

Filed on behalf of: Janssen Biotech, Inc.

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

ACCORD BIOPHARMA, INC., INTAS PHARMACEUTICALS LTD., AND
BIO-THERA SOLUTIONS, LTD.,
Petitioner,

v.

JANSSEN BIOTECH, INC.,
Patent Owner.

IPR2026-00259
Patent No. 12,291,566

**DECLARATION OF DR. NIGIL HAROON, M.D., PH.D., M.B.A.
IN SUPPORT OF
PATENT OWNER'S PRELIMINARY RESPONSE**

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I. Introduction

1. I have been retained by Janssen Biotech, Inc. (“Janssen”) to provide my opinion concerning the validity of U.S. Patent No. 12,291,566 (“the ’566 Patent”), which has been challenged by Accord Biopharma, Inc., Intas Pharmaceuticals Ltd., and Bio-Thera Solutions, Ltd. (collectively, “Petitioners”). The ’566 Patent covers methods of treating ankylosing spondylitis (“AS”) via intravenous (“IV”) administration of golimumab, an antibody that inhibits tumor necrosis factor (“TNF” or “TNF α ”).

II. Summary of Opinions

2. Based on materials cited in this declaration and my over 20 years of clinical expertise treating patients suffering from AS, I conclude that Petitioners have not demonstrated either anticipation or obviousness of the ’566 Patent independent claims.

III. Qualifications

3. I am a professor of medicine and rheumatology at the University of Toronto and a clinician scientist in the field of spondyloarthritis¹ (“SpA”), a class of diseases that includes AS and psoriatic arthritis (“PsA”). I serve as Head of

¹ While the nomenclature for these diseases continues to evolve, this category of diseases has commonly been referred to as SpA.

the Division of Rheumatology at the University Health Network and Sinai Health in Toronto. I am also the chair of Translational Research and Drug Discovery in inflammatory arthritis at the University of Toronto and University Health Network. University Health Network has been ranked as the Number One publicly funded hospital and Number Two hospital in the world according to Newsweek.

4. I earned my Bachelor of Medicine and Bachelor of Surgery (M.B.B.S.) (the equivalent to an M.D. in North America) from the University of Kerala in 1998. I then completed my residency in internal medicine at South Gujarat University in 2003. I completed my clinical fellowship in clinical immunology and rheumatology at Sanjay Gandhi Postgraduate Institution of Medical Sciences in 2007. I completed a clinical and research fellowship in Adult Rheumatology with a focus on SpA at the University of Toronto from 2008 to 2012. In 2012, I earned my Ph.D. in the functional genomics of SpA from the Institute of Medical Sciences, University of Toronto. I also hold an MBA in Health and Life Sciences from Rotman School of Business.

5. My practice includes treating patients as well as consulting for clinical development of new therapies. I treat forty patients weekly for diseases like SpA and other rheumatologic conditions, including rheumatoid arthritis

(“RA”). I have received numerous awards in recognition of my contributions in the field of medicine and rheumatology.

6. I currently hold many leadership positions in SpA working groups. I am the chair of the Spondyloarthritis Research and Treatment Network, called SPARTAN. I also serve on the Medical and Scientific Advisory Board of the Spondylitis Association of America and the Canadian Spondylitis Association.

7. I have authored over 100 peer-reviewed publications, book chapters, and guidelines concerning SpA. My research spans subjects in the treatment of SpA, including predicting radiographic progression, finding novel therapeutic targets, and exploring the genetic basis of AS. I am an author and committee member in the last three treatment recommendations on axial SpA (2015, 2019, 2026) from the ACR/SPARTAN/SAA (the latest one will be published in 2026). In 2013, I received the Bruckel Award from the Spondylitis Association of America in recognition of my contributions to the care and understanding of the treatment of SpA. I am also a named inventor on a U.S. patent application on methods of treating SpA.

8. In total, I have over 20 years of experience treating patients with SpA and consulting on the development of treatments for SpA. I am familiar with the various clinical endpoints used to evaluate efficacy of therapies for SpA. Through clinical, academic, and professional experiences, I have made

significant impact in shaping clinically meaningful endpoints and best practices for SpA management.

9. Additional information regarding my experience, publications, and honors is included in my *Curriculum Vitae*, which I understand is attached as Ex.2055. I am receiving compensation at my standard consulting rate of \$750 USD per hour, plus reimbursement for reasonable expenses. My compensation is not dependent on my opinions or on the outcome of this matter.

IV. Summary of Materials Reviewed and Considered

10. All of the opinions contained in this Declaration are based on the documents I reviewed and my knowledge and professional judgment. In forming the opinions expressed in this Declaration, while drawing on my experience in the field of rheumatology, I reviewed the Petition and the following documents:

Ex.	Description
1004	U.S. Patent No. 12,291,566 to Harrison et al. (May 6, 2025) (“566 Patent”)
1005	Declaration of Dr. Roy M. Fleischmann in Support of IPR Petition
1014	U.S. National Library of Medicine, ClinicalTrials.gov, NCT02186873, “ <i>A Study of Golimumab in Participants with Active Ankylosing Spondylitis</i> ” (Version 24, October 27, 2015), available at https://clinicaltrials.gov/study/NCT02186873? (“NCT873-V24”)
1015	<i>SIMPONI (golimumab) injection, for subcutaneous use</i> , FOOD AND DRUG ADMINISTRATION (June 2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125289s024lbl.pdf (“PI2015-Simponi”)

Ex.	Description
1016	R. D. Inman, et al., <i>Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis</i> , 58 ARTHRITIS & RHEUMATISM 11:3402-3412 (Nov. 2008) (“Inman”)
1024	U.S. Patent Publication 2009/0123378 to Wong et al. (May 14, 2009) (“Wong”)
1032	<i>SIMPONI ARIA (golimumab) injection, for intravenous use</i> , FOOD AND DRUG ADMINISTRATION (July 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125433s000lbletd.pdf (“PI2013-Aria”)
1033	D. van der Heijde, et al., <i>The Effect of Golimumab Therapy on Disease Activity and Health-related Quality of Life in Patients with Ankylosing Spondylitis: 2-year Results of the GO-RAISE Trial</i> , 41 THE JOURNAL OF RHEUMATOLOGY 6:1095-1103 (2014) (“Van der Heijde”)
1034	<i>Administrative and Correspondence Documents, Application Number: 125433Orig1s000</i> , CENTER FOR DRUG EVALUATION AND RESEARCH, (September 30, 2013) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125433review.pdf (“CDER Review”)
1038	Y. Zhuang, et al., <i>Golimumab Pharmacokinetics After Repeated Subcutaneous and Intravenous Administrations in Patients with Rheumatoid Arthritis and the Effect of Concomitant Methotrexate: An Open-Label, Randomized Study</i> , 34 CLINICAL THERAPEUTICS 1:77-90 (Jan. 2012) (“Zhuang”)
2002	Prosecution History for U.S. Patent No. 12,291,566 B2 (“566 Patent PH”) (EXCERPT)
2052	Eur. Meds. Agency, Sci. Meds. Health, Comm. for Med. Prods. for Hum. Use (Day 120 Assessment Report, EMA/416184/2014), Withdrawal Assessment Report: Simponi (golimumab), EMEA/H/C/000992/X/0047 (Janssen Biologics B.V., Applicant) (Oct. 24, 2013)

Ex.	Description
2053	Ctr. for Drug Evaluation & Rsch., Clinical Pharm. & Biopharmaceutics Rev., Simponi (Golimumab), BLA Appl. No. 125289 (submitted June 24, 2008) (EXCERPTS)
2056	Press Release, Johnson & Johnson, <i>Janssen Receives Two U.S. FDA Approvals for Simponi Aria® (Golimumab) for the Treatment of Adults With Active Psoriatic Arthritis or Active Ankylosing Spondylitis</i> (Oct. 20, 2017), https://www.jnj.com/media-center/press-releases/janssen-receives-two-us-fda-approvals-for-simponi-aria-golimumab-for-the-treatment-of-adults-with-active-psoriatic-arthritis-or-active-ankylosing-spondylitis
2058	NIH, Nat'l Lib. of Med., Nat'l Ctr. for Biotechnology Info., ClinicalTrials.gov, <i>An Efficacy and Safety Study of Golimumab in Participants With Ulcerative Colitis</i> (Janssen Rsch. & Dev., LLC, ClinicalTrials.gov ID NCT00488774) (updated June 14, 2013), https://clinicaltrials.gov/study/NCT00488774
2059	NIH, Nat'l Lib. of Med., Nat'l Ctr. for Biotechnology Info., ClinicalTrials.gov, <i>Study of Adalimumab in Patients With Axial Spondyloarthritis</i> (AbbVie, ClinicalTrials.gov ID NCT00939003) (updated Sept. 9, 2014), https://clinicaltrials.gov/study/NCT00939003
2062	NIH, Nat'l Lib. of Med., Nat'l Ctr. for Biotechnology Info., ClinicalTrials.gov, <i>A Study of Ixekizumab (LY2439821) in bDMARD-Naive Participants With Radiographic Axial Spondyloarthritis (COAST-V)</i> (Eli Lilly & Co., ClinicalTrials.gov ID NCT02696785) (updated Nov. 19, 2019), https://clinicaltrials.gov/study/NCT02696785
2063	NIH, Nat'l Lib. of Med., Nat'l Ctr. for Biotechnology Info., ClinicalTrials.gov, <i>A Study of Ixekizumab (LY2439821) in TNF Inhibitor Experienced Participants With Radiographic Axial Spondyloarthritis (COAST-W)</i> (Eli Lilly & Co., ClinicalTrials.gov ID NCT02696798) (updated June 17, 2020), https://clinicaltrials.gov/study/NCT02696798

Ex.	Description
2066	FDA, Cosentyx Prescribing Information (revised Jan. 2016) (“Cosentyx”)
2067	FDA, Kevzara Prescribing Information (revised Apr. 2018) (“Kevzara”)
2068	FDA, Remicade Prescribing Information (revised Oct. 2015) (“Remicade”)
2069	Jennifer J. Anderson et al, <i>Ankylosing Spondylitis Assessment Group Preliminary Definition of Short-Term Improvement in Ankylosing Spondylitis</i> , 44 ARTHRITIS RHEUMATISM 1876 (2001)
2071	Anthony D. Bai et al, <i>Intention-To-Treat Analysis May Be More Conservative Than Per Protocol Analysis in Antibiotic Non-Inferiority Trials: A Systematic Review</i> , 21 BMC MED. RSCH. METHODOLOGY 1–10 (2021)
2072	X. Baraliakos et al, <i>Radiographic Progression in Patients With Ankylosing Spondylitis After 4 Yrs of Treatment With the Anti-TNF-α Antibody Infliximab</i> , 46 RHEUMATOLOGY 1450 (2007)
2073	L.C. Doward et al, <i>Development of the ASQoL: A Quality of Life Instrument Specific to Ankylosing Spondylitis</i> , 62 ANNALS RHEUMATIC DISEASES 20 (2003)
2074	Mazen Elyan & Muhammad Asim Khan, <i>Diagnosing Ankylosing Spondylitis</i> , 33 J. RHEUMATOLOGY 12 (2006)
2076	Mohammad Ghasemi-rad et al, <i>Ankylosing Spondylitis: A State of the Art Factual Backbone</i> , 7 WORLD J. RADIOLOGY 236 (2015)
2077	H. Haibel et al, <i>Six Months Open Label Trial of Leflunomide in Active Ankylosing Spondylitis</i> , 64 ANNALS RHEUMATIC DISEASES 124 (2005)
2078	H. Haibel et al, <i>Open Label Trial of Anakinra in Active Ankylosing Spondylitis Over 24 Weeks</i> , 64 ANNALS RHEUMATIC DISEASES 296 (2005)

Ex.	Description
2079	H. Haibel et al, <i>No Efficacy of Subcutaneous Methotrexate in Active Ankylosing Spondylitis: A 16-Week Open-Label Trial</i> , 66 ANNALS RHEUMATIC DISEASES 419 (2007)
2080	CHARLES A. JANEWAY, JR., ET AL, IMMUNOBIOLOGY-THE IMMUNE SYSTEM IN HEALTH & DISEASE ch. 3-6 (5th ed 2001), (EXCERPT), https://www.ncbi.nlm.nih.gov/books/NBK27160/
2081	Arthur Kavanaugh et al, <i>Treatment of Psoriatic Arthritis in a Phase 3 Randomised, Placebo-Controlled Trial with Apremilast, An Oral Phosphodiesterase 4 Inhibitor</i> , 73 ANNALS RHEUMATIC DISEASES 1020 (2014)
2083	R.J. Lories & D.L.P. Baeten, <i>Differences in Pathophysiology Between Rheumatoid Arthritis and Ankylosing Spondylitis</i> , 27 CLINICAL EXPERIMENTAL RHEUMATOLOGY S10 (2009)
2084	Peter Machado et al, <i>Ankylosing Spondylitis Disease Activity Score (ASDAS): Defining Cut-Off Values for Disease Activity States and Improvement Scores</i> , 70 ANNALS RHEUMATIC DISEASES 47 (2011)
2085	W.P. Maksymowych and M.A. Brown, <i>Genetics of Ankylosing Spondylitis and Rheumatoid Arthritis: Where Are We At Currently, and How Do They Compare?</i> , 27 CLINICAL EXPERIMENTAL RHEUMATOLOGY S20 (2009)
2086	Dennis McGonagle et al, <i>Classification of Inflammatory Arthritis by Enthesitis</i> , 352 LANCET 1137 (1998)
2087	D.R. Mould & R.N. Upton, <i>Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development—Part 2: Introduction to Pharmacokinetic Modeling Methods</i> , 2 CPT: PHARMACOMETRICS SYS. PHARMACOLOGY 1–14 (2013)
2088	Philip Ian Murray & Saaeha Rauz, <i>The Eye and Inflammatory Rheumatic Diseases: The Eye and Rheumatoid Arthritis, Ankylosing Spondylitis, Psoriatic Arthritis</i> , 30 BEST PRAC. RSCH. CLINICAL RHEUMATOLOGY 802 (2016)

Ex.	Description
2089	Dušan Mustur et al, <i>Assessment of Functional Disability and Quality of Life in Patients with Ankylosing Spondylitis</i> , 137 SERBIAN ARCHIVES MED. 524 (2009)
2090	Makoto Naganuma et al, <i>Recent Trends and Future Directions for the Medical Treatment of Ulcerative Colitis</i> , 9 CLINICAL J. GASTROENTEROLOGY 329 (2016)
2091	Karel Pavelka et al, <i>A Study to Evaluate the Safety, Tolerability, and Efficacy of Brodalumab in Subjects With Rheumatoid Arthritis and an Inadequate Response to Methotrexate</i> , 42 J. RHEUMATOLOGY 912 (2015)
2092	M. Rudwaleit et al, <i>MRI in Predicting a Major Clinical Response to Anti-Tumour Necrosis Factor Treatment in Ankylosing Spondylitis</i> , 67 ANNALS RHEUMATIC DISEASES 1276 (2008)
2093	Rita Rugienė et al, <i>The Quality of Life and Functional Ability in Patients with Ankylosing Spondylitis</i> , 15 ACTA MEDICA LITUANICA 99 (2008)
2094	P. Rutgeerts et al, <i>Randomised Clinical Trial: A Placebo-Controlled Study of Intravenous Golimumab Induction Therapy for Ulcerative Colitis</i> , 42 ALIMENTARY PHARMACOLOGY THERAPEUTICS 504 (2015) (“Rutgeerts”)
2095	P. Rutgeerts et al, <i>Supplemental Appendix</i> (2015) (“Rutgeerts App’x”)
2096	Georg Schett et al, <i>Structural Damage in Rheumatoid Arthritis, Psoriatic Arthritis, and Ankylosing Spondylitis: Traditional Views, Novel Insights Gained From TNF Blockade, and Concepts for the Future</i> , 13 ARTHRITIS RSCH. THERAPY S4 (2011)
2098	Joachim Sieper et al, <i>Assessment of Short-Term Symptomatic Efficacy of Tocilizumab in Ankylosing Spondylitis: Results of Randomised, Placebo-Controlled Trials</i> , 73 ANNALS RHEUMATIC DISEASES 95 (2014)

Ex.	Description
2099	Joachim Sieper et al, <i>Sarilumab for the Treatment of Ankylosing Spondylitis: Results of a Phase II, Randomised, Double-Blind, Placebo-Controlled Study (ALIGN)</i> , 74 ANNALS RHEUMATIC DISEASES 1051 (2015)
2100	Joachim Sieper et al, <i>Secukinumab Efficacy in Anti-TNF-Naive and Anti-TNF-Experienced Subjects With Active Ankylosing Spondylitis: Results from the MEASURE 2 Study</i> , 76 ANNALS RHEUMATIC DISEASES 571 (2017)
2101	I.-H. Song et al, <i>Different Response to Rituximab in Tumor Necrosis Factor Blocker–Naive Patients With Active Ankylosing Spondylitis and in Patients in Whom Tumor Necrosis Factor Blockers Have Failed, A Twenty-Four–Week Clinical Trial</i> , 62 ARTHRITIS RHEUMATISM 1290 (2010)
2102	I-H Song et al, <i>Treatment of Active Ankylosing Spondylitis With Abatacept: An Open-Label, 24-Week Pilot Study</i> , 70 ANNALS RHEUMATIC DISEASES 1108 (2011)
2105	Carlos Taxonera et al, <i>Clinical Outcomes of Golimumab as First, Second or Third Anti-TNF Agent in Patients with Moderate-to-Severe Ulcerative Colitis</i> , 23 INFLAMMATORY BOWEL DISEASES 1394 (2017)
2107	R.N. Upton & D.R. Mould, <i>Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development: Part 3—Introduction to Pharmacodynamic Modeling Methods</i> , 3 CPT: PHARMACOMETRICS SYS. PHARMACOLOGY 1–16 (2014)
2109	D. van der Heijde et al, <i>Proposal of a Linear Definition of the Bath Ankylosing Spondylitis Metrology Index (BASMI) and Comparison With the 2-Step and 10-Step Definitions</i> , 67 ANNALS RHEUMATIC DISEASES 489 (2008)
2110	Désirée van der Heijde et al, <i>ASDAS, a Highly Discriminatory ASAS-Endorsed Disease Activity Score in Patients With Ankylosing Spondylitis</i> , 68 ANNALS RHEUMATIC DISEASES 1811 (2009)

Ex.	Description
2111	Désirée van der Heijde et al, <i>Tofacitinib in Patients With Ankylosing Spondylitis: A Phase II, 16-Week, Randomised, Placebo-Controlled, Dose-Ranging Study</i> , 76 ANNALS RHEUMATIC DISEASES 1340 (2017)
2112	Désirée van der Heijde et al, <i>Supplementary Information: Tofacitinib in Patients With Ankylosing Spondylitis: A Phase II, 16-Week, Randomised, Placebo-Controlled, Dose-Ranging Study</i> (Ex. 2111) (2017)
2113	Karin A. van Schie et al, <i>Therapeutic TNF Inhibitors Can Differentially Stabilize Trimeric TNF by Inhibiting Monomer Exchange</i> , 6 NATURE SCI. REPS. 1–10 (2016)
2114	Ronald F. van Vollenhoven, <i>Sex Differences in Rheumatoid Arthritis: More Than Meets the Eye...</i> , 7 BMC MED. 1–4 (2009)
2116	J.E. WARE & M. KOSINSKI, SF-36 PHYSICAL & MENTAL HEALTH SUMMARY SCALES: A MANUAL FOR USERS OF VERSION 1 (2d ed. 1994) (EXCERPTS)
2117	Michael E. Weinblatt, <i>Methotrexate in Rheumatoid Arthritis: A Quarter Century of Development</i> , 124 TRANSACTIONS AM. CLINICAL CLIMATOLOGICAL ASS’N 16 (2013)
2118	John Brockbank & Dafna Gladman, <i>Diagnosis and Management of Psoriatic Arthritis</i> , 62 DRUGS 2447 (2002)
2119	Paul A.C. Lord et al., <i>Predictors of Response to Anti-TNF Therapy in Ankylosing Spondylitis: Results from the British Society for Rheumatology Biologics Register</i> , 49 RHEUMATOLOGY 563 (2010)
2120	Philip J. Mease, <i>Is There a Role for Rituximab in the Treatment of Spondyloarthritis and Psoriatic Arthritis?</i> , 39 J. RHEUMATOLOGY 2235 (2012)
2121	Masatsugo Ono et al, <i>Structural Basis for Tumor Necrosis Factor Blockade with the Therapeutic Antibody Golimumab</i> , 27 PROTEIN SCIENCE 1038 (2018)

Ex.	Description
2122	Eric M. Ruderman, <i>The Role of Concomitant Methotrexate in Biologic Therapy for Rheumatoid Arthritis</i> , 71 BULL. HOSP. JOINT DISEASES S29 (2013)
2123	Lars Fugger & Arne Svejgaard, <i>Association of MHC and Rheumatoid Arthritis HLA-DR4 and Rheumatoid Arthritis: Studies in Mice and Men</i> , 2 ARTHRITIS RSCH. 208 (2000)

11. My opinions are additionally guided by my appreciation of how a person of ordinary skill in the art (“POSA”) would have understood the claims of the ’566 Patent at the time of the alleged invention, which I have been asked to assume is February 7, 2017. I refer to this date as the “priority date” below.

V. Legal Standards

12. I am not a lawyer. In forming my opinions, I have applied the legal standards that counsel provided to me, which are set forth below.

A. Claim Construction

13. I understand that claim terms must be construed as they would be understood by a POSA, following review of the claim language, the specification, and the prosecution history. I also understand that, unless a patentee provides a different definition in the patent specification, a claim term should be given its plain and ordinary meaning as it would be understood by a POSA at the time of the invention, considering the teachings of the claims themselves, the patent’s specification, and the prosecution history. Accordingly, unless a claim term has

been defined in the patent specification, either explicitly or by clear implication, I have applied the term's plain and ordinary meaning.

B. Anticipation

14. I understand that a prior art reference anticipates a claim only if it discloses all of the claim limitations combined in the same way as recited in the claim.

15. I understand that there may be “inherent anticipation” only when the reference discloses a method that must necessarily result in the unstated limitation. I understand that inherency may not be established by probabilities or possibilities.

C. Obviousness

16. I understand that obviousness depends on underlying factual determinations, including (1) the scope and content of the prior art, (2) any differences between the claimed subject matter and the prior art, (3) the level of skill in the art, and (4) objective indicia of non-obviousness where available in evidence.

17. I understand that, in addition to showing that a combination of prior art references discloses every element of a claim, Petitioners must also prove that a POSA would have a motivation to combine those references and that a POSA would have had a reasonable expectation of success in doing so.

VI. A Person of Ordinary Skill in the Art

18. I understand that patents are to be read from the perspective of a theoretical person of ordinary skill in the art (again, a “POSA”) in the relevant field at the time of the invention. To determine the qualifications of a POSA at the time of the invention (February 7, 2017), I have been asked to consider the following factors: (1) the educational level of the inventors; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) education level of active workers in the field. Regarding point (1), I have been informed that the inventors held M.D.s or Ph.D.s by the priority date.

19. In my opinion, a POSA for the ’566 Patent would have been a medical doctor and/or clinical researcher with a Ph.D. and significant experience treating and/or researching SpA, including AS. In my experience, while medical doctors typically have sufficient baseline knowledge to treat both RA and AS, the clinical researchers developing AS treatments have more specialized knowledge than medical doctors. These individuals do not necessarily also have such specialized knowledge or research experience in the development of RA treatment, because, as I describe below, RA is a wholly distinct disease from AS. Similarly, clinical researchers who specialize in RA may not have specialized knowledge or research experience in the development of AS treatment. The

POSA would have collaborated with others, including scientists skilled in related fields typically employed in pharmaceutical development, such as pharmacokineticists, biostatisticians, and formulators.

VII. Scientific Background and State of the Art

20. In this section, I explain the technical background relevant to the '566 Patent claims and my analysis.

A. Simponi and Simponi Aria

21. While Simponi and Simponi Aria both contain the active ingredient golimumab, they differ in their routes of administration, approved indications, and dosing regimens. Simponi is injected subcutaneously ("SC"). By the priority date, Simponi was approved to treat RA at 50 mg once a month with concomitant methotrexate ("MTX"), PsA at 50 mg once a month with or without MTX, AS at 50 mg once a month, and ulcerative colitis ("UC") at 200 mg SC injection at week 0, followed by 100 mg at week 2, then 100 mg every 4 weeks. Ex.1015 (PI2015-Simponi). Simponi Aria is administered via an IV infusion. At the priority date, Simponi Aria was only approved to treat RA at 2 mg/kg in an IV infusion over 30 minutes at weeks 0, 4, and then every 8 weeks with concomitant MTX. Ex.1032 (PI2013-Aria). In October 2017, Simponi Aria received FDA approval to treat PsA and AS via 2 mg/kg in an IV infusion at

weeks 0 and 4, and then every 8 weeks. Ex.2056 at 1-3 (Oct. 20, 2017 J&J Press Release).

B. TNF

22. TNF is a pro-inflammatory signaling protein (cytokine). TNF causes tissue injury, including damage to cartilage and bone. As a result, TNF plays a role in several inflammatory and autoimmune diseases, including AS.

23. Golimumab is a monoclonal antibody therapy designed to block TNF. Ex.1015 (PI2015-Simponi). An anti-TNF antibody may bind to TNF and prevent TNF from binding to its receptors, thus disrupting TNF-mediated inflammation cascades in the body. The TNF inhibitors available at the priority date were known to have differential effects upon binding to TNF. Ex.2113 at 4 (van Schie 2016). Subsequently, it was shown that golimumab binds to a different site on TNF compared to the other inhibitors. Ex.2121 (Ono 2018).

C. Ankylosing Spondylitis

24. AS is a chronic inflammatory disease affecting several joints, including in the spine, pelvis, and peripheral joints. Ex.2074 at 15 (Elyan 2006). In severe cases, AS may lead to substantial loss of mobility and disability. Ex.2089 at 524, 526 (Mustur 2009).

25. Patients with AS often have elevated TNF levels. As discussed, it was known that a TNF inhibitor could prevent a cascade of reactions that would

otherwise lead to the inflammatory and immune responses associated with AS. However, the precise pathogenesis of AS, and TNF's role therein, was not fully known. Ex.2072 at 1452 (Baraliakos 2007).

26. At the '566 Patent priority date, clinicians would rely on several metrics to measure AS disease activity and impact on patients:

- a. Ankylosing Spondylitis Disease Activity Score ("ASDAS");
- b. Bath Ankylosing Spondylitis Functional Index ("BASFI");
- c. Bath Ankylosing Spondylitis Metrology Index ("BASMI");
- d. 36-item Short Form Health Survey ("SF-36") Physical Component Summary ("PCS") and Mental Component Summary ("MCS");
- e. Ankylosing Spondylitis Quality of Life Questionnaire ("ASQoL");
- f. Assessment in Ankylosing Spondylitis 20 ("ASAS20").

27. ASDAS, BASFI, BASMI, ASQoL, and ASAS20 are unique to AS.

28. ASDAS is the ASAS International Working Group's metric for assessing disease activity in AS and other SpA diseases. Ex.2110 at 1811 (van der Heijde 2009). An ASDAS score is based on a weighted combination of (1) back pain, (2) duration of morning stiffness, (3) peripheral joint pain and/or swelling, (4) general well-being, and (5) either erythrocyte sedimentation rate ("ESR") or C-reactive protein ("CRP") level. *Id.* at 1812 (Table 1). Inactive disease is defined as less than 1.3 ASDAS, a reduction in ASDAS of 1.1

indicates clinically important improvement, and a reduction in ASDAS of 2.0 indicates major improvement. Ex.2084 at 50 (Machado 2011) (Fig. 1).

29. BASFI is a patient-reported functional index. The metric is a set of ten questions—eight related to functional anatomy and two on the patient’s ability to cope with everyday life. Ex.2089 at 525 (Mustur 2009). BASFI is measured 0-to-10, with higher scores indicating maximal impairment. *Id.*

30. BASMI assesses the axial spine and hip mobility based on five metrics. Ex.2109 at 489 (van der Heijde 2008). The five BASMI clinical measures are (1) tragus-to-wall distance, (2) cervical rotation, (3) lumbar flexion, or the modified Schober test, (4) lateral spinal flexion, and (5) intermalleolar distance. *Id.* The linear definition of BASMI score is calculated by the mean of each of the five metrics and is measured 0-to-10.² *Id.* at 490 (Table 3).

31. The SF-36 survey assesses physical and mental factors of a patient’s health status. *See* Ex.2116 at 5-6 (Ware 1994). A patient’s responses to questions across eight components contribute to a composite score, which is summarized into a mental component (MCS) and physical component (PCS) to address each factor. *See id.*

² Alternative methods of calculating BASMI, including a discrete BASMI index, are also well-established.

32. ASQoL is a patient-reported functional and health index. Ex.2073 (Doward 2003) (Abstract). It serves as an indicator of overall health status and captures the impact of AS on the patient’s physical and mental health and quality of life. *Id.* at 25. Patient responses to the ASQoL questionnaire are measured 0-to-18, with higher scores indicating poorer quality of life. *Id.* at 22, 24.

33. ASAS20 is an outcome measure based on a patient’s self-assessment of disease. Ex.2069 at 1884 (Anderson 2001). The ASAS International Working Group defines the metric as a greater than or equal to 20% improvement from baseline in at least three of four categories and the absence of deterioration from baseline in the fourth category. *Id.* (Table 9). The four ASAS20 domains are (1) Patient Global Assessment of Disease Activity (measured 0-to-10), (2) Total Back Pain (measured 0-to-10), (3) Function (assessed by BASFI, measured 0-to-10), and (4) Inflammation (the average of two morning stiffness-related questions from the Bath Ankylosing Spondylitis Disease Activity Index (“BASDAI”) measured 0-to-10). *Id.* (Tables 9-10).

34. Although these metrics differ, they represent attempts to understand and characterize the state of a patient’s AS disease at a given time.

1. RA and AS Are Different Diseases

35. RA belongs to a class of seropositive rheumatologic diseases that is clinically distinct from the SpA family, which includes AS. Several key

differences distinguish these two conditions and render extrapolation of treatment plans between them methodologically unsound. Brockbank & Gladman 2002 provides a helpful visual of some key differences:

Table II. Distinguishing clinical features of psoriatic arthritis (PsA), rheumatoid arthritis (RA) and the other spondyloarthritides					
Clinical feature	PsA	RA	AS	Reactive	IBD
Gender	M = F	F > M	M > F	M > F	M = F
Peripheral joint pattern	Oligo/poly, asymmetric	Poly-articular, symmetric	Oligo-articular, lower limb	Oligo-articular, lower limb	Oligo-articular, lower limb
DIP joint	+++	+	–	–	–
Dactylitis	+++	–	+	++	+
Enthesitis	++	–	++	+++	++
Spondylitis	++	–	+++	+	++
Sacroiliitis	Asymmetric	–	Symmetric	Asymmetric	Symmetric
Eye involvement	+	++	++	+++	+
Nodules/Sjögren's	–	+++	–	–	–
Skin/nail lesions	+++	–	–	++	–
Rheumatoid factor positive	–	+++	–	–	–
AS = ankylosing spondylitis; DIP = distal interphalangeal; F = female; IBD = inflammatory bowel disease; M = male; + indicates low frequency of occurrence; ++ indicates medium frequency of occurrence; +++ indicates very high frequency of occurrence; – indicates feature did not occur.					

Ex.2118 at 2450 (Brockbank & Gladman 2002) (Table II).

36. The tissues affected by RA and AS differ substantially. RA patients experience inflammation primarily in the synovial compartment of peripheral joints (i.e., joints in the hands, feet, and wrists). Ex.2083 at S-11-12 (Lories 2009). RA patients also commonly develop rheumatoid nodules, or benign lumps below the skin. *Id.* at S-12.

37. The hallmark of AS, by contrast, is severe inflammation in the sacroiliac joint, which is the junction between the base of the spine and the pelvis. Ex.2076 at 237 (Ghasemi-rad 2015). AS patients also commonly experience inflammation in the enthesal tissue (the sites of bony insertion of ligaments and tendons throughout the body) and axial joints (i.e., joints in the

spine, hip, and shoulders). Ex.2074 at 15 (Elyan 2006). Spinal inflammation causes AS patients pain and can progress into loss of mobility. *Id.*

38. Although not the main feature, the disease may also cause inflammation in the peripheral joints, skin, eyes, and gut. *Id.*; Ex.2083 at S-10-11 (Lories 2009). The pathogenesis of RA and AS differ significantly with RA being predominantly a synovitis (inflammation of the joints with bone destruction) while AS has a major component of enthesitis (inflammation of the tissues surrounding the joints with bone formation). Ex.2086 (McGonagle 1998). AS also presents with features of extra-articular manifestations (“EMM”), such as significant presence of inflammatory bowel disease (“IBD”), psoriasis, and uveitis. Ex.2076 at 241 (Ghasemi-rad 2015). The EMMs differ between AS and RA, including atlanto-axial dislocation, interstitial lung disease, vasculitis, neuropathy, and amyloidosis as seen in RA patients but not in AS patients.

39. The pattern of structural damage also differs: RA patients have progressive bone erosion accompanied by cartilage destruction, whereas AS patients have new bone formation, including syndesmophytes (bony growths or calcification on the spine) and ankylosis, or spinal fusion. *Id.* at 242; Ex.2096 at 1 (Schett 2011). Severe cases are colloquially referred to as “bamboo spine,” in which calcification causes all cartilage in the spine to become bone, fusing the spine and leading to immobility. Ex.2076 at 238 (Ghasemi-rad 2015). Eye

involvement differs as well. The eye involvement in RA is predominantly inflammation of the covering of the eyes leading to scleritis or episcleritis and dryness of eyes due to lacrimal gland dysfunction (sicca syndrome). The eye involvement in AS is characterized by internal inflammation affecting the uveal tract (uveitis/iritis). Ex.2088 (Murray 2016).

40. At the pathogenic level, RA and AS differ in their immunological mechanisms. The human immune system works as two sets of connected responses: innate and adaptive immunity, each implicating different types of cells. Innate immunity is the body's first line of generalized defense that quickly recognizes common regions of pathogens to combat a broad range of threats without specificity. It is mediated in part by macrophages and mast cells (i.e., white blood cells). Ex.2083 at S-12 (Lories 2009). In contrast, adaptive immunity is a slower response that recognizes specific antigens and is associated with specialized helper B-cells that produce antibodies to bind and destroy specific pathogens. *Id.* By the priority date, it was believed that RA was primarily driven by activation of the adaptive immune system, whereas AS was driven predominantly by the innate immune system. *Id.* For example, therapy targeting B cells (rituximab) had limited efficacy in AS patients but was well known as effective in RA. Ex.2101 at 1290 (Song 2010) (Abstract).

41. In contrast to RA patients, AS patients are typically seronegative for the autoantibody called rheumatoid factor. Ex.2074 at 19 (Elyan 2006).

Rheumatoid factors are an important product of B cells, which constitute a prominent pathogenic cell population in RA. Ex.2120 at 2235 (Mease 2012). A patient's production of this antibody has thus become a key focus in RA treatment. *Id.*

42. The genetic underpinnings of the two diseases also diverge. Researchers identified a strong correlation between AS and the human leukocyte antigen B27 ("HLA-B27") marker that is encoded in the major histocompatibility complex ("MHC") I locus of chromosome 6. Ex.2076 at 238-39 (Ghasemi-rad 2015). By the priority date, it was understood that more than 80% of patients with AS carried HLA-B27. *Id.* at 239. RA has a stronger correlation with MHC Class II genes: HLA-DR1 and -DR4. Ex.2123 (Fugger & Svejgaard 2000) (Abstract). While each of RA and AS have many implicated genes, there is very little overlap between the two. Ex.2085 at S-24 (Maksymowych 2009).

43. The patient populations affected by RA and AS exhibit distinct demographic profiles. At the priority date, the RA patient population was approximately 75% female, whereas the AS population was approximately 75%

male.³ Ex.2093 at 99 (Rugiene 2008); Ex.2114 at 2 (Vollenhoven 2009).

Disease onset also differs: RA patients tend to develop symptoms later in life, while AS typically presents in younger individuals, often in their teens through their twenties. Ex.2074 at 12, 14 (Elyan 2006).

2. Treatments for RA and AS Are Different

44. Due to these differences, it was well established at the priority date that RA and AS require different treatment strategies.

45. The chronology of FDA-approved therapies for RA reveals a treatment landscape that evolved in distinct phases over more than six decades. The earliest available therapies, dating to the pre-1982 era, consisted almost exclusively of corticosteroids and nonsteroidal anti-inflammatory drugs (“NSAIDs”), which are agents that addressed symptoms of pain and inflammation but did not modify the underlying disease course or prevent progressive joint destruction.

46. Beginning in the mid-1980s through the late 1990s, a series of conventional synthetic disease-modifying antirheumatic drugs (“csDMARDs”) entered the RA drug landscape, representing the first therapeutic class capable of

³ This understanding has changed since 2017 with improved insight into non-radiographic axial SpA.

slowing radiographic disease progression, with MTX emerging as the anchor drug in most DMARD regimens. Ex.2117 at 18-19 (Weinblatt 2013). A paradigm shift occurred beginning in 1998 with the approval of the first biologic agents targeting TNF, interleukin-1 (“IL-1”) receptors, T-cells, CD20, IL-6 receptors, and Janus kinase (“JAK”). These products demonstrated sustained inhibition of bone erosion and structural damage in RA patients.

47. The treatment landscape for AS evolved far more slowly and with substantially fewer approved drug classes than RA: whereas RA saw the introduction of conventional synthetic DMARDs such as MTX and leflunomide beginning in the mid-1980s, these agents were shown to have no meaningful efficacy for spinal symptoms of AS, Ex.2079 (Haibel 2007) (Abstract), leaving NSAIDs as the sole pharmacological option for decades.

48. The first biologic TNF therapies did not receive AS-specific approvals until 2003 to 2013, lagging four to five years behind the same molecules’ RA approvals and reflecting a narrower evidentiary base. Critically, whereas RA patients gained access to non-TNF biologics targeting IL-1, IL-6, CD20, and T-cell costimulation between 2001 and 2017, studies on those same mechanisms in AS showed limited or no efficacy. *See* Ex.2102 (Song 2011); Ex.2098 (Sieper 2014); Ex.2101 (Song 2010); Ex.2078 (Haibel 2005).

49. The approval of an IL-17A inhibitor in early 2016 represented the first non-TNF biologic mechanism validated for AS. Ex.2066 at 1 (Cosentyx Label (2016)). This milestone had no parallel in the RA landscape, where IL-17 inhibition was explored but failed to demonstrate efficacy, despite success with other non-TNF inhibitors. Ex.2091 at 916 (Pavelka 2015). By the end of 2018, the AS treatment availabilities remained comparatively limited, comprising NSAIDs, TNF inhibitors, and an IL-17A inhibitor, while JAK inhibitors, which had already been available for RA since 2012, had not yet received AS approval. Thus, in addition to the differences in immune activation seen, the clear differences in response to different therapeutic agents speak to the distinct pathogenic mechanisms in AS and RA.

50. In developing treatment strategies for AS, a POSA would consider the differences from RA with predominant enthesal and innate immune mediated disease in AS while there is more adaptive immune system mediated synovitis in RA. Ex.2102 at 1109 (Song 2011). Overall, the potential differences of age group, sex distribution, and the presence of musculoskeletal disease in AS would weigh on the mind for potential pharmacokinetic and pharmacodynamic (“PK/PD”) and treatment differences in the two diseases.

51. As such, not every biologic effective in RA is equally effective in AS. Tocilizumab, for example, is approved for RA but failed in AS. *See*

Ex.2098 at 95, 99 (Sieper 2014) (“TCZ is not an effective treatment for patients with AS.”). Similarly, not every anti-TNF agent effective in RA is effective in AS at the same dosage: infliximab requires a higher, more frequent dose for AS than for RA. *See* Ex.2068 (Remicade Label). To treat RA, Remicade (infliximab) is prescribed in conjunction with MTX, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks, but its approved regimen for AS is 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks without concomitant MTX. *Id.*

52. These disease distinctions carry implications for immunogenicity and treatment protocols. Use of MTX in RA had been shown to prolong treatment efficacy, which had not been shown in AS. Ex.2122 at S-31 (Ruderman 2013); Ex.2079 (Haibel 2007) (Abstract). This difference is reflected in the prescribing requirements: whereas all RA patients must receive concomitant MTX with Simponi, no such requirement applies to AS patients. Ex.1015 at 1 (PI2015-Simponi).

D. Antibodies

53. Antibodies are proteins each made up of several distinct polypeptides (amino acids connected in sequence by peptide bonds). An antibody’s 3D structure is dictated primarily by the sequences of these amino acids. The Y-shaped 3D structure of a typical antibody is made up of two pairs of polypeptide chains: two identical “heavy” chains and two identical “light”

chains. The heavy and light chains each contain a so-called “variable region” connected to a “constant region.”

54. Within both the heavy and light chain variable domains, there are three segments where amino acid sequence variability is especially concentrated—these are called hypervariable regions, designated HV1, HV2, and HV3. *See* Ex.2080 at 1 (Janeway 2001). Structurally, the hypervariable sequences correspond to three loops located at the outer edge of the domain. *Id.* When the heavy and light chain variable domains pair together, these hypervariable loops from each domain are brought together, creating a single combined binding site at the tip of each arm of the Y-shaped antibody molecule. *Id.*

55. Because these loops form a surface that is complementary in shape to the antigen, they are more commonly referred to as complementarity-determining regions, or CDRs (CDR1, CDR2, and CDR3). *Id.* Because CDRs from both the heavy and light chain variable domains contribute to the antigen-binding site, it is the combination of the heavy and light chain—not either alone—that determines the antibody’s final antigen specificity. *Id.* “[A]s the amino acid sequences of the CDRs are different in different antibodies, so are the shapes of the surfaces created by these CDRs.” *Id.* at 2. Thus, in terms of antigen binding, the six CDRs determine the function and specificity of an

antibody, and a POSA would understand these sequences to be a definitive feature of that antibody.

E. IV and SC Formulations Have Different Pharmacokinetic Profiles

56. PK/PD parameters differ materially between SC and IV administration. PK describes the time course of drug exposure in patients at the population level. Ex.2087 at 1 (Mould 2013). PD describes what the drug does to the body. Ex.2107 at 1 (Upton 2014). The literature demonstrates that IV administration of golimumab produces substantially higher peak serum concentration (“C_{max}”), or highest amount of product in the blood after administration, and area under the curve (“AUC”), or total drug exposure, compared to SC administration. *See* Ex.1038 (Zhuang). Despite its higher C_{max}, serum concentration levels after IV administration drop very quickly.

57. During the development of IV golimumab for RA, the FDA raised two significant concerns about Janssen’s proposal to submit a supplemental Biologics License Application (“BLA”) for IV golimumab. First, the FDA determined that IV and SC golimumab are “two separate and distinct products because they have different pharmacokinetic characteristics, dosing regimens, and product presentations.” Ex.1034 at 127 (CDER Review). Second, because the IV regimen results in “greater maintenance dose” and “greater exposure,” the FDA concluded that the IV formulation faced a heightened risk of malignancy.

Id. “Given the differences of the IV and SC regimens,” the FDA required “evidence of independent substantiation of the efficacy of IV golimumab.” *Id.*

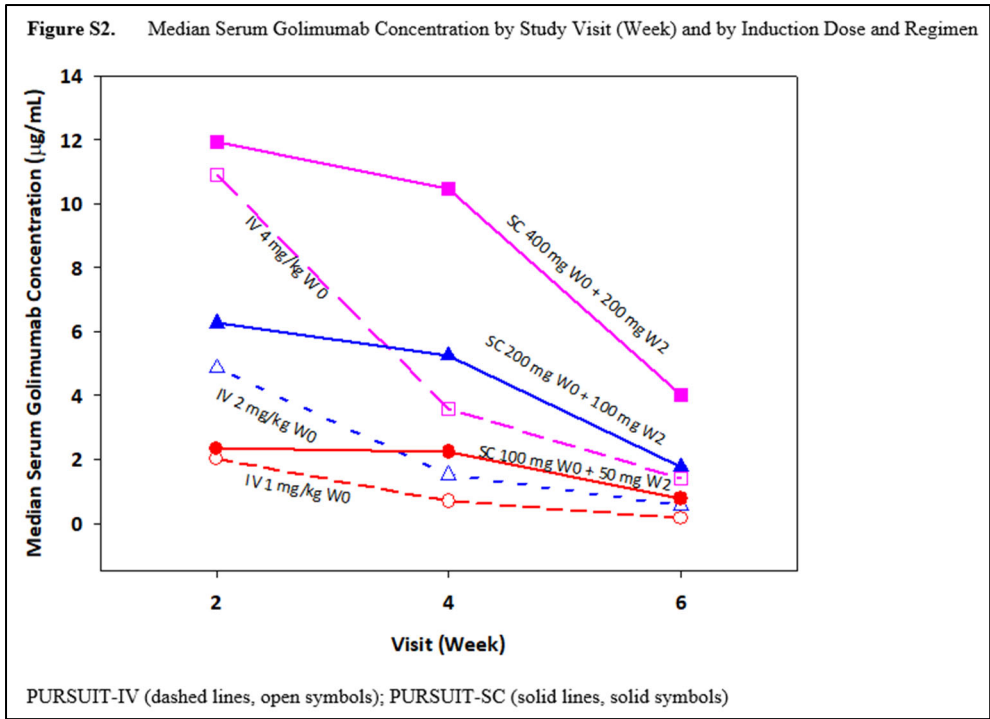
58. Other regulatory authorities shared these concerns. In 2013, the European Medicines Agency (“EMA”) denied approval for Simponi IV because of the threat that the PK/PD profile posed to patient safety. Ex.2052 at 59 (Oct. 24, 2013, EMA Simponi Withdrawal Assessment Report). The EMA withdrawal report stated the “C_{max} that is 6 times higher and AUC which is 3 times higher than that of SC administration, raises uncertainty regarding the safety profile” and concluded that these safety risks outweighed the insufficient efficacy advantages identified. *Id.*

59. While the high peaks in C_{max} seen in IV administration raised safety concerns, the correspondingly sharper troughs—reflecting accelerated drug clearance—could give a POSA independent concerns about whether the IV formulation could maintain sustained therapeutic exposures necessary for effective treatment. *See* Ex.2095 at 13 (Rutgeerts Supplemental Appendix) (Fig. S2). Moreover, IV administration had been shown to produce far more variability in these parameters compared to SC administration, where gradual absorption yields steadier serum concentrations. *Id.*

60. Janssen’s experience with intravenous golimumab in UC provides instructive clinical context for the subsequent AS development program. The

Phase II/III UC induction study was designed to evaluate IV golimumab at doses intended to achieve systemic drug exposures comparable to the approved SC regimen (PURSUIT-IV). Ex.2094 at 509-10 (Rutgeerts 2015). “[T]he 1-, 2- and 4-mg/kg IV golimumab single infusion induction regimens were expected to provide comparable systemic drug exposure (area under the concentration-time curve) as the three SC golimumab induction regimens assessed in PURSUIT-SC.” *Id.* However, the study failed to demonstrate a “dose-response” and achieved “lower than expected” efficacy, which was “less than observed in the SC induction study” (PURSUIT-SC). *Id.* at 504; *see* Ex.2090 at 332 (Naganuma 2016).

61. Rutgeerts et al. studied three dose levels in each of SC and IV. Ex.2094 at 510 (Rutgeerts 2015). At each corresponding IV and SC dose level, serum golimumab concentration levels for the IV dosage dropped at a faster rate than its SC counterpart, as shown in the figure below. *Id.*



Ex.2095 at 13 (Rutgeerts Supplemental Appendix) (Fig. S2). This figure also shows that the trough or lowest serum concentration (“ $C_{\min}$ ”) drops lower in the IV dose level compared to its corresponding SC dose. The gradual reduction in serum golimumab concentration after SC administration is starkly different from the steeper drops seen after IV administration. Thus, this figure exemplifies how SC administration creates a “reservoir” effect. In other words, SC administration injects the drug product into the patient’s subcutaneous tissue, which then releases the product into the bloodstream gradually. This is slow and steady drug exposure as compared to the IV administration, which infuses the entire dose directly into the bloodstream, causing the high $C_{\max}$ to quickly drop. As I discuss below, these substantial differences in PK profile raised serious concerns

regarding the predictability, safety, and efficacy of the IV product prior to the patented invention.

62. Thus, the clinical results did not support continuing to pursue approval, and therefore the Phase III study was terminated. Ex.2094 at 510 (Rutgeerts 2015); Ex.2058 (NCT774). Rutgeerts et al. noted “[t]he overall benefit from a single golimumab infusion was lower than expected across all efficacy measures and in comparison with PURSUIT SC.” Ex.2094 at 510. Despite Simponi’s long-established UC indication, Simponi Aria has never received FDA approval for UC. This unsuccessful translation from SC to IV formulations within the same molecule and disease state underscores the inherent PK and PD uncertainties that confronted investigators at the inception of the Simponi Aria AS clinical trials.

63. Accordingly, results from a study on one route of administration cannot reliably be assumed to apply to the other.

VIII. The ’566 Patent (Ex.1004)

64. The ’566 Patent is titled “Anti-TNF Antibodies, Compositions, and Methods for the Treatment of Active Ankylosing Spondylitis.” Ex.1004 (’566 Patent) (Title). It discloses “methods utilizing anti-TNF antibodies having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) comprising SEQ ID NO:37 for use in the safe and effective treatment of active Ankylosing

Spondylitis.” *Id.* (Abstract). SEQ ID NOS: 36 and 37 correspond to golimumab. *Id.* at 79:4-5.

65. The ’566 Patent describes a clinical study performed to show that golimumab is effective to treat AS when administered intravenously, with or without MTX. *Id.* at 78:60-110:46. For example, the clinical study demonstrated that, 16 weeks after the start of treatment, AS patients receiving 2 mg/kg IV golimumab at weeks 0, 4, and every 8 weeks thereafter, achieved improvements in several criteria, including ASAS20. *Id.* at 105:27-106:19. Some patients in the study continued treatment with stable doses of MTX, sulfasalazine (“SSZ”), and hydroxychloroquine (“HCQ”), while others did not. *Id.* at 96:17-38.

66. The ’566 Patent has three independent claims. Independent claim 1 of the ’566 Patent recites:

1. A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising: administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising:

- a. a heavy chain (HC) complementary determining region (CDR) 1 comprising an amino acid sequence of SEQ ID NO: 1;
- b. a HC CDR2 comprising an amino acid sequence of SEQ ID NO: 2; wherein position 1 of SEQ ID NO: 2 is phenylalanine, position 2 of SEQ ID NO: 2 is methionine, position 3 of SEQ ID NO: 2 is serine,

position 4 of SEQ ID NO: 2 is tyrosine, position 10 of SEQ ID NO: 2 is lysine, position 11 of SEQ ID NO: 2 is tyrosine, and position 17 of SEQ ID NO: 2 is glycine;

c. a HC CDR3 comprising an amino acid sequence of SEQ ID NO: 3; wherein position 4 of SEQ ID NO: 3 is isoleucine, position 5 of SEQ ID NO: 3 is alanine, and position 9 of SEQ ID NO: 3 is asparagine;

d. a light chain (LC) CDR1 comprising an amino acid sequence of SEQ ID NO: 4; wherein position 7 of SEQ ID NO: 4 is tyrosine;

e. a LC CDR2 comprising an amino acid sequence of SEQ ID NO: 5; and

f. a LC CDR3 comprising an amino acid sequence of SEQ ID NO: 6, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via IV infusion at a dose of 2 mg/kg, administered over 30±10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, and wherein a patient treated with the composition achieves an Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at 4 weeks of treatment or at 2 weeks of treatment.

Id. at 131:34-67 (claim 1).

67. Independent claim 3 of the '566 Patent recites:

3. A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising: administering a composition comprising a safe and

effective amount of at least one isolated mammalian anti-TNF antibody comprising:

- a. a heavy chain (HC) complementary determining region (CDR) 1 comprising an amino acid sequence of SEQ ID NO: 1;
- b. a HC CDR2 comprising an amino acid sequence of SEQ ID NO: 2; wherein position 1 of SEQ ID NO: 2 is phenylalanine, position 2 of SEQ ID NO: 2 is methionine, position 3 of SEQ ID NO: 2 is serine, position 4 of SEQ ID NO: 2 is tyrosine, position 10 of SEQ ID NO: 2 is lysine, position 11 of SEQ ID NO: 2 is tyrosine, and position 17 of SEQ ID NO: 2 is glycine;
- c. a HC CDR3 comprising an amino acid sequence of SEQ ID NO: 3; wherein position 4 of SEQ ID NO: 3 is isoleucine, position 5 of SEQ ID NO: 3 is alanine, and position 9 of SEQ ID NO: 3 is asparagine;
- d. a light chain (LC) CDR1 comprising an amino acid sequence of SEQ ID NO: 4; wherein position 7 of SEQ ID NO: 4 is tyrosine;
- e. a LC CDR2 comprising an amino acid sequence of SEQ ID NO: 5; and
- f. a LC CDR3 comprising an amino acid sequence of SEQ ID NO: 6, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via IV infusion at a dose of 2 mg/kg, administered over 30±10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, and wherein at week 16 of treatment patients treated with the anti-TNF antibody achieve a mean change from baseline in one or more criteria selected from the group consisting of:

Bath Ankylosing Spondylitis Functional Index (BASFI)=-2.4±2.1 Standard Deviation (SD), Bath Ankylosing Spondylitis Metrology Index (BASMI)=-0.4±0.6 SD, 36-item Short-Form Health Survey Physical Component Summary (SF-36 PCS)=8.5±7.5 SD, 36-item Short-Form Health Survey Mental Component Summary (SF-36 MCS)=6.5±9.1 SD, and Ankylosing Spondylitis Qualify of Life questionnaire (ASQoL)=-5.4±5.0 SD.

Id. at 132:37-133:12 (claim 3).⁴

68. Independent claim 5 of the '566 Patent recites:

5. A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising: administering a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising:

a. a heavy chain (HC) complementary determining region (CDR) 1 comprising an amino acid sequence of SEQ ID NO: 1;

b. a HC CDR2 comprising an amino acid sequence of SEQ ID NO: 2; wherein position 1 of SEQ ID NO: 2 is phenylalanine, position 2 of SEQ ID NO: 2 is methionine, position 3 of SEQ ID NO: 2 is serine, position 4 of SEQ ID NO: 2 is tyrosine, position 10 of SEQ ID NO: 2

⁴ I understand that “Qualify” is a clerical error and that this limitation relates to ASQoL.

is lysine, position 11 of SEQ ID NO: 2 is tyrosine, and position 17 of SEQ ID NO: 2 is glycine;

c. a HC CDR3 comprising an amino acid sequence of SEQ ID NO: 3; wherein position 4 of SEQ ID NO: 3 is isoleucine, position 5 of SEQ ID NO: 3 is alanine, and position 9 of SEQ ID NO: 3 is asparagine;

d. a light chain (LC) CDR1 comprising an amino acid sequence of SEQ ID NO: 4; wherein position 7 of SEQ ID NO: 4 is tyrosine;

e. a LC CDR2 comprising an amino acid sequence of SEQ ID NO: 5; and

f. a LC CDR3 comprising an amino acid sequence of SEQ ID NO: 6, wherein said anti-TNF antibody is administered via intravenous (IV) infusion at a dose of 2 mg/kg, administered over 30±10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, and wherein ≥65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.

Id. at 133:17-134:20 (claim 5).

69. I understand that during prosecution of the '566 Patent, the Examiner initially issued multiple rejections on the pending claims, including a rejection as obvious via Wong (Ex.1024) in view of Zhuang (Ex.1038), but ultimately allowed the claims because the prior art did not disclose the dosage and infusion time to treat AS. Ex.2002 at -383-84.

IX. Summary of the Art

A. NCT02186873 (“NCT873-V24”) (Ex.1014)

70. NCT873-V24 is a version of a clinical trial protocol titled “A Study of Golimumab in Participants with Active Ankylosing Spondylitis.” The protocol discusses administering golimumab IV to AS patients.

71. NCT873-V24 is missing several parameters found in the ’566 Patent claims and specifications that a POSA would understand to impact the likelihood of the study achieving the claimed clinical endpoints. Key differences include patient population criteria, such as “active” AS, spinal fusion, and medical history.

72. The ’566 Patent claims methods for treating “active” AS, which is defined in the specification. *See, e.g.*, Ex.1004 at cls. 1, 3, 5 (’566 Patent). Example 9 states that patients have “active” AS if they meet BASDAI ≥ 4 and Visual Analogue Scale (“VAS”) ≥ 4 . *Id.* at 79:59-65, 88:48-53, 89:51-54. At the priority date, BASDAI and VAS measured pain on a sliding scale from 0-to-10 cm. *Id.* at 97:60-98:3. NCT873-V24 does not disclose these criteria for active AS, and a POSA would not have understood that protocol to necessarily require the same BASDAI score or VAS score.

73. In my experience, how clinicians consider AS disease to be active can vary. The definition of active disease can be different even while designing

clinical trials. While BASDAI may be employed, a different threshold for inclusion could be used. For example, in Haibel et al.'s pre-priority study of leflunomide in AS, patients were permitted to enter the study with each of BASDAI and spinal pain as low as 3. Ex.2077 (Haibel 2005). BASDAI may be completely avoided in the definition of active AS.

74. Different baseline BASDAI and VAS levels may reflect different severity of disease and may therefore also affect whether patients meet the other claimed clinical endpoints, as well. Studies have recognized baseline BASDAI as an important feature affecting rates of clinical response to TNF inhibitors. *See* Ex.2119 (Lord 2009) (Table 3). Thus, where NCT873-V24 is silent, the number of patients qualifying for studies can vary based on the definition of active disease, and this in turn can affect the achievement of the claimed clinical endpoints.

75. The '566 Patent specification defines complete ankylosis of the spine as having bridging syndesmophytes present at all intervertebral levels. The patient population may include 10% of subjects with that condition. *See, e.g.,* Ex.1004 at 88:66-89:4, 105:40-43 ('566 Patent). NCT873-V24 does not disclose whether there are any restrictions with respect to complete ankylosis of the spine. From my experience, different researchers use varied definitions of complete ankylosis of the spine. For example, the Phase III COAST-V and COAST-W

clinical studies of ixekizumab in radiographic axial SpA excluded any patient with complete ankylosis of the spine. Exs.2062-63 (NCT785, NCT798).

76. A POSA would understand that patients with complete spinal fusion have worsened functionality and irreversible structural damage representative of later disease state that was less likely to be ameliorated by the medical therapies available at the time. Including such patients in the study population could dilute the measurable treatment effect on functional and mobility endpoints, introducing uncertainty regarding whether the claimed clinical endpoints would be achieved. For example, complete spinal fusion affects ASAS20, because spinal fusion reflects late disease state. Similarly, it impacts the achievement of the BASFI and BASMI clinical endpoints, as spinal fusion is irreversible, so these patients could continue to experience restriction of mobility despite treatment.

77. The '566 Patent specification also requires the study subjects have “prior exposure to no more than one biologic anti-TNF α agent (other than golimumab),” and those patients that do have exposure to an additional agent “will be limited to at most 20% of the study population.” Ex.1004 at 88:62-65, 105:40-43 ('566 Patent). NCT873-V24, however, includes no inclusion or exclusion criteria based on other antibody treatments. A POSA would not have been able to predict the population criteria applied, as there are many studies that purposefully permit different levels of prior exposure. The Phase III COAST-V

and COAST-W clinical studies of ixekizumab in radiographic axial SpA are prime examples, as the former required patients to be TNF-inhibitor naive, and the latter required patients to be TNF-inhibitor experienced. Exs.2062-63 (NCT785, NCT798). In my opinion, whether subjects could meet the claimed clinical endpoints cannot be predicted without this information, which is missing from NCT873-V24.

78. Prior exposure to other TNF inhibitors can lead to reduced clinical efficacy of future antibody treatments, although the cause for this was unclear at the priority date. For instance, in the MEASURE 2 study of secukinumab in AS patients, around 39% of patients had experienced one TNF inhibitor in the past and had lower ASAS20 responses compared to biologic-naïve patients. Ex.2100 at 573-74 (Sieper 2017). Another study on golimumab in UC patients showed that patients who received SC golimumab as a first line therapy experienced a higher response compared to those who used the product as a third line. Ex.2105 (Taxonera 2017) (Abstract). NCT873-V24 could have enrolled more patients with prior exposure to TNF inhibitors, who would be expected to have diminished responses. In my opinion, this makes achievement of the claimed clinical endpoints unpredictable.

79. The '566 Patent specification details the discontinuation process and population set analysis, whereas NCT873-V24 is silent. *See, e.g.*, Ex.1004 at

82:25-30, 103:18-23 ('566 Patent). There are two ways to calculate efficacy analyses—as an intent-to-treat population or per-protocol population. *See* Ex.2081 at 1021-22 (Kavanaugh 2014). In Example 9 disclosed in the '566 Patent, researchers employed an intent-to-treat analysis, meaning that all randomized subjects were included in the analysis regardless of whether they completed the treatment program. *Id.* The same is not true of per-protocol studies. NCT873-V24 does not specify when and how patients should be withdrawn from the study for safety or lack of efficacy, or how that patient would be considered in the endpoint analysis. This missing analysis adds additional uncertainty about whether subjects would meet the claimed clinical endpoints. Ex.2071 (Bai 2021) (Abstract).

80. NCT873-V24 states “[a]dditional protocol-defined inclusion criteria apply” and “[a]dditional protocol-defined exclusion criteria apply” without providing more information. Ex.1014 at 8-9 (NCT873-V24). These additional inclusion and exclusion criteria could cause the clinical endpoints from NCT873-V24 to deviate even further from those claimed in the '566 Patent.

81. For example, a POSA would have been familiar with clinical trials in axial SpA that used objective evidence of inflammation in the form of magnetic resonance imaging (“MRI”) or inclusion criteria requiring either MRI or HLA-B27 expression, including the ABILITY-1 Phase III trial on

adalimumab. Ex.2059 at 5 (NCT003) (“Magnetic resonance imaging (MRI) indicating active sacroiliitis or positive human leukocyte antigen-B27 (HLA-B27) blood test in addition to meeting spondyloarthritis clinical criteria”).

Studies have shown better response to TNF inhibitor therapy in AS patients with MRI evidence of spinal inflammation. Ex.2092 at 1281 (Rudwaleit 2008). As mentioned above, a POSA would have also seen clinical trial protocols require prior primary failure of anti-TNF therapy, which had been shown to impact a patient’s likelihood of achieving the clinical endpoints. Because NCT873-V24 refers to additional inclusion and exclusion criteria without specifying what those criteria are, there is no way to confirm whether the claimed clinical endpoints would actually be achieved under NCT873-V24’s incomplete patient selection methodology.

B. PI2015-Simponi (Ex.1015)

82. PI2015-Simponi is a version of the prescribing information for Simponi, Janssen’s subcutaneous formulation of golimumab. PI2015-Simponi describes SC administration of golimumab to treat AS, but it does not disclose the ’566 Patent’s claimed administration route or meeting any of the claimed clinical endpoints. It notes that “[t]here was no clear evidence of improved ASAS response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).” Ex.1015 at 29 (PI2015-Simponi). The

AS study described in PI2015-Simponi assessed clinical results at week 14, as opposed to the '566 Patent's claimed week 16 clinical endpoint limitations.

C. PI2013-Aria (Ex.1032)

83. PI2013-Aria is a version of the prescribing information for Simponi Aria. It only describes IV golimumab with required concomitant MTX for the treatment of adults with active RA. It does not contain any clinical trial data on IV golimumab to treat active AS.

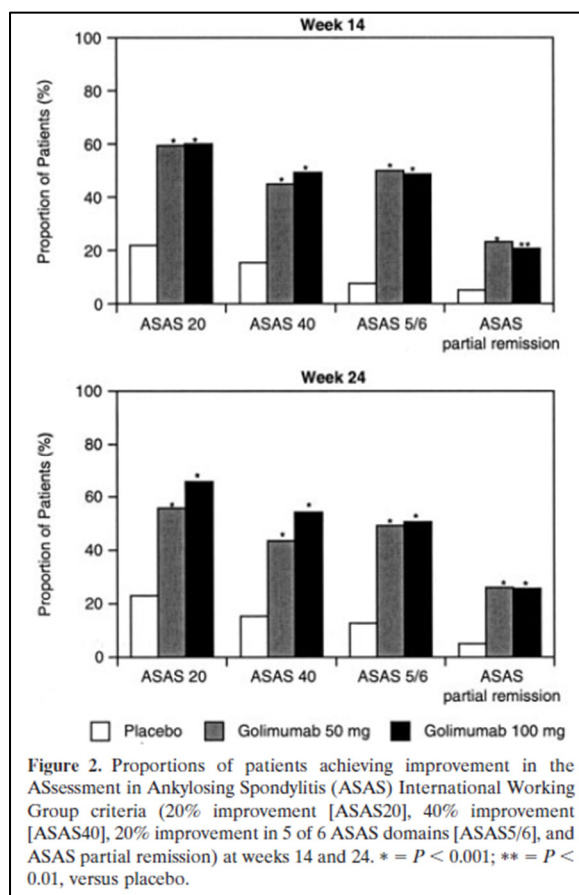
84. PI2013-Aria does not disclose any claimed clinical endpoints for AS, nor does it describe meeting any of the claimed clinical endpoints used to assess treatment of AS. It is directed exclusively to RA, a disease known by the priority date to have a different pathology, affected tissues, and patient population from AS, as well as requiring a different treatment strategy.

D. Inman (Ex.1016)

85. Inman discusses the results at weeks 14 and 24 of a Phase III clinical trial on SC administration of golimumab to treat active AS. The study's patient population excluded subjects with complete ankylosis of the spine and excluded subjects with any previous use of anti-TNF therapy. Ex.1016 at 3403. Inman does not contain any clinical trial data on IV golimumab to treat active AS.

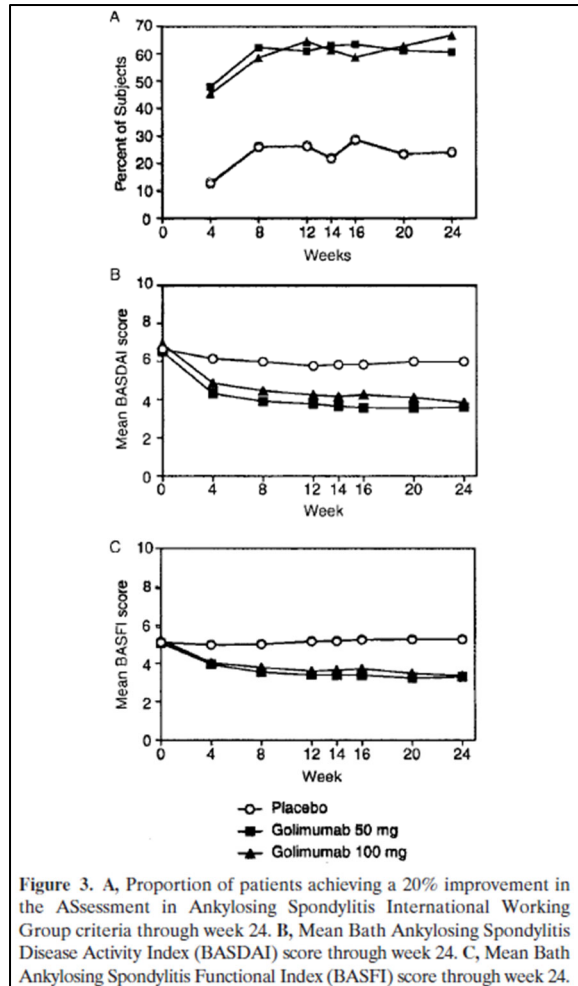
86. The study described by Inman compares results from two SC dosage regimens: 50 mg every four weeks ("q4w") and 100 mg q4w. Inman reported

that 59.4% and 60% of patients receiving 50 mg and 100 mg of SC golimumab, respectively, achieved ASAS20 at week 14, compared to 21.8% for subjects receiving placebo. Inman Figure 2 provides a visualization of these results:



Ex.1016 at 3406 (Inman) (Fig. 2).

87. Inman also reported mean BASDAI and BASFI scores for patients receiving SC golimumab at 50 or 100 mg q4w, or placebo. Inman Figure 3 provides a visualization of these results:



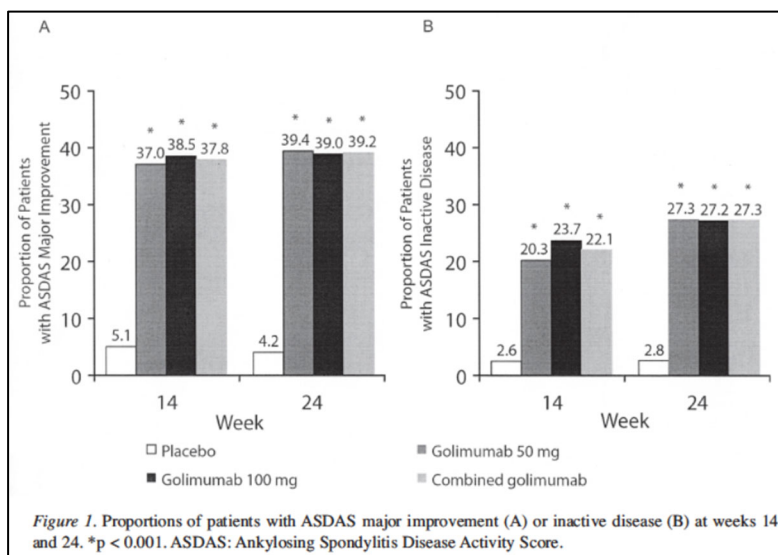
Id. (Fig. 3).

E. van der Heijde (Ex.1033)

88. Like Inman, van der Heijde provides two-year results from the same Phase III clinical trial on SC golimumab at 50 mg or 100 mg q4w for the treatment of AS. The study's patient population excluded subjects with complete ankylosis of the spine and excluded subjects with any previous use of anti-TNF therapy. Ex.1033 at 1096 & n.18; Ex.1016 at 3403 (Inman). Again, van der

Heijde does not contain any clinical trial data on IV golimumab to treat active AS.

89. Van der Heijde reports on the comparative efficacy of the two dosages for SC golimumab in ASDAS and SF-36 scores. It describes that “[s]ignificantly greater proportions of patients in Groups 2 [50 mg] and 3 [100 mg] achieved ASDAS major improvement when compared with Group 1 [placebo] at both Week 14 (37.0% and 38.5% vs 5.1%; $p < 0.001$) and Week 24 (39.4% and 39.0% vs 4.2%; $p < 0.001$; Figure 1).” Ex.1033 at 1097 (van der Heijde). Van der Heijde Figure 1 provides a visual representation of these results:



Ex.1033 at 1099 (van der Heijde) (Fig. 1).

X. Claim Construction

90. I understand that Petitioners have presented the following claim constructions for terms in the '566 Patent independent claims.

A. “Treating” in the Preamble Is Limiting

91. I understand that Petitioners argue that “treating” in the preamble should not be construed as limiting because they claim it does not modify the active step of “administering,” and that even if “treating” were limiting, it merely means administering the claimed dosing regimen to a patient “regardless of clinical benefit.” Pet. 35-36. In my opinion, this construction is inconsistent with a POSA’s reading of the claims.

92. A POSA would understand “treating” to require that administration be carried out as a therapy and that it actually constitutes treatment of active AS, not the mere injection of a biologic into a human without regard to therapeutic purpose. Both the specification and the claims support this construction: the specification repeatedly describes the therapeutic purpose of the invention, including the clinical trial designed to evaluate efficacy in treating AS, Ex.1004 ('566 Patent) (Example 9), while the claims recite specific AS-focused clinical endpoint values as a measure of treatment efficacy. Further, the preamble helps to inform the requirement that the treatment is “safe and effective.” Thus, in my

opinion, the preamble meaningfully limits the claims' practice of administering golimumab.

B. Claimed Clinical Endpoints Are Limiting

93. I understand Petitioners assert that the clinical endpoints recited in the claims are merely the "intended results" of the method and should not be considered when comparing the claims to the prior art. Pet. at 2, 36-38.

94. In my opinion, a POSA would understand the clinical endpoints are meaningful limitations because they define the specific efficacy that golimumab, the treatment administered in the active steps of the claims, is proven capable of achieving in the patented invention. As I discuss below, the claimed efficacy outcomes are not inherent in the active method step of administering golimumab, and a POSA would recognize that clinical efficacy is not predetermined by an administration regimen alone. Identical dosing regimens can yield materially different efficacy outcomes depending on variables including: (a) patient population demographics (disease duration, baseline disease activity severity, prior biologic exposure, comorbidities); (b) concomitant pharmacotherapy (MTX, corticosteroids); (c) treatment adherence and dropout rates; (d) the statistical analysis plan employed; and (e) inherent biological variability across patient populations. Thus, in my opinion, the claimed clinical endpoints meaningfully limit the claims' practice of administering golimumab.

XI. Ground 1: NCT873-V24 Does Not Anticipate the '566 Patent Claims⁵

95. In my opinion, NCT873-V24 does not anticipate the claims of the '566 Patent. At this stage, I have been asked to focus on the independent claims of the '566 Patent. I reserve the right to provide further opinions should the inter partes review proceed.

96. The NCT873-V24 clinical trial protocol does not disclose at least the following claim limitations:

- “at least one pharmaceutically acceptable carrier or diluent” (claims 1, 3);
- “administered over 30±10 minutes” (claims 1, 3, 5)
- “a patient treated with the composition achieves an Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at 4 weeks of treatment or at 2 weeks of treatment” (claim 1);
- “at week 16 of treatment patients treated with the anti-TNF antibody achieve a mean change from baseline in one or more criteria selected from the group consisting of: Bath Ankylosing Spondylitis Functional Index (BASFI)=−2.4±2.1 Standard Deviation (SD), Bath Ankylosing Spondylitis Metrology Index (BASMI)=−0.4±0.6 SD, 36-item Short-Form Health Survey Physical Component Summary (SF-36 PCS)=8.5±7.5 SD, 36-item

⁵ My opinions regarding Ground 1 apply to Ground 2 as well.

Short-Form Health Survey Mental Component Summary (SF-36 MCS)=6.5±9.1 SD, and Ankylosing Spondylitis Qualify of Life questionnaire (ASQoL)=−5.4±5.0 SD” (claim 3); and

- “≥65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment” (claim 5).

A. NCT873-V24 Does Not Expressly or Inherently Disclose “over 30±10 minutes”

97. NCT873-V24 does not disclose or describe any administration time, much less 30±10 minutes, for its IV infusion. Ex.1014. I understand that Petitioners admit as such. Pet. at 42. While I have been informed by counsel that Petitioners’ reliance on a second reference, PI2013-Aria, and a POSA’s understanding is legally improper, I further disagree with Petitioners’ statement that “[a] POSA would have understood that the same dose of IV golimumab in NCT873-V24 would be administered using the same infusion time as in the FDA-approved label.” Pet. 43.

98. As previously discussed in Section VII.C.1, a POSA would not extrapolate a treatment strategy for AS from a label indicated for a completely different disease. For example, a POSA would know that other TNF inhibitors were approved to treat AS at a higher, more frequent IV dosage than the approved regimen for RA. *See* Ex.2068 (Remicade Label). Regardless of the therapy, a treatment program for RA cannot be transposed into AS. Thus, in my

opinion, a POSA would not understand a study protocol that provides no administration time to necessarily instruct IV administration “over 30±10 minutes.”

B. NCT873-V24 Does Not Expressly or Inherently Disclose the Claimed Clinical Endpoints

99. Petitioners admit that NCT873-V24 does not provide any outcome from the clinical trial. Thus, I understand that Petitioners rely on inherent anticipation to assert that these limitations are disclosed by the reference. I also understand that inherent anticipation requires that the claimed clinical endpoints are “necessarily” met by NCT873-V24, and not just probable or possible.

100. In my opinion, a clinical trial protocol does not ensure any particular outcome. Clinical trials can and do fail. A POSA would understand that even two identically designed trials, run on different patient populations, could not be guaranteed to achieve the same clinical values due to potential variability in patient cohorts. Thus, the claimed clinical endpoints would not necessarily be achieved by the protocol in NCT873-V24. Having a study plan established does not ensure that efficacy will be achieved.

101. It is common knowledge to a POSA that many clinical trials studying therapeutics in treating AS have failed. For example, abatacept (Orencia) is a modulator that inhibits activity of T cells, which play key roles in the immune system response. Ex.2102 at 1108 (Song 2011). While already

approved for the treatment of RA, a Phase II clinical study of abatacept in patients with AS failed—the patients in the study experienced no significant changes in response for BASDAI, ASAS20, and ASDAS. *Id.* at 1109.

102. In 2014, sarilumab (Kevzara) failed to effectively treat AS patients in a Phase II clinical trial. Ex.2099 (Sieper 2015) (Abstract). However, sarilumab was later approved to treat RA. Ex.2067 (Kevzara Label).

103. Tocilizumab (Actemra) is a recombinant, humanized monoclonal antibody that binds to IL-6 receptors to inhibit IL-6-mediated signaling. Ex.2098 at 95 (Sieper 2014). By 2014, tocilizumab was widely approved as a treatment for adult patients with active RA and inadequate response to DMARD or anti-TNF therapy. *Id.* However, a Phase II-III clinical trial in patients with AS with similar non-response profiles failed. Researchers found tocilizumab was not effective in the treatment of AS and noted “[o]ther biologics, such as anakinra or abatacept, which have shown efficacy in RA, also failed in AS, suggesting a poorly understood difference in the inflammatory and immune-mediated pathways of different chronic conditions.” *Id.* at 99. Similarly, the study of IV golimumab in UC failed despite researchers’ reliance on knowledge of SC golimumab. Ex.2094 at 509-10 (Rutgeerts 2015); Ex.2058 (NCT774). These studies emphasize that the claimed clinical endpoints could not have been

inherently present in, or necessarily achieved by, the protocol as described in NCT873-V24, regardless of a POSA's knowledge or expectations.

104. In my opinion, the claimed clinical endpoints would not necessarily be met by the study protocol described in NCT873-V24. As discussed above in Section IX.A, many important factors of the clinical trial described in the '566 Patent are missing from the protocol version raised by Petitioners. Indeed, Example 9 of the '566 Patent describes many important procedures followed in the Phase III trial that impact the likelihood of success. Under these conditions, still some patients did not achieve ASDAS inactive disease by week 2 or 4, for instance. Ex.1004 ('566 Patent) (Table 9). A POSA would understand that, with key parameters absent from the practice as described, it would be scientifically inaccurate and inappropriate to assert that the claimed clinical endpoints would necessarily be achieved by NCT873-V24's discussion of administering golimumab.

105. Foremost, a POSA would understand that clinical endpoints are significantly influenced by the study's patient population. The specific clinical outcomes depend on the demographics, baseline disease activity, and other characteristics of the enrolled subjects. However, as I explained earlier, NCT873-V24 provides an incomplete picture of the study population described in the claimed invention. NCT873-V24 does not identify the patient population's

definition of “active” AS, spinal-fusion criteria, or prior biologic exposure criteria. These patient selection criteria would not have been known to a POSA from NCT873-V24 alone and bear directly on whether NCT873-V24 would meet the claimed clinical endpoints.

106. Without these key details, NCT873-V24 does not ensure the claimed clinical endpoints would be necessarily met.

XII. Ground 3: NCT873-V24, PI2013-Aria, PI2015-Simponi, van der Heijde, and Inman Do Not Render the ’566 Patent Claims Obvious

107. My opinions regarding Ground 1 also apply to Ground 3.⁶ A POSA would not understand the asserted combination of NCT873-V24, PI2013-Aria, PI2015-Simponi, van der Heijde, and Inman to render the ’566 Patent claims obvious.

A. The Combination of Art Does Not Expressly or Inherently Disclose the Claimed Clinical Endpoints

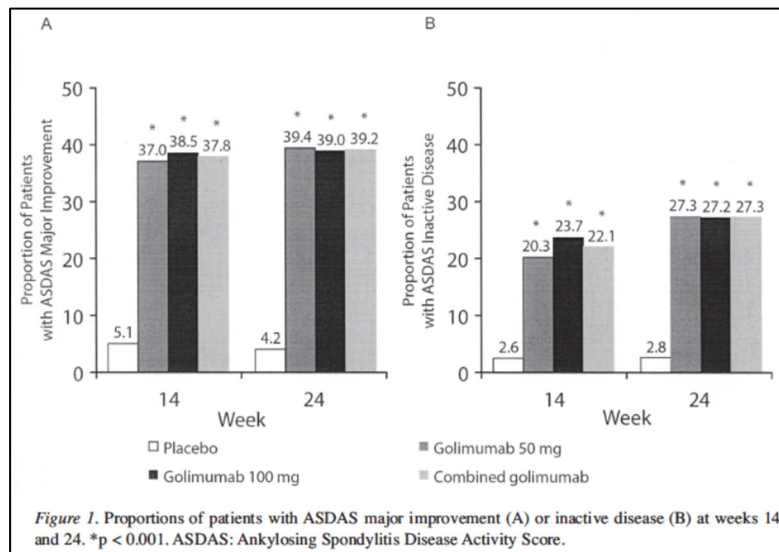
108. In my opinion, the data from the SC golimumab clinical trial reported in Inman and van der Heijde do not disclose achieving the clinical endpoint limitations in the ’566 Patent claims 1, 3, and 5.

⁶ As such, my earlier discussions regarding NCT873-V24, PI2015-Simponi, and PI2013-Aria, including their failure to disclose all limitations of the independent claims, apply accordingly to Ground 3.

1. **“a patient treated with the composition achieves an Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at 4 weeks of treatment or at 2 weeks of treatment” (claim 1)**

109. I understand Petitioners argue van der Heijde discloses the claimed ASDAS clinical endpoint. *See* Pet. 51-54. The data reported in van der Heijde differs materially from the claimed ASDAS clinical endpoint, such that a POSA would not have expected the claimed endpoint based on van der Heijde’s disclosure.

110. Van der Heijde reported ASDAS inactive disease data only at weeks 14 and 24 after SC administration—not at weeks 2 or 4 after IV administration as required by claim 1:



Ex.1033 at 1099 (van der Heijde) (Fig. 1).

111. Measurements taken ten or twenty weeks later than the claimed measurement dates would not inform a POSA of the claimed week 2 or week 4

results. The potential course of clinical response over that long period of time is not predictable, and disease activity scores at later timepoints cannot reliably be extrapolated backward to predict earlier outcomes.

112. I understand that Petitioners also argue that Inman’s reported improvements in ASAS20 would lead a POSA to expect “that at least some patients would have achieved ASDAS inactive disease by week 4.” *See* Pet. 51-54. However, a POSA would understand that ASAS20 and ASDAS are distinct metrics measuring different aspects of disease activity, as ASAS20 assesses symptomatic response based on patient-reported outcomes, whereas ASDAS measures overall disease activity by combining patient-reported symptoms with objective inflammatory markers. A POSA would thus know that improvement on one measure does not reliably predict achievement of inactive disease status on the other.

113. Additionally, Petitioners rely on a statement in van der Heijde that “significantly greater proportions ... had ASDAS inactive disease at weeks 14 and 24” to suggest this would have led a POSA to expect the claimed ASDAS clinical endpoint at week 2 or 4. *See* Pet. 51 (citing Ex.1033 at 1097 (van der Heijde)). This argument ignores that achieving ASDAS inactive disease requires reducing disease activity below an absolute threshold (<1.3), which depends on baseline disease severity and individual patient response—factors that cannot be

extrapolated from later-timepoint population data. Accordingly, the much later data in van der Heijde cannot be used to predict the claimed ASDAS clinical endpoint at weeks 2 and 4 and the rapid onset of inactive disease achieved by the '566 Patent.

114. Moreover, ASDAS inactive disease is difficult to achieve in clinical trials, especially where the patient's disease state is long established. A POSA would especially appreciate the rarity of a treatment achieving this clinical endpoint at week 2 or week 4. For instance, a contemporaneous study on tofacitinib in AS demonstrated clinical efficacy at week 12, but rates of ASDAS inactive disease were uniquely resistant, particularly at week 2 and week 4. Ex.2111 at 1341 (van der Heijde 2017); Ex.2112 at 13 (van der Heijde 2017 Supplementary Information) (Table S1). Combined with a POSA's understanding of the failed application of SC golimumab data to an IV formulation in the context of UC, as described above in Section VII.E, a POSA would not have expected the IV formulation to achieve the clinical endpoint so early. Thus, the references relied upon by the Petitioners would not render obvious the claimed clinical endpoint of ASDAS inactive disease.

2. “36-item Short-Form Health Survey Physical Component Summary (SF-36 PCS)=8.5±7.5 SD” (claim 3)

115. The SF-36 PCS data reported in van der Heijde differs materially from the claimed SF-36 PCS clinical endpoint, such that a POSA would not have

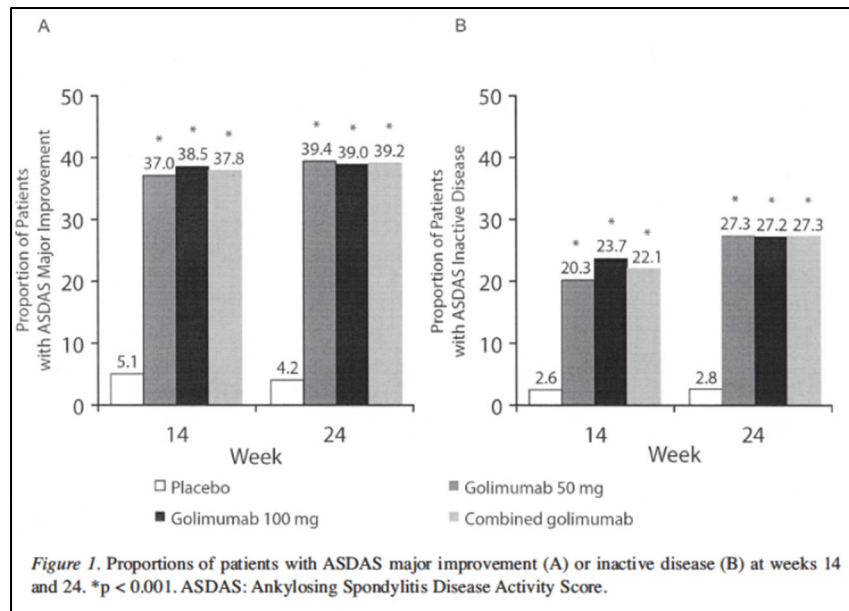
expected the claimed outcome based on van der Heijde's disclosure. Petitioners assert that "given that [v]an der Heijde reports mean changes in SF-36 PCS at week 14 of 8.8 and 8.9 for 50 and 100 mg SC doses, respectively, which are higher than the claimed mean changes, and given that a POSA would have known that IV golimumab has a higher bioavailability, C_{max} , and AUC than 100 mg SC golimumab, a POSA would have reasonably expected that an IV dose of 2 mg/kg of golimumab would achieve a mean change in SF-36 PCF [*sic*] of at least 8.5 ± 7.5 ." Pet. 56. This argument conflicts with the knowledge of a POSA as of the priority date.

116. Van der Heijde and Inman tested a different and potentially easier to treat patient population than the '566 Patent. For example, the van der Heijde and Inman patient population excluded subjects with complete ankylosis of the spine and excluded subjects with any previous use of anti-TNF therapy. Ex.1033 at 1096 & n.18 (citing Ex.1016, which describes patient population at 3403). The '566 Patent, by contrast, includes up to 10% subjects with complete ankylosing spondylitis and up to 20% subjects with prior exposure to an anti-TNF α agent. Ex.1004 at 88:62-65 ('566 Patent). As described above, including these patient populations can make achieving SF-36 PCS more challenging. Thus, by excluding these subjects, the reported SF-36 PCS in van der Heijde may have been artificially elevated relative to the more challenging patient population that

achieved the SF-36 PCS clinical endpoint claimed in the '566 Patent. For this reason, a POSA would not consider the SF-36 PCS reported in van der Heijde to be comparable to the clinical endpoint of claim 3 of the '566 Patent.

117. Petitioners ignore evidence that AUC and $C_{\max}$ are not necessarily correlated with efficacy. For example, while increased SC golimumab dosage may result in increased AUC and $C_{\max}$ (Ex.2053 at 21, 25 (BLA 125289 (SC) Clin. Pharm. Review), the contemporaneous literature reported that increase did not translate to meaningful improvement in clinical outcomes. *See* Ex.1016 at 3406 (Inman) (Figs. 2-3); Ex.1033 at 1099 (van der Heijde) (Fig. 1).

118. In the GO-RAISE trial, 50 mg and 100 mg SC golimumab doses produced comparable efficacy outcomes, indicating that dose-response relationships for golimumab are non-linear and that increased systemic exposure does not reliably translate into proportionately greater clinical benefit. Plainly, PI2015-Simponi states “[t]here was no clear evidence of improved ASAS response with the higher Simponi dose group (100 mg) compared to the lower Simponi dose group (50 mg).” Ex.1015 at 29 (PI2015-Simponi). Also, van der Heijde’s visualization of the ASDAS results emphasizes the similar efficacy between the tested dosages:



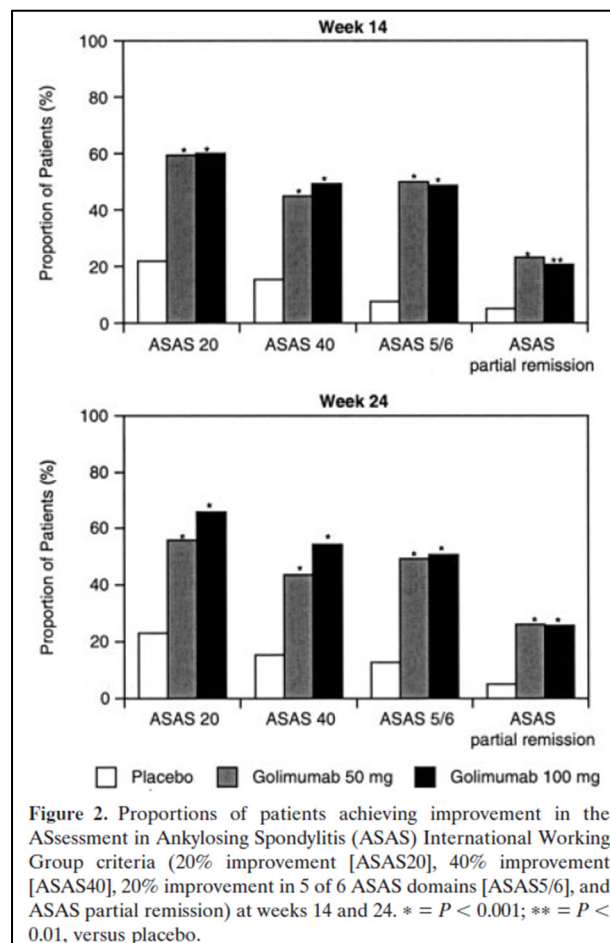
Ex.1033 at 1099 (van der Heijde) (Fig. 1). Given this efficacy plateau, a POSA would have had no basis to assume that any potentially greater drug exposure achieved through IV administration would translate into improved efficacy outcomes.

3. “≥65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment” (claim 5)

119. Petitioners argue that Inman disclosed the claimed ASAS20 clinical endpoint. *See* Pet. 58. The ASAS20 data reported in Inman differs materially from the claimed ASAS20 clinical endpoint, such that a POSA would not have expected the claimed outcome based on Inman’s disclosure.

120. Inman reported that 59.4% and 60.0% of patients receiving 50 mg and 100 mg SC golimumab, respectively, achieved ASAS20 at week 14—both below the claimed ≥65% threshold.

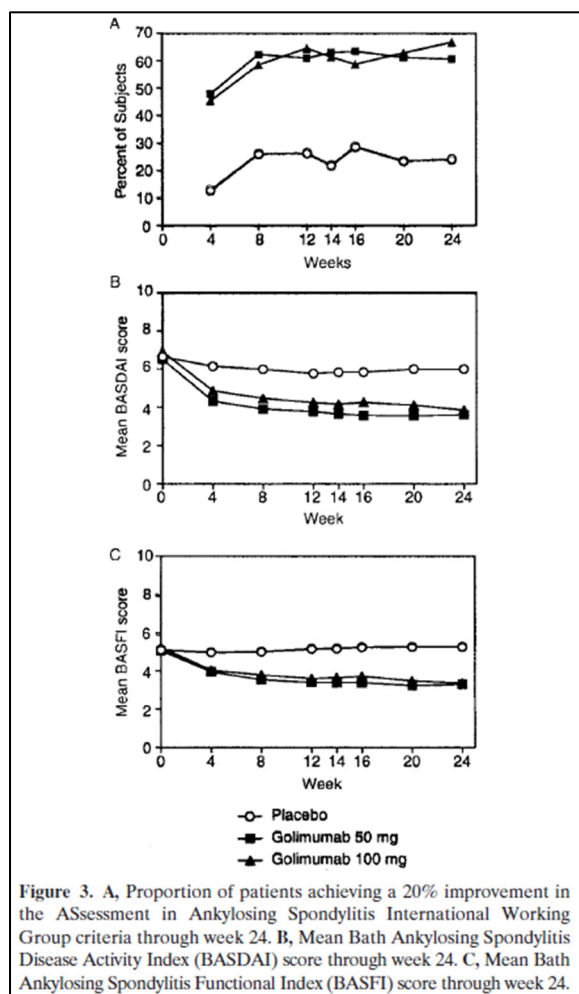
121. Inman also disclosed a smaller degree of improvement relative to placebo, as shown below:



Ex.1016 at 3406 (Inman) (Fig. 2). The reported placebo rate serves as an internal benchmark that allows for cross-study comparison in absence of head-to-head data. The magnitude of the treatment effect (also called the “delta” between active drug and placebo) provides a more scientifically valid comparison of therapeutic benefit between trials, compared to the ASAS20 rate itself. Inman’s data shows a delta of about 39%, which is inferior to the delta of about 47% reported in the ’566 Patent. This provides further evidence that a POSA could

not reliably extrapolate the data from Inman to predict week 16 outcomes as recited in claim 5.

122. Also, the Inman data itself demonstrates that doubling the SC golimumab dose from 50 mg to 100 mg did not meaningfully increase the ASAS20 response rate (59.4% vs. 60.0% at week 14).



Id. at 3406 (Fig. 3). As mentioned in Section VII.C, the BASDAI index (Figure 3C) overlaps with the domains of ASAS scores. This efficacy plateau refutes the assumption that higher drug exposure would necessarily lead to improved

efficacy outcomes. The non-linear dose-response relationship observed in Inman would undermine any expectation that IV golimumab would achieve a response rate exceeding 65% when SC golimumab failed to do so after doubling its dose.

123. Accordingly, the ASAS20 data in Inman is sufficiently distinct from the claimed clinical endpoint that a POSA would not have expected $\geq 65\%$ of patients to achieve ASAS20 at week 16 based on Inman's disclosure. The combination of NCT873-V24, PI2013-Aria, PI2015-Simponi, van der Heijde, and Inman thus fail to disclose the claimed clinical endpoints.

* * *

124. In conclusion, it is my opinion that Petitioners have not identified any prior art data that discloses or renders obvious achieving the claimed clinical endpoints.

B. A POSA Would Not Have Been Motivated to Combine the Plethora of Asserted References

125. I understand from counsel that to demonstrate obviousness, Petitioners must also show that a POSA would have been motivated to combine the asserted references to obtain the claimed invention. In my opinion, because a POSA would have known of the stark differences in disease pathogenesis, presentations and treatment strategies between AS and RA, a POSA would be unlikely to arrive at this combination of references.

126. A POSA would not have been motivated to combine references directed to RA and AS because the state of the art as of the priority date clearly indicated that RA and AS are pathologically and immunologically distinct diseases. Although TNF plays a role in both inflammatory diseases, they differ fundamentally in their underlying mechanisms: RA is associated with predominant adaptive immune inflammation, whereas AS is characterized by predominant innate immune system involvement. Moreover, RA primarily affects synovial tissue and peripheral joints, resulting in progressive bone erosion and cartilage destruction, whereas AS principally involves enthesal tissue and axial joints (i.e., the spine) and may lead to new bone formation, including syndesmophytes and spinal fusion. In my opinion, these substantial pathologic differences highlight that treatment outcomes observed in RA cannot be assumed to predict outcomes in AS. Accordingly, a POSA would have had no motivation to combine references relating to these distinct disease indications.

127. Moreover, during the relevant time, Simponi Aria was approved only for RA, not AS. In my experience, physicians were not relying on the dose and clinical endpoint information found in PI2013-Aria to treat AS with Simponi Aria “off label” ahead of the priority date, due to potential differences in dose requirements and how AS patients would respond. Accordingly, a POSA would

not have been motivated to rely on PI2013-Aria as a basis for treating AS patients.

128. For several reasons, extrapolating conditions and outcomes from one clinical trial to another, particularly across distinct disease indications, is not an accepted practice within my field. As an initial matter, irrespective of how the targeted diseases compare, every study population is unique. Different patient populations exhibit variable therapeutic responses, and there is no assurance that clinical trial outcomes will be replicated across studies. This concern is compounded by the well-documented demographic and clinical differences between AS and RA patient populations—AS patients are characteristically younger, predominantly male, and present with distinct disease duration and baseline characteristics compared to RA patients. Therefore, the shared active ingredient, dosing, and sponsor between the two studies would not have been enough to motivate a POSA to combine references about different studies in AS patients with a study on RA, as a POSA would recognize each reference to concern distinct patient populations.

129. Additionally, Petitioners incorporate references that only describe SC administration of golimumab, whereas the claims are directed to IV administration. As explained above in Section VII.E, a POSA would be familiar with substantial differences between the two administration routes.

130. A POSA would not have had a scientific rationale to combine five separate references that span across routes of administration and diseases without knowledge of the claimed invention itself. The asserted references include clinical trial protocols for IV golimumab in AS (NCT873-V24), prescribing information for IV golimumab in RA (PI2013-Aria), prescribing information for SC golimumab across multiple indications (PI2015-Simponi), and SC golimumab efficacy data in AS (van der Heijde and Inman)—requiring a POSA to bridge across fundamentally different PK profiles (IV versus SC), distinct disease pathologies (RA versus AS), and disparate patient populations, all without any reference suggesting that such a combination would yield the claimed clinical endpoints. In my opinion, because of the logical leaps required to reach this combination, a POSA would not have been motivated to combine these references.

C. A POSA Would Not Have Had a Reasonable Expectation of Success

131. I have been informed by counsel that to show obviousness, the Petitioners must also show that a POSA would have had a reasonable expectation of success of combining the prior art to achieve the claimed invention.

132. As of the priority date, a POSA would not have had a reasonable expectation of success. Rather, they would have been aware that an analogous extrapolation strategy (from SC to IV golimumab) had failed for UC. By the

priority date, it was known in the art that Janssen attempted to develop Simponi Aria for treating UC, an indication already approved for Simponi, Janssen's SC golimumab formulation.

133. In Janssen's UC clinical trials, despite administering an IV dose "expected to provide comparable systemic drug exposure" to the approved SC dose, researchers observed that IV golimumab did not produce a "dose-response" and achieved "lower than expected" efficacy, which was "less than observed in the SC induction study." Ex.2094 at 504, 509-10 (Rutgeerts 2015). Enrollment in the Phase III trial was stopped due to lack of efficacy in Phase II. *Id.* at 510. This high-profile failure in attempting to translate SC efficacy to IV in a TNF-mediated inflammatory condition would have significantly dissuaded a POSA from expecting that success in IV golimumab treatment of AS could be inferred from SC golimumab data for AS.

134. The substantial pharmacokinetic differences between IV and SC administration, as I described in Section VII.E, would have further reduced a POSA's expectation of success. IV administration produces higher peak concentrations, greater total exposure, faster clearance, and lower troughs than SC administration. Ex.1038 at 84 (Zhuang) (Table II); Ex.1015 at 19 (PI2015-Simponi); Ex.2095 at 13 (Rutgeerts Supplemental Appendix) (Fig. S2). These differences raised significant concerns.

135. A POSA would have recognized that actions taken by the FDA and other regulatory health agencies reflected and informed the perspective of POSAs. As of the priority date, these regulatory agencies had taken actions that conflict with Petitioners' obviousness theories. For example, the FDA concluded that IV golimumab faced heightened malignancy risk due to "greater exposure" and required "independent substantiation of the efficacy." Ex.1034 at 127 (CDER Review). The FDA further determined that IV and SC golimumab are "two separate and distinct products because they have different pharmacokinetic characteristics, dosing regimens, and product presentations," and required independent clinical data even in RA, where SC golimumab was already approved. *Id.*

136. Likewise, the EMA (the EU regulatory health agency) denied EU approval for Simponi IV in 2013, finding that "Cmax that is 6 times higher and AUC which is 3 times higher than that of SC administration, raises uncertainty regarding the safety profile." Ex.2052 at 59 (Oct. 24, 2013, EMA Simponi Withdrawal Assessment Report). In light of the conclusions reached by these authorities, a POSA would have understood that higher drug exposure could lead to increased immunosuppression, infusion reactions, and other adverse events. Thus, a POSA would have shared these concerns and would not have considered

IV golimumab treatment for AS to be “safe and effective” as claimed by the ’566 Patent.

137. Critically, the asserted references do not support the assumption that higher exposure necessarily leads to greater efficacy. Pre-priority data analyses of SC golimumab data demonstrated a plateau or saturation in efficacy between the 50 mg and 100 mg doses. *See* Ex.1016 at 3406 (Inman) (Figs. 2-3); Ex.1033 at 1099 (van der Heijde) (Fig. 1). The Simponi label states that “[t]here was no clear evidence of improved ASAS response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).” Ex.1015 at 29 (PI2015-Simponi). Indeed, the clinical trial data on IV golimumab in UC specifically indicated that “peak serum golimumab concentration is not a dominant driver of efficacy.” Ex.2094 at 511 (Rutgeerts 2015). This finding directly undermines Petitioners’ premise that higher C_{max} would translate to greater efficacy. Thus, a POSA could not have reasonably expected IV golimumab to treat AS with a level of efficacy required to meet the claimed clinical endpoints.

138. Moreover, achieving the claimed clinical endpoints at specific timepoints are not merely differences in degree. Rather, they represent qualitatively different therapeutic profiles that a POSA would not have predicted from the prior art. For example, achieving ASDAS inactive disease (<1.3) after

just 2 or 4 weeks of IV treatment is clinically significant given that SC data shows only approximately 20% of patients achieving inactive disease much later, at 14 weeks. Ex.1033 at 1099 (van der Heijde) (Fig. 1); Ex.2111 at 1341 (van der Heijde 2017). Reaching the claimed degree of inactive disease status cannot be reliably extrapolated from data concerning a different dosage form at a much later timepoint.

139. Lastly, a POSA would have recognized the inherent unpredictability of clinical development, particularly when extending a therapy to a new indication or route of administration. Therapeutic agents effective in RA—including tocilizumab (an IL-6 receptor blocker) and abatacept (a T-cell co-stimulation modulator)—failed in AS clinical trials, underscoring the distinct disease mechanisms and the unpredictability of extending results from one TNF-mediated condition to another. Ex.2102 at 1108-09 (Song 2011); Ex.2098 at 95, 99 (Sieper 2014).

140. As described above, there are multiple sources of uncertainty, including the documented failure of golimumab SC-to-IV extrapolation in UC, the pharmacokinetic differences that concerned both the FDA and EMA, the dose-plateau effect that contradicts higher-exposure assumptions, and the general unpredictability of clinical trials across disease indications. As a result, a POSA

would not have had a reasonable expectation that IV golimumab in AS would achieve the clinical endpoints recited in the '566 Patent independent claims.

XIII. Conclusion

All statements made herein of my own knowledge are true, and all statements made on information and belief are believed to be true. Further, I am aware that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001. I declare under penalty of perjury that the foregoing is true and correct.

Executed on 26/06/2026 (date), in TORONTO, ONTARIO (city, state).



Dr. Nigil Haroon