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.: 9,187,559
Issue Date: November 17, 2015
Title: Multiple-Variable Dose Regimen for Treating Idiopathic Inflammatory Bowel Disease

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PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 9,187,559 PURSUANT TO 35 U.S.C. §§ 311-319 AND 37 C.F.R. § 42

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Ex. No.[1]	Description	Referred To As	Reference Type[2]
1001	U.S. Patent No. 9,187,559, filed Feb. 20, 2015, issued Nov. 17, 2015	"'559 patent"	n/a
1002	Declaration of Ingvar Bjarnason, M.D.	"Bjarnason Decl."	n/a
1003	WOLFGANG A. RITSCHEL & GREGORY L. KEARNS, HANDBOOK OF BASIC PHARMACOKINETICS . . . INCLUDING CLINICAL APPLICATIONS (5th ed. 1999)	"Ritschel & Kearns"	102(b)
1004*	M. Schattenkirchner et al. *Long-Term Use of the Fully Human Anti-TNF Antibody D2E7 in Combination with Methotrexate in Active Rheumatoid Arthritis*, 43 ARTHRITIS & RHEUMATISM S228 [968] (2000)	"Schattenkirchner"	102(b)
1005	Declaration of Victoria L. Reines	"Reines Decl."	n/a
1006*	Alfons den Broeder et al., *A Single Dose, Placebo Controlled Study of the Fully Human Anti-Tumor Necrosis Factor-α Antibody Adalimumab (D2E7) in Patients with Rheumatoid Arthritis*, 29 J. RHEUMATOLOGY 2288 (2002)	"den Broeder"	102(b)
1007	Chaity Chaudhury et al., *The Major Histocompatibility Complex-Related Fc Receptor for IgG (FcRn) Binds Albumin and Prolongs Its Lifespan*, 197 J. EXPERIMENTAL MED. 315 (Feb. 2003)	"Chaudhury"	102(b)
1008	Roelien H. Enting et al., *A Prospective Study Evaluating the Response of*	"Enting"	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.

Ex. No.[1]	Description	Referred To As	Reference Type[2]
	Patients with Unrelieved Cancer Pain to Parenteral Opioids, 94 CANCER 3049 (2002)		
1009	U.S. Patent No. 5,405,837, filed May 18, 1993, issued Apr. 11, 1995	"'837 patent"	102(b)
1010	U.S. Patent No. 6,818,633, filed June 28, 2002, issued Nov. 16, 2004	"'633 patent"	102(e)
1011	B. Everts et al., *Morphine Use and Pharmacokinetics in Patients with Chest Pain Due to Suspected or Definite Acute Myocardial Infarction*, 2 EUR. J. PAIN 115 (1998)	"Everts"	102(b)
1012	U.S. Patent No. 6,855,340, filed May 23, 2003, issued Feb. 15, 2005	"'340 patent"	102(e)
1013	Ronald D. Schoenwald, Basic Principles, *in* PHARMACOKINETICS IN DRUG DISCOVERY AND DEVELOPMENT (Ronald D. Schoenwald ed., 2002)	"Schoenwald"	102(b)
1014	Frank M. Balis et al., *Pharmacokinetics of Subcutaneous Methotrexate*, 6 J. CLINICAL ONCOLOGY 1882 (1988)	"Balis"	102(b)
1015	*Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172 (Patent Owner's Response, Paper No. 37, Sept. 13, 2016)	"Patent Owner's Response in '135 IPR"	n/a
1016	MARK FELDMAN ET AL., SLEISENGER & FORDTRAN'S GASTROINTESTINAL AND LIVER DISEASE: PATHOPHYSIOLOGY/DIAGNOSIS/MANAGEMENT (7th ed. 2002)	"Feldman"	102(b)
1017	William J. Sandborn & Stephen B. Hanauer, *Antitumor Necrosis Factor Therapy for Inflammatory Bowel Disease: A Review of Agents, Pharmacology, Clinical Results, and Safety*, 5 INFLAMMATORY BOWEL DISEASES 119 (1999)	"Sandborn 1999"	102(b)

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1018*	Luke Timmerman, *Abbott's Humira, the 3rd-in-Class Drug That Toppled Lipitor as No. 1*, XCONOMY (Apr. 16, 2012), *available at* http://www.xconomy.com/national/2012/04/16/abbotts-humira-the-3rd-in-class-drug-that-toppled-lipitor-as-no-1/#	"Timmerman"	n/a
1019	U.S. 2003/0153503, filed Dec. 6, 2002, published Aug. 14, 2003	"'503 publication"	102(a)/ 102(e)
1020*	WO 02/100330, filed June 5, 2002, published Dec. 19, 2002	"WO '330"	102(b)
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1022*	Application No. 11/104,117, Declaration of John Collett (dated Mar. 17, 2014)	"Collett Decl."	n/a
1023*	Remicade® (infliximab) Package Insert (Centocor, Inc. revised June 2002)	"2002 Remicade® Package Insert"	102(b)
1024*	Application No. 11/104,117, Declaration of Diane R. Mould (dated Mar. 17, 2014)	"Mould Decl."	n/a
1025	Declaration of John Posner, Ph.D.	"Posner Decl."	n/a
1026*	2003 Humira™ (Adalimumab) Package Insert (Abbott Labs., Revised Jan. 2003)	"2003 Humira™ Package Insert"	102(b)
1027	Stephen B. Hanauer & Themistocles Dassopoulos, *Evolving Treatment Strategies for Inflammatory Bowel Disease*, 52 ANN. REV. MED. 299 (2001)	"Hanauer"	102(b)
1028	SN 11/104,117, Applicant Amendment and Response to December 16, 2013 Non-Final Office Action and accompanying Declarations (Mar. 18, 2014)	"Applicant Amendment and Response"	n/a

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1029	PHARMACEUTICS: THE SCIENCE OF DOSAGE FORM DESIGN (Michael E. Aulton ed. 2nd ed. 2002)	"Aulton"	102(b)
1030	Grant R. Wilkinson, *Chapter 1: Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, and Elimination in* GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS (Joel Hardman et al. eds., 10th ed. 2001)	"Goodman & Gilman"	102(b)
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1032	Affidavit of Christopher Butler	"Butler Affidavit"	n/a
1033*	U.S. Provisional Application No. 60/382,993, filed May 24, 2002	"the '993 application"	n/a
1034	William J. Sandborn & Stephen B. Hanauer, *Infliximab in the Treatment of Crohn's Disease: A User's Guide for Clinicians*, 97 AM. J. GASTROENTEROLOGY 2962 (2002)	"Sandborn & Hanauer"	102(b)
1035	Screenshot of https://web.archive.org/web/20030308015249/http://www.remicade.com:80/pdf/prescribing.pdf from the Way Back Machine	n/a	n/a
1036	SLEISENGER & FORDTRAN'S GASTROINTESTINAL AND LIVER DISEASE: PATHOPHYSIOLOGY, DIAGNOSIS, MANAGEMENT vol. 2 (Mark Feldman et al. eds., 6th ed. 1998)	"Sleisenger & Fordtran's Gastrointestinal and Liver Disease"	102(b)
1037	Jørn Brynskov et al., *Cytokines (Immunoinflammatory Hormones) and*	"Brynskov"	102(b)

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	Their Natural Regulation in Inflammatory Bowel Disease (Crohn's Disease and Ulcerative Colitis): A Review, 12 DIGESTIVE DISEASES 290 (1994)		
1038	S. C. Truelove et al., *Comparison of Corticosteroid and Sulphasalazine Therapy in Ulcerative Colitis*, BRIT. MED. J. 1708 (1962)	"Truelove"	102(b)
1039	Paul Rutgeerts et al., *A Comparison of Budesonide with Prednisolone for Active Crohn's Disease*, 331 NEW ENG. J. MED. 842 (1994)	"Rutgeerts"	102(b)
1040	K. Fellermann et al., *Mycophenolate Mofetil: Lack of Efficacy in Chronic Active Inflammatory Bowel Disease*, 14 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 171 (2000)	"Fellermann"	102(b)
1041	N. Svartz, *The Treatment of 124 Cases of Ulcerative Colitis with Salazopyrine and Attempts of Desensibilization in Cases of Hypersensitiveness to Sulfa*, 130 ACTA MEDICA SCANDINAVICA 465 (1948)	"Svartz 1948"	102(b)
1042	A. P. Dick et al., *Controlled Trial of Sulphasalazine in the Treatment of Ulcerative Colitis*, 5 GUT 437 (1964)	"Dick"	102(b)
1043	Robert W. Summers et al., *National Cooperative Crohn's Disease Study: Results of Drug Treatment*, 77 GASTROENTEROLOGY 847 (1979)	"Summers"	102(b)
1044	S. Candy et al., *A Controlled Double Blind Study of Azathioprine in the Management of Crohn's Disease*, 37 GUT 674 (1995)	"Candy"	102(b)
1045	Brian R. Stotland & Gary R. Lichtenstein, *Newer Treatments for Inflammatory Bowel Disease*, 34 DRUGS	"Stotland"	102(b)

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1046	G. Bianchi Porro et al., *Cyclosporin Treatment for Severe Active Ulcerative Colitis*, 336 LANCET 439 (1990)	"Porro"	102(b)
1047	Simon Lichtiger et al., *Cyclosporine In Severe Ulcerative Colitis Refractory to Steroid Therapy*, 330 NEW ENG. J. MED. 1841 (1994)	"Lichtiger"	102(b)
1048	M. A. C. Meijssen, *Cyclosporine and Inflammatory Bowel Disease: Buying Time*, 7 MEDIATORS OF INFLAMMATION 145 (1998)	"Meijssen"	102(b)
1049*	Lloyd Mayer et al., *Effect of Hydroxychloroquine in the Treatment of Active Ulcerative Colitis: Results of the Open Label Phase of the Controlled Trial*, 100 GASTROENTEROLOGY (1991)	"Mayer"	102(b)
1050*	Edouard Louis & Jacques Belaïche, *Hydroxychloroquine (Plaquenil®) for Recurrence Prevention of Crohn's Disease After Curative Surgery*, 19 GASTROENTÉROLOGIE CLINIQUE ET BIOLOGIQUE 233 (1995)	"Louis"	102(b)
1051	Richard A. Kozarek et al., *Methotrexate Induces Clinical and Histologic Remission in Patients with Refractory Inflammatory Bowel Disease*, 110 ANNALS INTERNAL MED. 353 (1989)	"Kozarek"	102(b)
1052	M. Lémann et al., *Methotrexate for the Treatment of Refractory Crohn's Disease*, 10 ALIMENTARY PHARMACOLOGY & THERAPEUTICS 309 (1996)	"Lémann"	102(b)
1053	Brian G. Feagan et al., *Methotrexate for the Treatment of Crohn's Disease*, 332 NEW ENG. J. MED. 292 (1995)	"Feagan 1995"	102(b)
1054	A. W. Segal et al., *Levamisole in the*	"Segal"	102(b)

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	Treatment of Crohn's Disease, 2 LANCET 382 (1977)		
1055	A. Hermanowicz et al., *Controlled Therapeutic Trial of Levamisole and Sulphasalazine in Acute Ulcerative Colitis*, 25 GUT 534 (1984)	"Hermanowicz"	102(b)
1056	Humira® (adalimumab) Package Insert (AbbVie Inc. revised April 2017), 2017 Physician's Desk Reference	"2017 Humira® Package Insert"	n/a
1057	DEREK WALLER & ANDREW RENWICK, PRINCIPLES OF MEDICAL PHARMACOLOGY (1994)	"Waller"	102(b)
1058	Remicade® (infliximab) Package Insert (Centocor, Inc., revised Sept. 12, 2005)	"2005 Remicade® Label"	n/a
1059	Stephan R. Targan et al., *A Short-Term Study of Chimeric Monoclonal Antibody cA2 to Tumor Necrosis Factor α For Crohn's Disease*, 337 NEW ENG. J. MED. 1029 (1997)	"Targan"	102(b)
1060	Daniel H. Present et al., *Infliximab for the Treatment of Fistulas in Patients with Crohn's Disease*, 340 NEW ENG. J. MED. 1398 (1999)	"Present"	102(b)
1061	William J. Sandborn et al., *An Intravenous Loading Dose of Azathioprine Decreases the Time to Response in Patients With Crohn's Disease*, 109 GASTROENTEROLOGY 1808 (1995)	"Sandborn 1995"	102(b)
1062	Brian G. Feagan et al., *A Comparison of Methotrexate with Placebo for the Maintenance of Remission in Crohn's Disease*, 342 NEW ENG. J. MED. 1627 (2000)	"Feagan 2000"	102(b)
1063	D. S. Rampton, *Methotrexate in Crohn's Disease*, 48 GUT 790 (2001)	"Rampton"	102(b)

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1064	C. P. Braegger et al., *Tumour Necrosis Factor Alpha in Stool as a Marker of Intestinal Inflammation*, 339 LANCET 89 (1992)	"Braegger"	102(b)
1065	William J. Sandborn et al., *An Engineered Human Antibody to TNF (CDP571) for Active Crohn's Disease: A Randomized Double-Blind Placebo-Controlled Trial*, 120 GASTROENTEROLOGY 1330 (2001)	"Sandborn 2001"	102(b)
1066	William J. Sandborn, *Strategies for Targeting Tumour Necrosis Factor in IBD*, 17 BEST PRAC. & RES. CLINICAL GASTROENTEROLOGY 105 (Feb. 2003)[3]	"Sandborn 2003"	102(b)
1067	https://www.ncbi.nlm.nih.gov/pubmed/12617886	n/a	n/a
1068	Remicade® (infliximab) Package Insert (Centocor, Inc. revised June 2002), 2003 Physicians' Desk Reference (57th ed. 2003)	"2002 Remicade® Package Insert"	102(b)
1069	Declaration of Mary Anne Donaldson	"Donaldson Decl."	n/a
1070*	U.S. Environmental Protection Agency, Office of Research and Development, EXPOSURE FACTORS HANDBOOK (Aug. 1997)	"EPA Handbook"	102(b)

[3] Sandborn 2003 was published in February 2003. Ex. 1067.

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Sandoz Inc. ("Sandoz" or "Petitioner") respectfully requests *Inter Partes* Review ("IPR") of claims 1-30 of U.S. Patent No. 9,187,559 (the "'559 patent," ex. 1001[4]) which is assigned to AbbVie Biotechnology Ltd. ("AbbVie" or "Patent Owner").

The '559 patent claims a subcutaneously administered dosing regimen for the TNF-α antibody adalimumab, the active ingredient in AbbVie's Humira® product, to treat idiopathic inflammatory bowel disease ("IBD") with a first dose of 160 mg and a second dose of 80 mg two weeks later. The '559 patent also has dependent claims directed to additional lower dosing beginning 4 weeks after the 160 mg dose. The patent describes the dosing regimen as taking place within two therapeutic phases – an "induction" or "loading" dose phase followed by a "treatment" or "maintenance" phase.

Simply put, the 4-week phase of higher induction dosing of the independent claims prior to initiating the first lower maintenance dose required by some of the dependent claims is intended to rapidly achieve sufficiently high adalimumab blood levels to induce remission of IBD.

[4] 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 taught all of the elements of the claims of the '559 patent and motivated a person of ordinary skill in the art ("POSA") to combine them with a reasonable expectation of success. A POSA knew that IBD, which includes both Crohn's disease ("CD") and ulcerative colitis ("UC"), is a debilitating and potentially life-threatening condition that should be brought into remission as quickly as possible. The prior art taught that the standard medical treatment of IBD requires both induction and maintenance regimens – the former to induce remission of IBD symptoms, and the latter to maintain remission of symptoms – and that different drugs or dosing regimens were used for induction as compared with maintenance regimens. It also taught that the TNF-α antibody infliximab was used to treat IBD by first inducing remission through more frequent dosing (5 $^{mg}/_{kg}$ at weeks 0, 2 and 6) prior to initiating less frequent maintenance dosing (5 $^{mg}/_{kg}$ every 8 weeks). More frequent dosing resulted in higher blood levels of that drug. The prior art taught that this infliximab induction regimen induced IBD remission in as little as four weeks.

Knowing that the TNF-α antibody infliximab had already been administered as an induction dosing regimen with higher drug levels to first induce IBD remission and then lower drug levels to maintain remission, a POSA would have been motivated to design an IBD induction dosing regimen for adalimumab. A POSA would have been able to determine the appropriate adalimumab doses for

both the induction of remission and maintenance phases of the claimed dosing regimen straight from AbbVie's own prior art publications.

A POSA would expect 40 mg every other week ("eow") to be an effective maintenance regimen for IBD. The 2003 Humira™ Package Insert (ex. 1026) described using a 40 mg eow maintenance dose for treating rheumatoid arthritis ("RA") and "maintain[ing]" the improvement in symptomatic relief through 52 weeks. AbbVie's WO '330 published patent application (ex. 1020) taught that the same 40 mg eow adalimumab dose was the most "prefer[red]" maintenance dose to treat IBD.

A POSA would also have guidance from the same prior art for higher adalimumab doses that could be used to induce IBD remission prior to 40 mg eow maintenance dosing. AbbVie's WO '330 published patent application taught a higher adalimumab dosing regimen of 80 mg eow that could be used to treat RA and IBD, and provided safety and efficacy data from RA clinical trials. Moreover, the 2003 Humira™ Package Insert disclosed that 80 mg adalimumab eow had been used to treat RA patients, and that much higher doses of adalimumab were safe. From this, a POSA would conclude that the higher 80 mg eow dosing is likely safe and effective in treating TNF-α disorders, and should be considered as a basis for an IBD induction dosing regimen.

Basic pharmacology and the known severity of IBD provided the motivation to modify this known 80 mg eow dosing regimen into the claimed 160 mg/80 mg induction doses. Based on adalimumab's known linear pharmacokinetics and 2 week half-life, a POSA would readily understand that if adalimumab was dosed at 80 mg eow, it would take 5 doses, or 10 weeks, to reach steady state blood levels. Because of the recognized need to induce rapid remission of IBD symptoms, a POSA would seek to more rapidly achieve the higher blood levels associated with 80 mg eow dosing using a modified dosing regimen. A POSA would also have in mind the prior art teaching that induction dosing of the TNF-α antibody infliximab was able to achieve remission of IBD symptoms within as few as 4 weeks.

Applying well-known dosing equations from prior art texts, a POSA would determine that an 80 mg dose preceded two weeks earlier by a double-sized loading dose of 160 mg would achieve the desired blood levels much more rapidly than would 80 mg eow dosing. Thus, a POSA treating IBD would have been motivated to administer an induction dose of 160 mg of adalimumab followed in two weeks by an 80 mg dose, as claimed in the '559 patent, and would have reasonably expected that this regimen would induce remission.

Accordingly, as further discussed herein, Petitioner has shown that there is a reasonable likelihood that the claims of the '559 patent are invalid over the prior art. This IPR should be instituted to cancel claims 1-30 of the '559 patent.

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 '559 patent is related to two of the patents that were at issue[5] in *AbbVie Inc. et al. v. Amgen Inc. et. al.*, No. 1:16-cv-00666-MSG (D. Del. filed Aug. 4, 2016), however that case has been dismissed pursuant to a stipulation filed on September 28, 2017. Petitioner was not a party to that action.

Petitioner is not aware of any reexamination certificates or pending prosecution concerning the '559 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.), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135 ("the '135 patent"), dated November 9, 2015; (2) *Boehringer Ingelheim GmbH v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00408 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (3) *Boehringer Ingelheim GmbH v. AbbVie Biotechnology*

[5] U.S. Patent Nos. 8,961,973; 8,986,693 and the '559 patent claim priority to the same application, SN 60/561,139 filed April 9, 2004.

Ltd., Case No. IPR2016-00409 (P.T.A.B), Petition for *Inter Partes* Review of U.S. Patent No. 8,889,135, dated December 29, 2015; (4) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00188 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,017,680 ("the '680 patent"), dated December 7, 2015; (5) *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, Case No. IPR2016-00189 (P.T.A.B.), Petition for *Inter Partes* Review of U.S. Patent No. 9,073,987 ("the '987 patent"), dated December 7, 2015. On May 17, 2016, the Board issued decisions instituting *inter partes* review for Case No. IPR2016-00172. On June 13, 2016, the Board issued decisions instituting *inter partes* review for Case Nos. IPR2016-00188 and IPR2016-00189. On July 7, 2016, the Board issued decisions instituting *inter partes* review for Case Nos. IPR2016-00408 and IPR2016-00409.

On May 16, 2017, the Board issued a Final Written Decision in IPR No. 2016-00172 on the '135 patent. On June 9, 2017, the Board issued Final Written Decisions in IPR2016-00188 and IPR2016-00189, on the '680 and '987 patents, respectively. All three patents were directed to a method of treating RA by administering 40 mg D2E7 (adalimumab) subcutaneously eow. *Coherus BioSciences, Inc. v. AbbVie Biotechnology Ltd.*, IPR Nos. 2016-00172, 2016-00188, 2016-00189 (P.T.A.B).

On July 6, 2017, the Board issued Final Written Decisions in Nos. IPR2016-00408 and IPR2016-00409, further finding the claims of the '135 patent unpatentable. *Boehringer Ingelheim GmbH v. AbbVie Biotechnology Ltd.*, Case Nos. IPR2016-00408, IPR2016-00409 (P.T.A.B). The patents that are the subjects in the identified administrative matters and the '559 patent however do not claim priority to any of the same applications.

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), IPR2017-01988 (U.S Patent No. 8,974,790), IPR2017-02105 (U.S. Patent No. 9,090,689), IPR2017-02106 (U.S. Patent No. 9,067,992), IPR2018-00002 (U.S. Patent No. 9,512,216). AbbVie is the patent owner of these patents, however only U.S. Patent Nos. 9,090,689, 9,067,992, 9,512,216, and the '559 patent claim priority to the same applications, the earliest of which is SN 60/561,139 filed on April 9, 2004.

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

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D. Service Information (37 C.F.R. § 42.8(b)(4))

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

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E. Fee Payment Authorization (37 C.F.R. § 42.103(a))

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

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

As required by 37 C.F.R. § 42.104(a), Petitioner certifies that the '559 patent is eligible for IPR and that Petitioner is not barred or estopped from requesting IPR on the ground identified herein.

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

A. Effective Filing Date of the '559 Patent

For purposes of this Petition only, the effective filing date of the challenged claims is April 9, 2004. Sandoz reserves the right to challenge the effective filing date of the '559 patent in any other proceeding.

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

Petitioner requests *inter partes* review and cancellation of claims 1-30 of the '559 patent on one ground pursuant to 35 U.S.C. § 103 as set forth herein. Petitioner's detailed statement of the reasons for the relief requested is set forth below in the section titled "Statement of Reasons for the Relief Requested." In accordance with 37 C.F.R. § 42.6(c), copies of the exhibits are filed herewith. In addition, the Petition is accompanied by the declarations of Ingvar Bjarnason, M.D. (ex. 1002) and of John Posner, Ph.D. (ex. 1025).

The Petition contains one ground for invalidating the '559 patent which includes only publications that are 102(b) prior art based on the April 9, 2004 priority date.

The challenged claims are unpatentable in view of the teachings of the following prior art publications:

Reference	Publication Date	Type of Prior Art
2003 Humira™ Package Insert	Mar. 31, 2003	102(b)
WO 2002/100,330 A2	Dec. 19, 2002	102(b)
2002 Remicade® Package Insert	Dec. 3, 2002	102(b)
Hanauer	2001	102(b)
Goodman & Gilman	2001	102(b)

The 2003 Humira™ Package Insert was publicly available on the FDA's website no later than March 31, 2003 as demonstrated by the Internet Archive and the Wayback Machine service which it provides. Exs. 1026, 1031, 1032. The 2002 Remicade® Package Insert was publicly available on Centocor, Inc.'s www.remicade.com website no later than March 8, 2003 as demonstrated by the Internet Archive and the Wayback Machine service which it provides. Exs. 1023, 1035. Additionally, the 2002 Remicade® Package Insert was also available in the 2003 Physicians' Desk Reference (57th ed.), which has a received date stamp of December 3, 2002 from the Arnold & Porter Library. Exs. 1068; 1069 (affirming that the 2003 Physicians' Desk Reference was published, available in libraries and

publicly accessible as of December 3, 2002). Dr. Bjarnason confirms that these package inserts were publicly accessible from a number of sources, including the FDA website, the manufacturer's website, the Physicians' Desk Reference, and in print form accompanying the commercial drug product, and were, in fact, regularly accessed by physicians as of their respective dates. Ex. 1002 at ¶¶10, 69, 77. Hanauer was published in Volume 52 dated 2001 of the Annual Review of Medicine and stamped received on December 19, 2001 by the West Virginia University ("WVU") Health Science Library which demonstrates it was published in 2001, available for purchase by libraries and the general public in 2001 and publicly available in the WVU library in 2001. Ex. 1027. Dr. Bjarnason confirms that the Annual Review of Medicine was a long-published and well-known journal that he has personally accessed, and that was both familiar to and accessible by the POSA. Ex. 1002 at ¶¶10, 64. Goodman & Gilman was published in 2001 by McGraw-Hill Companies, Inc. and stamped received on August 24, 2001 by the Library of Congress which demonstrates it was published in 2001, available for purchase by libraries and the general public in 2001 and publicly available in the Library of Congress in 2001. Ex. 1030. Dr. Posner confirms that physicians were widely familiar with editions of Goodman & Gilman, and could readily have accessed them at virtually any medical or pharmacy school library. Dr. Posner

himself has been using editions of Goodman & Gilman since the 1960s. Ex. 1025 at ¶ 45 n.3.

These prior art references and the knowledge of a POSA are supported and informed by the wider body of prior art concerning the treatment of IBD and related diseases. *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (explaining that *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007) "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.'"). The additional background art publications discussed in Section VI, each of which is Section 102(b) or 102(e) prior art, illustrate this wider body of prior art.

The challenged claims are unpatentable based upon the following ground:

Table 1 – Ground for *Inter Partes* Review

Claims	Priority Date	Statutory Basis and Prior Art
1-30	April 9, 2004	Obvious under § 103(a) over the 2003 Humira™ Package Insert and WO '330 in view of Goodman & Gilman, the 2002 Remicade® Package Insert and Hanauer

Section VI and the Declarations of Ingvar Bjarnason, M.D. (ex. 1002) and John Posner, Ph.D. (ex. 1025) further describe the grounds for the invalidation of the '559 patent. Ex. 1002 at ¶¶ 91-115; Ex. 1025 at ¶¶ 62-100.

Dr. Bjarnason is an expert in the field of gastroenterology and has decades of experience in treating patients having IBD. Ex. 1002 at ¶¶ 3-10. Dr. Posner is a clinical pharmacologist, medical professor, and drug development expert with more than three decades of experience in the development of both small molecule and biologic pharmaceuticals. Ex. 1025 at ¶¶ 3-14. Dr. Posner has extensive knowledge of the process by which drug dosing regimens are determined and optimized and, throughout his career, has designed and executed pharmacokinetic studies of new molecular entities. *Id.*

Drs. Bjarnason and Posner are qualified to provide opinions as to what a POSA would have understood, known, or concluded as of April 9, 2004 (and one year before) and are therefore competent to testify in this proceeding.

V. SUMMARY OF THE '559 PATENT

A. Background of the '559 Patent

The '559 patent issued with 30 claims directed to a "multiple-variable dose method" for treating idiopathic IBD. Ex. 1001 at claim 1. Claims 1 and 4 are the only independent claims. Claim 1 recites:

> 1. A multiple-variable dose method for treating idiopathic inflammatory bowel disease in a human subject in need thereof, comprising subcutaneously administering to the human subject:
>
> > a first dose of 160 mg of adalimumab administered to the human subject within a day; and

> a second dose of 80 mg of adalimumab administered to the human subject within a day, wherein the second dose is administered two weeks following administration of the first dose.[6]

Id. Independent claim 4 also includes the 160/80 mg dosing of claim 1, but further requires that the 160 mg dose be "administered as a set of four injections of 40 mg of adalimumab . . . within a day" and that the 80 mg dose be "administered as a set of two injections of 40 mg of adalimumab . . . within a day." *Id.* at claim 4.

The dependent claims recite various additional limitations, including: (i) administering 40 mg adalimumab two weeks following the 80 mg dose; (ii) administering additional 40 mg adalimumab doses two weeks apart; (iii) using a pre-filled syringe; (iv) where the subject has CD or UC; and (v) where the subject has a Crohn's Disease Activity Score ("CDAI") of < 150.

The '559 specification explains that the goal of the multiple-variable dose regimen is "inducing remission" of IBD by administering "at least one induction dose of a TNFα inhibitor." *Id.* at 2:52-59. The specification defines the term "[m]ultiple-variable dose regimen" as a treatment schedule "based on administering different amounts of TNFα inhibitor at various time points throughout the course of treatment. In one embodiment, the invention describes a multiple-variable dose method of treatment comprising an induction phase and a

[6] The '559 patent equates adalimumab (Humira®) with "D2E7" "a human anti-TNF mAb." Ex. 1001 at 23:25-26, 16:26-27.

treatment phase, wherein a TNFα inhibitor is administered at a higher dose during the induction phase than the treatment phase." *Id.* at 11:40-48. Thus, the specification states that the induction or loading dose "is larger in comparison to the maintenance or treatment dose." *Id.* at 11:62-65. "The induction dose is often used to bring the drug in the body to a steady state amount, and may be used to . . . achieve maintenance drug levels quickly." *Id.* at 11:66-12:1. On the other hand, the treatment or maintenance dose "is the amount of TNFα [inhibitor] taken by a subject to maintain or continue a desired therapeutic effect" after the subject takes the "induction dose." *Id.* at 12:16-20.

The patent explains that one example of an "induction phase treatment[]" is "a 160 mg dose followed by an 80 mg dose." *Id.* at 63:53-58.

The '559 patent discloses two clinical trials with various dosing regimens of adalimumab to treat CD. The '559 patent does not disclose any UC clinical trials.

Example 1 was a multiple-variable dose study of adalimumab treating CD patients. *Id.* at 73:43-75:21. The patients were divided into four groups and subjects received a "loading dose" at week 0 and a "treatment dose" at week 2. *Id.* at 74:1-8. The four groups were (Week 0/Week 2): (i) 160 mg/80 mg D2E7; (ii) 80 mg/40 mg D2E7; (iii) 40 mg/20 mg D2E7; or (iv) placebo/placebo. *Id.* Each of the induction doses could be calculated by doubling the previously disclosed treatment doses. Table 1 discloses the percentage of patients achieving clinical

remission (defined as a Crohn's Disease Activity Index of ≤ 150) at week 4 of treatment:

TABLE 1

D2E7 induces clinical remission in treatment groups at Week 4

	Placebo	40/20 mg	80/40 mg	160/80 mg
CDAI ≤ 150	12%	18%	24%	36%*

(*denotes p = 0.001)
(Placebo n = 74; 20 mg n = 74; 40 mg n = 75; 80 mg n = 76)

Only 36% of the patients achieved remission from the 160/80 mg dose at week 4. *Id.* at tbl. 1.

Example 2 assessed administration of 80 mg of adalimumab subcutaneously at week 0 and 40 mg at week 2 to CD patients who could not continue to be successfully treated with infliximab. *Id.* at 75:30-40. The study concluded that this dosing regimen "was well tolerated and was clinically beneficial." *Id.* at 76:16-20.

The data from the examples merely demonstrate (at most) the unsurprising result that higher doses of adalimumab yield somewhat greater efficacy at week 4 for CD patients.

Additionally, the '559 specification describes the well-known association between RA and IBD and that both conditions are mediated by TNF-α. Describing the admitted prior art, it explains that TNF-α "has been implicated in playing a role in the pathophysiology of a variety of autoimmune diseases . . . [and] has been

implicated in activating tissue inflammation and causing joint destruction in rheumatoid arthritis." *Id.* at 24:13-17. TNF-α "has been implicated in the pathophysiology of inflammatory bowel disorders including Crohn's disease (see e.g., Tracy et al. (1986) *Science* 234:470; Sun et al. (1988) *J. Clin. Invest.* 81:1328; MacDonald et al. (1990) *Clin. Exp. Immunol.* 81:301)." *Id.* at 28:51-55. Therefore, "TNFα inhibitors, including human antibodies, and antibody portions such as D2E7, may be used in a multiple-variable dose method to treat autoimmune diseases, . . . includ[ing] rheumatoid arthritis" (*id.* at 24:37-41) and "Crohn's disease." *Id.* at 25:14-17.

B. Person of Ordinary Skill in the Art

As explained by Dr. Bjarnason in his declaration, a POSA developing a treatment for IBD would have an M.D. with at least 3 years' experience post-residency treating patients for IBD. Ex. 1002 at ¶ 40.

As explained by Dr. Posner in his declaration, a POSA developing a dosing regimen for IBD would have a Ph.D. in pharmacology, pharmacokinetics, or a related field and at least 3 years of experience working on the pharmacokinetics/pharmacodynamics of biologic drugs. Ex. 1025 at ¶ 36.

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

The claim terms in the '559 patent are presumed to take on their ordinary and customary meaning based on the broadest reasonable interpretation 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). For purposes of this petition only, Sandoz does not assert that any special meanings apply to claim terms in the '559 patent.

The preambles to independent claims 1 and 4 ("A multiple-variable dose method for treating idiopathic[7] inflammatory bowel disease in a human subject in need thereof" (ex. 1001 at claims 1, 4)) are statements of intended use and are not limiting. *See Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.*, 320 F.3d 1339, 1345 (Fed. Cir. 2003) (statements of intended use typically do not limit the scope of a claim because they "usually do no more than define a context in which the invention operates."). If the Board concludes that the preambles should be construed, the term "treating" in claims 1 and 4 should be given its broadest reasonable interpretation of "reducing the signs and/or symptoms of idiopathic inflammatory bowel disease," by inducing remission and/or maintaining symptom remission, without requiring any specific level of therapeutic effect. The specification of the '559 patent supports this interpretation:

> [t]his invention provides a multiple-variable dose method of treating a TNFα-related disorder in which the administration of a TNFα inhibitor is beneficial. . . . As used herein, the term "a disorder in which TNFα activity is detrimental" is intended to include diseases and other

[7] Dr. Bjarnason explains that "idiopathic" means that the initial cause of the disease is unknown, and that both Crohn's disease and UC are idiopathic forms of IBD. Ex. 1002 at ¶ 43 n.4.

> disorders in which the presence of TNFα in a subject suffering from the disorder has been shown to be or is suspected of being either responsible for the pathophysiology of the disorder or a factor that contributes to a worsening of the disorder. Accordingly, 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 13:40-42, 23:27-36.

This construction is further consistent with the fact that where dependent claims (claims 13, 14, 16, 19, 25 and 28) of the '559 patent require specific levels of efficacy as measured by achievement of CDAI score, those claims expressly so state.

The declaration of Dr. Bjarnason further supports this interpretation of the preambles of claims 1 and 4. Ex. 1002 at ¶¶ 43-44.

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

This petition meets the threshold requirement for *inter partes* review because it establishes "a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition." 35 U.S.C. § 314(a). As explained below, for 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 ’559 patent’s independent claims require a subcutaneously administered IBD dosing regimen of 160 mg adalimumab followed in two weeks by 80 mg. This dosing regimen was obvious.

AbbVie’s own prior art had already taught the use of adalimumab to treat IBD, and subcutaneously administered adalimumab dosing regimens for TNF-α disorders, including RA and IBD. In particular, the prior art described the FDA-approved adalimumab 40 mg eow maintenance dosing regimen to treat RA (ex. 1026) and that the preferred maintenance regimen for treating IBD (among a number of other TNF-α-mediated conditions) was likewise 40 mg eow (ex. 1020).

The only information not expressly disclosed in the prior art was the precise 160 mg/80 mg induction dosing regimen required by the claims. The prior art, however, taught that IBD therapy required both induction of remission and maintenance of remission, that induction of remission was generally achieved by dosing to obtain higher blood levels of a therapeutic drug through higher or more frequent dosing and that, based on known adalimumab dosing regimens a 160 mg/80 mg adalimumab dose was an obvious way to achieve the higher blood levels needed to induce IBD remission.

In particular, more than one year before April 9, 2004, the prior art taught that:

- AbbVie's FDA-approved method for maintaining remission of RA symptoms was the subcutaneous injection of 40 mg adalimumab eow (2003 Humira™ Package Insert, ex. 1026* at 9); and

- AbbVie's "prefer[red]" maintenance regimen for treating IBD was the same subcutaneous injection of 40 mg adalimumab eow (WO '330, ex. 1020* at 27:39).

From this, a POSA would reasonably expect that subcutaneous injection of 40 mg adalimumab eow was an obvious way to maintain remission of IBD symptoms. Ex. 1002 at ¶ 90.

The prior art also taught that:

- IBD can be treated by first inducing remission of symptoms before initiating therapy to maintain remission (Hanauer, ex. 1027 at 300-01);

- the FDA had approved a dosing regimen for inducing CD remission using the TNF-α antibody infliximab that increased infliximab drug levels by more frequent dosing (5 $^{mg}/_{kg}$ at weeks 0, 2 and 6) compared to the subsequent maintenance dosing (5 $^{mg}/_{kg}$ every 8 weeks) (2002 Remicade® Package Insert, ex. 1023* at 4; ex. 1068 at 1181); and

- higher induction doses of drugs could be used for other disorders (*infra* Section VI.B.3).

From this, a POSA would reasonably expect that an adalimumab dosing regimen greater than the 40 mg eow maintenance dose would induce IBD remission. Ex. 1002 at ¶¶ 90, 94. To arrive at that adalimumab dosing regimen, a POSA would need to look no further than the same AbbVie WO '330 published

patent application. That reference disclosed a higher dose of adalimumab for TNF-α disorders, including RA and IBD, of 80 mg eow, that is supported with RA clinical data. Ex. 1020* at 4:34–5:2, 34:14–35:26. A POSA would understand this to mean that 80 mg eow dosing was likely safe and effective against TNF-α disorders and should be considered as a basis for an IBD induction dosing regimen. Additionally, a POSA would reasonably expect an 80 mg eow adalimumab dosing regimen to provide some degree of efficacy in inducing IBD remission. Ex. 1002 at ¶ 95.

Furthermore, a POSA would have been motivated to modify this known 80 mg eow adalimumab dose into the claimed 160 mg/80 mg dosing regimen because the prior art taught that:

- IBD is a debilitating and potentially life-threatening disease (*infra* Section VI.B.4);
- the TNF-α antibody infliximab administered with an induction dosing regimen achieved remission of CD symptoms in as little as 4 weeks (Hanauer, ex. 1027 at 306);
- 80 mg eow dosing alone would require 10 weeks to reach steady state blood levels (ex. 1025 at ¶ 62) as adalimumab exhibited linear pharmacokinetics and had an approximately two week half-life (ex. 1026* at 2);
- the severe symptoms of IBD required more rapid relief, which could be achieved by more rapidly reaching these steady state blood levels (*infra* Section VI.B.4-VI.B.5);
- based on well-known dosing equations from prior art texts and the known pharmacokinetics of adalimumab, a double-

sized 160 mg dose would achieve the desired blood levels much more rapidly than would 80 mg eow dosing alone (*infra* Section VI.C.1(b)); and

- an 80 mg dose 2 weeks after the 160 mg dose would maintain the blood levels at the heightened level for a total of 4 weeks, at which time 40 mg eow maintenance dosing would begin (Ex. 1025 at ¶¶ 82-83).

Accordingly, it would have been obvious to a POSA to treat IBD by subcutaneously administering the claimed 160 mg/80 mg adalimumab induction regimen.

The prior art also renders all of the other dependent claim limitations obvious. Several dependent claims require a subsequent 40 mg dose two weeks after the 80 mg dose, or multiple 40 mg doses administered two weeks apart. As just explained, the 40 mg adalimumab eow maintenance regimen was described in AbbVie's prior art published patent application for treating IBD and was approved for use in maintaining remission of RA. AbbVie's prior art 2003 Humira™ Package Insert disclosed 40 mg pre-filled adalimumab syringes for subcutaneous injection rendering obvious claims requiring subcutaneous administration of adalimumab in multiples of 40 mg and use of 40 mg pre-filled syringes. Ex. 1026* at 1. Claims adding a requirement to achieve a specified "Crohn's Disease Activity Index (CDAI) score" are also obvious because the '559 patent admits these results are inherent in the claimed method. Ex. 1001 at 73:40-75:21. Finally, it was obvious to use these claimed methods of treating IBD specifically for CD or

UC because AbbVie's prior art WO '330 patent taught treating CD and UC with adalimumab using the same dosing regimens, which is further supported by the long history of using the same drugs and dosing regimens to treat CD and UC. *See infra* Section VI.C.6; Ex. 1020* at 27:37-39, 32:25-26; Ex. 1002 at Section VI.B.

B. Prior Art Patents and Printed Publications Relied on in This Petition

1. AbbVie's Prior Art Taught Several Adalimumab Dosing Regimens for TNF-α Disorders

(a) The 2003 Humira™ Package Insert (ex. 1026) Taught 40 mg eow for Maintenance of RA Remission and that Much Higher Doses Were Safe

The "recommended dose of HUMIRA" in the 2003 Humira™ Package Insert for RA "is 40 mg administered every other week as a subcutaneous injection." Ex. 1026* at 9. The clinical studies portion of the package insert states that the improvement in arthritis "was maintained to week 52." *Id.** at 3. A POSA would understand this 40 mg eow to be an acceptable maintenance therapy for RA. Ex. 1002 at ¶ 80. As acknowledged by the '559 patent, there was a well-known association between RA and IBD. *Supra* Section V.A. Moreover, there was a long history of treating RA and IBD with the same drugs. *See infra* Table 2; ex. 1002 at Section VI.B.

The 2003 Humira™ Package Insert also included data demonstrating adalimumab's safety profile at much higher doses. Ex. 1026* at 9 ("10 $^{mg}/_{kg}$ have

been administered to patients in clinical trials without evidence of dose-limiting toxicities.").

(b) AbbVie's WO '330 (ex. 1020) Taught the Same 40 mg EOW Dose As a Preferred Maintenance Regimen To Treat IBD and That Higher Doses Were Possible

AbbVie placed its maintenance regimen of biweekly/eow subcutaneous injection of 40 mg adalimumab to treat IBD squarely in the prior art in the WO '330 published patent application.

WO '330 "provides methods for biweekly dosing regimens for the treatment of TNF-α associated disorders, preferably via a subcutaneous route." Ex. 1020* at 4:2-3. "Biweekly dosing," it explained, "has many advantages over weekly dosing including, but not limited to, a lower number of total injections, decreased number of injection site reactions (*e.g.*, local pain and swelling), increased patient compliance (*i.e.*, due to less frequent injections), and less cost to the patient as well as the health care provider." *Id.** at 4:3-7.

The most preferable antibodies used for treatment "are recombinant human antibodies that specifically bind to human TNFα." *Id.** at 4:12-13. D2E7 (adalimumab) is "[t]he most preferred recombinant antibody of the invention."[8] *Id.** at 4:27; *see also id.** at 12:17-18. The TNF-α-related diseases treated by

[8] WO '330 provides the amino acid sequences for D2E7 and notes that U.S. Patent No. 6,090,382, which it incorporated by reference, provides a further description. *Id.** at 4:27-33.

biweekly subcutaneous injection of a recombinant human TNF-α antibody, such as adalimumab, include sepsis, autoimmune diseases (including RA), infectious diseases, malignancies, transplant rejections, pulmonary disorders, bone disorders, cardiac disorders and "intestinal disorder[s]." *Id.** at 4:34-5:2. WO '330's sole example of an "intestinal disorder[]" is "idiopathic inflammatory bowel disease, which includes two syndromes, Crohn's disease and ulcerative colitis." *Id.** at 32:25-26. The most preferable dose is "about 40 mg." *Id.** at 27:37-39.

WO '330 does not disclose using a separate higher dosing regimen for inducing IBD remission, nor does it state that the dosing regimen should be discontinued or modified after the passage of time or cessation of symptoms. In fact, it states the 40 mg eow dose is a "prophylactically effective amount," (*id.** at 27:12) indicating that it can be used to prevent the resumption of more serious symptoms. A POSA would therefore understand WO '330's teaching of 40 mg eow IBD therapy as well-suited for a maintenance therapy for controlling potential IBD flare ups or maintaining remission. Ex. 1002 at ¶ 90.

Accordingly, the most preferred maintenance regimen taught by WO '330 is a subcutaneous biweekly injection of 40 mg adalimumab to treat IBD as one of several TNF-α-related diseases.

WO '330 also described RA clinical trials involving biweekly subcutaneous doses of placebo, 20 mg, 40 mg or 80 mg adalimumab for up to 24 weeks and

suggested each of these doses as possible ways to treat IBD. Ex. 1020* at 34:28-35:26, 27:37-39, 5:2. The study concluded that these doses "were statistically significantly more effective than placebo given weekly" for RA and did not report any adverse events. *Id.** at 35:22-26.

2. The Prior Art Taught That IBD Treatment Required Both Induction and Maintenance Therapies

(a) Before the Advent of TNF-α Antibodies, the Prior Art Taught the Need for Using Different Drugs for Induction and Maintenance Therapies

Treatment of IBD flare ups has long been known to involve two dosing phases. The first phase is to induce remission of the disease so that the patient's symptoms are noticeably reduced. Ex. 1002 at ¶ 62; Ex. 1027 at 300-01. Then, because IBD frequently recurs, a second phase is used to maintain the remission of symptoms. Ex. 1027 at 300-01. Hanauer described the use of aminosalicylate, corticosteroids and cyclosporine as "[i]nductive therapies" for "inducing remission of active" UC and the use of aminosalicylate, azathioprine and 6-mercaptopurine as "[m]aintenance therapies" for "maintaining remission to prevent relapse." *Id.* at 300. Likewise, Hanauer described the use of aminosalicylate, metronidazole, ciprofloxacin, corticosteroid, azathioprine, 6-mercaptopurine, methotrexate, infliximab and cyclosporine as "[i]nductive therapies" for "inducing remission of active" CD and the use of aminosalicylate, azathioprine, 6-mercaptopurine and methotrexate as "[m]aintenance of remission" therapies for "maintaining

remission" of CD. *Id.* at 300-01. Accordingly, a POSA knew that treatment of IBD can involve an induction phase and a maintenance phase. Ex. 1002 at ¶¶ 62, 66.

(b) The Prior Art Taught That the TNF-α Antibody Infliximab Induces Remission of CD with Higher Doses While Maintaining Remission with Lower Doses

Hanauer described clinical trials for the TNF-α antibody infliximab that "have begun to define a role for infliximab as both an inductive and maintenance agent for CD." Ex. 1027 at 306. The FDA approved Remicade® (infliximab) in 2002 for remission and maintenance of remission of CD. The prior art 2002 Remicade® Package Insert stated that infliximab is indicated for both "inducing and maintaining clinical remission" of CD. Ex. 1023* at 2; ex. 1068 at 1179.[9] Different dosing regimens were required for induction and maintenance: "[t]he recommended dose of REMICADE is 5 $^{mg}/_{kg}$ given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 $^{mg}/_{kg}$ every 8 weeks thereafter

[9] Although initially there was some concern that infliximab could not be used for long term maintenance of remission because of the risk from long-term suppression of the immune system (*see, e.g.*, ex. 1027 at 311), clinical trials for both infliximab and adalimumab demonstrated the long-term safety of these TNF-α inhibitors; the FDA had in the prior art approved their long-term use. Ex. 1023* at 4; Ex. 1068 at 1181; Ex. 1026* at 9.

for the treatment of moderately to severely active Crohn's disease." Ex. 1023* at 4; Ex. 1068 at 1181.[10]

The approved infliximab dosing regimen for inducing remission of CD delivered a total of 15 $^{mg}/_{kg}$ over a 6 week period while the approved maintenance dosing regimen delivered 5 $^{mg}/_{kg}$ every 8 weeks. *Id.* The prior art taught that a loading dose could be a larger dose or more frequent doses. Ex. 1030 at 27 (Loading doses "may be given at the onset of therapy . . . . [and] tend to be large."); Ex. 1029 at 284-85 ("[A] large single dose of the drug may be administered initially . . . ."); Ex. 1023* at 4, Ex. 1068 at 1181 ("The recommended dose of REMICADE is 5 $^{mg}/_{kg}$ given as an induction regimen at 0, 2 and 6 weeks followed by a maintenance regimen of 5 $^{mg}/_{kg}$ every 8 weeks thereafter . . . ."); Ex. 1025 at ¶ 46. Accordingly, the infliximab dosing regimen for IBD followed the well-known prior art model of administering greater quantities or higher frequency of drug to induce remission followed by less frequent or lower dosing to maintain remission. *See, e.g.*, ex. 1030 at 27; ex. 1029 at 284-85; ex. 1012 at 27:60-28:4. A POSA would immediately recognize that the infliximab induction regimen of more frequent 5 $^{mg}/_{kg}$ doses relative to maintenance dosing less frequently using the same 5 $^{mg}/_{kg}$ dose delivers more drug to the patient per

[10] Although the FDA did not approve infliximab for the treatment of UC until 2005 (ex. 1058 at 20), prior art clinical trials demonstrated that UC could be treated with infliximab. *See, e.g.*, ex. 1017 at 129.

unit of time during the induction period. Ex. 1025 at ¶ 59. Similarly, administering higher adalimumab induction doses of 160 mg/80 mg prior to beginning 40 mg eow maintenance dosing at week 4 as required by the '559 claims, delivers more drug to the patient per unit of time during the induction phase to induce remission. Ex. 1002 at ¶¶ 99-100. Therefore, the POSA would understand that administering higher doses of adalimumab during the induction phase would similarly induce remission.

3. The Prior Art Also Taught the Use of Higher Induction Doses of Drugs To Treat Other Disorders

It was well known that, within a certain dosing range, higher drug doses tend to produce a greater therapeutic effect. As Goodman & Gilman, a leading prior art pharmaceutical text, explained, "the intensity of a drug's effect is related to its concentration above a minimum effective concentration, whereas the duration of this effect is a reflection of the length of time the drug level is above this value." Ex. 1030 at 25; Ex. 1025 at ¶¶ 46-52.

Several prior art examples demonstrate the known use of higher induction doses relative to maintenance doses. Ex. 1002 at ¶¶ 71-76; Ex. 1019 at ¶ 206 ("Alternatively, stimulation of endogenous erythropoietin may be achieved by 1) administering a loading dose followed by a maintenance dose, 2) administering an induction dose to rapidly achieve erythropoietin levels within a target range, followed by a lower maintenance dose to maintain hematocrit within a desired

target range, or 3) repeated intermittent dosing."); Ex. 1012[11] at 28:26-35 ("Induction doses contemplated are generally about 180 mg per day. Daily maintenance doses contemplated are generally between about 20 mg and about 180 mg; between about 25 and about 160 mg; between about 50 and about 150 mg; between about 30 and about 125 mg; between about 40 mg and about 100 mg; between about 35 and about 80 mg; between about 20 and about 65 mg; between about 30 mg and about 50 mg; about 40 mg; or in any particular range using any of the foregoing recited exemplary doses or any value intermediate between the particular stated ranges."); Ex. 1010 at 11:62-64 ("The desired dose is administered at appropriate intervals in unit dosage forms, usually with a relatively higher induction dose and lower, less frequent maintenance doses."); Ex. 1009 at 4:11-62 (describing treatment in three phases including: (1) an "'induction phase' . . . in which the IMP DH activity of the patient is sharply reduced by a high dose of tiazofurin" with a "prefer[red]" dose of "4,400 mg/m^2" tiazofurin; (2) a "'consolidation phase' . . . in which the gains achieved in the induction phase are consolidated" with "lower doses of tiazofurin" "[p]referably . . . about 2,200 mg/m^2" tiazofurin; and (3) "'maintenance phase' . . . in which the patient is

[11] U.S. Patent No. 6,855,340 ("the '340 patent," ex. 1012) is prior art to the '559 patent under pre-AIA 35 U.S.C. 102(e) and its date for prior art purposes is May 24, 2002, the filing date of the '993 provisional application. For example, claim 1 of the '340 patent is supported by claims 1, 2 and the specification of the '993 application. *See, e.g.*, ex. 1033* at claim 1; claim 2; 7:26-29.

maintained in remission" using "gradually tapered" doses of ribavirin until using "the lowest possible dose to maintain remission.").

4. IBD Was Known To Cause Severe Symptoms That Required a Rapid Therapeutic Response

Feldman (ex. 1016) explains that for patients with CD, "coping with diarrhea, pain, malaise, and decreased energy takes a toll [on the patient] and their families." Ex. 1016 at 2032. "Depression and anxiety often diminish daily functioning that is already impaired by the physical manifestations of the disease, and psychosocial functioning has a large impact on the patient's quality of life." *Id.* "Frequent complications [of CD] include stricture and fistula, which often necessitate surgery." *Id.* at 2005; *see also id.* at 2030-31 ("Surgery plays an integral role in the treatment of Crohn's disease, both to control symptoms and treat complications. By the 20th year from the onset of symptoms, roughly three fourths of patients will have had surgery."). Accordingly, "the primary goals of therapy are to induce and maintain remission." *Id.* at 2022.

Like CD, UC can result in life-altering symptoms for people afflicted by this disease. Feldman explains that moderate UC results in more than four stools a day. *Id.* at 2048. And patients with severe UC have more than six stools daily with blood and may require hospitalization. *Id.* at 2048, 2059. Patients with severe UC "whose condition deteriorates during the first few days of intravenous therapy require surgery, as do those who fail to improve." *Id.* at 2059. Thus, the treatment

goals for UC (like CD) are to induce and maintain remission. *Id.* at 2059-60. UC patients are treated with regimens that "allow rapid control of [the] disease." *Id.* at 2059.

5. The Prior Art Taught How To Determine a Loading Dose for Drugs with a Long Half-Life Like Adalimumab

It was well known, as Waller explained, that "[a] therapeutic problem may arise when a rapid effect is required for a drug which has a long or very long half-life," and that this "delay between the initiation of treatment and the attainment of steady state may be avoided by the administration of a *loading dose*."[12] Ex. 1057 at 36. The term "loading dose" has been used by some references to refer "to a single or multiple dose administered initially to rapidly achieve the desired pharmacological level." Ex. 1019 at ¶ 93.

Goodman & Gilman likewise explained: "[a] loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated." Ex. 1030 at 27. It generally takes approximately five half-lives to reach steady state, irrespective of the size or frequency of dosing. Ex.

[12] The '559 patent uses "loading dose" and "induction dose" interchangeably. Ex. 1001 at 11:62-63.

1025 at ¶ 49; Ex. 1029 at 284.[13] For a drug like adalimumab with a two week half-life, absent a loading dose, it would take almost 10 weeks to reach full therapeutic effect. Ex. 1025 at ¶ 49.

Thus, "[t]o reduce the time required for onset of the full therapeutic effect, a large single dose of the drug may be administered initially in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug and is approximately equal to the value of C^{ss}_{max} required." Ex. 1029 at 284-85; *see also* ex. 1030 at 27 ("The 'loading dose' is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly."). "Thereafter smaller, equal doses are administered respectively at suitable fixed intervals so as to maintain the plasma concentrations of the drug" and these doses "are known as maintenance doses." Ex. 1029 at 285.

Aulton also disclosed how to determine an appropriate induction dose. "As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug." Ex. 1029 at 285; *see also* ex. 1003 at 353 (tbl. 28-1) ("If the dosing interval

[13] "[S]teady state" is when "the amount of drug eliminated from the body over each dosing time interval is equal to the amount that was absorbed into the body compartment following administration of the previous dose." Ex. 1029 at 280; Ex. 1025 at ¶ 48. At steady state, with constant dosing intervals and the same dose, a patient's blood concentrations will stay between consistent C_{max} and C_{min} values. Ex. 1029 at 280 (fig. 19.4); Ex. 1025 at ¶ 48.

τ is equal to or somewhat shorter than the elimination half-life $t_{1/2}$, then the dose Ratio R [of Induction Dose/Treatment Dose] should be 2:1."). This allows a patient to achieve blood levels close to steady-state blood levels from the induction dose alone. Ex. 1029 at 285 (fig. 19.8); *see* ex. 1025 at ¶¶ 50, 72.

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

loading dose= target C_p x (V_{ss}/F)[14]

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

C. Ground for *Inter Partes* Review: 2003 Humira™ Package Insert and WO '330 in View of Goodman & Gilman, the 2002 Remicade® Package Insert and Hanauer Render Claims 1-30 Obvious

1. 160 mg/80 mg Adalimumab Dosing Was Obvious (All Claims)

(a) A POSA would use 80 mg eow as the basis for an IBD induction therapy

The POSA knew that pharmaceutical treatment of IBD required both induction and maintenance therapies. *See supra* Section VI.B.2. Induction and maintenance of IBD typically required either different drugs or, in the case of the

[14] Ex. 1030 at 25. "V_{ss}" refers to distribution volume at steady state, "F" refers to bioavailability and target C_p refers to target plasma concentration. *Id.* at 22, 23, 27.

TNF-α antibody infliximab, different dosing regimens. *See supra* Section VI.B.2(b). For example, Hanauer described the use of numerous "[i]nductive therapies" for "inducing remission of active [IBD] and then maintaining remission to prevent relapse." Ex. 1027 at 300-01 (citations omitted). Administering greater quantities of drug, through higher doses or more frequent dosing, are alternative ways to achieve higher drug blood levels to induce remission. Ex. 1025 at ¶¶ 47, 59. The prior art 2002 Remicade® Package Insert taught that infliximab could be used for "inducing . . . remission" of CD by administering 5 $^{mg}/_{kg}$ at 0, 2 and 6 weeks, and that it could be used for "maintaining clinical remission" of CD by administering 5 $^{mg}/_{kg}$ every 8 weeks thereafter. Ex. 1023* at 2-4; Ex. 1068 at 1179-81. Basic pharmacological principles known to a POSA taught that higher doses, within a certain range, normally yield greater efficacy. Ex. 1030 at 24-25; Ex. 1025 at ¶ 49. Several examples demonstrate application of this principle underlying the use of higher induction doses preceding maintenance dosing at a lower dosing level. *See supra* Section VI.B.3. Accordingly, a POSA would be aware that IBD is treated using an induction followed by a maintenance dosing regimen, and a POSA would have been motivated to determine an IBD induction dosing regimen for adalimumab.

In selecting that higher dose, a POSA would know that the 40 mg adalimumab eow maintenance dosing regimen had been approved to treat RA and

that WO ’330 disclosed the same maintenance regimen as being “prefer[red]” for treating IBD. Ex. 1026* at 9; Ex. 1020* at 27:39. As discussed above, a POSA would have been motivated to look for a higher dose to use for an IBD induction dose. WO ’330 disclosed such a higher dose – 80 mg eow for several TNF-α related disorders, including IBD and RA. Ex. 1020* at 4:34-5:2, 27:37-39. In addition, WO ’330 disclosed several weekly adalimumab dosing regimens, including 40 mg and 80 mg weekly. *Id.** at 33:18-34:28. However, as WO ’330 explained, a POSA would prefer eow dosing because, it is more “convenient” for the patient, more likely to result in “patient compliance” and “less cost[ly].” *Id.** at 4:3-9.

Thus, WO ’330 would point a POSA toward the 80 mg eow adalimumab dose as a good basis for selecting an IBD loading dose because (a) it taught that 80 mg eow was effective for RA (as demonstrated by clinical study data), and suggested that the same dose would also be effective for IBD, and (b) 80 mg eow was a higher dose than the 40 mg eow dose described for maintenance treatment of IBD.

The choice of an 80 mg eow adalimumab dose was further confirmed by the 2003 Humira™ Package Insert, which also reported that 80 mg adalimumab eow had been used in a clinical study (“Study I”) to treat RA patients.

Based on the prior art disclosures, therefore, a POSA would reasonably expect that an induction dose that would provide comparable drug levels to the disclosed 80 mg eow dose would be effective in inducing IBD remission in at least some patients.[15]

(b) Goodman & Gilman and the 2003 Humira™ Package Insert Made It Obvious to Administer a 160 mg Loading Dose of Adalimumab Prior to an 80 mg Dose Two Weeks Later To Provide Rapid Patient Relief

In choosing an induction dosing regimen, a POSA, as Dr. Posner explains, would have understood from the two week half-life disclosed by the 2003 Humira™ Package Insert that it would take about 10 weeks of 80 mg eow dosing to achieve steady state blood levels of adalimumab. Ex. 1025 at ¶ 66. Given the need to provide IBD patients with rapid relief (*supra* Section VI.B.4), the 2003 Humira™ Package Insert provided all of the information needed for a POSA to determine that adalimumab had suitable pharmacokinetics for a loading dose and for determining an appropriate size for that dose to rapidly achieve blood levels associated with 80 mg eow dosing.

Adalimumab, according to the 2003 Humira™ Package Insert, had a known half-life of "approximately 2 weeks." Ex. 1026* at 2. While a POSA would reasonably select the prior art higher 80 mg eow as a basis for determining a

[15] Notably, in Example 1 of the '559 patent, only 36% of the patients treated with the claimed dosing regimen achieved remission. Ex. 1001 at 74:27-75:21.

loading dose to induce remission of IBD, *supra* Section VI.C.1(a), a POSA would also know it would take approximately 5 such biweekly doses, or 10 weeks, for a patient to reach steady-state blood levels. Ex. 1025 at ¶ 49. Accordingly, a POSA would have been motivated to provide IBD patients with a higher loading dose prior to any 80 mg dose to more rapidly reach steady state blood levels and thereby provide more rapid relief of IBD symptoms. *Id.* at ¶ 62.

To determine a desirable loading dose for adalimumab, a POSA would use the higher 80 mg eow dose as a starting point. *Id.*; *see also* ex. 1029 at 284-85. Dr. Posner explains, the prior art taught that for drugs whose treatment dosage interval corresponds to the half-life, a POSA would understand that the loading dose should be twice the treatment dose. Ex. 1025 at ¶ 50; Ex. 1029 at 285 ("As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug."); *see also* ex. 1003 at 352-53 ("If the dosing interval τ is equal to or somewhat shorter than the elimination half-life $t_{1/2}$, then the dose Ratio R [of induction dose/treatment dose] should be 2:1."). Therefore, a POSA would understand that one appropriate adalimumab loading dose is 160 mg (twice an 80 mg dose). As shown in Aulton's Figure 19.8, this regimen allows a patient to achieve blood levels close to steady-state from the loading dose alone. *See* ex. 1029 at 285; ex. 1025 at ¶¶ 50, 72.

The determination of a 160 mg adalimumab loading dose using the principle set forth in Aulton and Ritschel & Kearns is demonstrated by established pharmacokinetic calculations. As explained above, Goodman & Gilman provides the following standard equation to determine an induction or loading dose "with the aim of achieving the target concentration rapidly" (ex. 1030 at 27):

$$\text{loading dose} = \text{target } C_p \times (V_{ss}/F)$$[16]

A POSA would know the target plasma concentration (C_p) would be at or near the C_{max} achieved at steady state because that is the amount eventually achieved by administering twice the FDA-approved 40 mg eow dosing regimen for RA (*i.e.*, 80 mg eow). Ex. 1025 at ¶ 51 n.6. The C_{max} at steady state can be determined from the steady state C_{min}. As shown by Dr. Posner, using the steady state C_{min} of 5 $^{\mu g}/_{ml}$ from 40 mg eow dosing provided in the 2003 Humira™ Package Insert (ex. 1026* at 2), the fact that adalimumab exhibits first order pharmacokinetics and that it is administered with a frequency near its half-life, a POSA would know that the target plasma concentration (C_{max} at steady state) is 20 $^{\mu g}/_{ml}$ because the steady state C_{min} occurs one half-life from the C_{max} by virtue of dosing on the half-life and 80 mg is twice 40 mg. Ex. 1025 at ¶ 76. In other words, the steady state C_{min} is $^1/_2$ of the steady state C_{max}, therefore the C_{max}

[16] *Supra* n.14.

achieved by 80 mg eow dosing after reaching steady state is 20 $^{\mu g}/_{ml}$.[17] The 2003 Humira™ Package Insert states that V_{ss} ranged from 4.7 to 6.0 L and bioavailability (F) was 64%. Ex. 1026* at 2. Using those values a POSA could calculate that an appropriate loading dose of adalimumab to achieve blood levels associated with 80 mg eow at steady state would be between 147 mg[18] and 188 mg[19], depending on whether 4.7 L or 6.0 L is used for distribution volume. Ex. 1025 at ¶¶ 77-80. Accordingly, a 160 mg adalimumab loading dose would have been an obvious choice for a POSA to select (particularly since adalimumab was available in 40 mg pre-filled syringes, making dosing convenient with 4 syringes) and to have reasonably expected would succeed in achieving a more rapid therapeutic benefit in IBD patients.[20]

Moreover, a POSA would also have had a reasonable expectation that an adalimumab loading dose would be successful in increasing blood levels predictably because the prior art 2003 Humira™ Package Insert stated that

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[17] $C_p = C_{max}$ (steady state) = 2 x C_{min} (steady state) = 2 x C_{min} (40 mg eow steady state) x 2 = 2 x 5 $^{\mu g}/_{ml}$ x 2 = 20 $^{\mu g}/_{ml.}$

[18] loading dose= target 20 $^{\mu g}/_{ml}$ x (4.7 L / .64%) = 147 mg.

[19] loading dose= target 20 $^{\mu g}/_{ml}$ x (6.0 L / .64%) = 188 mg.

[20] Although loading doses for some drugs can impose added risks necessitating dividing the dose into several smaller doses administered over a relatively brief period of time, adalimumab's substantial safety margin (demonstrated by the 2003 Humira™ Package Insert), would likely render this unnecessary for adalimumab. Ex. 1025 at ¶ 85.

adalimumab exhibits linear pharmacokinetics and thus, "steady state [blood levels] increased approximately proportionally with dose following . . . 40 and 80 mg . . . subcutaneous dosing."[21] Ex. 1026* at 2; *see* ex. 1025 at ¶ 68. Thus, it would have been obvious that combining an initial 160 mg loading dose two weeks before an 80 mg dose would be efficacious and could result in more rapid relief. Furthermore, a POSA would reasonably expect induction of remission of IBD in at least some patients at the end of the 4 week induction period (*i.e.*, two weeks after the 80 mg dose and before the first 40 mg maintenance dose) because as taught by Hanauer, clinical testing of infliximab demonstrated induction of IBD remission 4 weeks after one dose of TNF-α inhibitor. Ex. 1027 at 306.

A POSA would also have known that a 160 mg and an 80 mg dose were both well within the range of adalimumab doses that the prior art had established were safe and well tolerated based on published clinical trial results. WO '330 described a study where patients received either 20, 40 or 80 mg weekly doses of adalimumab subcutaneously for 12 weeks which would result in adalimumab

[21] The prior art 2003 Humira™ Package Insert disclosed that both intravenously and subcutaneously administered adalimumab exhibited "linear" pharmacokinetics. Ex. 1025 at ¶ 68; Ex. 1026* at 2. For drugs with linear, or first order, pharmacokinetics, drug plasma concentrations are predictable because they are proportional to the dose. Ex. 1025 at ¶¶ 67-68; *see also* ex. 1013 at 18 ("In a linear pharmacokinetic model, plasma concentrations are additive, which is a useful principle for predicting multiple dosing profiles and for estimating dosing regimens in chronic conditions. This principle is referred to as the superposition principle, which states that the concentration of drug remaining in the body at any time is added to the concentration remaining from previous doses.").

blood levels equivalent to 40, 80 and 160 mg eow doses. Ex. 1020* at 34:14-27; Ex. 1025 at ¶¶ 87-88.[22] In addition, the 2003 Humira™ Package Insert explained that "[m]ultiple doses up to 10 $^{mg}/_{kg}$ have been administered to patients in clinical trials without evidence of dose-limiting toxicities." Ex. 1026* at 9. Using an average human weight of 70 kg (ex. 1070* at 14), 10 $^{mg}/_{kg}$ corresponds to an average dose of 700 mg, far beyond the claimed 160 mg loading dose. Thus, even without considering the well-known pharmacokinetic principles discussed above, a POSA would reasonably expect that an induction dose of 160 mg could be safely administered to patients and, by virtue of it being a larger dose, would provide more rapid relief. Ex. 1025 at ¶¶ 84-89.

Supporting the choice of a 160 mg/80 mg induction dosing regimen, a POSA would select dosage amounts which are a multiple of 40 mg. Because adalimumab was commercially available in the prior art in 40 mg syringes, the most convenient doses would be a multiple of 40 mg such as 80, 120 or 160 mg. Ex. 1026* at 1. As shown on the 2003 Humira™ Package Insert, AbbVie had a single commercial embodiment for its Humira® product, a 40 mg pre-filled syringe. *Id.* Accordingly, both AbbVie, and a POSA trying to make a biosimilar form of Humira®, had every incentive to select an induction dose that was a whole

[22] Additionally, a 1 $^{mg}/_{kg}$ (approximately 70 mg) subcutaneous dose of adalimumab had been described in the prior art disclosure of AbbVie's clinical trials for RA and was stated to be "very well tolerated." Ex. 1004* at 4.

number multiple of the then-existing 40 mg pre-filled syringe (*i.e.*, 80, 120, 160 mg) to avoid the burden of developing a new dosing format. *See* ex. 1034 at 2964 ("One strategy for increasing the dose [of infliximab] is to round up to the nearest 100-mg increment (100-mg vials), increasing the dose further as needed in 100-mg increments up to a maximal dose of 10 $^{mg}/_{kg}$."). Thus, a POSA, like AbbVie, would have been motivated to use an induction dosing regimen comprised of whole number multiples of 40 mg. Ex. 1025 at ¶ 90.[23]

In addition, a POSA would know there were only a limited number of reasonable, higher induction doses from which to choose, such as 80 mg and 160 mg, which are multiples of the standard 40 mg dose, and would reasonably expect any of them to induce remission to some degree in IBD patients. *See KSR Int'l Co.*, 550 U.S. at 421 ("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 has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under §103.").

[23] While Humira® is currently available in 10 mg and 20 mg injections, those forms were not commercially available in 2004. Moreover, the 10 mg and 20 mg doses are only used for pediatric conditions. The current dosage for all adult conditions is 40 mg, or a multiple thereof including 80 and 160, all administered by one or more pre-filled 40 mg syringes or self-injectors. Ex. 1056 at 1-2.

2. A POSA Would Have Been Motivated to Combine the Known 40 mg EOW Adalimumab Dosing for IBD with the Obvious 160 mg/80 mg IBD Induction Dose and Reasonably Expect Success (Claims 2, 3, 5, 6)

IBD therapies include both induction of remission and maintenance of remission. *Supra* Section VI.B.2. A POSA knew that the TNF-α antibody infliximab was approved for both induction and maintenance of remission using different dosing regimens. *Supra* Section VI.B.2(b). As explained above, 160 mg/80 mg is an obvious IBD induction dosing regimen. *Supra* Section VI.C.1. Furthermore, because WO '330 specifically disclosed subcutaneous administration of 40 mg adalimumab eow as a "most prefer[red]" maintenance regimen to treat IBD, a POSA would know that this obvious induction dosing regimen could be combined with the known maintenance dosing regimen to induce IBD remission and maintain that remission. Ex. 1020* at 12:11-18; 27:37-39; 32:18-26; Ex. 1002 at ¶¶ 101-02. This conclusion would be supported by the 2003 Humira™ Package Insert, which described using a 40 mg eow maintenance regimen for treating RA and "maintain[ing]" the improvement in symptomatic relief through 52 weeks. Ex. 1026* at 3. A POSA would therefore expect 40 mg eow to be an effective maintenance regimen for IBD.

3. The 2003 Humira™ Package Insert Taught Administering Adalimumab in Multiples of 40 mg Injections (Claim 4)

The prior art 2003 Humira™ Package Insert disclosed 40 mg pre-filled syringes for subcutaneous injection, stating that "HUMIRA is supplied in single-use, 1 mL pre-filled glass syringes . . . for subcutaneous administration." Ex. 1026* at 1. A POSA would have been motivated by this knowledge and the convenience of a pre-filled syringe to administer doses such as 160 mg and 80 mg as multiple 40 mg injections using the existing 40 mg pre-filled adalimumab syringes.

4. The 2003 Humira™ Package Insert Taught "subcutaneous injection . . . using a pre-filled syringe" (Claims 7, 8, 21, 22, 23 and 30)

The prior art 2003 Humira™ Package Insert disclosed pre-filled syringes for subcutaneous injection, stating that "HUMIRA is supplied in single-use, 1 mL pre-filled glass syringes . . . for subcutaneous administration." Ex. 1026* at 1. The prior art thus taught the limitation "subcutaneous injection . . . using a pre-filled syringe" as required by claims 7, 8, 21, 22, 23 and 30. A POSA would have been motivated by this knowledge and the convenience of a pre-filled syringe to select this dosing method of administration.

5. Achieving a CDAI Score of <150 Is an Inherent Result of the Claimed Dosing Regimen (Claims 13, 14, 16, 19, 25 and 28)

Several claims of the ’559 patent require that the patient achieve a Crohn’s Disease Activity Index (CDAI) score of <150. *See, e.g.*, ex. 1001 at claim 13. This result, according to the ’559 patent itself, is inherently achieved by some percentage of patients who are administered the claimed adalimumab dosing regimen, without the need for any additional steps. The ’559 patent discloses that 36% of patients who received the claimed 160/80 mg adalimumab regimen had CDAI scores of <150. *Id.* at 74:27-47. Accordingly, the addition of these limitations specifying the clinical endpoints inherent in this method of treatment cannot save the claims from invalidation. *Par Pharm., Inc. v. Twi Pharm., Inc.*, 773 F.3d 1186, 1194–95 (Fed. Cir. 2014) (“We have recognized that inherency may supply a missing claim limitation in an obviousness analysis.”). Therefore, claims 13, 14, 16, 19, 25 and 28 are obvious.

6. It Was Obvious To Use the Same Methods for Treating Both CD and UC (Claims 9, 10, 11, 12, 15, 17, 18, 20, 24, 26, 27 and 29)

Claims 9, 11, 15, 18, 24 and 27 specify that the human subject being treated with the claimed methods has Crohn’s disease and claims 10, 12, 17, 20, 26 and 29 specify that the human subject has UC. For all of the reasons explained above concerning the obvious adalimumab induction and maintenance therapies for IBD

in general, a POSA would reasonably expect the same obvious methods could be used successfully for either CD or UC.

WO ’330 disclosed the treatment of both Crohn’s disease and UC with adalimumab, citing a single range of doses for all conditions treated. Ex. 1020* at 4:34-5:2; 32:18-26; 27:37-39. This disclosure was entirely consistent with the POSA’s understanding that Crohn’s disease and UC are closely related, TNF-α-mediated conditions, that were historically treated with the same drugs at the same or similar dosing regimens. Ex. 1002 at Section VI.B. As shown in Table 2, steroids, sulphasalazine, azathioprine, cyclosporine, hydroxychloroquine, methotrexate, and levamisole were all used to treat CD and UC using similar or identical doses and dosing regimens. *Id.* at ¶¶ 49-58.

Table 2 – Small Molecule Drugs Used to Treat CD and UC at the Same or Similar Dose

Drug	IBD dosing regimen	
	UC	CD
Prednisolone (Ex. 1002 at ¶ 51)	20 $^{mg}/_{day}$	25-40 $^{mg}/_{day}$
Prednisone (*id.*)	10-60 mg (median 20 mg) daily	
Sulphasalazine (*id.* at ¶ 52)	Up to 6 $^{g}/_{day}$	1 $^{g}/_{15\ kg}$ (= 5 g for a 75 kg person)
Azathioprine (*id.* at ¶ 53)	1.5 – 2.5 $^{mg}/_{kg}/_{day}$	1.5 – 4 $^{mg}/_{kg}/_{day}$
Cyclosporine (*id.* at ¶ 54)	8.5 $^{mg}/_{kg}/_{day}$ orally for 5-6 weeks or 4 $^{mg}/_{kg}/_{day}$ intravenously for at least 10 days 4 $^{mg}/_{kg}/_{day}$ intravenously for up to 14 days, if improvement, then oral dose was administered as 6 to 8 $^{mg}/_{kg}/_{day}$ 4 $^{mg}/_{kg}/_{day}$ intravenously comparable with 12-16 $^{mg}/_{kg}/_{day}$ orally	5-7.5 $^{mg}/_{kg}/_{day}$ orally
Hydroxy-chloroquine (*id.* at ¶ 55)	400 $^{mg}/_{day}$	400 $^{mg}/_{day}$
Methotrexate (*id.* at ¶ 56)	25 $^{mg}/_{week}$ for 12 weeks, tapered down to 7.5 $^{mg}/_{week}$	same
Levamisole (*id.* at ¶ 57)	150 mg twice a week for the first two weeks, then once a week thereafter	50 mg 8-hourly (= 150 $^{mg}/_{day}$) for 3 consecutive days every 2 weeks

Thus, based on the disclosure of WO ’330, in light of the well-established knowledge in the relevant field, a POSA would approach the development of

dosing regimens for adalimumab with the reasonable expectation of success that induction and maintenance dosing regimens reasonably understood to be effective in treating IBD would be effective in treating both CD and UC. Ex. 1002 at Sections VI.B, VII.E.

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

During the prosecution of application no. 11/104,117 (the "'117 application" which issued as U.S. Patent No. 8,889,136), of which the application for the '559 patent is a continuation, AbbVie argued that a POSA would not apply the induction dose teachings of Aulton to a subcutaneously administered large molecule, such as an antibody. Ex. 1028 at 17. AbbVie submitted the declarations of Dr. John Collett, Ph.D. and Dr. Diane Mould, Ph.D. in support of its argument. Exs. 1022, 1024. The '117 application contained claims directed to an induction dose regimen of adalimumab for the treatment of CD. As explained by Dr. Posner, none of AbbVie's criticisms are correct or undermine the applicability of Aulton to determining the appropriate range of induction doses for adalimumab. Ex. 1025 at ¶¶ 91-99. As Dr. Posner explains, there is no basis for limiting Aulton to "small" molecules or for excluding subcutaneous administration. *Id.* The same principles can apply to biologics and small molecules. *Id.* Indeed, Ritschel & Kearns provides the same loading dose guidance as Aulton without any specific reference to route of administration or molecule. *See* ex. 1003 at 352-53.

Further, neither of the prior declarations AbbVie submitted during prosecution of the ’117 application addressed the fact that the 2003 Humira™ Package Insert explicitly disclosed that subcutaneously administered adalimumab exhibits linear pharmacokinetics. Ex. 1026* at 2; Ex. 1025 at ¶ 94. This data confirms that a POSA would have understood that Aulton’s teachings were in fact applicable to subcutaneously administered adalimumab. Thus, as Dr. Posner explains, based on the known pharmacokinetics for adalimumab, a POSA would reasonably expect that a subcutaneously administered adalimumab induction dose would proportionally increase a patient’s blood levels relative to the maintenance dose. Ex. 1025 at ¶¶ 82-83.

8. No Secondary Considerations Such as Commercial Success or Unexpected Results Demonstrate Nonobviousness

AbbVie has repeatedly made contradictory arguments of commercial success attempting to support the patentability of its varied portfolio of secondary D2E7-related patents. There can be no nexus between Humira®’s commercial success and the claims of the ’559 patent because at different times AbbVie has attributed the commercial success of Humira® to entirely different patents. The Federal Circuit, moreover, 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 '559 patent that drives Humira®'s sales. For example, in defending the alleged patentability of a patent claiming an adalimumab formulation against a petition for *inter partes* review of U.S. Patent No. 8,916,158 ("the '158 patent"), AbbVie argued that the commercial success of Humira® was "driven in large part by" its formulation. Ex. 1021 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 Humira®'s commercial success 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 160 mg/80 mg

induction regimen followed by 40 mg maintenance dosing to treat IBD. Moreover, the very evidence that AbbVie submitted, supposedly in support of its response to the '158 formulation patent petition, acknowledged that the commercial success of Humira® was due to its initial patent on 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. 1018* at 5 (cited as Ex. 2003 in the '158 IPR).

When trying to defend its RA dosing patent (the '135 patent), AbbVie attributed Humira®'s commercial success, not to its IBD multi-variable 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. 1015 at 58. In the Final Written Decision for the '135 IPR, the Board recognized that AbbVie has inconsistently argued that different attributes of Humira® have led to its commercial success in different proceedings: "[t]hus, Patent Owner has relied on features other than the dosing regimen recited in the '135 patent claims as driving the commercial success of HUMIRA®." *Coherus BioSciences Inc. v. AbbVie Biotechnology Ltd.*, No. IPR2016-00172, Final Written Decision, Paper No. 60, at 40 (P.T.A.B. May 16, 2017). The Board stated: "it is

not clear whether the sales of HUMIRA® are due to the dosing regimen recited in the '135 patent, or the formulation that Patent Owner argued was the driver of commercial success in another *inter partes* review, or the known and patented fully human D2E7 antibody." *Id.* at 41.

Accordingly, AbbVie cannot save the claims of the '559 patent from invalidity by asserting that the commercial success of Humira® is due to the methods claimed in the '559 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).

As explained *supra* Section V.A, the CD clinical trial results do not show any unexpected benefits. The '559 patent discloses two CD clinical trials and no trials for UC. The studies simply demonstrated that various adalimumab induction dosing regimens are effective in treating Crohn's disease and that the higher dose is somewhat more effective.

9. The Prior Art Combination Described Above Renders Claims 1-30 of the '559 Patent Obvious

For the reasons discussed above and summarized in the tables below, claims 1-30 of the '559 patent are obvious over the 2003 Humira™ Package Insert and WO '330 in view of Goodman & Gilman, the 2002 Remicade® Package Insert and Hanauer.

Independent Claims 1 and 4

'559 Patent Claim Language	Prior Art Disclosures
Claim 1	
A multiple-variable dose method for treating idiopathic inflammatory bowel disease in a human subject in need thereof,	"This invention provides methods of treating disorders in which the administration of an anti-TNFa antibody is beneficial. These methods include the biweekly, subcutaneous administration of isolated human antibodies, or antigen-binding portions thereof, that bind to human TNFa with high affinity, a low off rate and high neutralizing capacity. . . . The most preferred recombinant, neutralizing antibody of the invention is referred to herein as D2E7 . . . ." Ex. 1020* at 12:11-18. "The human antibodies, and antibody portions of the invention can be used to treat autoimmune diseases . . . including rheumatoid arthritis." *Id.** at 30:33-35. "The human antibodies, and antibody portions, of the invention, also can be used to treat intestinal disorders, such as idiopathic inflammatory bowel disease, which includes two syndromes, Crohn's disease and ulcerative colitis." *Id.** at 32:24-26. Adalimumab is dosed "most preferably [at] about 40 mg" to treat the

’559 Patent Claim Language	Prior Art Disclosures
	conditions in the application, including RA and IBD (CD and UC). *Id.** at 27:37-40; *Id.** at 30:33-35; *Id.** at 32:24-26.
comprising subcutaneously administering to the human subject:	WO ’330 “provides methods for biweekly dosing regimens for the treatment of TNFα associated disorders, preferably via a subcutaneous route.” Ex. 1020* at 4:2-3.
a first dose of 160 mg of adalimumab administered to the human subject within a day; and	D2E7 is dosed “most preferably [at] about 40 mg” to treat the conditions in the application, including RA and IBD (CD and UC). Ex. 1020* at 27:37-40; *Id.** at 30:33-35; *Id.** at 32:24-26. For the reasons stated *supra* Section VI.C.1(b), a POSA would have been motivated to include a 160 mg adalimumab dose prior to the 80 mg dose and reasonably expect that to be efficacious.
a second dose of 80 mg of adalimumab administered to the human subject within a day, wherein the second dose is administered two weeks following administration of the first dose.	Adalimumab is dosed “most preferably [at] about 40 mg” to treat the conditions in the application, including RA and IBD (CD and UC). Ex. 1020* at 27:37-40; *Id.** at 30:33-35; *Id.** at 32:24-26. “As a general rule, the loading dose should be twice the size of the maintenance dose if the selected dosage time interval corresponds to the biological half-life of the drug.” Ex. 1029 at 285. For the reasons stated *supra* Section VI.C.1(a), a POSA would have been motivated to include an 80 mg adalimumab dose prior to 40 mg eow dosing and reasonably expect that to be

’559 Patent Claim Language	Prior Art Disclosures
	efficacious.
Claim 4	
A multiple-variable dose method for treating idiopathic inflammatory bowel disease in a human subject in need thereof,	See Claim 1.
comprising subcutaneously administering to the human subject:	
a first dose of 160 mg of adalimumab administered as a set of four injections of 40 mg of adalimumab administered to the human subject within a day; and	See Claim 1. “HUMIRA is supplied in single-use 1 mL pre-filled glass syringes . . . . Each syringe delivers 0.8 mL (40 mg) of drug product.” Ex. 1026* at 1.
a second dose of 80 mg of adalimumab administered as a set of two injections of 40 mg of adalimumab administered to the human subject within a day, wherein the second dose is administered two weeks following administration of the first dose.	

Dependent Claims 2, 3, 5, 6 (40 mg eow maintenance dosing)

’559 Patent Claim Language	Prior Art Disclosures
Claims 2, 5	WO ’330, in its own words, “provides methods for biweekly dosing regimens for the treatment of TNFα associated disorders, preferably via a subcutaneous route.” Ex. 1020* at 4:2-3. Adalimumab is dosed “most preferably [at] about 40 mg” to treat the conditions in the application, including RA and IBD (CD and UC). Ex. 1020* at 27:37-40; *Id.** at 30:33-35; *Id.** at 32:24-26.
The method of claim [1, 4] wherein the method further comprises administering to the human subject a subsequent subcutaneous injection of 40 mg of adalimumab two weeks following administration of the second dose.	
Claims 3, 6	
The method of claim [2, 5] wherein the method further comprises administering to the human subject additional subsequent subcutaneous injections of 40 mg of adalimumab,	

wherein the subsequent subcutaneous injections are administered two weeks apart.	

Dependent Claims 7, 8, 21, 22, 23, 30 (pre-filled syringe)

’559 Patent Claim Language	Prior Art Disclosures
Claims 7, 8, 22, 23, 30	“HUMIRA is supplied in single-use 1 mL pre-filled glass syringes . . . . Each syringe delivers 0.8 mL (40 mg) of drug product.” Ex. 1026* at 1.
The method of claim [2, 3, 4, 5, 6] wherein each subcutaneous injection is administered to the human subject using a pre-filled syringe.	
Claim 21	
The method of claim 1, wherein each subcutaneous administration is with a pre-filled syringe.	

Dependent Claims 9, 11, 15, 18, 24, 27 (Crohn’s Disease)

’559 Patent Claim Language	Prior Art Disclosures
Claims 9, 11, 15, 18, 24, 27	
The method of claim [1, 2, 3, 4, 5, 6] wherein the human subject has Crohn’s disease.	See Claim 1.

Dependent Claims 10, 12, 17, 20, 26, 29 (ulcerative colitis)

’559 Patent Claim Language	Prior Art Disclosures
Claims 10, 12, 17, 20, 26, 29	
The method of claim [1, 2, 3, 4, 5, 6] wherein the human subject has ulcerative colitis.	See Claim 1.

Dependent Claims 13, 14, 16, 19, 25, 28 (CDAI score of <150)

’559 Patent Claim Language	Prior Art Disclosures
Claims 13, 14, 16, 19, 25, 28	
The method of claim [9, 11, 15, 18, 24, 27] wherein the human subject achieves a Crohn’s Disease Activity Index (CDAI) score of <150.	“Table 1 shows the percentage of patients with clinical remission (CDAI<150) at week 4 of the dosing regimen. As shown below in Table 1, thirty percent of patients who received 80/40 mg or 160/80 mg of D2E7 achieved clinical remission compared with 12% who received placebo . . . . Patients in the highest dose group, 160/80 mg, achieved a statistically significant remission rate of 36% versus a placebo rate of 12%.” Ex. 1001 at 74:27-47.[24]

VII. CONCLUSION

Petitioner has demonstrated a reasonable likelihood that claims 1-30 of the ’559 patent are unpatentable as obvious in view of the prior art identified herein. Petitioner therefore requests that the Board grants *inter partes* review for each of those claims.

[24] The ’559 patent is not prior art but its disclosure demonstrates the result is inherent for some portion of treated patients. *Supra* Section V.A.

Dated: November 6, 2017

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that this brief complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a), this Petition contains 13,159 words as counted by the word processing program used for its preparation (Microsoft Word 2010), including figure labels and annotations, which were manually counted.

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

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CERTIFICATE OF SERVICE

I hereby certify that true and correct copies of the foregoing Sandoz Inc.'s Petition for *Inter Partes* Review of U.S. Patent No. 9,187,559 and Exhibits 1001 – 1070 were served on November 6, 2017 via Federal Express to the correspondence address for the attorney of record for AbbVie Biotechnology Ltd., the assignee of the '559 patent.

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