UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SWISS PHARMA INTERNATIONAL AG,

Petitioner

v.

Patent Owner of
U.S. Patent No. 8,815,236 to Burke et al.
Appl. No. 13/676,866 filed Nov. 14, 2012
Issued Aug. 26, 2014

IPR Trial No. TBD

PETITION FOR *INTER PARTES*
REVIEW OF U.S. PATENT NO. 8,815,236
PURSUANT TO 35 U.S.C. § 312 AND 37 C.F.R. § 42.108

TABLE OF CONTENTS

TABLE OF AUTHORITIES

Cases **Page(s)**

Statutes

Other Authorities

EXHIBIT LIST

Exhibit No.	Description	Short Reference
Ex. 1001	U.S. Patent No. 8,815,236 to Burke et al., titled "Method for Treating Multiple Sclerosis And Crohn's Disease"	'236 patent
Ex. 1002	Declaration of Dr. Christian Schöneich	Schöneich Decl.
Ex. 1003	Curriculum Vitae of Dr. Christian Schöneich	Schöneich CV
Ex. 1004	List of Prior Art and Other Materials Considered by Dr. Christian Schöneich	Schöneich Materials Considered
Ex. 1005	Declaration of Scott Bennett, Ph.D.	Bennett Decl.
Ex. 1006	Curriculum Vitae of Scott Bennett, Ph.D.	Bennett CV
Ex. 1007	List of Materials Considered by Scott Bennett, Ph.D.	Bennett Materials Considered
Ex. 1008	Declaration of Rachel J. Watters	Watters Decl.
Ex. 1009	Curriculum Vitae of Rachel J. Watters	Watters CV
Ex. 1010	U.S. Patent Publication 2001/0014326 A1 to Andya, et al., for Application No. 09/809,511, filed march 14, 2001	Andya
Ex. 1011	Declaration of Dr. Staley Brod	Brod Decl.
Ex. 1012	Curriculum Vitae of Dr. Staley Brod	Brod CV
Ex. 1013	List of Prior Art and Other Materials Considered by Dr. Staley Brod	Brod Materials Considered

Exhibit No.	Description	Short Reference
Ex. 1014	B. W. van Oosten, et al., Increased MRI Activity and Immune Activation in Two Multiple Sclerosis Patients Treated with the Monoclonal Anti-Tumor Necrosis Factor Antibody cA2, 47 Neurology 1531 (1996)	van Oosten
Ex. 1015	Bruce E. Sands, et al., Infliximab in the Treatment of Severe, Steroid-Refractory Ulcerative Colitis: A Pilot Study, 7 Inflammatory Bowel Diseases 83 (2001)	Sands
Ex. 1016	BLA 98-0012, Correspondence with FDA re Pharmacology Review of the infliximab BLA, dated 5/21/1998	BLA Correspondence
Ex. 1017	Fiona H. Gordon, et al., A Randomized Placebo-Controlled Trial of a Humanized Monoclonal Antibody to α4 Integrin in Active Crohn's Disease, 121 Gastroenterology 268 (2001)	Gordon
Ex. 1018	U.S. Patent No. 5,840,299 to Bendig, issued 11/24/1998	Bendig
Ex. 1019	L.A. Sorbera, et al., Natalizumab Treatment of IBD Treatment of Multiple Sclerosis, 25 Drugs of the Future 917 (2000)	Sorbera
Ex. 1020	John Stephen White, et al., Proteins, Peptides and Amino Acids: SourceBook 108-112 (2002)	White
Ex. 1021	Larry M. Cummins, et al., Preparation and Characterization of an Intravenous Solution of IgG From Human Immunodeficiency Virus-Seropositive Donors, 77 Blood 1111 (1991)	Cummins
Ex. 1022	Orthoclone®, in Physicians' Desk Reference 1837 (50th ed. 1996)	Orthoclone

Exhibit No.	Description	Short Reference
Ex. 1023	Thomas Aversano, et al., A Chimeric IgG4 Monoclonal Antibody Directed Against CD18 Reduces Infarct Size in a Primate Model of Myocardial Ischemia and Reperfusion, 25(3) JACC 781 (1995)	Aversano
Ex. 1024	Zenapax®, in Physicians' Desk Reference 2696 (54th ed. 2000)	Zenapax
Ex. 1025	Jenny Bell & Jean Colaneri, Zenapax: Transplant's First Humanized Monoclonal Antibody, 25(4) ANNA Journal 429 (1998)	Bell
Ex. 1026	Malathy Subramanian et al., Effect of Histidine Oxidation on the Loss of Potency of a Humanized Monoclonal Antibody, in AAPS Pharmsci S-29 (Oct. 2001)	Subramanian
Ex. 1027	Xylocaine®, in Physicians' Desk Reference 638 (54th ed. 2000)	Xylocaine
Ex. 1028	Naropin®, in Physicians' Desk Reference 609 (54th ed. 2000)	Naropin
Ex. 1029	Pharmaceutical Formulation Development of Peptides and Proteins 146-47, 150-52, 160-65, 171(Sven Frokjaer and Lars Hovgaard eds., Taylor & Francis Ltd. 2000)	Frokjaer
Ex. 1030	Collected FDA and PTO information	FDA and PTO Info
Ex. 1031	Protein Formulation and Delivery Preface, 139-158 (Eugene J. McNally ed., Marcel Dekker, Inc. 2000)	McNally
Ex. 1032	Remington: The Science and Practice of Pharmacy 250-51, 819, 1265 (2000)	Remington

Exhibit No.	Description	Short Reference
Ex. 1033	Alfred Martin, et al., Physical Pharmacy 222-39, 391-92 (1983)	Martin
Ex. 1034	Chemical Stability of Pharmaceuticals: A Handbook for Pharmacists 8-32 (Kenneth A. Connors, et al., eds., 1986)	Connors
Ex. 1035	Fundamental Immunology 47-57 (William E. Paul ed., Lippincott-Raven, 4th edition, 1999)	Paul
Ex. 1036	Cellular and Molecular Immunology (Abul K. Abbas et al. W.B. Saunders Co., 3rd edition, 1997)	Abbas
Ex. 1037	F. Mikulandra, The Effect of High Birth Weight (4000 g or More) on the Weight and Height of Adult Men and Women, 24 Coll. Antropol. 133-136 (2000)	Mikulandra
Ex. 1038	Confidential Report, J. Deistung, P. Challis & R. Pardon, Preformulation Study on the Humanised Monoclonal Antibody (Sept. 1994) (on file with European Patent Office)	Preformulation Study
Ex. 1039	Confidential Report, J. Deistung, P. Challis & R. Pardon, Preformulation Study on the Humanised Monoclonal Antibody (Sept. 1994) (from prosecution history of U.S. Patent No. 8,900,577)	‘577 Preformulation Study
Ex. 1040	Minutes of Oral Proceedings of May 21, 2010, by Examining Division, European Patent Office, with Andrea Schüssler, Representative for Applicants (June 7, 2010) (on file with European Patent Office)	EPO minutes
Ex. 1041	Response to the Noting of loss of rights pursuant Rule 112(1) EPC dated November 24, 2015, in the prosecution of European Patent Application 10 005 235.6 – 1405, dated February 3, 2016.	EPO Response

Exhibit No.	Description	Short Reference
Ex. 1042	U.S. Patent No. 8,349,321 ("the '321 patent") to Burke et al., titled "Immunoglobin Formulation And Method of Preparation Thereof"	'321 patent
Ex. 1043	Claims as filed for Appl. No. 13/676,866 dated 11/14/2012	Original Claims
Ex. 1044	Non Final Rejection for Appl. No. 12/572,978 dated 2/11/2011	'978 Non-Final Rejection
Ex. 1045	U.S. Patent No. 6,914,128 to Salfeld, issued 7/5/2005	Salfeld
Ex. 1046	Response to Non Final Rejection for Appl. No. 12/572,978 dated 8/11/2011	'978 Response 1
Ex. 1047	Wang et al., 185 International Journal of Pharmaceutics 129-188 (1999).	Wang
Ex. 1048	Cleland et al., 10 Critical Reviews in Therapeutic Drug Carrier Systems, 307-377 (2000).	Cleland
Ex. 1049	Non-Final Rejection after RCE for Appl. No. 12/572,978 dated 5/10/2012	RCE Non Final Rejection
Ex. 1050	Response to Final Rejection for Appl. No. 12/572,978 dated 1/27/2012	'978 Response 2
Ex. 1051	Notice of Allowance for Appl. No. 12/572,978 dated 10/11/2012	'978 Notice of Allowance
Ex. 1052	Amendment and Response to Restriction Requirement for Appl. No. 13/676,866 dated 2/11/13	'866 Response 1
Ex. 1053	Response to Non Final Rejection for Appl. No. 13/676,866 dated 7/15/13	'866 Response 2
Ex. 1054	Final Rejection for Appl. No. 13/676,866 mailed 9/19/13	'866 Final Rejection

Exhibit No.	Description	Short Reference
Ex. 1055	Response After Final Rejection for Appl. No. 13/676,866 dated 3/18/14	‘866 Response 3
Ex. 1056	Notice of Allowance for Appl. No. 13/676,866 dated 4/10/14	‘866 Notice of Allowance
Ex. 1057	Declaration of Dr. David Sachar	Sachar Decl.
Ex. 1058	Curriculum Vitae of Dr. David Sachar	Sachar CV
Ex. 1059	List of Prior Art and Other Materials Considered by Dr. David Sachar	Sachar Materials Considered
Ex. 1060	W. A. Sheremata, et al., A Safety and Pharmacokinetic Study of Intravenous Natalizumab in Patients with MS, 52 Neurology 1072 (1999)	Sheremata
Ex. 1061	U.S. Patent Pub. No. US2015/0030590, published January 29, 2015	Panzara

Pursuant to 35 U.S.C. § 311 *et seq.* and 37 C.F.R. § 42.1 *et seq.*, Swiss Pharma International AG ("Petitioner") hereby submits this petition for *inter partes* review ("Petition") of U.S. Patent No. 8,815,236 ("the '236 patent") (Ex. 1001). Petitioner respectfully submits that claims 1-16 and 21-22 (the "Challenged Claims") are unpatentable under 35 U.S.C. § 103 in view of the prior art discussed herein.

I. INTRODUCTION

The Challenged Claims cover methods for treatment through administration of an old therapeutically active agent paired with a standard well-known formulation repeatedly and successfully used with numerous other therapeutically active agents from the same class of compounds. The therapeutically active agent is natalizumab, known to effectively treat both multiple sclerosis ("MS") and Crohn's disease ("CD") years before the earliest effective filing date for the '236 patent. Natalizumab is a monoclonal antibody ("mAb") belonging to the immunoglobulin G ("IgG") class of compounds. The formulation recited by the Challenged Claims is also old. Numerous prior art IgG mAb formulations, including multiple FDA-approved prior art formulations, contain the exact same combination of three excipients recited by the Challenged Claims – (1) phosphate buffer, (2) sodium chloride and (3) polysorbate 80. Given the repeated success of this formulation with other IgG mAb actives, the rationale for its combination with

natalizumab is strong. Further, protein formulators skilled in the art looked to this formulation with these other IgG mAb actives because they reasonably expected it to work. Consequently, its combination with natalizumab to treat known disease states in the Challenged Claims is obvious.

The remaining limitations, such as the specifics of administration and the concentration or pH of the formulation, were commonly known and appear in the prior art, are necessarily satisfied or recite nothing more than result effective variables subject to routine optimization. It is well-settled that differences in concentration and pH do not support patentability in the absence of some evidence of criticality or unexpected results – neither of which is present here.

Indeed, the allegedly unexpected results that Applicants relied upon to gain allowance of U.S. Patent No. 8,349,321 ("the '321 patent"), parent to the '236 patent, arose from a "Preformulation Study" that Applicants themselves publicly admitted is inaccurate, non-reproducible and unsupportive of the conclusion of unexpected results. Specifically, on July 6, 2010, a year before presenting the Preformulation Study during prosecution of the '321 patent, Applicants' representative admitted to the European Patent Office (EPO) that the study was "based on preliminary data which was not accurate . . . [and] could not be reproduced." (Ex. 1040 at 1.) Yet, Applicants never told the Examiner about this problem, and in fact relied on the Preformulation Study as a primary basis for

overcoming the Examiner's repeated obviousness rejections. Unexpected results do not rescue the '236 patent here. Thus, there is a reasonable likelihood that at least one, if not all, of the Challenged Claims of the '236 patent are obvious. Petitioner respectfully requests that the Board institute an *inter partes* review of the '236 patent pursuant to 35 U.S.C. § 314 and 37 C.F.R. § 42.108.

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

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

Petitioner certifies that Swiss Pharma International AG is a real party-in-interest. Petitioner is a subsidiary that is owned by Medana Pharma SA, Polfa Warsaw SA (also known and registered as Warszawskie Zakłady Farmaceutyczne Polfa S.A.) and Pharmaceutical Works Polpharma SA (also known and registered as Zakłady Farmaceutyczne Polpharma SA). Polfa Warsaw SA and Medana Pharma SA are in turn owned by Zakłady Farmaceutyczne Polpharma SA (also known as Pharmaceutical Works Polpharma SA).

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

Petitioner is concurrently filing two additional petitions for *inter partes* review that will address certain claims of the '321 patent and U.S. Patent No. 8,900,577 ("the '577 patent"). The '236 and '577 patents are related to each other and to the '321 patent as continuations or divisionals.

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

Petitioner designates the following as lead and back-up counsel, all with Axinn, Veltrop & Harkrider LLP:

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A power of attorney is submitted herewith pursuant to 37 C.F.R. § 42.10(b).

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

Service of any documents via hand-delivery may be made at the postal mailing addresses of lead and back-up counsel identified above with courtesy copies to the respective email addresses stated above. Petitioner consents to electronic service at these same email addresses.

III. FEE PAYMENT AUTHORIZATION (37 C.F.R. § 42.103)

In accordance with 37 C.F.R. § 42.103(a), Petitioner authorizes the Patent Office to charge Deposit Account No. 013050 for the fees set forth in 37 C.F.R. § 42.15(a). If payment of additional fees is due during this proceeding, the Patent Office is authorized to charge such fees to Deposit Account No. 013050, and credit any overpayment to the same account.

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

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '236 patent is available for *inter partes* review and that Petitioner is neither barred nor estopped from requesting *inter partes* review.

V. IDENTIFICATION OF CHALLENGE AND GROUNDS (37 C.F.R. § 42.104(b))

Pursuant to 37 C.F.R. §§ 42.22(a)(1) and 42.104(b)(1)-(2), Petitioner respectfully requests *inter partes* review and cancellation of Challenged Claims 1-16, 21 and 22. Independent claim 1 is representative:

> 1. A method of treatment, comprising administering to a patient with multiple sclerosis a therapeutic amount of a stable, aqueous pharmaceutical formulation comprising from about 20 mg/ml to about 150 mg/ml of natalizumab, about 10 mM phosphate buffer, about 140 mM sodium chloride, and polysorbate 80 present in an amount of about 0.001% to 2% (w/v), wherein the multiple sclerosis is treated by administration of the stable, aqueous pharmaceutical formulation.

(Ex. 1001 at 17:62-18:2.) Independent claim 9 is identical to claim 1, except that it is for the treatment of MS, not CD. The dependent claims each depend from either claim 1 or 9 and specify the route of administration as intravenous (claims 2 & 10), the administration to be over a series of treatments (claims 3 & 11), a 20 mg/ml natalizumab concentration in the formulation (claims 4 & 12), a 0.02% polysorbate 80 concentration (claims 5 & 13), and specific pH ranges for the formulation

(claims 6-8 and 14-16). Independent claims 21 & 22 collect the various limitations from several dependent claims and combine them into single independent claims for methods of treatment for MS and CD, respectively.

A. Effective Filing Date of the '236 Patent

The '236 patent was filed as Appl. No. 13/676,866 on November 14, 2012. It is a divisional of Appl. No. 12/572,978, filed on October 2, 2009, which issued as the '321 patent. Appl. No. 12/572,978 is a continuation of Appl. No. 10/773,406, which in turn claims priority to provisional Appl. No. 60/445,818, filed on February 10, 2003. For purposes of this petition only, Petitioner has assumed that the earliest effective filing date of the Challenged Claims is February 10, 2003. Petitioners do not otherwise concede same for other purposes.

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

The scope and content of the prior art is described in Section VII.A, and the two proposed grounds of invalidity are described in Sections VII.B and VII.C. The Declarations of Dr. Christian Schöneich (Ex. 1002), Dr. Staley Brod (Ex. 1011) and Dr. David Sachar (Ex. 1057) support each of these grounds. As more fully set forth in their declarations, Dr. Schöneich is an expert in protein formulation (Ex. 1002 at ¶¶ 5-10, 85), Dr. Brod is an expert in the treatment of MS (Ex. 1011 at ¶¶ 5-14, 38) and Dr. Sachar is an expert in the treatment of CD (Ex. 1057 at ¶¶ 5-10, 36). Each is qualified to provide opinions as to what a person of ordinary skill

in the art would have understood, known or concluded as of February 10, 2003.

Petitioner respectfully requests institution on each of the Challenged Claims based on two independent Grounds:

- Ground 1 – Obviousness over either van Oosten (Ex. 1014) or Zenapax (Ex. 1024) in view of Sorbera (Ex. 1019); and
- Ground 2 – Obviousness over Gordon (Ex. 1017) in view of either Orthoclone (Ex. 1022) or Aversano (Ex. 1023).

VI. SUMMARY OF THE '236 PATENT AND PROSECUTION HISTORY

The '236 patent relates to aqueous formulations comprising various therapeutically active proteins, especially antibodies and immunoglobulins. According to the '236 patent specification, "the invention provides for a stable, aqueous pharmaceutical formulation comprising an immunoglobulin (or other protein), a phosphate buffer, a polysorbate and sodium chloride." (Ex. 1001 at 1:58-61.) The '236 patent teaches that virtually all proteins are interchangeable in this formulation, stating that "[a]lthough discussion of the formulation is provided mainly in reference to an antibody or immunoglobulin, other proteins are contemplated as interchangeable in the formulations disclosed." (Id. at 2:64-67.)

Consistent with the '236 patent's statement concerning interchangeability, all originally-filed independent claims broadly recite formulations comprising proteins or immunoglobulins without restriction, along with a phosphate buffer, a

polysorbate, and sodium chloride. (Ex. 1043 at 1, 4 and 5 (claims 1, 29 and 33).) No original independent claim specifically recited natalizumab, which originally appeared only in dependent claims. (See, e.g., id. at 2 (claims 14-16).)

In response to allowance of the formulation claims in the '321 patent (parent to the '236 patent), however, Applicants amended the then pending claims of the '236 patent to recite certain aspects of the allowable formulation. It is thus instructive to review prosecution of the application leading to the '321 patent.

In that case, the Examiner rejected the original claims as anticipated by U.S. Pat. No. 6,914,128 ("Salfeld") (Ex. 1045) and as obvious over Salfeld in view of Gordon (Ex. 1017). (Ex. 1044 at 7.) The Examiner explained that Salfeld discloses an aqueous pharmaceutical formulation as claimed (id. at 5) and that although "[Salfeld] . . . does not particularly teach natalizumab," Gordon cures the deficiency (id. at 8). In response, Applicants filed a series of successively narrowing amendments to focus exclusively on the natalizumab active. Notwithstanding statements in their specification concerning interchangeability and their original decision to broadly claim formulations comprising any and all proteins and immunoglobulins, Applicants argued that "[t]he art teaches that antibodies are not readily interchangeable in formulations . . . ." (Ex. 1046 at 8-9 (citing Wang, Ex. 1047; Cleland, Ex. 1048).)

Applicants also relied heavily on the aforementioned "Preformulation

Study" (Ex. 1038),[1] as evidence that phosphate buffer, polysorbate 80 and sodium chloride represented an "unlikely combination of excipients" and that "inclusion of [] sodium chloride or [] Tween [polysorbate] 80 in the formulation had the effect of accelerating the degradation processes." (Ex. 1046 at 10-11.) Applicants publicly admitted, however, the Preformulation Study "was not accurate . . . [and] could not be reproduced," though they never made or disclosed that admission to the Examiner. (Ex. 1040 at 1.)

Ultimately, the Examiner presiding over prosecution of the '321 patent withdrew his obviousness rejection. (Ex. 1049 at 3.) Although he did not provide reasons for allowance, Applicants' heavy reliance on the Preformulation Study just prior to withdrawal of the Examiner's obviousness rejection likely played a significant role. (Ex. 1050 at 5.) In allowing the claims of the '236 patent, the Examiner pointed to the allowable subject matter of the '321 patent. (Ex. 1056 at 6 (citing "U.S. Pat. 8,349,431," a clear typographical error).) The formulation, as opposed to the method limitations, thus established the basis for allowance.

A. Level of Ordinary Skill in the Art

[1] As Dr. Schoneich explains, during prosecution of EP Appln. No. 04709508.8 ("EP '508"), Applicants submitted to the EPO Ex.1038, the same document as the "Preformulation Study" referenced by Applicants during the prosecution of the '321 patent and the related '577 patent (Ex. 1039). (Ex. 1002 at ¶ 195.)

A person of ordinary skill in the art of the '236 patent would have held a Ph.D. or other post-graduate training in protein chemistry or a related field with at least a few years of practical industrial or academic experience preparing protein formulations. (Ex. 1002 at ¶ 83.) The experience includes practical familiarity with assays for assessing protein stability and solubility so as to optimize a protein formulation based on the results. One of ordinary skill could also confer with medical doctors who have at least three years of knowledge or experience in treating patients with CD, MS or other disease states treatable with IgG mAbs. (Id. at ¶ 83; see also Ex. 1011 at ¶ 34; Ex. 1057 at ¶ 34.)

B. Claim Construction (37 C.F.R. § 42.104(b)(3))

A patent claim term in *inter partes* review is to be given the "broadest reasonable construction in light of the specification" as commonly understood by those of ordinary skill in the art. See In re Cuozzo Speed Techs., LLC, 793 F.3d 1268, 1275 (Fed. Cir. 2015), cert. granted 84 U.S.L.W. 3218 (U.S. Jan. 15, 2016) (No. 15-446); 7 C.F.R. § 42.100(b). Consistent with this standard, and without conceding that these terms should be construed the same way in a district court proceeding, Petitioner provides proposed constructions of certain of the claim terms as set forth below for purposes of this Petition only.

1. "Stable"

The '236 patent expressly defines this term by stating that "[a] 'stable'

formulation is one in which the protein therein essentially retains its physical stability and/or chemical stability and/or biological activity upon storage. By 'stable' is also meant a formulation which exhibits little or no signs of instability, including aggregation and/or deamidation." (Ex. 1001 at 5:57-62.) Although this passage offers alternate definitions, the broadest reasonable interpretation of "stable" merely requires that the formulation retains any one of physical, chemical or biological stability upon storage. (Ex. 1002 at ¶ 27.)

2. **"Phosphate buffer"**

The '236 patent does not expressly define "phosphate buffer," but does expressly define "buffer" to mean "a buffered solution that resists changes in pH by the action of its acid-base conjugate components." (Ex. 1001 at 6:39-41.) Accordingly, the broadest reasonable construction of "phosphate buffer" is "a buffered solution comprising one or more phosphate salts that resists changes in pH by the action of its acid-base conjugate components." (Ex. 1002 at ¶ 29.)

3. **"Series of treatments"**

The '236 patent does not expressly define "series of treatments," but it contrasts a series with a one-time administration. The '236 patent thus makes clear that the broadest reasonable construction of "series of treatments" is "at least two treatments." (Ex. 1011 at ¶ 47; Ex. 1057 at ¶ 47.)

VII. DETAILED EXPLANATION (37 C.F.R. § 42.104(b)(4)-(5))

As mentioned, this case is about the routine administration of a known therapeutically active agent provided in a known formulation. At the time of the earliest effective filing date of the '236 patent, the IgG mAb natalizumab and its indications, including treatment of CD and MS, were known. And the three excipients recited in the Challenged Claims – phosphate buffer, sodium chloride and polysorbate 80 – were also known.

Specifically, prior art by van Oosten (Ex. 1014) teaches an aqueous formulation containing these very same excipients with an IgG mAb that, like natalizumab, was known to treat CD. Furthermore, Gordon teaches a natalizumab formulation containing a buffer and polysorbate 80, which later undergoes dilution with saline thus adding sodium chloride. (Ex. 1017 at 7.) The buffer used in that formulation served the same buffering function as phosphate buffer. For these reasons, and as discussed in detail below, the scope and content of the prior art points directly to the claimed subject matter of the '236 patent.

A. Scope and Content of the Prior Art

The Declarations of Scott Bennett (Ex. 1005) and Rachel J. Watters (Ex. 1008) establish the prior art status of all printed publications identified in this section of the Petition. Unless otherwise indicated, all such publications were publicly available prior to February 10, 2002 – one year before the earliest possible

effective filing date of the ‘236 patent – qualifying them as prior art under 35 U.S.C. 102(b). Furthermore, with the exception of Gordon (Ex. 1017), Bendig (Ex.1018) and Sheremata (Ex. 1060), none of the prior art relied upon here appears in the references cited section of the ’236 patent.

1. The IgG mAb Natalizumab

Natalizumab was known at least as early as November 24, 1998. (Ex. 1018 at Figs. 6 and 7; Ex. 1061 at ¶ 0051 (stating Natalizumab was described in Ex. 1018); see also Ex. 1002 at ¶ 65.) The prior art classified natalizumab as a humanized IgG mAb. (Ex. 1017 at 6.) As Dr. Schöneich explains, a person of ordinary skill would have known that all IgG mAbs, including natalizumab, share key structural characteristics that impact their general compatibility with the excipients used in aqueous formulations. (Ex. 1002 at ¶ 33 and discussed starting at p. 40.) The prior art also confirms the efficacy (at least 3 mg/kg) and safety (up to 6 mg/kg) of natalizumab for the treatment of MS and CD. (Ex. 1019 at 3-4.)

2. Prior Art IgG Formulations

The prior art is replete with IgG and IgG mAb formulations having the same excipients as those in the Challenged Claims at the same or similar concentrations.

a. Prior Art IgG Formulations Comprising Phosphate Buffer and Sodium Chloride

Commercial protein manufacturers routinely stored and shipped IgG antibodies in formulations containing phosphate buffered saline, often abbreviated

as PBS. (Ex. 1020 at 14 (USBio I19903-31 using "PBS"), 16 (Sigma F7381 using "phosphate buffered saline"); publicly available as of April 2002 (Ex. 1005 at 54).) A person of ordinary skill recognizes that PBS contains phosphate buffer and saline, which is an aqueous solution of sodium chloride. (Ex. 1002 at ¶ 36.) For example, White discloses 20 mg/ml IgG formulations that use 10 mM phosphate buffered saline. (Ex. 1020 at 16 (e.g., Sigma F 7381).) These excipients help ensure the long-range stability of the IgG active drug substances. (Ex. 1002 at ¶ 35.) For example, Cummins reports 12 month stability (0° to 8° C storage) of a 5% (50 mg/ml) IgG solution in normal saline, disclosing "no changes detected in pH, [or] percentage of monomeric IgG." (Ex. 1021 at 6, 8; Ex. 1002 at ¶ 79.)

b. Prior Art IgG mAb Formulations Containing Phosphate Buffer, Sodium Chloride and Polysorbate 80

Because IgG mAb actives may aggregate, and thereby compromise stability, it was also well-known in the art to include a surfactant with such formulations. (Ex. 1002 at ¶¶ 58-59 (discussing Ex. 1029 at 15-20).) As Dr. Schöneich explains, typical prior art IgG mAb formulations include a buffer to maintain a specific pH over time, sodium chloride to provide tonicity of the formulation and a surfactant to disperse the IgG mAb and thereby prevent aggregation. (Ex. 1002 at ¶ 40, 48-49, 58-59; Ex. 1029 at 12-13, 15-20; Ex. 1031 at 13-14; Ex. 1032 at 6, 9; Ex. 1033 at 8.)

At least four prior art IgG mAb formulations employ phosphate buffer, sodium chloride and the surfactant polysorbate 80, as recited by the Challenged Claims. These prior art formulations employ these excipients at nearly the same concentrations as the most narrow of the Challenged Claims, claims 21 and 22:

Table 1: Prior Art IgG mAb Formulations[2]

Ingredient	Claims	Orthoclone	Aversano	van Oosten	Zenapax
IgG mAb	20 mg/ml	1 mg/ml	5 mg/ml	10 mg/ml	5 mg/ml
Phosphate Buffer	~ 10 mM	16.4 mM	10 mM	10 mM	67 mM
Sodium Chloride	~ 140 mM	147 mM	150 mM	150 mM	78.7 mM
Polysorbate 80	0.001% to 2% (w/v)	0.02%	0.01%	0.01%	0.02%
pH	6.1	7.0 ±0.5	6.5	7.2	6.9

Orthoclone (Ex. 1022)

Orthoclone, approved by FDA in 1992, is a formulation comprising the IgG mAb muromonab-CD3. (Ex. 1022 at 3; Ex. 1030 at 1.) The formulation contains

[2] Dr. Schöneich provides routine conversions of units of measurement to compare reported values in the prior art to the claims. (Ex. 1002 at ¶¶ 64-79.)

1 mg/ml muromonab-CD3, 0.45 mg/ml monobasic sodium phosphate and 1.8 mg/ml of dibasic sodium phosphate – equivalent to 16.4 mM phosphate buffer (see Ex. 1002 at ¶ 71; see also p. 11, above for construction of phosphate buffer), 147 mM sodium chloride and 0.02% polysorbate 80 in water for injection. (Ex. 1022 at 3.) The formulation has a pH of 7.0 ±0.5 and is supplied in ampules. (Id.) The formulation is stored at 2º C to 8º C. (Id. at 7.) Because Orthoclone was FDA approved, it retained its biological activity, i.e., was stable, at least long enough to be shipped from the manufacturer to the site of use. According to Remington, Orthoclone had a shelf-life of one year. (Ex. 1032 at 8.)

Aversano (Ex. 1023)

Aversano, published in 1995, discloses a formulation comprising the IgG mAb designated CLB54. (Ex. 1023 at 4, 5.) The formulation contains 5 mg/ml CLB54, 10 mM phosphate buffer, 150 mM sodium chloride and 0.01% polysorbate 80 and has a pH of 6.5. (Id. at 5; Ex. 1002 at ¶ 72.)

van Oosten (Ex. 1014)

van Oosten, published in 1996, discloses a formulation containing the IgG mAb infliximab. (Ex. 1014 at 5 ("[e]ach vial contained . . . 10 mg/ml cA2."); Ex. 1015 at 4 (disclosing that cA2 is also known as "infliximab").) Like natalizumab, infliximab was known to treat CD. (Ex. 1014 at 4.) The formulation

contains 10 mg/ml infliximab, 10 mM phosphate buffer, 150 mM sodium chloride and 0.01% polysorbate 80, and has a pH of 7.2. (Id. at 5; Ex. 1002 at ¶ 73.)

Zenapax (Ex. 1024)

Zenapax, approved by FDA in 1997, is a formulation comprising the IgG mAb daclizumab. (Ex. 1024 at 2; Ex. 1030 at 3.) The formulation contains 5 mg/ml daclizumab, 3.6 mg sodium phosphate monobasic monohydrate and 11 mg sodium phosphate dibasic heptahydrate – equivalent of 67 mM of phosphate buffer (see Ex. 1002 at ¶ 74), 78.7 mM sodium chloride and 0.02 % polysorbate 80 and has a pH of 6.9. (Ex. 1024 at 2; Ex. 1002 at ¶ 74.) According to another prior art reference by Bell, the "[s]helf life of Zenapax is 1 year" and "[v]ials should be stored between 36° – 46° F" (equivalent to 2º C to 8º C). (Ex. 1025 at 4.)

3. Prior Art Natalizumab Formulations and Treatment

In August 2001, clinical researchers reported a natalizumab formulation containing a buffer and the surfactant polysorbate 80, which later undergoes dilution with saline to add sodium chloride. (Ex. 1017 at 7.) Gordon reports a clinical trial for the treatment of CD with an aqueous natalizumab formulation comprising 5 mg/ml natalizumab, "50 mmol/L of histidine buffer and 0.02% polysorbate 80, adjusted to pH 6."[3] (Id. at 7.) This formulation then undergoes

[3] As Dr. Schöneich explains, Gordon teaches a formulation containing natalizumab, histidine and polysorbate 80 stored in a vial. (Ex. 1002 at ¶ 68.)

dilution through the addition of 0.9% saline (sodium chloride and water). Post-dilution, Gordon further teaches that "[p]atients received a single 3 mg/kg intravenous infusion of natalizumab." (Id.)

The buffer employed by Gordon was histidine, used to maintain the formulation pH at 6.0. (Id.) According to scientifically authoritative prior art texts, only a few buffers were suitable for the pH disclosed in Gordon, including phosphate, citrate and histidine buffers. (Ex. 1029 at 13.)

Shortly after Gordon published, in October 2001, Subramanian reported that the use of both histidine and citrate buffers in an IgG mAb formulation containing polysorbate 80 results in "accelerated potency loss" of the IgG mAb active drug. (Ex. 1002 at ¶ 76-77; Ex. 1026 at 4.) According to Subramanian, histidine reacts undesirably with polysorbate 80 to form an impurity that degrades the IgG mAb. (Ex. 1026 at 4.) This helps explain Applicants' later alleged discovery, as reported during the prosecution of the related '321 patent, that Gordon was unstable. (Ex. 1002 at ¶ 77.) And given that Subramanian did not criticize sodium phosphate in this way, suggests how one of ordinary skill could fix it. (Id.)

Furthermore, although Gordon teaches dilution of its natalizumab formulation with saline prior to administration, nearly all the prior art aqueous IgG formulations include sodium chloride as part of the commercial formulation. In fact, it was well known that formulating at isotonic conditions was highly desired

to allow for patient comfort. (Ex. 1011 at ¶ 29; Ex. 1032 at 6.) Isotonic formulations are highly desirable because non-isotonic formulations, i.e., those that are hyper or hypotonic, "cause tissue irritation, pain on injection, and electrolyte shifts." (Ex. 1032 at 6.) "An isotonic solution, therefore, is the choice as a vehicle for many drugs that have to be administered parenterally." (Id. at 8.) To make that choice, skilled formulators could simply follow the teachings of Andya, which states that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm" and that "[i]sotonicity can be measured using a[n] . . . ice-freezing type osmometer." (Ex. 1010 at ¶ 0051.) The '236 patent appears to have copied this passage directly from Andya. (Ex. 1001 at 6:33-38.)

4. Administration of Prior Art Formulations

The prior art discloses administration of the prior art IgG mAb formulations via intravenous ("i.v.") injection. (Ex. 1022; Ex. 1014; Ex. 1024; Ex. 1017; Ex. 1019; Ex. 1060). Further, natalizumab can be administered in a series. Sorbera reports efficacy treating MS with "2 i.v. infusions (3 mg/kg) of natalizumab given 4 weeks apart." (Ex. 1019 at 3). Gordon reports that treating CD with a single 3 mg/kg dose might be suboptimal and suggests "that larger and/or more frequent doses might result in improved efficacy." (Ex. 1017 at 10.)

B. Ground 1 – The Challenged Claims are Obvious under 35 U.S.C. § 103(a) over van Oosten or Zenapax in view of Sorbera

Each of the primary references in Ground 1 – van Oosten (Ex. 1014) and

Zenapax (Ex. 1024) – discloses an IgG mAb formulation comprising the identical excipients recited by the claims – phosphate buffer, sodium chloride and polysorbate 80. Although van Oosten and Zenapax respectively contain infliximab and daclizumab as opposed to natalizumab, a single modification through the secondary reference – Sorbera (Ex. 1019) – cures this deficiency. Sorbera teaches that natalizumab, like the infliximab of van Oosten, is an IgG mAb that is useful for treating CD. In other words, these actives qualify as simple substitutes under the case law. In addition, modifying Zenapax with Sorbera combines known elements (the Zenapax excipients and natalizumab) according to known methods of manufacture. (Ex. 1002 at ¶ 92.) Each combination of prior art references thus discloses all of the structural limitations recited by the Challenged Claims, as exemplified by claim 1:

Claim 1	Prior Art
A method of treatment, comprising	**van Oosten:** "In . . . human immune-mediated diseases . . . , such as Crohn's disease (CD) . . ., intravenous treatment with . . . cA2 resulted in significant improvement lasting for 2 to 4 months after a single infusion." (Ex. 1014 at 4.) **Zenapax:** "ZENAPAX is used as part of an immunosuppressive regimen." (Ex. 1024 at 3.) **Sorbera:** "[N]atalizumab . . . has displayed efficacy against both multiple sclerosis and IBD" "of which Crohn's disease and ulcerative colitis are the most common forms." (Ex. 1019 at 2-3.)
administering to a patient with multiple sclerosis a therapeutic amount of a stable, aqueous	**van Oosten:** "In . . . Crohn's disease (CD) . . . , intravenous treatment with the humanized monoclonal anti-TNF antibody cA2 resulted in significant improvement . . . ." (Ex. 1014 at 4.) "[W]e treated two

pharmaceutical formulation comprising	rapidly progressive MS patients with intravenous infusions of . . . cA2." (Id. at Abstract.) "Each vial contained 20 ml of a solution. . . ." (Id. at 5.) **Zenapax:** "ZENAPAX® (Daclizumab)" "is supplied as a clear, sterile, colorless concentrate for further dilution and intravenous administration." (Ex. 1024 at 2.) **Sorbera:** "[N]atalizumab . . . has displayed efficacy against both multiple sclerosis and IBD" "of which Crohn's disease and ulcerative colitis are the most common forms." (Ex. 1019 at 2-3.) "2 i. v. infusions (3 mg/kg) of natalizumab [was] given 4 weeks apart." (Id. at 3.)
from about 20 mg/ml to about 150 mg/ml of natalizumab,	**van Oosten:** "Each vial contained . . . 10.0 mg/ml cA2. . . ." (Ex. 1014 at 5.) **Zenapax:** "Each milliliter of ZENAPAX contains 5 mg of Daclizumab. . . ." (Ex. 1024 at 2.) **Sorbera:** "2 i. v. infusions (3 mg/kg) of natalizumab given 4 weeks apart." (Ex. 1019 at 3.)
about 10 mM phosphate buffer,	**van Oosten:** "Each vial contained . . . 0.01 M sodium phosphate." (Ex. 1014 at 5.) **Zenapax:** "Each milliliter of ZENAPAX contains . . . 3.6 mg sodium phosphate monobasic monohydrate, 11 mg sodium phosphate dibasic heptabydrate. . . ." (Ex. 1024 at 2.)
about 140 mM sodium chloride, and	**van Oosten:** "Each vial contained . . . 0.15 M sodium chloride. . . ." (Ex. 1014 at 5.) **Zenapax:** "Each milliliter of ZENAPAX contains . . . 4.6 mg sodium chloride. . . ." (Ex. 1024 at 2.)
polysorbate 80 present in an amount of about 0.001% to 2% (w/v),	**van Oosten:** "Each vial contained . . . 0.01% polysorbate 80. . . ." (Ex. 1014 at 5.) **Zenapax:** "Each milliliter of ZENAPAX contains . . . 0.2 mg polysorbate 80. . . ." (Ex. 1024 at 2.)
wherein the multiple sclerosis is treated by administration of the stable, aqueous pharmaceutical formulation.	**van Oosten:** "In . . . human immune-mediated diseases . . . , such as Crohn's disease (CD) . . . , intravenous treatment with . . . cA2 resulted in significant improvement lasting for 2 to 4 months after a single infusion." (Ex. 1014 at 4.) **Sorbera:** "[N]atalizumab . . . has displayed efficacy

	against both multiple sclerosis and IBD" "of which Crohn's disease and ulcerative colitis are the most common forms." (Ex. 1019 at 2-3.)

The only other limitations are result effective variables subject to routine optimization. As the C.C.P.A. long ago explained, "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." In re Aller, 220 F.2d 454, 456 (C.C.P.A. 1955). See also In re Applied Materials, Inc., 692 F.3d 1289, 1295-96 (Fed. Cir. 2012). That is, optimization of result effective variables is "within the grasp of one of ordinary skill in the art." Id. at 1295. There is no such evidence of criticality or unexpected results here as discussed further below.

1. Challenged Claims 1 and 9

The limitations of independent claims 1 and 9 are identical as recited in the headings of sub-paragraphs (a) through (g) below, except that claim 1 is directed to the treatment of MS while claim 9 is directed to the treatment of CD:

a. "A method of treatment"

The preamble is not limiting because the body of claims 1 and 9 fully sets forth all of the limitations, and the preamble merely states the intended purpose of those limitations. See Pitney Bowes, Inc. v. Hewlett-Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999). To the extent the preamble is a limitation, van Oosten

(Ex. 1014 at 4), Zenapax (Ex. 1024 at 2) and Sorbera (Ex. 1019 at 3) each disclose a method of treatment.

b. "administering to a patient with [MS / CD] a therapeutic amount <u>of a stable, aqueous pharmaceutical formulation</u>"

Each of van Oosten (Ex. 1014 at 4), Zenapax (Ex. 1024 at 2) and Sorbera (Ex. 1019 at 3) disclose intravenous administration of their aqueous pharmaceutical formulation. Furthermore, the van Oosten and Sorbera formulations would be administered to a patient with either MS or CD because van Oosten reports favorable efficacy on CD (Ex. 1014 at 4) and Sorbera discloses that the natalizumab was efficacious when administered to patients with both MS and CD, a form of IBD. (Ex. 1019 at 3.) van Oosten and Zenapax disclose formulations that are necessarily aqueous. van Oosten, for example, teaches that its formulation is a "solution," which necessarily requires a solvent. (Ex. 1002 at ¶ 97; Ex. 1014 at 5.) Similarly, Zenapax teaches a colorless concentrate in a volume of 5 milliliters. (Ex. 1024 at 2.) Absent identification of a specific solvent in both, a person of ordinary skill in the protein formulation art would have recognized that the solvent in question is necessarily water and the formulation is thus aqueous. (Ex. 1002 at ¶ 97.) Water is of course safe for pharmaceutical administration and routinely used in parenteral formulations. (<u>Id.</u>) Indeed, other

IgG mAb formulations, e.g., Orthoclone, teach ampules containing buffered solutions "in water for injection." (Ex. 1022 at 3.)

With respect to the "stable" limitation, van Oosten reports favorable efficacy on CD, which demonstrates that its formulation necessarily retained its biological activity after storage and prior to administration. (Ex. 1002 at ¶ 98.) Zenapax likewise qualifies as stable, with Bell expressly teaching that Zenapax has a shelf life of 1 year. (Ex. 1025 at 4.)

It is also a basic and fundamental goal of formulation science to prepare stable formulations that retain their biological activity under storage. (Ex. 1002 at ¶ 35; Ex. 1031 at 7 ("This book is written to assist pharmaceutical scientists in the development of stable protein formulations.").) For the same reasons the claimed formulations achieve that goal, so do the modified natalizumab formulations in Petitioner's proposed combinations. Stable formulations containing various IgG mAbs and the claimed excipients at similar concentrations were well-known in the prior art and approved by FDA on multiple occasions, e.g., Zenapax and Orthoclone. (Ex. 1024 at 2; Ex. 1022 at 3.) In addition, Cummins reports the extended stability of a 50 mg/ml IgG formulation containing just phosphate buffer and sodium chloride for a full twelve months. (See Ex. 1021 at 6, 8.) As Dr. Schöneich thus explains, the combination of natalizumab and the claimed excipients at optimized concentrations would necessarily or inherently create a

stable formulation, especially under the broad definition of "stable" provided by the '236 patent. (Ex. 1002 at ¶¶ 98-99, 159.) Indeed, an otherwise obvious formulation claim cannot become non-obvious simply by adding an inherent property to its limitations. See Santarus, Inc. v. Par Pharm., Inc., 694 F.3d 1344, 1354 (Fed. Cir. 2012).

c. "from about 20 mg/ml to about 150 mg/ml of natalizumab"

There are various reasons why one of ordinary skill would be motivated to replace the IgG mAbs in either van Oosten (infliximab) or Zenapax (daclizumab) with natalizumab. First, infliximab and natalizumab are known substitutes that treat the same disease. Second, substitution of daclizumab for natalizumab combines known elements according to known methods.

van Oosten teaches that administration of its infliximab formulation results in significant improvement in patients with CD. (Ex. 1014 at 4.) Because Sorbera teaches that natalizumab effectively treats CD, the prior art motivates one of ordinary skill to substitute it for infliximab. See In re Huellmantel, 324 F.2d 998, 1000 (C.C.P.A. 1963). Infliximab and natalizumab qualify as simple substitutes because their functions, i.e., treatment of CD, were well-known in the art. And this simple substitution would have yielded the predictable results of achieving that function. (Ex. 1002 at ¶ 102.) Indeed, the scope and content of the prior art demonstrates that the excipients employed in the van Oosten formulation were

compatible and worked well with various IgG mAb actives. (Id. at ¶ 103.) For example, each of van Oosten (Ex. 1014 at 5), Zenapax (Ex. 1024 at 2), Aversano (Ex. 1023 at 5) and Orthoclone (Ex. 1022 at 3) relied upon this same combination of excipients to create stable, pharmaceutically acceptable formulations. (Ex. 1002 at ¶ 103.) The result of pairing these same excipients with natalizumab is no different.[4] (Id. at ¶ 104.) In fact, the '236 patent teaches that all proteins are "interchangeable" with these excipients. (Ex. 1001 at 2:64-67.)

Alternatively, adding the natalizumab of Sorbera to the Zenapax excipients (which are identical to those of the Challenged Claims) merely combines known elements according to known methods. More than ten years before the earliest effective filing date, formulators prepared commercial formulations of Orthoclone using these very same excipients. (Ex. 1002 at ¶ 71; Ex. 1030 at 1.) And, the Zenapax formulation was approved in 1997, more than 5 years before the earliest

[4] The fact that FDA ultimately approved a lyophilized powder as opposed to the aqueous infliximab formulation of van Oosten does not teach away. Galderma Labs., L.P. v. Tolmar, Inc., 737 F.3d 731, 738 (Fed. Cir. 2013) ("A reference does not teach away . . . [if it] does not criticize, discredit, or otherwise discourage investigation into the invention claimed"). Further, the NDA holder for infliximab publicly stated that "there were no significant differences between the liquid and the two lyophilized formulations of cA2." (Ex. 1016 at 12.)

effective filing date. (Ex. 1030 at 3.) Thus, to achieve the claimed natalizumab formulation, one of ordinary skill would have needed only to follow well-known methods for creating the final formulation, i.e., combining the IgG mAb in question with optimized excipient solutions. (Ex. 1002 at ¶ 105.)

One of ordinary skill would also have recognized that each ingredient in the Petitioner's modified formulations would retain its original function. (Id. at ¶ 106.) Phosphate buffer would buffer the formulation to a certain pH, sodium chloride would provide the desired isotonicity and polysorbate 80 would prevent agglomeration of the IgG mAb. (Id. at ¶¶ 106-07.) And, because the modified formulations would be stable, natalizumab would retain its function to treat CD and MS. (Ex. 1011 at ¶ 44; Ex. 1057 at ¶ 44.)

Finally, for the same reasons substitution of natalizumab in place of infliximab yields predictable results, so is the substitution of natalizumab for daclizumab. (Ex. 1002 at ¶ 108.) After all, as stated in the '236 patent, antibodies in general are "interchangeable" in the claimed formulation. (Ex. 1001 at 2:64-67.)

With respect to the "from about 20 mg/ml to about 150 mg/ml" limitation – that is nothing more than routine optimization of a result effective variable. The "normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages." In re Peterson, 315 F.3d

1325, 1330 (Fed. Cir. 2003). While van Oosten and Zenapax include IgG mAb concentrations of 10 mg/ml and 5 mg/ml, respectively (Ex. 1014 at 5; Ex. 1024 at 2), IgG formulations containing between 5 and 50 mg/ml were known in the art. (Ex. 1017 at 7; Ex. 1020 at 16 (e.g., Sigma F 7381 F 9636 or F 7256); Ex. 1021 at 6). One of ordinary skill would have simply calculated the appropriate concentration of natalizumab for storage in vials over a range of volumes. (Ex. 1002 at ¶ 109; Ex. 1011 at ¶ 27.)

For example, Sorbera discloses that 3 mg of natalizumab per kg of body weight (3 mg/kg) is therapeutically effective. (Ex. 1019 at 3.) Because the average adult male weighs 78.5 ±11.8 kg, 235.5 mg (3 mg/kg * 78.5 kg) of natalizumab would have been considered necessary for a single treatment. (Ex. 1002 at ¶ 110 (citing Ex. 1037 at 6, Table 1).) Given that vials for aqueous pharmaceuticals come in a range of different volumes, including, for example, 5, 10, 20, 25 and 50 ml (see Ex. 1024 at 2; Ex. 1027 at 3; Ex. 1028 at 6), a person of ordinary skill in the art would have routinely tested natalizumab over a range of concentrations that encompasses the concentrations recited in the Challenged Claims. (Ex. 1002 at ¶ 111.) No single concentration is critical because a single vial or multiple vials in combination are added to standard intravenous infusion bags for administration of 3 mg/kg. (Ex. 1011 at ¶¶ 26-27.)

d. <u>"about 10 mM phosphate buffer"</u>

van Oosten discloses that its aqueous formulation comprises 10 mM phosphate buffer. (Ex. 1014 at 5; Ex. 1002 at ¶ 112.) van Oosten thus expressly teaches this limitation.

Zenapax discloses an aqueous pharmaceutical formulation comprising 67 mM phosphate buffer. This concentration is unnecessarily high (as it provides more than 1000 times the necessary buffering capacity) and is subject to routine optimization. (Ex. 1002 at ¶¶ 113-15.)

As an initial matter, buffer concentration is a result effective variable because it was known in the art to maintain the pH of pharmaceutical formulations over time. (Ex. 1002 at ¶ 40 (discussing Ex. 1029 at 12-13).) This is in line with existing IgG mAb formulations, where pH varies between 6.0 (Gordon, Ex. 1017) and 7.2 (Orthoclone, Ex. 1022). One of ordinary skill seeking to maintain pH in this range would thus explore the minimum buffer capacity necessary to achieve this pH range through basic mathematical calculations. (Ex. 1002 at ¶¶ 43-46, 114.) Buffer capacity (β) is routinely calculated using the following well-known equation: $\beta = \Delta A / \Delta pH$, where ΔA is the change in acid brought about by degradation and ΔpH is the change in pH that can be tolerated. (Ex. 1002 at ¶ 43 (citing Ex. 1033 at 13).) Applying this equation to Zenapax and taking into

account the level of degradation of the active drug expected over time,[5] Dr. Schöneich calculates that only a minimum of about 0.065 mM phosphate buffer would have been required to maintain a pH of 6.9 ±0.1. (Id. at ¶ 113.)

Protein formulators, however, routinely seek to maintain pH by including excess buffer concentrations. (Id. at ¶ 44.) van Oosten, for example, requires a minimum buffer concentration of about 0.116 mM phosphate buffer, but sets its phosphate buffer concentration at 10 mM – an excess of about 86 times. (Id. at ¶ 45 (citing Ex. 1014 at 5).) Further, a commercially available research formulation of an IgG antibody that contains 20 mg/ml protein, in 10 mM phosphate buffered saline at a pH of 7.4 would have required only 0.24 mM phosphate buffer, but contains an excess of about 40 times. (Ex. 1002 at ¶ 46 (citing Ex. 1020 at 16 (Sigma F 7381 F 9636 or F 7256, for example)).)

With respect to 20 mg/ml of natalizumab at pH 6.0 (as disclosed in Ex. 1017 at 7) or pH 6.1 (Petitioner's optimized formulation), one of ordinary skill would calculate the minimum buffer concentration of phosphate buffer to equal 1.036 mM and 0.85 mM, respectively, and would have routinely tested a range of excess buffer concentrations to ensure proper maintenance of the desired pH. (Ex. 1002 at ¶ 114.) One of ordinary skill would thus explore a buffer

[5] If not stated otherwise, shelf life allows for no more than 10% degradation. (Ex. 1002 at ¶ 44 (discussing Ex. 1034 at 11).)

concentration between 10 and 100 mM phosphate buffer to achieve the claimed concentration. (Id.)

Finally, a buffer concentration of about 10 mM is in no way critical. (Id. at ¶ 115.) According to Dr. Schöneich, once a minimum amount of phosphate buffer has been ascertained, amounts in excess of the minimum, even up to 10 to 100 times the required minimum buffering capacity, will not negatively impact the formulation. (Id. at ¶¶ 45-47 (discussing Ex. 1014 at 5; Ex. 1020 at 16; Ex. 1033 at 14).) Indeed, the '236 patent specification discloses a wide range of buffer acceptable concentrations:

> Additional liquid formulations of antibody at high concentration, from 20-200 mg/mL may consist of phosphate or other suitable buffer (such as histidine, citrate, acetate or succinate) in the concentration range of 2 to 50 mM, to provide buffering in the pH range of 3.0 to 7.0.

(Ex. 1001 at 16:54-58.) Dr. Schöneich confirms that a buffer concentration of "about 10 mM" does not represent the only concentration that will maintain a pH of about 6.0 or 6.1 for a 20 mg/ml to 150 mg/ml antibody formulation. (Ex. 1002 at ¶ 115.)

e. "about 140 mM sodium chloride"

van Oosten and Zenapax respectively teach concentrations of sodium chloride of 150 mM and 78.7 mM. (Ex. 1014 at 5; Ex. 1024 at 2.) One of ordinary skill would, however, would routinely optimize the concentration of sodium

chloride to achieve isotonicity because the prior art motivates a person of ordinary skill to formulate to isotonic conditions. (Ex. 1011 at ¶ 29; Ex. 1032 at 6.)

It was known in the art, per the teachings of Andya, that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm" and that "[i]sotonicity can be measured using a[n] . . . ice-freezing type osmometer." (Ex. 1010 at ¶ 0051.) For example, Orthoclone, van Oosten and Aversano teach isotonic formulations. (Ex. 1002 at ¶ 57.) As Dr. Schöneich explains, 250 to 350 mOsm is present when a solution has a freezing point between -0.46° C and -0.64° C. (Ex. 1002 at ¶ 52 (citing the cryoscopic method, Ex. 1033 at 23-25).) To determine the appropriate concentration of sodium chloride, one of ordinary skill would simply calculate the concentration of sodium chloride necessary to depress the freezing point of the solution to within that range. (Ex. 1002 at ¶ 54.) Using this method, Dr. Schöneich calculated that a natalizumab formulation comprising a 10 mM phosphate buffer concentration requires a sodium chloride concentration between 127 mM and 180 mM, which encompasses the claimed concentration. (Id. at ¶ 56.) Furthermore, the exact concentration of sodium chloride cannot be critical because isotonicity permits a range of sodium chloride concentrations, confirmed by Dr. Schöneich's calculations and by Challenged Claim 1 itself, which requires "about 140 mM sodium chloride."

f. "polysorbate 80 present in an amount of about 0.001% to 2% (w/v)"

Both van Oosten and Zenapax expressly satisfy the claim limitation reciting "in an amount of about 0.001% to 2%." (Ex. 1014 at 5 (reciting 0.1 mg/ml (0.01%)); Ex. 1024 at 2 (reciting 0.2 mg/ml (0.02%)).) "It is . . . an elementary principle of patent law that when, as by a recitation of ranges or otherwise, a claim covers several compositions, the claim is 'anticipated' if *one* of them is in the prior art." Aventis Pharma S.A. v. Hospira, Inc., 675 F.3d 1324, 1333 (Fed. Cir. 2012) (citing Titanium Metals Corp. v. Banner, 778 F.2d 775, 782 (Fed. Cir. 1985).)

g. "wherein the [MS / CD] is treated by administration of the stable, aqueous pharmaceutical formulation"

van Oosten reports favorable efficacy on CD (Ex. 1014 at 4) and Sorbera discloses that the natalizumab was efficacious when administered to patients with both MS and CD (Ex. 1019 at 3), satisfying this claim limitation for claims 1 and 9. (Ex. 1011 at ¶¶ 37-50; Ex. 1057 at ¶¶ 37-51.)

2. Challenged Claims 2 and 10: "intravenous administration"

Claims 2 and 10 require the administration to be "by intravenous administration." Each of van Oosten (Ex. 1014 at 4), Zenapax (Ex. 1024 at 2) and Sorbera (Ex. 1019 at 3) disclose intravenous administration of their aqueous pharmaceutical formulation. (Ex. 1011 at ¶ 46; Ex. 1057 at ¶ 46.)

3. Challenged Claims 3 and 11: "series of treatments"

Claims 3 and 11 require the administration to be "over a series of treatments." As explained in Section VI.B, the broadest reasonable interpretation of "series of treatments" would be "at least two treatments." (Ex. 1011 at ¶ 47; Ex. 1057 at ¶ 47.) Zenapax recommends administration "every 14 days for a total of five doses." (Ex. 1024 at 2.) And van Oosten states that "[b]oth patients received two infusions." (Ex. 1014 at 5.) Thus both Zenapax and van Oosten teach a series of treatments. Sorbera and Gordon confirm administration of natalizumab over a series of treatments. Sorbera teaches that administration of "2 i.v. infusions (3 mg/kg) of natalizumab given 4 weeks apart" effectively treats MS. (Ex. 1019 at 3.) Gordon characterizes the effects of a single dose of natalizumab for CD as short lived, and teaches that "more frequent doses might result in improved efficacy." (Ex. 1017 at 10.) Because Sorbera's series of treatments to patients with MS demonstrated efficacy, and a single treatment in Gordon was reported as "short lived," one of ordinary skill would pursue administration of natalizumab in series. (Ex. 1011 at ¶ 47; Ex. 1057 at ¶ 48.)

4. Challenged Claims 4 and 12: "natalizumab is present in an amount of 20 mg/mL"

Claims 4 and 12 further require "natalizumab . . . in an amount of about 20 mg/mL." As discussed starting at page 27, the specific claimed concentration of natalizumab is nothing more than routine optimization of a result effective variable, which would cover 20 mg/ml.

5. Challenged Claims 5 and 13: "polysorbate 80 is present in an amount of about 0.02% (w/v)"

Claims 5 and 13 require polysorbate 80 in "an amount of about 0.02%." Zenapax expressly satisfies the claim limitation reciting 0.02% polysorbate 80. (Ex. 1024 at 2.) While van Oosten's formulation contains 0.1 mg/ml (i.e., 0.01%) polysorbate 80, this concentration is also a result effective variable subject to routine optimization. (Ex. 1002 at ¶¶ 58-60; Ex. 1029 at 15-20.)

Those of ordinary skill knew how to increase or decrease the amount of polysorbate 80 so as to strike a balance between preventing aggregation of the antibody active and avoiding instability. (Ex. 1002 at ¶ 60.) For example, Gordon discloses 0.02% of polysorbate 80 in a natalizumab formulation. (Ex. 1017 at 7.) In addition, methods for determining the optimum concentration of polysorbate 80 involved routine storage stability tests that had been standard in the art for decades. (Ex. 1002 at ¶ 60 (discussing stability tests in Ex. 1031 at 9-10).)

Further, no single concentration of polysorbate 80 within the claimed range is critical. (Ex. 1002 at ¶ 122.) The '236 patent discloses that polysorbate 80 may be present in amounts between 0.001% to 2.0%. (Ex. 1001 at 1:61-63.) Similarly, because claims 5 and 13 recite a concentration of polysorbate 80 that is "about 0.02%," a precise concentration of polysorbate 80 is not critical. As Dr. Schöneich explains, more than one polysorbate concentration is suitable to prevent IgG mAb aggregation. (Ex. 1002 at ¶¶ 60, 122.)

6. Challenged Claims 6-8 and 14-16: "pH is about 6.0 ±0.5"

Claims 6 and 14 require a "pH of about 3.0 to about 7.0." Claims 7 and 15 require that the "pH is about 5.5 to about 6.5." And claims 8 and 16 require that the "pH is about 6.0 ±0.5." van Oosten and Zenapax both teach maintaining their formulations at a set pH. In the case of van Oosten, that pH is 7.2, satisfying claims 6 and 14. (Ex. 1014 at 5.) And in the case of Zenapax, that pH is 6.9, also satisfying claims 6 and 14. (Ex. 1024 at 2.)

Regardless, optimizing the pH of a formulation containing natalizumab would have been a matter of routine optimization accomplished through stability and solubility studies known in the art for decades. (Ex. 1002 at ¶ 136.) Formulation pH has long been known to impact the desired solubility of the therapeutically active antibody. (Ex. 1002 at ¶ 38 (discussing Ex. 1031 at 13-14).) Those of ordinary skill routinely tested protein formulations, including antibody formulations, within a pH range of 5 to 7. (Ex. 1002 at ¶ 38 (citing Ex. 1031 at 13-14).) Prior art formulations of other IgG mAbs confirm widespread usage and knowledge of this preferred pH range, spanning 6.0 to 7.2. (See, e.g., Ex. 1017 at 7; Ex. 1024 at 2; Ex. 1014 at 5; Ex. 1022 at 3; Ex. 1023 at 5.)

7. Challenged Claims 21 and 22

Claims 21 and 22 collect the various limitations from several dependent claims and combine them into single independent claims for methods of treatment

for MS and CD, respectively. Nothing suggests that the consolidation of these limitations resulted in a nonobvious combination.

For example, claims 21 and 22 require "intravenously administering to a patient" the claimed formulation, but as discussed starting on page 33 above, each of van Oosten (Ex. 1014 at 4), Zenapax (Ex. 1024 at 2) and Sorbera (Ex. 1019 at 3) disclose intravenous administration of their aqueous pharmaceutical formulation. Claims 21 and 22 require "20 mg/ml natalizumab," but as discussed on page 27 above, the concentration of natalizumab is nothing more than routine optimization of a result effective variable. Claims 21 and 22 require "8.18 mg/mL of sodium chloride," but again, as discussed on page 31, van Oosten and Zenapax respectively teach concentrations of sodium chloride of 8.76 mg/ml (i.e., 150 mM) and 4.6 mg/ml (i.e., 78.7 mM), and sodium chloride concentration is nothing more than routine optimization of a result effective variable. Again, claims 21 and 22 require "0.2 mg/mL of polysorbate 80," but as discussed on page 35, Zenapax discloses 0.2 mg/ml polysorbate 80 and polysorbate 80 concentration is nothing more than routine optimization of a result effective variable. (See p. 35, above.)

As to pH, claims 21 and 22 require "the formulation has a pH of 6.1." van Oosten and Zenapax both teach maintaining their formulations at a set pH. In the case of van Oosten, that pH is 7.2. (Ex. 1014 at 5.) And in the case of Zenapax, that pH is 6.9. (Ex. 1024 at 2.) Optimizing the pH of a formulation

containing natalizumab, as discussed starting at page 36 above, would have been a matter of routine optimization accomplished through solubility studies known in the art for decades. (Ex. 1002 at ¶ 39.) In fact, Gordon teaches that its natalizumab formulation has a pH of 6.0. (Ex. 1017 at 7.) And a specific pH of 6.1 is in no way critical. (Ex. 1002 at ¶¶ 136.) Orthoclone teaches that its pH may vary by as much as "±0.5." (Ex. 1022 at 3.) Likewise, all experimental examples in the '236 patent list a pH of "6.0 ±0.5." (Ex. 1001 at 15:30-17:11.) Thus, a person of ordinary skill would have expected a range of pH values, including 6.1, to help maintain the stability of the formulation. (Ex. 1002 at ¶¶ 136.)

8. Reasonable Expectation of Success

A person of ordinary skill in the art would have had at least a reasonable expectation of producing a stable formulation by substituting natalizumab for van Oosten's infliximab and Zenapax's daclizumab. (Ex. 1002 at ¶ 144.) Likewise, one of ordinary skill would have had at least a reasonable expectation of successfully implementing that natalizumab formulation as a method of treatment for MS and CD. (Ex. 1011 at ¶ 44; Ex. 1057 at ¶ 44.) As the Federal Circuit has repeatedly explained, absolute predictability is not required: "[o]bviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." Pfizer, Inc. v. Apotex, Inc., 480 F.3d 1348, 1364 (Fed. Cir. 2007). In this case, the prior art demonstrates the

stability of multiple IgG mAb formulations containing the excipients recited by the Challenged Claims of the ‘236 patent. Furthermore, key overlapping structural characteristics shared by IgG mAbs means they behave comparably in formulations containing identical excipients. And the excipients of the optimized natalizumab formulation would not have impacted the ability of the active to treat MS and CD. (Ex. 1011 at ¶ 44; Ex. 1057 at ¶ 44.)

As discussed above in Sections VII.B.1-7, one of ordinary skill would have reasonably expected that the claimed natalizumab formulation could have been made through routine experimentation. Each and every excipient recited by the claims –phosphate buffer, sodium chloride and polysorbate 80 – was not only individually known but had been repeatedly and successfully used together in prior art IgG mAb formulations to create stable formulations years before the ‘236 patent. (Ex. 1002 at ¶ 145.) Furthermore, given the extensive literature discussing how to optimize concentrations for such excipients, one of ordinary skill could have readily prepared the claimed formulation through routine testing. (Ex. 1002 at ¶¶ 38-63; Ex. 1031 at 9, 10.)

Similarly, one of ordinary skill would have reasonably expected such an optimized formulation to achieve its intended purpose of remaining “stable” under storage, especially under the ‘236 patent’s broad definition of this term. (Ex. 1002 at ¶ 145.) Stable formulations containing various IgG mAbs and the claimed

excipients were both well-known in the prior art and approved by FDA on multiple occasions, e.g., Orthoclone and Zenapax. (Ex. 1022 at 3; Ex. 1024 at 2.) Cummins reports 12 month stability (0° to 8°C storage) of a 50 mg/ml IgG solution in normal saline alone. (Ex. 1021 at 6, 8.) And White discloses several commercially available formulations ready for shipment around the country, each comprising 20 mg/ml concentrations of IgG in 5 mM or 10 mM PBS. (Ex. 1020 at 14 (USBio I1903-31) and 16 (Sigma F 7381, F 9636 and F 7256).)

According to Dr. Schöneich, the existence of prior art formulations employing such high concentrations of IgG actives leads a person of ordinary skill to expect that a 20 mg/ml natalizumab formulation comprising these same excipients would also retain biological activity under storage. (Ex. 1002 at ¶ 145.) One of ordinary skill would, therefore, have reasonably expected the combination of natalizumab and the claimed excipients at optimized concentrations to be a stable final formulation.

Furthermore, IgG mAbs represent a specific population of proteins sharing key structural characteristics germane to formulation development. These shared characteristics would have provided a person of ordinary skill in the art with a reasonable expectation that a formulation useful for one IgG mAb would be useful for another. (Ex. 1002 at ¶ 145.)

Among those characteristics are the primary amino sequence and secondary, tertiary and quaternary structures of the antibodies. (Ex. 1002 at ¶ 33 (discussing Ex. 1035 at 8-23 and Ex. 1036 at 11-21).) As Dr. Schöneich explains, IgG mAbs share essentially identical secondary, tertiary and quaternary structures, which structures are important to ensuring comparable behavior in identical formulations. (Ex. 1002 at ¶ 33 (discussing Ex. 1035 at 8-15).) In addition, the primary amino acid sequence of different IgG mAb actives can share 95% identity. (Ex. 1035 at 8-9.) But even when the primary acid amino acid sequence differs by a greater percentage, many of the amino acid changes are conservative and would not affect the behavior of the IgG mAb actives within the same formulation. (Ex. 1002 at ¶ 33.) For example, the four prior art IgG mAbs that were developed for clinical use have differences in subtype (IgG_1 vs. IgG_4) and species (humanized vs. chimeric vs. mouse). (Ex. 1002 at ¶ 145 (referring to Ex. 1024; Ex. 1023; Ex. 1014; Ex. 1022).) Yet, all four formulations (see Table 1, above at p. 15) were successfully formulated with the same three excipients. (Ex. 1002 at ¶ 145.) Thus, a person of skill would have had a reasonable expectation that one IgG mAb would exhibit similar behavior as another in the optimized formulation.

Accordingly, a person of ordinary skill in the art would have had at least a reasonable expectation that natalizumab formulated with a combination of

phosphate buffer, sodium chloride and polysorbate 80 would qualify as stable. (Id. at ¶ 145.)

Applicants' contrary argument during prosecution of the parent '321 patent based on Wang (Ex. 1047) and Cleland (Ex. 1048) not only overstates the teachings of those references, but also ignores express statements in the '236 patent regarding "interchangeable" proteins and antibodies. Wang and Cleland do not stand for the proposition that the knowledge and experience of skilled antibody formulators can be swept aside during development of comparable antibody formulations employing different IgG mAb actives. Although Wang and Cleland generically discuss issues when formulating proteins in general, neither focuses on formulations comprising IgG mAbs in particular. And neither states that antibodies in general, let alone IgG mAbs, are not readily interchangeable in formulations. (Ex. 1002 at ¶ 148.) Perhaps more importantly, there is no indication that Wang or Cleland appreciated that multiple IgG mAb prior art formulations successfully relied upon the exact same excipients at similar concentrations. (Id.) Furthermore, this tribunal should not permit Patent Owner to reinstate its arguments over Wang and Cleland given its prior representation to the Patent Office that all proteins are "interchangeable" in such formulations. (Ex. 1001 at 2:64-67.)

Given the foregoing, the general disclosures in Wang and Cleland cannot rebut the reasonable expectation of success created by Petitioner's combination of prior art. If that were the case, all new protein formulations would qualify as non-obvious and patentable. But that simply is not law:

> A rule of law equating unpredictability to patentability, applied in this case, would mean that any new salt … would be separately patentable, simply because the formation and properties of each salt must be verified through testing. This cannot be the proper standard since the expectation of success need only be reasonable, not absolute.

Pfizer, 480 F.3d at 1364. Like the situation in Pfizer, Patent Owner cannot claim that every new protein formulation is non-obvious simply because testing would be required to determine whether the protein actives are interchangeable.

Lastly, one of ordinary skill would have had at least a reasonable expectation of successfully implementing that natalizumab formulation in a method of treatment for MS and CD. Natalizumab was of course known to effectively treat both disease states. (Ex. 1019 at 3; Ex. 1011 at ¶ 44; Ex. 1057 at ¶ 44.)

C. Ground 2 –The Challenged Claims are Obvious under 35 U.S.C. § 103(a) over Gordon in View of Orthoclone or Aversano

Gordon teaches a natalizumab formulation containing all of the claimed excipients, with the exception of histidine buffer in place of phosphate buffer. Each of the secondary references, Orthoclone or Aversano, teaches IgG mAb formulations with precisely the same excipients recited by the Challenged Claims –

phosphate buffer, sodium chloride and polysorbate 80. A person of ordinary skill would have been motivated to replace the histidine buffer of Gordon with phosphate buffer of the secondary references because Subramanian reported that formulations containing histidine buffer combined with polysorbate 80 impair the biological activity of an IgG mAb. Not only had phosphate buffer worked with numerous prior art IgG mAb formulations, such a modification represents simple substitution of one known element for another. The following chart reflects these combinations, as exemplified by claim 1:

Claim 1	Prior Art
A method of treatment, comprising	**Gordon:** "A single 3-mg/kg natalizumab infusion was well tolerated." (Ex. 1017 at 6.) "[A] small phase I study in 26 healthy male volunteers have shown that a single 3-mg/kg intravenous dose is safe and well tolerated." (Id. at 7.) **Orthoclone:** "ORTHOCLONE OKT3 (muromonab-CD3) Sterile Solution . . . functions as an immunosuppressant. (Ex. 1022 at 3.) **Aversano:** "Nineteen closed-chest baboons (10 control, 9 treated with CLB54) had the left anterior descending coronary artery occluded for 90 min, followed by 4 h of reflow. CLB54 (mean [-+SD] 11 +-2 mg/kg body weight) or saline solution was administered intravenously 20 min before reflow." (Ex. 1023 at Abstract.)
administering to a patient with multiple sclerosis a therapeutic amount of a stable, aqueous pharmaceutical formulation comprising	**Gordon:** "A single 3-mg/kg natalizumab infusion was well tolerated by Crohn's disease patients." (Ex. 1017 at 6.) "A multicenter study of natalizumab in patients with active multiple sclerosis and a small phase I study in 26 healthy male volunteers have shown that a single 3-mg/kg intravenous dose is safe and well tolerated." (Id. at 7.) **Orthoclone:** "ORTHOCLONE OKT3 (muromonab-

	CD3) Sterile Solution is a murine monoclonal antibody to the CD3 antigen of human T cells." (Ex. 1022 at 3.) "The recommended dose of ORTHOCLONE OKT3 for the treatment of acute renal, steroid-resistant cardiac, or steroid resistant hepatic allograft rejection is 5 mg per day in a single (bolus) intravenous injection for 10 to 14 days." (Id. at 6.) "Store in a refrigerator at 2° to 8°C (36° to 46°F)." (Id. at 7.) **Aversano:** "CLB54 . . . was administered intravenously 20 min." (Ex. 1023 at Abstract.)
from about 20 mg/ml to about 150 mg/ml of natalizumab,	**Gordon:** "Natalizumab (5 mg/mL) was formulated in a solution." (Ex. 1017 at 7.) **Orthoclone:** "The antibody is a biochemically purified IgG_{2a} immunoglobin" and that "[e]ach 5 mL ampule of ORTHOCLONE OKT3 Sterile Solution contains 5 mg (1 mg/mL) of muromonab-CD3 in a clear colorless solution." (Ex. 1022 at 3.) **Aversano:** "The chimeric CLB54 monoclonal antibody used in this study is a human/mouse genetic reconstruction of a murine monoclonal IgG4 molecule that binds selectively to the neutrophil CD18 receptor." (Ex. 1023 at 5.) "It was supplied as a sterile, nonpyrogenic solution of 5 mg of monoclonal IgG4 per milliliter of buffer solution." (Id.)
about 10 mM phosphate buffer,	**Gordon:** "[S]olution [had] 50 mmol/L histidine buffer." (Ex. 1017 at 7.) **Orthoclone:** "Each ampule contains a buffered solution (pH 7.0 ±0.5) of monobasic sodium phosphate (2.25 mg), dibasic sodium phosphate (9.0 mg). . . ." (Ex. 1022 at 3.) **Aversano:** "[S]terile, nonpyrogenic solution . . . contain[s] . . . 0.01 mol/liter of sodium phosphate. . . ." (Ex. 1023 at 5.)
about 140 mM sodium chloride, and	**Orthoclone:** "Each 5 mL ampule . . . contains a buffered solution [of] . . . sodium chloride (43 mg) . . . in water." (Ex. 1022 at 3.) **Aversano:** "[S]terile, nonpyrogenic solution . . . contain[s] 0.15 mol/liter of sodium chloride. . . ." (Ex. 1023 at 5.)
polysorbate 80 present in	**Gordon:** "[S]olution . . . was diluted to 100 mL in

an amount of about 0.001% to 2% (w/v),	0.9% saline for administration." (Ex. 1017 at 7.) **Orthoclone:** "Each 5 mL ampule . . . contains . . . polysorbate 80 (1.0 mg). . . ." (Ex. 1022 at 3.) **Aversano:** "[S]terile, nonpyrogenic solution . . . contain[s] . . . 0.01% of polysorbate 80. . . ." (Ex. 1023 at 5.)
wherein the multiple sclerosis is treated by administration of the stable, aqueous pharmaceutical formulation.	**Gordon:** "At week 2, the CDAI decreased significantly from baseline after infusion of natalizumab (mean 45 points) but not placebo (mean 11 points)." (Ex. 1017 at Abstract.) "Seven (39%) natalizumab-treated patients achieved remission at week 2, compared with 1 (8%) treated with placebo." (Id.) "A single 3-mg/kg natalizumab infusion was well tolerated by Crohn's disease patients." (Id.) "A multicenter study of natalizumab in patients with active multiple sclerosis and a small phase I study in 26 healthy male volunteers have shown that a single 3-mg/kg intravenous dose is safe and well tolerated." (Id. at 7.)

1. Challenged Claims 1 and 9

The features of the independent claims 1 and 9 are identical as recited in the headings of sub-paragraphs (a) through (g) below, except that claim 1 is directed to the treatment of MS while claim 9 is directed to the treatment of CD:

a. "A method of treatment"

To the extent the preamble is a limitation, Gordon (Ex. 1017 at 6), Orthoclone (Ex. 1022 at 3) and Aversano (Ex. 1023 at Abstract) each disclose a method of treatment.

b. administering to a patient with [MS / CD] a therapeutic amount of a stable, aqueous pharmaceutical formulation"

Each of Gordon (Ex. 1017 at 7), Orthoclone (Ex. 1022 at 3) and Aversano (Ex. 1023 at Abstract) disclose intravenous administration of their aqueous pharmaceutical formulation. Furthermore, the formulation would be administered to a patient with either MS or CD because Gordon reports favorable efficacy on CD and discloses that natalizumab was administered to patients with active MS as well. (Ex. 1017 at 6, 7.) Sorbera confirms that natalizumab was effective for MS as well as CD. (Ex. 1019 at 3.)

Gordon teaches that its formulation is in "solution," which necessarily requires a solvent. (Ex. 1017 at 7.) As previously mentioned, absent identification of a specific solvent, a person of ordinary skill in the protein formulation art would have recognized that the solvent in question is necessarily water and the formulation is thus aqueous. (Ex. 1002 at ¶ 158.) Water is of course safe for pharmaceutical administration and routinely used in parenteral formulations. (Id. at ¶¶ 97, 158.) Furthermore, Orthoclone and Aversano also disclose this limitation. As mentioned, Orthoclone teaches a buffered solution "in water for injection." (Ex. 1022 at 3.) Like Gordon, Aversano teaches that its formulation is in "solution," which necessarily requires water, for the same reasons as described for Gordon. (Ex. 1023 at 5.)

As to stability, under the broad definition for "stable," Gordon qualifies as stable inasmuch as the formulation was necessarily stored prior to administration.

(Ex. 1002 at ¶ 159.) Gordon's formulation was made and shipped from "Elan Pharma Ltd." in England. (Ex. 1017 at 6.) Aversano and Orthoclone also disclose stable formulations. Aversano's formulation was made and shipped from "Centocor, Inc." (Ex. 1023 at 5.) As an FDA-approved formulation shipped around the country, Orthoclone also qualifies as "stable." (Ex. 1002 at ¶ 71.) In fact, Remington's indicated that Orthoclone had a shelf-life of 1 year. (Ex. 1032 at 8.) As Dr. Schöneich also points out, various prior art formulations comprising the identical combination of claimed excipients qualified as stable. (Ex. 1002 at ¶ 159 (citing Ex. 1014; Ex. 1024; Ex. 1022; and Ex. 1023).) According to Dr. Schöneich, the combination of natalizumab and the claimed excipients at optimized concentrations create a stable formulation, especially under the broad definition provided by the '236 patent. (Ex. 1002 at ¶ 159.) Indeed, the modified Gordon formulation substituting phosphate buffer for histidine, which satisfies all limitations of claims 1 and 9, is inherently stable. See Santarus, 694 F.3d at 1354.

c. "from about 20 mg/ml to about 150 mg/ml of natalizumab"

Although Gordon only discloses that the aqueous formulation includes 5 mg/ml natalizumab (Ex. 1017 at 7), this difference in concentration represents nothing more than routine optimization of a result effective variable. In this regard, Petitioner incorporates by reference its discussion starting on page 27.

d. "about 10 mM phosphate buffer"

Gordon's natalizumab formulation includes a histidine buffer, which one of ordinary skill would have readily exchanged with the phosphate buffer of Orthoclone or Aversano because (1) the classic teaching/suggestion/motivation or "TSM" rationale points directly toward use of phosphate buffer and, independently (2) such use is no more than a simple substitution of one known buffer for another with predictable results.

Turning first to TSM – shortly after Gordon published, Subramanian taught those of ordinary skill that histidine buffer combined with polysorbate 80 caused accelerated degradation of IgG mAb actives. (Ex. 1026 at 4.) One of ordinary skill looking for an alternative to histidine buffer would quickly zero in on phosphate buffer. (Ex. 1002 at ¶ 162.) As discussed above in the Scope and Content section, numerous IgG mAb formulations repeatedly and successfully used polysorbate 80 with a phosphate buffer and sodium chloride. In fact, FDA approved two of these formulations – Orthoclone and Zenapax – and the combined use of these excipients was common practice in the field for antibody and other protein formulations. (Ex. 1022; Ex. 1024.)

Such extensive and successful use of these inactive ingredients with other IgG mAbs would have motivated one of ordinary skill reviewing Gordon, which discloses natalizumab along with polysorbate 80 and the problematic histidine

buffer, to incorporate phosphate buffer in place of histidine. (Ex. 1002 at ¶ 163.) The skilled artisans' choices were limited, given that only a few buffers had been previously approved by FDA for maintaining a pH of about 6.0, including, for example, histidine, phosphate buffer and sodium citrate. (Ex. 1029 at 13.)

Furthermore, unlike the histidine and citrate buffers criticized by Subramanian, phosphate buffer was known to be compatible with both IgG mAbs and polysorbate 80 without the prospect of accelerated potency loss. (Ex. 1002 at ¶ 163 (discussing Ex. 1022 at 3; Ex. 1024 at 2).) Even putting Subramanian aside, there exists a rationale for selection of the phosphate buffer of Orthoclone inasmuch as this excipient qualifies as a simple substitute for Gordon's histidine. It was well-known that both histidine and phosphate buffer were safe buffers whose function was to maintain the pH of IgG mAb formulations over time. (Ex. 1002 at ¶ 164.) Indeed, Frokjaer teaches that both phosphate and histidine buffers were among the group of a few buffers used in protein formulations at pH of about 6.0. (Ex. 1029 at 13.)

Further, simple substitution of histidine with phosphate buffer would lead to the predictable result of a stable formulation. (Ex. 1002 at ¶ 165.) Numerous stable formulations comprising an IgG mAb active along with the combination of excipients polysorbate 80, sodium chloride and phosphate buffer, were known in the prior art. At least two of these formulations were FDA-approved. (Ex. 1022;

Ex. 1024.) Thus, simple substitution of histidine with phosphate buffer would have led to the predictable result of a stable formulation. (Ex. 1002 at ¶ 165.)

The "about 10 mM" concentration is also subject to routine optimization. As discussed starting at page 29, those of ordinary skill routinely calculated optimal buffer concentrations using mathematical equations well-known in the prior art and such concentration is not critical. Aversano, for example, uses 10 mM phosphate buffer. (Ex. 1023 at 5.)

e. <u>"about 140 mM sodium chloride"</u>

To answer whether Gordon satisfies the sodium chloride limitation, some brief background is necessary. More specifically, Gordon expressly teaches two formulations – (1) a pre-dilution formulation and (2) a post-dilution formulation. (Ex. 1017 at 7.) To be clear, Petitioner's focus for purposes of Ground 2 is the pre-dilution formulation.

The prior art motivates sodium chloride addition to the pre-dilution formulation because isotonic conditions are necessary for patient comfort. (Ex. 1002 at ¶ 169; Ex. 1011 at ¶ 29; Ex. 1032 at 6.) As discussed starting at page 31, the prior art teaches that "[i]sotonic formulations will generally have an osmotic pressure from about 250 to 350 mOsm." (Ex. 1010 at ¶ 0051.) And sodium chloride was the excipient of choice for achieving isotonic conditions. (Ex. 1002 at ¶ 49; Ex. 1032 at 9.) In addition, numerous IgG mAb formulations

employing phosphate buffer and polysorbate 80 also include sodium chloride for this very reason. For example, multiple FDA-approved prior art formulations, including both Orthoclone and Zenapax, include sodium chloride. (Ex. 1022 at 3; Ex. 1024 at 2.) Thus, a person of ordinary skill in the art would have added sodium chloride to the formulation prior to dilution.

It also bears noting that a person of ordinary skill reading Gordon would have understood its pre-dilution formulation to necessarily contain sodium chloride. Extrinsic sources, including Bendig and the '236 patent itself, confirm that Gordon's pre-dilution formulation contains sodium chloride. See Schering Corp. v. Geneva Pharm., 339 F.3d 1373, 1382-83 (Fed. Cir. 2003) (evidence external to a prior art reference, created after the patent-in-suit was filed, may be used to establish that each claimed element was necessarily present in the prior art). Bendig, assigned to Elan Pharmaceuticals (Ex. 1030 at 5), the same entity sponsoring Gordon's research (Ex. 1017 at 12; Ex. 1002 at ¶¶ 65, 68), discloses a preferred formulation of natalizumab, 50 mM histidine buffer and 150 mM sodium chloride at a pH of 6.0 without dilution. (Ex. 1018 at 14:18-21.) The '236 patent, also originally filed by Elan Pharmaceuticals, reports that polysorbate 80 was added to the original formulation used in clinical trials, i.e., the Bendig formulation. (Ex. 1001 at 11:23-29.) The inference is thus strong that Gordon

built on the work of Bendig and added polysorbate 80 to Bendig's pre-dilution formulation containing histidine buffer and 150 mM sodium chloride.

Moreover, a person of ordinary skill would have recognized the presence of sodium chloride in the pre-dilution formulation because without it the post-dilution formulation would not qualify as isotonic. The prior art of course teaches that isotonic conditions are highly desirable for intravenous administration. (Ex. 1011 at ¶ 29; Ex. 1032 at 6.) As the '236 patent itself states, "[i]ntravenous administration requires the final formulation to be isotonic." (Ex. 1001 at 11:21-22.) If Gordon's pre-dilution formulation truly does not contain salt, its dilution with 0.9% saline would result in an undesirably hypotonic solution. (Ex. 1002 at ¶ 168.) That is because the amount of saline added is insufficient to bring the diluted solution within the range of osmotic pressures identified by the prior art as isotonic. (Ex. 1010 at ¶ 0051; Ex. 1002 at ¶ 168.) Thus, the only way the post-dilution solution could qualify as isotonic is if the pre-dilution formulation already contained sufficient sodium chloride to make it so. (Ex. 1002 at ¶ 168.) According to Dr. Schöneich, a person of ordinary skill reading Gordon would conclude that the pre-dilution formulation already included sodium chloride. (Id.)

Finally, as to the concentration of about 140 mM sodium chloride, as discussed above starting at page 31, the concentration of sodium chloride required by Challenged Claims 1 and 9 is subject to routine optimization. As Dr. Schöneich

explains, achieving isotonic conditions for a 10 mM phosphate buffered formulation requires sodium chloride to be at a concentration of between 127 mM to 180 mM which encompasses the claimed concentration. (Ex. 1002 at ¶ 56.) A formulator with Gordon in hand would have included a sufficient concentration of sodium chloride in the pre-dilution formulation before placing it in a vial. (Ex. 1002 at ¶ 170.)

f. "polysorbate 80 present in an amount of about 0.001% to 2% (w/v)"

Gordon's natalizumab formulation includes 0.02% polysorbate 80 (Ex. 1017 at 7), Aversano discloses a formulation with 0.01% polysorbate 80 (Ex. 1023 at 5), and Orthoclone discloses a formulation with 0.02% polysorbate 80 (Ex. 1022 at 3), all within the claimed range. (Ex. 1002 at ¶ 171.)

g. "wherein the [MS / CD] is treated by administration of the stable, aqueous pharmaceutical formulation"

Gordon reports favorable efficacy on CD and discloses that natalizumab was administered to patients with active MS as well. (Ex. 1017 at 6, 7.) Any uncertainty regarding the efficacy of natalizumab in the treatment of MS would be resolved by the disclosure of Sorbera which confirms that natalizumab was effective for MS as well as CD. (Ex. 1019 at 3, 4.).

2. Challenged Claims 2 and 10: "intravenous administration"

Claims 2 and 10 require the administration to be "by intravenous administration." Gordon (Ex. 1017 at 7), Orthoclone (Ex. 1022 at 3) and Aversano (Ex. 1023 at 5) each disclose intravenous administration of its active, Gordon expressly disclosing intravenous administration of natalizumab.

3. Challenged Claims 3 and 11: "series of treatments"

Claims 3 and 11 require the administration to be "over a series of treatments." As explained in Section VI.B, the broadest reasonable interpretation of "series of treatments" would be "at least two treatments." Gordon characterizes the effects of a single dose of natalizumab for CD as short lived, and teaches that "more frequent doses might result in improved efficacy." (Ex. 1011 at ¶ 59; Ex. 1057 at ¶ 60; Ex. 1017 at 10.) Thus, Gordon itself teaches and suggests administration of natalizumab in series. Further, Sorbera teaches that administration of "2 i.v. infusions (3 mg/kg) of natalizumab given 4 weeks apart" effectively treats MS. (Ex. 1019 at 3.) Thus, the teachings in Gordon and Sorbera would motivate one of ordinary skill to pursue administration of natalizumab in series of treatments. (Ex. 1011 at ¶ 59; Ex. 1057 at ¶ 48.)

4. Challenged Claims 4 and 12: "natalizumab is present in an amount of 20 mg/mL"

Claims 4 and 12 further require "natalizumab . . . in an amount of about 20 mg/mL." Gordon discloses 3 mg of natalizumab per kg of body weight

(3 mg/kg) is therapeutically effective. (Ex. 1017 at 7.) And the specific concentration of natalizumab is nothing more than routine optimization of a result effective variable. (See p. 27, above.)

5. Challenged Claims 5 and 13: "polysorbate 80 is present in an amount of about 0.02% (w/v)"

Claims 5 and 13 require polysorbate 80 in "an amount of about 0.02%." Gordon's natalizumab formulation includes 0.02% polysorbate 80. (Ex. 1017 at 7; Ex. 1002 at ¶ 182.) Thus, Gordon satisfies this limitation.

6. Challenged Claims 6-8 and 14-16: "pH is about 6.0 ±0.5"

Claims 6 and 14 require a "pH of about 3.0 to about 7.0." Claims 7 and 15 require that the "pH is about 5.5 to about 6.5." And claims 8 and 16 require that the "pH is about 6.0 ±0.5." Gordon's natalizumab formulation has a pH of 6.0. (Ex. 1017 at 7.)

7. Challenged Claims 21 and 22

Claim 21 and 22 collect the various limitations from several dependent claims and combine them into single independent claims for methods of treatment for MS and CD, respectively. As with Ground 1, nothing suggests that the consolidation of these limitations resulted in a nonobvious combination. As discussed starting on page 55, Gordon (Ex. 1017 at 7), Orthoclone (Ex. 1022 at 3) and Aversano (Ex. 1023 at Abstract) disclose intravenous administration of their aqueous pharmaceutical formulation. As discussed starting on page 27, the

concentration of natalizumab is nothing more than routine optimization of a result effective variable. As discussed starting on page 51, Gordon teaches the use of sodium chloride, and as discussed starting on page 31, sodium chloride concentration is nothing more than routine optimization of a result effective variable. And as discussed starting on page 54, Gordon and Aversano each disclose that 0.2 mg/ml polysorbate 80 and polysorbate 80 concentration is nothing more than routine optimization of a result effective variable.

Even the limitations to pH do not render claims 21 and 22 nonobvious as Gordon discloses a pH of 6.0, the precise requirement of claims 21 and 22. One of ordinary skill would have expected a formulation with a pH of 6.0 to exhibit the same properties as a formulation with a pH of 6.1 because the proton concentration between pH of 6.0 and 6.1 is similar. (Ex. 1002 at ¶ 142.) Thus, a formulation at pH 6.0 would exhibit the same formulation characteristics as one at pH 6.1 (id.), which would mean the efficacy of the natalizumab would remain unchanged (Ex. 1011 at ¶ 62; Ex. 1057 at ¶ 51). Orthoclone confirms this point, teaching that its pH may vary by as much as "±0.5," far greater a range than the difference between the pH of 6 as disclosed by Gordon and the pH of 6.1 of the Challenged Claim. (Ex. 1022 at 3.) This is also confirmed by each example in the '236 patent, which recites pH 6.0 ±0.5. (Ex. 1001 at 16:19-17:36.) The claimed pH is also

subject to routine optimization. (See p. 36, above). There is nothing special about a pH of 6.1. (Ex. 1002 at ¶ 142.)

8. Reasonable Expectation of Success

The person of ordinary skill in the art would also have had a reasonable expectation that the combination of Gordon (Ex. 1017) and Orthoclone (Ex. 1022) or Aversano (Ex. 1023) would successfully result in the claimed stable natalizumab formulation. See Pfizer, 480 F.3d at 1364. As discussed in great detail starting at page 38 above, those of ordinary skill recognized that the claimed formulation could be made and would work for its intended purpose. Once again, the prior art reports several stable IgG mAb formulations with excipients identical to those recited by the Challenged Claims. And the IgG mAb actives in these formulations share key structural characteristics leading to comparable behavior in comparable formulations.

D. Statement of No Redundancy

Neither vertical nor horizontal redundancy is present here. With respect to Ground 1, the rationale for modifying van Oosten with Sorbera (simple substitution) is different than the motivation to modify Zenapax with Sorbera (combining known elements). The alternate combinations of Ground 2 are also distinct because the secondary references, Orthoclone and Aversano, each present different concentrations of excipients, making routine optimization necessary in

some cases but not others. Finally, Ground 1 and 2 themselves are not redundant because each presents entirely different primary references leading to distinct substitutions and rationales. Ground 1 starts with a formulation satisfying all formulation components and replaces the active IgG mAb with natalizumab. Ground 2 starts with a known natalizumab formulation and substitutes one of the formulation excipients, i.e., a buffer. The Grounds thus do not qualify as vertically or horizontally redundant.

E. Secondary Considerations of Nonobviousness Fail to Overcome the Strong *Prima Facie* Showing of Obviousness

Petitioners are not aware of any evidence of secondary considerations of nonobviousness sufficient to rescue the Challenged Claims from the strong case for *prima facie* obviousness discussed herein. See, e.g., Q.I. Press Controls, B.V. v. Lee, 752 F.3d 1371, 1379-80 (Fed. Cir. 2014). During prosecution of the '321 patent, Applicants alleged unexpected results, but the Preformulation Study they relied upon was "based on preliminary data which was not accurate . . . [and] could not be reproduced" – by their own admission. (Ex. 1040 at 1.)

Furthermore, as Dr. Schöneich explains in his declaration, even if the Preformulation Study data were accurate and reproducible, such data does not support unexpected results. (Ex. 1002 at ¶ 202.) For example, the protein concentration for the only formulation using polysorbate 80 (which also contained sodium chloride) purportedly increased, rather than decreased as would have been

expected if the protein was degrading. (Ex. 1002 at ¶ 203; Ex. 1038 at 20, Table 2.) In addition, that same formulation was able to maintain a stable pH over 8 weeks – the same pH as in a similar formulation without the polysorbate 80. (Ex. 1038 at 19, Table 1.) And a different formulation using phosphate buffer maintains the exact same pH over time both with and without sodium chloride. (Id..) According to Dr. Schöneich, these results do not support the Patent Owner's assertions in support of the alleged unexpected results that "the inclusion of sodium chloride or polysorbate 80 was found to accelerate the degradation process." (Ex. 1002 at ¶ 213; see also Ex. 1046 at 10.)

Commercial success also cannot rescue the '236 patent. To the extent commercial success, if any, exists, it can only trace back to the natalizumab active, which was well-known in the prior art before the '236 patent. (Ex. 1011 at ¶ 25.) And as the Federal Circuit has explained, "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." Ormco Corp. v. Align Technology, Inc., 463 F.3d 1299, 1312 (Fed. Cir. 2006).

VIII. CONCLUSION

Given the foregoing, Petitioner respectfully submits that it has shown a reasonable likelihood that Challenged Claims 1-16, 21 and 22 of the '236 patent are obvious. Petitioner requests, therefore, that the Board institute *inter partes* review for each of these claims.

Respectfully submitted,
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CERTIFICATE OF SERVICE

I hereby certify that a true and correct copy of **PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,815,236 PURSUANT TO 35 U.S.C. § 312 AND 37 C.F.R. § 42.108** was served on April 18, 2016 via *FedEx Priority Overnight* service to the corresponding address for the subject patent pursuant to 37 C.F.R § 42.105:

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