week (Ex.1034)

Japan Chemical Week, published September 13, 2001, reported the development of TNF-α inhibitors in the treatment of RA, inflammatory bowel diseases ("IBD"), PsA and PsO. Ex.1034 at 1. Commenting on the then-approved TNF-α inhibitors infliximab and etanercept, Japan Chemical Week identified AbbVie's "D2E7" product, stating that it is "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, IBD, psoriasis, [and] psoriatic arthritis . . . ." *Id.*

Thus, Japan Chemical Week described the logical progression of TNF-α inhibitors, including adalimumab, in treating PsO and PsA as well as RA and IBD. *Id.*

4. Marzo-Ortega (Ex.1004*)

Marzo-Ortega reported the efficacy of treating PsA and PsO with $3^{mg}/_{kg}$ infliximab. Ex.1004* at 6. Marzo-Ortega notes 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." *Id.* Marzo-Ortega further explains that because a dose of $3^{mg}/_{kg}$ infliximab has proven to treat RA, the researchers decided to use that identical dose to treat patients with PsA and PsO. *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 at weeks 0, 2, 6 and 14. *Id.* PASI was used to assess psoriasis improvement. *Id.* In the patients who had reached their "week 4 assessment. . . . PASI improved by 80%. . . . These preliminary results suggest a dramatic beneficial effect on skin and joint disease in patients with PsA and skin psoriasis on methotrexate." *Id.*

5. Mease 2000 (Ex.1017)

Mease 2000 described a clinical trial testing the safety and efficacy of treating PsA and PsO with etanercept administered 25mg twice-weekly subcutaneously. Ex.1017 at 385.

Mease first applied the well-known prior art premise that drugs known to treat RA are prime candidates for treating PsA and PsO to etanercept: "[e]tanercept, a [TNF] inhibitor, has shown efficacy in the treatment of [RA]. [PsA] and [PsO] 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.

By way of background to the PsA and PsO clinical trials on etanercept, Mease stated that "[t]umour-necrosis-factor inhibition with etanercept has previously been shown to diminish the activity of rheumatoid arthritis." *Id*. at 385. Mease further associated using etanercept to treat PsA and PsO to the prior success of treating RA with etanercept at the same dose and dosing schedule:

> [t]here is a need for a new therapy to treat both psoriatic arthritis and psoriasis. Etanercept has been shown in previous trials to be effective against rheumatoid arthritis with no serious toxic effects. In two randomised controlled trials of etanercept (25 mg subcutaneously twice weekly) in patients with active DMARD-refractory rheumatoid arthritis, 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 showed that the same twice weekly subcutaneous dosing of 25mg etanercept that was successful in treating RA was also safe and effective in treating PsA and PsO. *Id.* at 387-89.

Mease concluded that "[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." *Id.* at 389.

6. Chaudhari (Ex.1036)

Chaudhari described a study in which 5 and $10^{mg}/_{kg}$ infliximab was administered to treat "moderate to severe plaque psoriasis." Ex.1036 at 1843. Chaudhari explained that TNF-α "is believed to have a major role" in psoriasis as "increased concentrations [of TNF-α] have been detected in psoriatic skin lesions." *Id*. at 1842. Chaudhari further stated that "TNF-α therefore has a potential role in both of the major pathological lesions in psoriasis. Consequently, blockade of TNF-α activity should, in theory, reduce inflammation and keratinocyte proliferation and differentiation abnormalities in psoriasis." *Id*.

Chaudhari stated that infliximab's prior approval for the treatment of RA and Crohn's formed the "scientific rationale for blocking TNF-α in psoriasis . . . [that] led us to design a . . . trial of infliximab monotherapy in patients with moderate to severe psoriasis." *Id*. at 1843.

Chaudhari explained that infliximab was effective in the treatment of patients with moderate to severe plaque psoriasis: "patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area" participated in the study. *Id.* Patients received either placebo, 5 or $10^{mg}/_{kg}$ infliximab administered at weeks 0, 2 and 6. *Id.* Non-responders in the placebo group by week 10 received either 5 or $10^{mg}/_{kg}$ infliximab at weeks 10, 12 and 16. *Id.* Non-responders in the $5^{mg}/_{kg}$ group received "a single infusion of infliximab 10 $^{mg}/_{kg}$ . . .

whereas non-responders in the infliximab 10 $^{mg}/_{kg}$ group were dropped from the study." *Id.* PGA and PASI were the clinical endpoints used to assess efficacy. *Id.* at 1844. Eighty-two percent of the $5^{mg}/_{kg}$ group and 91% of the $10^{mg}/_{kg}$ group "achieved the primary endpoint of a good, excellent, or clear rating on the PGA at week 10, compared with only" 18% of the placebo group. *Id.* Additionally, 82% of the $5^{mg}/_{kg}$ group and 73% of the $10^{mg}/_{kg}$ group achieved PASI 75 compared with 18% of the placebo group. *Id.* Chaudhari concluded that "[p]atients who received infliximab in this study experienced a higher degree of clinical benefit and a more rapid time to response than patients who received placebo." *Id.* at 1845.

C. The Prior Art Taught that RA and PsO Shared Certain Disease Characteristics and Were Often Treated by the Same Drugs at the Same or Similar Doses and Dosing Regimens

1. RA and PsO Are Chronic Diseases

The prior art taught that RA and PsO are "autoimmune inflammatory" diseases. Ex.1015 at 500; Ex.1011 at 489 ("Inflammatory and autoimmune diseases, includ[e] rheumatoid arthritis, . . . psoriasis . . . ."). The prior art also taught that both RA and PsO are chronic remitting and relapsing diseases. Ex.1002 at ¶¶56-58; *see also* ex.1008 at 21 (describing "[c]hronic plaque psoriasis" as "the most common manifestation" of psoriasis); ex.1030 at 1325 ("Different patterns of [RA] have been described. The two main patterns are chronic persistent and the

relapsing-remitting disease course."); ex.1031 at 198 ("Psoriasis is a common, chronic, recurrent, inflammatory disease of the skin . . . .").

Salfeld taught that "D2E7 [is] a good therapeutic candidate for treatment of chronic diseases." Ex.1054* at 3. A POSA reading Salfeld would therefore know that adalimumab is "a good therapeutic candidate for treatment of" PsO. *Id.*; Ex.1002 at ¶75.

2. RA and PsO Are Known To Be TNF-α-Related Disorders

Prior art publications widely reported the connection between the proinflammatory cytokine TNF-α and both RA and PsO. In 1994, Ettehadi reported finding elevated TNF-α activity in psoriatic skin lesions. *See generally* ex.1013; *see also* ex.1017 at 385 ("Psoriatic arthritis and psoriasis are disease states in which tumour necrosis factor, a proinflammatory cytokine, is present in increased concentrations in joints and in the skin."); ex.1019 at S34-35 ("It is thought that TNF-α resides at the apex of an inflammatory cytokine cascade that is responsible for the pathophysiology of RA . . . . TNF-α has been linked to the pathogenesis of PsA and psoriasis because of its ability to upregulate adhesion molecules and to trigger an inflammatory cytokine cascade."); ex.1009 at 301 ("TNF is believed to have a primary role in inflammatory conditions (for example, RA and other autoimmune diseases) . . . . TNF is present at high levels in the joint fluid and tissue of patients with RA and PsA."). Chaudhari cited Ettehadi in

describing the researchers' rationale for initiating its successful infliximab PsO clinical trial. Ex.1036 at 1842 ("The cytokine TNF-α in particular is believed to have a major role in this process: increased concentrations have been detected in psoriatic skin lesions.").

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

3. The Prior Art Taught the Use of TNF-α Inhibitors To Treat RA and PsO

Based on the role of TNF-α, prior art publications taught the use of TNF-α inhibitors to treat RA and PsO. Ettehadi concluded, based on finding "elevated TNF-α in psoriatic lesions[,] . . . [that] the use of TNF-α and TNF receptor antibodies and recombinant soluble TNF receptors, may be of value in the treatment of inflammatory dermatoses." Ex.1013 at 150. Thus in 1994, Ettehadi accurately predicted the development of TNF-α inhibitors and their use in treating TNF-α related disorders such as PsO.

Many others followed suit. Mease 2000 successfully treated PsA and PsO with etanercept and stated that "blocking tumour necrosis factor in both psoriatic arthritis and psoriasis may offer a new therapeutic option for patients with both diseases." Ex.1017 at 389.[29] Similarly, Kalden stated: "anti-TNF-α therapy offers

[29] 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

patients with PsA and psoriasis a new therapeutic option for the control of their disease." Ex.1019 at S36. Chaudhari similarly stated that "[t]he scientific rationale for blocking TNF-α in psoriasis . . . led us to design a . . . trial of infliximab monotherapy in patients with moderate to severe psoriasis." Ex.1036 at 1843.

4. The Prior Art Taught that Adalimumab, as a TNF-α Blocker, Was a Prime Candidate To Treat PsO

Lorenz specifically named 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 available art establishing the role of TNF-α in chronic inflammatory diseases, including RA, Crohn's disease, PsO and PsA, Lorenz restated the known relationship between TNF-α and PsO and PsA: "TNF-α plays a pivotal role in the pathogenesis of PsA and psoriasis." *Id.* at S19. Citing the successful PsO and PsA clinical trial reports by Chaudhari (infliximab) and Mease 2000 (etanercept), 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 anti-TNF-α therapies available to treat "chronic inflammatory

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2002 Mease stated that "[i]nhibitors of TNF thus appear to have excellent potential for treating PsA and psoriasis." Ex.1009 at 303.

diseases" caused by TNF-α and PsO is identified as one of the "[n]ew indications for TNF-α-targeting therapies." *Id.* at S17-19.

Like Lorenz, Japan Chemical Week identified adalimumab, in addition to infliximab and etanercept, as TNF-α inhibitors that would be used to treat PsO: "D2E7 . . . [is] likely to have wider applications, covering not only RA and IBD but also psoriasis, indicating further development of markets." Ex.1034 at 1.

AbbVie's development of Humira® for the PsO indication was premised directly on the prior art's teaching that TNF-α inhibition could treat PsO. On March 3, 2003, AbbVie's predecessor, Abbott Laboratories (hereinafter "AbbVie"), published a press release announcing that it would initiate clinical trials to explore the use of Humira® to treat PsO. Ex.1049* at 1. AbbVie explained its rationale for the clinical trials, stating: (1) "[p]soriasis . . . [is an] autoimmune disorder[] in which . . . tumor necrosis factor-alpha . . . 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.*

5. The Prior Art Demonstrated That TNF-α Inhibitors Could Treat RA and PsO With the Same or Similar Doses and Dosing Regimens

Prompted by TNF-α's known role in triggering RA and PsO, researchers soon demonstrated that TNF-α inhibitors were effective in treating both diseases.

Ex.1002 at ¶¶59-72. Furthermore, the prior art taught that drugs used to treat RA could also be used to treat PsO using the same or similar doses and dosing regimens as used for RA. For example, the prior art established that the TNF-α inhibitors infliximab and etanercept were effective in treating both RA and PsO using the same or similar doses and dosing regimens. *See infra* Table 2.

a. Infliximab

(1) The Prior Art Taught That 3, 5 and 10 $^{mg}/_{kg}$ Effectively Treated RA

Multiple prior art references taught that 3, 5 and 10 $^{mg}/_{kg}$ 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 patients receiving 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.

(2) The Prior Art Taught That 3, 5 and 10 $^{mg}/_{kg}$ Effectively Treated PsO

Multiple prior art references taught that 3, 5 and 10 $^{mg}/_{kg}$ infliximab effectively treated PsO.

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 PsO and PsA was based on infliximab's efficacy in treating RA at that exact dose. *Id.* ("[I]nfliximab at a dose of $3^{mg}/_{kg}$ in combination with methotrexate has proven effective in rheumatoid arthritis. We therefore aimed to assess the efficacy of infliximab at a dose [of] $3^{mg}/_{kg}$ in combination with methotrexate in the treatment of patients with PsA and skin psoriasis."). Wollina administered 300mg infliximab to two 100kg patients (for a dose of $3^{mg}/_{kg}$) at weeks 0, 2, 4 and 8 in combination with methotrexate and found it to be effective in treating PsO. Ex.1050 at 128.

Chaudhari administered 5 or $10^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 and found it to be effective in treating moderate to severe plaque psoriasis. Ex.1036 at 1843-45. Van den Bosch administered $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 and found it effective in treating psoriatic skin disease. Ex.1037 at 429, 432. Ogilvie administered $5^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6 in combination with methotrexate or sulphasalazine and found it to be effective in treating psoriatic skin lesions. Ex.1033 at 587-89.

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

Mease 2000 described a clinical trial in which 25mg etanercept administered subcutaneously twice weekly effectively treated PsO and PsA: "[e]tanercept was also effective in improving the skin lesions of psoriasis in the trial." Ex.1017 at

386, 388 (citation omitted). 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 rheumatoid arthritis with no serious toxic effects" at a dose of "25 mg subcutaneously twice weekly."[30] *Id.* at 389.

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

Drug	RA		PsO	
	Reference	**Dosing Regimen**	**Reference**	**Dosing Regimen**
$3^{mg}/_{kg}$ Infliximab	Remicade® Package Insert (ex.1027 at 1087)	$3^{mg}/_{kg}$ infliximab at weeks 0, 2 and 6, then every 8 weeks thereafter in combination with MTX	Marzo-Ortega (ex.1004* at 6)	$3^{mg}/_{kg}$ at weeks 0, 2, 6 and 14, in combination with MTX
			Wollina (ex.1050 at 128)	300mg (equivalent to $3^{mg}/_{kg}$[31]) at weeks 0, 2, 4 and 8 in combination with MTX
5 or $10^{mg}/_{kg}$ 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	Chaudhari (ex.1036 at 1843)	5 or $10^{mg}/_{kg}$ at weeks 0, 2, 6
	Perkins (ex.1040 at 2206)	patients received single infusion of either 5, 10, or	Van den Bosch (ex.1037 at 429)	$5^{mg}/_{kg}$ at weeks 0, 2 and 6

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

[31] 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		PsO	
	Reference	Dosing Regimen	Reference	Dosing Regimen
		$20^{mg}/_{kg}$ infliximab in combination with MTX		
	Remicade® Package Insert (ex.1027 at 1085)	$10^{mg}/_{kg}$ at weeks 0, 2 and 6, then every 4 or 8 weeks thereafter in combination with MTX	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 Insert (ex.1006 at 23)	25mg twice weekly	2002 Enbrel® Package Insert (ex.1006 at 10-11)	25mg twice weekly

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

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

Support for the use of the same or similar doses and dosing regimens for TNF-α inhibitors in treating both RA and PsO is also based on the practice of using

earlier generations of drugs to treat both diseases with the same doses and 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. As demonstrated in Table 3, various forms of methotrexate, cyclosporine, hydrocortisone, cortisone, dexamethasone, prednisolone and betamethasone were all approved in the prior art for use in treating RA and PsO at the same or similar maintenance doses and dosing regimens.

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

Drug	Reference	RA dosing regimen	PsO dosing regimen
Trexall® (methotrexate)	Ex.1024* at 10	1. "Single oral doses of 7.5 mg once weekly." 2. "Divided oral dosages of 2.5 mg at 12-hour intervals for 3 doses given as a course once weekly." "Dosages in each schedule may be adjusted gradually to achieve an optimal response, but not ordinarily to exceed a total	1. Single doses of 10 to 25mg per week (oral, intramuscular, or intravenous) until adequate response is achieved 2. "Divided oral dose schedule: 2.5 mg at 12-hour intervals for three doses." "Dosages in each schedule may be gradually adjusted to achieve optimal clinical response; 30 $^{mg}/_{week}$ should not

Drug	Reference	RA dosing regimen	PsO dosing regimen
		weekly dose of 20 mg."	ordinarily be exceeded."
Gengraf™ (cyclosporine)	Ex.1035 at 460	The initial dose is 2.5 $^{mg}/_{kg}/_{day}$ taken twice a day as a divided dose	
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 PsO at the same dosage regimen.

7. Prior Art Package Inserts for Approved TNF-α Inhibitors Disclosed Doses and Dosing Regimens for RA and PsO

The prior art established the ability of TNF-α inhibitors to treat PsO and RA, and showed that they could do so using the same dosage regimens. Therefore one would expect a POSA to review the FDA approved labels for known TNF-α inhibitors, such as adalimumab, etanercept and infliximab, to treat RA and PsO.

a. Enbrel® Package Inserts

Like Humira®, Enbrel® is a TNF-α inhibitor. Ex.1005 at 1551-52; Ex.1006 at 1. Enbrel® was first approved to treat RA. Ex.1005 at 1553. In 2002, Enbrel® was approved to treat PsA using exactly the same dose and dosing regimen as was approved to treat RA: "[t]he recommended dose of ENBREL for adult patients with rheumatoid arthritis or psoriatic arthritis is 25 mg given twice weekly as a subcutaneous injection 72-96 hours apart . . . ." Ex.1006 at 23; *see also* ex.1019 at S38 (noting that in January 2002, etanercept was approved by the FDA to treat PsA).

The clinical trial data included in the package insert for PsA also demonstrates Enbrel®'s ability to treat the related condition, PsO, at the same 25mg twice per week dose. Ex.1006 at 10-12. The patients in the PsA trial all "had plaque psoriasis." *Id.* at 10. The package insert reported that the skin lesions were "improved with ENBREL, relative to placebo, as measured by" PASI score. *Id.* at 11. The data also demonstrated an improvement in PGA. *Id.* at tbl. 4. Thus, although the FDA had not yet approved Enbrel® for treatment of PsO, it had approved Enbrel® for the treatment of psoriasis plaques in patients having PsA and the drug had demonstrated efficacy in reducing those plaques using the very same clinical endpoints described in the '689 patent. Ex.1001 at 41:35–42:8; Ex.1002 at ¶92.

Accordingly, the 2002 Enbrel® Package Insert taught that etanercept could be administered using the same dose and dosing regimen to treat both RA and PsO. Ex.1002 at ¶92.[32]

b. Remicade® Package Insert

The Remicade® Package Insert states: "[t]he recommended dose of REMICADE [for RA] is 3 $^{mg}/_{kg}$ given as an intravenous infusion followed with additional 3 $^{mg}/_{kg}$ doses at 2 and 6 weeks after the first infusion then every 8 weeks thereafter." Ex.1027 at 1087. Remicade® is administered in combination with methotrexate to treat RA. *Id.*

Additionally, the clinical studies found doses of $3^{mg}/_{kg}$ or $10^{mg}/_{kg}$ infliximab administered at weeks 0, 2 and 6, and then every 4 or 8 weeks thereafter in combination with methotrexate to be effective. *Id.* at fig.1.

[32] In November 2016, the FDA approved Enbrel® for treating psoriasis based on the same type of PASI and PGA data already in the 2002 Enbrel® Package Insert. *Compare* ex.1048 *with* ex.1006. Although the 2016 Enbrel® Package Insert included a higher initial dose for the treatment of psoriasis, calling for "50 mg twice weekly for [the first] 3 months," the same total weekly amount of 50 mg is indicated for ongoing treatment of psoriasis (after the first 3 months) as was previously indicated for RA and PsA. Ex.1048 at 1; Ex.1006 at 23. In addition, the data in the 2002 Enbrel® Package Insert demonstrated that even without the 3 month period of higher dosing, 25 mg twice per week was effective in treating psoriasis. Ex.1006 at 11-12. Data in the 2016 Enbrel® Package Insert confirms this. Ex.1048 at 16; Ex.1002 at ¶92 n.11.

D. Ground 1: Keystone Combined with Lorenz and Chaudhari Render Claims 1, 4, 7, 10, 13, 16 and 19 Obvious

Ground 1 assumes a July 18, 2003 priority date. Keystone disclosed the 40mg adalimumab eow subcutaneous dosing regimen to treat RA. Lorenz taught that D2E7 could be used to treat PsO and PsA. Chaudhari taught that a TNF-α inhibitor (like adalimumab) could treat patients with moderate to severe plaque psoriasis. Lorenz and the background art described *supra* Tables 2 and 3, provided the motivation to combine those references and the reasonable expectation of success that the claimed dosing regimen would treat PsO, because the prior art taught that the same drugs, including TNF-α inhibitors, used to treat RA could generally be used to treat PsO, including in patients with PsA with the same dosing regimens.

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.* It would therefore be obvious to a POSA to administer 20, 40, or 80mg D2E7 eow subcutaneously to treat RA.

The only difference between Keystone and the claimed dosing regimen is that the claimed dosing regimen recites the treatment of "moderate to severe chronic plaque psoriasis" (ex.1001 at claim 1) instead of the treatment of RA.

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

Lorenz taught that anti-TNF-α blockers were effective in treating PsO and PsA. Lorenz reviewed the successful clinical trial reports of infliximab, etanercept, and adalimumab (D2E7) in treating RA. *See generally* 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 discussed in detail the clinical trial successes of infliximab (including Chaudhari) and etanercept (including Mease 2000) in the treatment of PsO and PsA. *Id.* at S18-19.

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.* As Drs. Helfgott and Plott state, a POSA reading Lorenz would clearly understand that adalimumab was an obvious therapeutic agent for the treatment of PsA and PsO. Ex.1002 at ¶46; Ex.1012 at ¶63.

Japan Chemical Week confirms that a POSA would understand Lorenz and the art reviewed therein as teaching the use of D2E7 to treat PsO. Japan Chemical Week 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." Ex.1034 at 1.

Accordingly, the prior art clearly taught that adalimumab would have applications in the treatment of not only RA and IBD, but also PsO and PsA.

3. The Known RA Adalimumab Dosing Regimen of 40mg eow by Subcutaneous Injection Was an Obvious Choice for the Treatment of PsO

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

For example, Marzo-Ortega demonstrated the efficacy of infliximab in treating PsA and PsO 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 PsO infliximab dose could be lowered from $5^{mg}/_{kg}$, which was successful in a previous PsO 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 rheumatoid arthritis. We therefore aimed to assess the efficacy of

infliximab at a dose [of] $3^{mg}/_{kg}$ in combination with methotrexate in the treatment of patients with PsA and skin psoriasis.").

Mease 2000 similarly reported the success of the subcutaneous administration of 25mg etanercept twice weekly to treat PsA and PsO, which is the same etanercept dosing regimen proven to treat RA. Ex.1017 at 385, 389; *see also* ex.1005 at 1554 (The FDA-approved dose of Enbrel® (etanercept) for treating RA is 25mg administered twice weekly subcutaneously.).

As Drs. Helfgott and Plott explain, a POSA would be motivated to use the same adalimumab dosing regimen (40mg eow) shown to be effective in treating RA to also treat PsO and PsA, because a POSA would know that other TNF-α inhibitors (*i.e.*, infliximab and etanercept) could be used to treat each of these conditions at the same dosing regimen. Ex.1002 at ¶¶98-102, 122; Ex.1012 at ¶¶76-78, 95. Additionally, a POSA would know that TNF-α was implicated in RA and PsO, 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 PsO. Accordingly, a POSA would have a reasonable expectation that the RA dosing regimen would effectively treat PsO. Ex.1002 at ¶¶102, 122; Ex.1012 at ¶¶78, 95-96.

4. Keystone Taught "filling adalimumab into vessels"

Keystone taught the subcutaneous administration of adalimumab. Ex.1003 at A481. A POSA would understand that a syringe can either be filled by the person administering the drug or it can be pre-filled by the manufacturer. Ex.1002 at ¶96 n.13; *see KSR Int'l. Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) ("When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp."). Thus, by disclosing subcutaneous administration of adalimumab, Keystone rendered filling adalimumab into vessels obvious.

5. A POSA Would Have Been Motivated to Combine Keystone with Lorenz and Chaudhari 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 PsO; (2) the use of TNF-α inhibitors to treat both RA and PsO using the same or similar dosing regimens; and (3) adalimumab's known potential for treating PsO provide an overwhelming motivation for a POSA to combine Keystone with Lorenz and Chaudhari, with a reasonable expectation that 40mg subcutaneously-administered adalimumab eow would effectively treat PsO.

As explained above, the background prior art provided a POSA with a wealth of information about how to select drugs, doses and dosing regimens to

treat PsO based on known treatments for RA thus providing further motivation for using the RA dosing regimen in PsO:

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

A POSA would understand all of 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. . . .").

In summary, the success of TNF-α inhibitors (*supra* Table 2) as well as other drugs (*supra* Table 3) in treating RA and PsO using the same or similar doses and dosing regimens, serve as a motivation to combine the teachings of Lorenz and Chaudhari with Keystone.[33] Table 2 summarizes numerous prior art references,

[33] Methotrexate was administered in combination with adalimumab in Keystone. Ex.1003 at A481. This, however, is irrelevant to the analysis because claim 1 of the '689 patent is open-ended and covers the administration of adalimumab by

including Marzo-Ortega, Mease 2000, Chaudhari, Ogilvie, Van den Bosch, Wollina, Perkins, Feldmann, the 2002 Enbrel® Package Insert and the Remicade® Package Insert, which demonstrate the successful treatment of PsO with the same infliximab and etanercept doses that had been used to treat RA and provides a reasonable expectation of success that the claimed method of administering 40mg adalimumab subcutaneously eow would be effective in treating PsO.

6. Keystone Combined with Lorenz and Chaudhari Renders Obvious Claims 1, 4, 7, 10, 13, 16 and 19

Claims 1 and 7 of the '689 patent are obvious over the prior art for the reasons stated *supra* VI.D.1-VI.D.5.

a. Keystone Combined with Lorenz and Chaudhari Taught That the Vessels Were Syringes (Claims 4, 10)

Claims 4 and 10 depend from claims 1 and 7, respectively and additionally require that the "vessels are syringes." Ex.1001 at claims 4, 10. For the reasons discussed in the context of claims 1 and 7, claims 4 and 10 are obvious.

Additionally, as discussed *supra* VI.D.4, Keystone teaches a subcutaneous injection, and therefore discloses this claim limitation. Ex.1003 at A481. As Dr.

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itself, with methotrexate or any other drug. Ex.1001 at claim 1 ("A method of administering adalimumab . . . comprising . . . ."). In any event, the skilled artisan would understand that co-administration of methotrexate was optional because prior clinical trials showed that several D2E7 doses all effectively treated RA without co-administration of methotrexate. *See, e.g.*, ex.1007* at 3; ex.1042 at I72.

Helfgott explains, a subcutaneous injection is not possible without a syringe. Ex.1002 at ¶¶104, 125.

Accordingly, the additional claim limitation, "wherein said vessels are syringes" is obvious over Keystone combined with Lorenz and Chaudhari.

b. Keystone Combined With Lorenz and Chaudhari Taught the Claimed Treatment of a Patient Having Both PsO and PsA and Achieving the Claimed Clinical Endpoints (Claims 16 and 19)

Claims 16 and 19 depend from claim 7, and additionally require that "said patient has both psoriasis and psoriatic arthritis." Ex.1001 at claims 16, 19. As explained above, for all of the same reasons that a POSA would reasonably expect a TNF-α inhibitor that treats RA to treat PsO using the same dose and dosing regimen, the POSA would reasonably expect the claimed dosing regimen to treat patients with PsO, including in patients that have PsA.

Treating PsO patients with the claimed method, which is obvious for the reasons explained above, would inherently treat the percentage of PsO patients which also have PsA. Lorenz taught that "psoriatic arthritis (PsA) occurs in approximately 6–20% of psoriasis patients." Ex.1028 at S18; *see Par Pharm., Inc. v. Twi Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) ("We have recognized that inherency may supply a missing claim limitation in an obviousness analysis."). Additionally, Lorenz described Mease 2000, the results of which

showed that etanercept treated psoriasis in patients with PsA. Ex.1028 at S19; *see also* ex.1017.

Claims 16 and 19 also require a patient to achieve specific clinical outcomes. Claim 16 requires achieving "at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment" and claim 19 requires achieving "at least a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment." Ex.1001 at claims 16, 19. However, both of these endpoints are the obvious result of anti-TNF-α therapy. Chaudhari, in describing the infliximab PsO trial, reported that 82% of the $5^{mg}/_{kg}$ infliximab group and 73% of the $10^{mg}/_{kg}$ infliximab group achieved a 75% improvement in PASI score and that 82% of the patients in the $5^{mg}/_{kg}$ infliximab group and 91% of the patients in the $10^{mg}/_{kg}$ infliximab group achieved PGA scores of good, excellent, or clear. Ex.1036 at 1844. As Drs. Helfgott and Plott explain, the recited clinical endpoints are the obvious result of successful TNF-α blockade and adalimumab, like infliximab, was known in the prior art to successfully block TNF-α at the claimed dosing regimen of 40mg eow. Ex.1002 at ¶¶112-13, 133-34; Ex.1012 at ¶¶85-87, 103-05.

Moreover, both of these recited endpoints, according to the '689 patent itself, are inherently achieved by administering 40mg eow of adalimumab to PsO

patients. Ex.1001 at 41:11–42:31. In other words, these results are achieved by administering 40mg adalimumab eow without the need for any additional steps.

Accordingly, 40mg eow dosing of adalimumab in PsO is obvious, and the addition of these limitations specifying the clinical endpoints inherent in this method of treatment cannot save the claims from invalidation. *Par Pharm., Inc.*, 773 F.3d at 1194–95.

c. Keystone Combined with Lorenz and Chaudhari Taught Treating Patients Having "at least 5% body surface area . . . affected by the psoriasis" (Claim 13)

Claim 13, which depends from claim 7 requires that the treated patient has "at least 5% body surface area (BSA) . . . affected by the psoriasis." Ex.1001 at claim 7. A POSA, however, expected that patients having 5% or more BSA affected by PsO could be effectively treated using TNF-α inhibitors. Chaudhari reported effective treatment of patients having "moderate to severe plaque psoriasis involving at least 5% of the body surface area" with a TNF-α inhibitor. Ex.1036 at 1843.

For the same reasons stated *supra* VI.D.6.b, Keystone combined with Lorenz and Chaudhari taught the methods of treatment that inherently provided the claimed clinical endpoints.

E. Ground 2: Keystone Combined with Mease 2000 and Chaudhari Render Claims 1, 4, 7, 10, 13, 16 and 19 Obvious

As explained *supra* IV.A, AbbVie is only entitled to a July 18, 2003 date of priority. Nevertheless, even in the event that AbbVie obtains the benefit of the July 19, 2002 filing date, as set forth in Ground 2, claims 1, 4, 7, 10, 13, 16 and 19 of the '689 patent are invalid.

Thus, Ground 2 relies on the same recited combination of prior art as Ground 1 with the exception of Lorenz. While Lorenz taught the use of adalimumab to treat PsO in Ground 1, that use was also obvious from Keystone in view of Mease 2000 and Chaudhari.

Keystone taught that 40mg of adalimumab subcutaneously administered eow successfully blocked TNF-α and treated the signs and symptoms of RA. Ex.1003 at A481. As described *supra* VI.B.5–VI.B.6, VI.C.5, Mease 2000 and Chaudhari described the use of etanercept and infliximab, respectively to successfully treat PsO with the same dosing regimens that had been used to successfully treat RA.

Mease 2000 and Chaudhari additionally taught that TNF-α is associated with RA and PsO (ex.1017 at 385; ex.1036 at 1842-43), and described the use of the TNF-α inhibitors etanercept and infliximab to treat PsO lesions. Ex.1017 at 385-88 (etanercept); Ex.1036 at 1843-46 (infliximab). Both Mease 2000 and Chaudhari concluded that blocking TNF-α would be useful in the treatment of PsO. Ex.1017 at 389 ("[B]locking tumour necrosis factor in both psoriatic arthritis

and psoriasis may offer a new therapeutic option for patients with both diseases."); Ex.1036 at 1846 ("[T]he clinical response to anti-TNF-α monotherapy in this trial suggests that, among the many cytokines and growth factors overexpressed in psoriatic plaques, TNF-α has a pivotal role in the pathogenesis of psoriasis.").

Accordingly, a POSA would know based on (1) Keystone's description of adalimumab's success in treating RA and (2) the teachings of Mease 2000 and Chaudhari that the TNF-α inhibitors etanercept and infliximab were successful in treating RA, PsO and PsA, and therefore the TNF-α inhibitor adalimumab was a prime candidate for treating PsO. Ex.1002 at ¶121; Ex.1012 at ¶95.

Moreover, a POSA would be motivated by Mease 2000 or Chaudhari to use adalimumab at the prior art RA 40mg eow dosing regimen disclosed in Keystone to treat PsO because etanercept and infliximab were shown in the art to treat both RA and PsO at the same dosing regimens. *See also supra* Table 2. For the above reasons, a POSA would also have a reasonable expectation that adalimumab at the 40mg eow dosing regimen would succeed in treating the signs and symptoms of PsO, including in patients with PsA. Ex.1002 at ¶¶102, 122; Ex.1012 at ¶¶78, 95-96.

The study disclosed in Chaudhari assessed "patients who had moderate to severe plaque psoriasis involving at least 5% of the body surface area," and found that, when treated with infliximab, these patients "experienced a high degree of

clinical benefit and rapid time to response in the treatment of moderate to severe plaque psoriasis compared with patients who received placebo." Ex.1036 at 1842-43. Accordingly, a POSA would understand that Chaudhari explicitly taught treating patients with moderate to severe plaque psoriasis. Ex.1002 at ¶¶47-49.

As explained with regard to Ground 1, *supra* VI.D.6, Keystone combined with Mease 2000 and Chaudhari additionally describe the limitations of dependent claims 4, 10, 13, 16, and 19 and render them obvious. Additionally, as discussed *supra* VI.D.6.b, Mease 2000, described in Lorenz, taught the treatment of patients having both PsO and PsA with TNF-α inhibitors as recited in claims 16 and 19.

F. No Secondary Considerations Such As Commercial Success or Long-Felt Need and Failure of Others 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 '689 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. *See Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377

(Fed. Cir. 2005) (where "market entry by others was precluded [due to blocking patents], the inference of non-obviousness of [the asserted claims], from evidence of commercial success, is weak."); *Coal. for Affordable Drugs II LLC v. NPS Pharm., Inc.*, No. IPR2015-01093, Final Written Decision, Paper 67, at 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 '689 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 PsO. 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 (U.S. Patent No. 8,889,135), AbbVie attributed Humira®’s commercial success, not to its PsO 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.1064 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 '689 patent from invalidity by asserting that the commercial success of Humira® is due to the methods claimed in the '689 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.*, 550 U.S. at 417) (citation omitted).

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.1064 at 55; *see also 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.1064 at 55-56 (noting that Enbrel® requires two doses per week and Remicade® is administered intravenously instead of

subcutaneously); *see also 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.") (internal quotation marks omitted).

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.1064 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. *See 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.

G. Summary of Grounds for Invalidity

The claim charts below provide a summary of the prior art disclosures that render obvious each claim limitation in the '689 patent for Grounds 1 and 2. The charts for the dependent claims hereby incorporate all of the grounds in the independent and any other dependent claims from which they depend.

Independent Claims 1 and 7 Are Obvious Over Keystone (ex.1003) Combined with Chaudhari (ex.1036) and Lorenz (ex.1028) [GROUND 1]
Or
Independent Claims 1 and 7 Are Obvious Over Keystone (ex.1003) Combined with Chaudhari (ex.1036) and Mease 2000 (ex.1017) [GROUND 2]

'689 Patent Claim Language	**Prior Art Disclosures**
Claim 1	
A method of administering adalimumab	"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.
for treatment of moderate to severe chronic plaque psoriasis,	"Several open-label studies have investigated the use of anti-TNF-α agents in the treatment of PsA and psoriasis." Ex.1028 at S18. Patients had "moderate to severe plaque psoriasis involving at least 5% of the body surface area." Ex.1036 at 1843.

’689 Patent Claim Language	Prior Art Disclosures
	Or
	“This randomised, double-blind, placebo-controlled, 12 week study assessed the efficacy and safety of etanercept . . . in 60 patients with psoriatic arthritis and psoriasis.” Ex.1017 at Abstract. Patients had “moderate to severe plaque psoriasis involving at least 5% of the body surface area.” Ex.1036 at 1843.
comprising filling adalimumab into vessels	“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. “[G]iven every other week subcutaneously.” Ex.1003 at A481.
and subcutaneously administering	“[G]iven every other week subcutaneously.” Ex.1003 at A481.
40 mg of said adalimumab	“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.
to a patient having moderate to severe chronic plaque psoriasis	“[T]reatment was efficacious and safe in PsA and psoriasis.” Ex.1028 at S18 (citation omitted). Patients had “moderate to severe plaque psoriasis involving at least 5%

’689 Patent Claim Language	Prior Art Disclosures
	of the body surface area.” Ex.1036 at 1843.
	Or
	“Only patients with plaque psoriasis affecting greater than or equal to 3% of body surface area were assessed for skin disease.” Ex.1017 at 386. “This randomised, double-blind, placebo-controlled, 12 week study assessed the efficacy and safety of etanercept . . . in 60 patients with psoriatic arthritis and psoriasis.” Ex.1017 at Abstract. Patients had “moderate to severe plaque psoriasis involving at least 5% of the body surface area.” Ex.1036 at 1843.
every other week.	“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.

’689 Patent Claim Language	Prior Art Disclosures
Claim 7	
A method of preparing adalimumab	See claim 1.
for treating moderate to severe chronic plaque psoriasis,	
comprising filling adalimumab into vessels and	
providing said adalimumab for treatment,	

’689 Patent Claim Language	Prior Art Disclosures
wherein said treatment comprises subcutaneously administering	
40 mg of said adalimumab	
to a patient having moderate to severe chronic plaque psoriasis	
every other week.	

Dependent Claims 4, 10, 13, 16 and 19 Are Obvious Over Keystone (ex.1003) Combined with Chaudhari (ex.1036) and Lorenz (ex.1028) [GROUND 1]
Or
Dependent Claims 4, 10, 13, 16 and 19 Are Obvious Over Keystone (ex.1003) Combined with Chaudhari (ex.1036) and Mease 2000 (ex.1017) [GROUND 2]

’689 Patent Claim Language	Prior Art Disclosures
Claim 4: The method of claim **1**, wherein said vessels are syringes.	“[G]iven every other week subcutaneously.” Ex.1003 at A481.
Claim 10: The method of claim **7**, wherein said vessels are syringes.	

’689 Patent Claim Language	Prior Art Disclosures
Claim 13	
The method of claim **7**, wherein at least 5% body surface area (BSA) of the patient is affected by the psoriasis.	Patients had “moderate to severe plaque psoriasis involving at least 5% of the body surface area.” Ex.1036 at 1843.
	or

<table>
<tr><th>’689 Patent Claim Language</th><th colspan="2">Prior Art Disclosures</th></tr>
<tr><td></td><td colspan="2">Patients had “moderate to severe plaque psoriasis involving at least 5% of the body surface area.” Ex.1036 at 1843.

“Of the 19 patients in each treatment group who were evaluable for psoriasis (≥3% of body surface area involvement) . . . .” Ex.1017 at 388.</td></tr>
<tr><td colspan="3">Claim 16</td></tr>
<tr><td rowspan="2"></td><td>Inherency argument</td><td>Obviousness argument</td></tr>
<tr><td>“Of the one hundred forty-eight adult patients enrolled in the [PsO] study, 29% also had a medical history of psoriatic arthritis (PsA).” Ex.1001 at 42:9-11.[34]</td><td>See supra VI.D.6.b; ex.1028 at S19 (describing Mease 2000, where etanercept treated psoriasis in patients with PsA) (Ground 1 only).

“[PsA] occurs in approximately 6-20% of psoriasis patients.” Ex.1028 at S18 (citation omitted) (Ground 1 only).

“This randomised, double-blind, placebo-controlled, 12</td></tr>
<tr><td>The method of claim 7, wherein said patient has both psoriasis and psoriatic arthritis</td><td></td><td></td></tr>
</table>

[34] The ’689 patent is not prior art but its disclosure demonstrates the result is inherent for some portion of treated patients. *See supra* VI.D.6.b.

’689 Patent Claim Language	Prior Art Disclosures	
		week study assessed the efficacy and safety of etanercept . . . or placebo in 60 patients with psoriatic arthritis and psoriasis.” Ex.1017 at Abstract (Ground 2 only).

'689 Patent Claim Language	**Prior Art Disclosures**	
	Inherency argument	**Obviousness argument**
and achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment.	"[A]t [w]eek 12, statistically significantly greater percentages of patients achieved a PASI 75 response or better on D2E7 than those on a placebo treatment." Ex.1001 at 41:24-26.[35]	"The change in PASI score was a secondary endpoint. Nine of 11 (82%) in the infliximab 5 $^{mg}/_{kg}$ group and eight of 11 (73%) patients in the infliximab 10 $^{mg}/_{kg}$ group had at least 75% improvement in the PASI score . . . ." Ex.1036 at 1844 (Grounds 1 and 2); *see also supra* VI.D.6.b; ex.1002 at ¶¶112-13, 133-34; ex.1012 at ¶¶85-87, 103-05.
Claim 19		
The method of claim **7**, wherein said patient has both psoriasis and psoriatic arthritis	**Inherency argument**	**Obviousness argument**
	See claim 16.	See claim 16.
and achieves at least a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment.	**Inherency argument**	**Obviousness argument**
	"At [w]eek 12, 49% of patients on D2E7 receiving 40 mg eow . . . achieved a PGA of	"Nine of 11 (82%) patients in the infliximab 5 $^{mg}/_{kg}$ group and ten of 11 (91%) in

[35] *See supra* n.34.

’689 Patent Claim Language	Prior Art Disclosures	
	‘clear’ or ‘almost clear’ . . . .” Ex.1001 at 42:5-8.[36]	the infliximab 10 $^{mg}/_{kg}$ group achieved the primary endpoint of a good, excellent, or clear rating on the PGA at week 10 . . . .” Ex.1036 at 1844; *see also supra* VI.D.6.b; ex.1002 at ¶¶112-13, 133-34; ex.1012 at ¶¶85-87, 103-05.

VII. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that claims 1, 4, 7, 10, 13, 16 and 19 of the ’689 patent are unpatentable as obvious in view of the prior art identified herein. Petitioner therefore requests that the Board institute *inter partes* review for each of those claims.

[36] *See supra* n.34.

Dated: September 14, 2017

Respectfully submitted,
/s/ David K. Barr
David K. Barr (Reg. No. 31,940)
David.Barr-PTAB@apks.com
Arnold & Porter Kaye Scholer LLP
250 West 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

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 13,308 words as counted by the word processing program used for its preparation (Microsoft Word 2010).

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

Dated: September 14, 2017

/s/ David K. Barr

David K. Barr (Reg. No. 31,940)
David.Barr-PTAB@apks.com
Arnold & Porter Kaye Scholer
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560

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. 9,090,689 and Exhibits 1001 – 1069 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 '689 patent.

Foley Hoag, LLP (wAVR)
Patent Group, Seaport West
155 Seaport Blvd.
Boston, MA 02210-2600

Dated: September 14, 2017

/s/ David K. Barr
David K. Barr (Reg. No. 31,940)
David.Barr-PTAB@apks.com
Arnold & Porter Kaye Scholer
250 W. 55th Street
New York, NY 10019
T: 212-836-7560
F: 212-836-6560