

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.

IPR2026-00257
Patent No. 11,041,020

**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. 11,041,020 (the “’020 Patent”), which has been challenged by Accord Biopharma, Inc., Intas Pharmaceuticals Ltd., and Bio-Thera Solutions, Ltd. (collectively, “Petitioners”). The ’020 Patent covers methods of treating psoriatic arthritis (“PsA”) via intravenous (“IV”) administration of golimumab, an antibody that inhibits tumor necrosis factor (“TNF” or “TNF α ”).

II. Summary of Opinions

2. Based on the materials cited in this declaration and my over 20 years of clinical expertise treating patients suffering from PsA, I conclude that Petitioners have not demonstrated either anticipation or obviousness of the ’020 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 PsA and ankylosing spondylitis (“AS”). I serve as Head

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

of 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 M.B.A. 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 (“axSpA”) (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 a

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
1001	U.S. Patent No. 11,041,020 to Harrison et al. (June 22, 2021)
1005	Declaration of Dr. Roy M. Fleischmann in Support of IPR Petition
1011	U.S. National Library of Medicine, ClinicalTrials.gov, NCT02181673, “ <i>A Study of Golimumab in Participants with Active Psoriatic Arthritis</i> ” (Version 23, January 8, 2016), available at https://clinicaltrials.gov/study/NCT02181673? (“NCT673-V23”)
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

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)
1025	International Publication WO 2008/063213 A2 to Medich et al. (May 29, 2008)
1032	<i>SIMPONI ARIA (golimumab) injection, for intravenous use</i> , FOOD AND DRUG ADMINISTRATION (July 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125433s000lbl.pdf
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)
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
1035	M. K. Doyle et al., <i>Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial</i> , 52 RHEUMATOLOGY 7:1214-9 (2013)
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)
1041	A. Kavanaugh, et al., <i>Golimumab, a New Human Tumor Necrosis Factor α Antibody, Administered Every Four Weeks as a Subcutaneous Injection in Psoriatic Arthritis</i> , 60 ARTHRITIS & RHEUMATISM 4, 976-986 (Apr. 2009)

Ex.	Description
1042	A. Kavanaugh, et al., <i>Golimumab in Psoriatic Arthritis, One-Year Clinical Efficacy, Radiographic, and Safety Results From a Phase III, Randomized, Placebo-Controlled Trial</i> , 64 ARTHRITIS & RHEUMATISM 8, 2504-2517 (2012)
1043	A. Kavanaugh, et al., <i>Patient-Reported Outcomes and the Association With Clinical Response in Patients With Active Psoriatic Arthritis Treated With Golimumab: Findings Through 2 Years of a Phase III, Multicenter, Randomized, Double-Blind, Placebo-Controlled Trial</i> , 65 ARTHRITIS CARE & RESEARCH 10, 1666-73 (Oct. 2013)
1044	A. Kavanaugh, et al., <i>Clinical efficacy, radiographic and safety findings through 5 years of subcutaneous golimumab treatment in patients with active psoriatic arthritis: results from a long-term extension of a randomised, placebo-controlled trial (the GO-REVEAL study)</i> , 73 ANN. RHEUM. DIS. 1689-1694 (Apr. 19, 2014)
2001	Prosecution History for U.S. Patent No. 11,041,020 B2 (EXCERPT)
2052	Eur. Meds. Agency (EMA), Sci. Meds. Health, Comm. for Med. Prods. for Hum. Use (Day 120 Assessment Report, EMA/416184/2014), <i>Withdrawal Assessment Report: Simponi (golimumab)</i> , EMEA/H/C/000992/X/0047 (Janssen Biologics B.V., Applicant) (Oct. 24, 2013)
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, Janssen Receives Two U.S. FDA Approvals for Simponi Aria® (Golimumab) for the Treatment of Adults With Active Psoriatic Arthritis or Active Ankylosing Spondylitis (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

Ex.	Description
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
2061	FDA, Actemra Prescribing Information (revised Oct. 2013) ("ACTEMRA® (tocilizumab) Label")
2062	FDA, Remicade Prescribing Information (revised Oct. 2015) ("REMICADE® (infliximab) Label")
2063	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)
2064	B. Bruce & J.F. Fries, <i>The Health Assessment Questionnaire (HAQ)</i> , 23 CLINICAL EXPERIMENTAL RHEUMATOLOGY S14 (2005)
2065	L. Congi & E. Roussou, <i>Clinical Application of the CASPAR Criteria for Psoriatic Arthritis Compared to Other Existing Criteria</i> , 28 CLINICAL EXPERIMENTAL RHEUMATOLOGY 304 (2010)
2066	A. Farid et al., <i>Narrow Band Ultraviolet B Therapy Deactivates Th1/Th17 Pathway and Activates Th2 Cytokines Secretion in Egyptian Psoriatic Arthritis Patients</i> , 13 J. RADIATION RSCH. APPLIED SCIS. 356 (2020)
2067	David T. Felson et al., <i>American College of Rheumatology Preliminary Definition of Improvement in Rheumatoid Arthritis</i> , 38 ARTHRITIS RHEUMATISM 727 (1995)
2068	Oliver FitzGerald et al., <i>Concepts of Pathogenesis in Psoriatic Arthritis: Genotype Determines Clinical Phenotype</i> , 17 ARTHRITIS RSCH. THERAPY 1–11 (2015)
2069	FITZPATRICK'S DERMATOLOGY IN GENERAL MEDICINE 427 (Irwin M. Freedberg eds., 6th ed. 2003)

Ex.	Description
2071	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)
2072	Dafna D. Gladman, <i>Effectiveness of Psoriatic Arthritis Therapies</i> , 33 SEMINARS ARTHRITIS RHEUMATISM 29 (2003)
2073	D.D. Gladman et al., <i>Psoriatic Arthritis: Epidemiology, Clinical Features, Course, and Outcome</i> , 64 ANNALS RHEUMATIC DISEASES ii14 (2005)
2074	Deepak R. Jadon et al., <i>Psoriatic Arthritis Mutilans: Characteristics and Natural Radiographic History</i> , 42 J. RHEUMATOLOGY 1–8 (2015)
2075	CHARLES A. JANEWAY, JR., ET AL., IMMUNOBIOLOGY-THE IMMUNE SYSTEM IN HEALTH & DISEASE ch. 3-6 (5th ed. 2001), https://www.ncbi.nlm.nih.gov/books/NBK27160/ (EXCERPT)
2076	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)
2077	Gabrielle H. Kingsley et al., <i>A Randomized Placebo-Controlled Trial of Methotrexate in Psoriatic Arthritis</i> , 51 RHEUMATOLOGY 1368 (2012)
2078	Mayke B.G. Koek et al., <i>Home Versus Outpatient Ultraviolet B Phototherapy for Mild to Severe Psoriasis: Pragmatic Multicentre Randomised Controlled Non-Inferiority Trial (PLUTO Study)</i> , 338 BRIT. MED. J. 1–11 (2009)
2079	Monalyn Labitigan et al., <i>Higher Rates and Clustering of Abnormal Lipids, Obesity, and Diabetes in Psoriatic Arthritis Compared with Rheumatoid Arthritis</i> , 66 ARTHRITIS CARE RSCH. 600 [1–16] (2014)
2080	R.J. Lories & D.L.P. Baeten, <i>Differences in Pathophysiology Between Rheumatoid Arthritis and Ankylosing Spondylitis</i> , 27 CLINICAL EXPERIMENTAL RHEUMATOLOGY S10 (2009)

Ex.	Description
2081	Iain B. McInnes et al., <i>Secukinumab, a Human Anti-Interleukin-17A Monoclonal Antibody, in Patients with Psoriatic Arthritis (FUTURE 2): A Randomised, Double-Blind, Placebo-Controlled, Phase 3 Trial</i> , S0140-6736(15)61134-5 LANCET 1–10 (2015)
2082	Philip J. Mease et al., <i>Etanercept Treatment of Psoriatic Arthritis – Safety, Efficacy, and Effect on Disease Progression</i> , 50 ARTHRITIS RHEUMATISM 2264 (2004)
2083	Philip J. Mease, <i>Is There a Role for Rituximab in the Treatment of Spondyloarthritis and Psoriatic Arthritis?</i> , 39 J. RHEUMATOLOGY 2235 (2012)
2084	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)
2085	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)
2086	Makoto Naganuma et al., <i>Recent Trends and Future Directions for the Medical Treatment of Ulcerative Colitis</i> , 9 CLINICAL J. GASTROENTEROLOGY 329 (2016)
2087	Masatsugu Ono et al., <i>Structural Basis for Tumor Necrosis Factor Blockade with the Therapeutic Antibody Golimumab</i> , 27 PROTEIN SCI. 1038 (2018)
2088	Eric M. Ruderman, <i>The Role of Concomitant Methotrexate in Biologic Therapy for Rheumatoid Arthritis</i> , 71 BULL. HOSP. JOINT DISEASES S29 (2013)
2089	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 2015”)
2090	P. Rutgeerts et al., <i>Supplemental Appendix</i> (2015) (“Rutgeerts App’x”)

Ex.	Description
2091	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)
2092	Georg Schett et al., <i>Oral Apremilast in the Treatment of Active Psoriatic Arthritis – Results of a Multicenter, Randomized, Double-Blind, Placebo-Controlled Study</i> , 64 ARTHRITIS RHEUMATISM 3156 (2012)
2094	William Taylor et al., <i>Classification Criteria for Psoriatic Arthritis – Development of New Criteria From a Large International Study</i> , 54 ARTHRITIS RHEUMATISM 2665 (2006)
2096	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)
2097	Désirée van der Heijde et al., <i>Psoriatic Arthritis Imaging: A Review of Scoring Methods</i> , 64 ANNALS RHEUMATIC DISEASES ii61 (2005)
2098	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)
2099	Ronald F. van Vollenhoven, <i>Sex Differences in Rheumatoid Arthritis: More Than Meets the Eye...</i> , 7 BIOMED CENT. MED. 1–4 (2009)
2100	J.E. WARE & M. KOSINSKI, SF-36 PHYSICAL & MENTAL HEALTH SUMMARY SCALES: A MANUAL FOR USERS OF VERSION 1 (2d ed. 1994) (EXCERPTS)
2101	Michael E. Weinblatt, <i>Methotrexate in Rheumatoid Arthritis: A Quarter Century of Development</i> , 124 TRANSACTIONS AM. CLINICAL CLIMATOLOGICAL ASS’N 16 (2013)

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 '020 Patent at the time of the alleged invention, which I have been asked to assume is January 30, 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 (January 30, 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 '020 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 SpA, the clinical researchers developing PsA 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 PsA and the SpA family. Similarly, clinical researchers who specialize in RA may not have specialized knowledge or research experience in the development of PsA 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 '020 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 at 1 (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 at 1 (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. TNF²

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 PsA.

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.2098 at 4 (van Schie 2016). Subsequently, it was shown that golimumab binds to a different site on TNF compared to the other inhibitors. Ex.2087 (Ono 2018).

C. Psoriatic Arthritis

24. PsA is a chronic inflammatory disease associated with psoriasis and multiple clinical domains that require comprehensive treatment. PsA disease presentation spans across joints (sacroiliac and peripheral), ligaments, tendons, and the skin. Ex.2069 at 427 (*Fitzpatrick's Dermatology*). In aggressive cases, patients with PsA may experience severe bone and joint damage (also called “arthritis mutilans”), which can lead to mobility impairment. Ex.2072 at 34

² TNF was previously referred to as TNF α . These terms are interchangeable.

(Gladman 2003); Ex.2074 at 1 (Jadon 2015). PsA patients often initially present with psoriasis before developing arthritis symptoms. Ex.2072 at 34 (Gladman 2003).

25. PsA disease pattern can affect both axial and peripheral joints. Ex.2069 at 427 (*Fitzpatrick's Dermatology*). As a member of the seronegative SpA group of diseases, PsA is known to be associated with the HLA-B27 gene and inflammation in the periarticular structures (including enthesitis or inflammation in the point where connective tissues meet bone). Ex.2073 at ii15 (Gladman 2005).

26. At the '020 Patent priority date, clinicians would rely on several metrics to measure PsA disease activity and patient outcomes:

- a. Health Assessment Questionnaire Disability Index score ("HAQ-DI");
- b. Enthesitis;
- c. Dactylitis;
- d. 36-item Short Form Health Survey ("SF-36") Physical Component Summary ("PCS") and Mental Component Summary ("MCS");
- e. Total Modified van der Heijde-Sharp score ("vdH-S");
- f. American College of Rheumatology 20 score ("ACR20").

27. HAQ-DI serves as a functional index designed to measure the degree of a patient's disability. Ex.2064 at S-16 (Bruce 2005). This assessment tool evaluates a patient's ability to perform activities of daily living by analyzing difficulty levels across eight distinct categories of physical function. *Id.*

28. Clinicians rely on enthesitis and dactylitis as key indicators for detecting and monitoring PsA. Enthesitis refers to inflammatory changes occurring at the sites where tendons, ligaments, or joint capsules attach to bone, with the lower extremities and pelvic region being the most frequently affected areas. Ex.2069 at 427 (*Fitzpatrick's Dermatology*). Dactylitis, sometimes referred to as "sausage digits," involves diffuse swelling of the fingers or toes. *Id.*

29. The SF-36 survey assesses physical and mental factors of a patient's health status. *See, e.g.*, Ex.2100 at 5 (Ware 1994 Excerpts). A patient's responses to questions across eight components contribute to a score measured from 0-to-100, which are summarized into a mental component (MCS) and physical component (PCS) to address each factor. *See id.* at 3, 28-29, 171.

30. Joint damage in PsA patients is quantified using the total modified vdH-S score, which is derived from radiographic (x-ray) images. *See, e.g.*, Ex.2097 at ii63 (van der Heijde 2005). Under this scoring system, clinicians evaluate multiple joints and assign numerical values based on the extent of

erosion (with a maximum of 320 points) and the degree of joint space narrowing (with a maximum of 208 points). *See id.* A patient's total score can reach a maximum of 528 points, with higher values indicating more advanced disease progression. *See id.*

31. ACR20 is a composite outcome measure that incorporates joint measurements along with the patient's self-reported assessment of disease activity. *See* Ex.2067 at 733-34 (Felson 1995). According to American College of Rheumatology criteria, ACR20 response requires at least 20% improvement from baseline in both swollen joint count and tender joint count, as well as at least 20% improvement from baseline in three of five additional parameters, including patient's assessment of pain (visual analog scale), patient's global assessment of disease activity, physician's global assessment of disease activity, function (HAQ-DI), and acute phase reactants (ESR or CRP). *See id.*

32. Each of these metrics serves as a tool to understand and characterize the state of a patient's PsA disease and response to treatment at a given time.

1. RA and PsA Are Different Diseases

33. RA belongs to a distinct class of rheumatologic diseases that is clinically distinct from the SpA family, including PsA. Several key differences distinguish these two conditions and render extrapolation of treatment plans

between them methodologically unsound. Gladman 2003 provides a visual summary of these differences:

Table 1: Clinical Features of PsA and RA		
Feature	PsA	RA
Rheumatoid factor	Uncommon	Common
Nail lesions	Common	Uncommon
Psoriasis	Common	Uncommon
Pattern of joint involvement	Asymmetric/symmetric*	Symmetric
Peripheral joint involvement	Common	Common
Distal interphalangeal joint involvement	Common	Uncommon
Spondylitis	Common	Uncommon
Sacroiliitis	Common	Uncommon

*Often initially asymmetric before becoming symmetric as disease progresses.
Adapted from Rahman and Gladman (3).

Ex.2072 at 30 (Table 1) (Gladman 2003).

34. In my opinion, RA is a unique disease that should not be conflated with PsA. From an immunologic standpoint, RA and PsA arise through distinct pathways. 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.2080 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 PsA was driven predominantly by the innate immune system. *Id.*

35. In contrast to RA patients, PsA patients are predominantly seronegative for the autoantibody called rheumatoid factor. Ex.2069 at 428 (*Fitzpatrick's Dermatology*). Rheumatoid factors are an important product of B cells, which constitute a prominent pathogenic cell population in RA. Ex.2083 at 2235 (Mease 2012). A patient's production of this antibody has thus become a key focus in RA treatment. *Id.*

36. The genetic underpinnings of the two diseases also diverge. Although multiple genes are associated with the two diseases, by the priority date, the major histocompatibility ("MHC") genes associated with PsA were the MHC Class I genes: HLA-C6 and HLA-B27, while RA was linked with MHC Class II genes: HLA-DR1 and -DR4. Ex.2068 (Abstract) (FitzGerald 2015); Ex.2071 (Abstract) (Fugger & Svejgaard 2000).

37. The affected populations also differ. The RA population is approximately 75% female, while the PsA population is distributed

approximately equally across male and female patients. Ex.2073 at ii14 (Gladman 2005); Ex.2099 at 2 (van Vollenhoven 2009). PsA patients are also typically younger at disease onset. In addition, PsA patients tend to have higher body mass index (“BMI”) compared to RA patients. In a study by Labitigan et al., there were more obese patients with PsA compared to RA patients, and normal body weight was more likely to be seen among RA patients. Ex.2079 at 6 (Labitigan 2014).

38. The anatomic distribution of inflammation and other symptoms is different as well. RA patients experience inflammation primarily in synovial tissue and peripheral joints. Ex.2080 at S-10-11 (Lories 2009). PsA affects a wider set of involved tissues and clinical domains, as described above.

39. The extra-articular manifestations differ between PsA and RA, including atlanto-axial dislocation, interstitial lung disease, vasculitis, neuropathy, and amyloidosis as seen in RA patients but not in PsA patients. In contrast, the extra-articular manifestations in PsA patients are predominantly psoriasis in the skin and inflammatory bowel disease.

40. The eye involvement is distinct 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). Whereas, the eye involvement in PsA is characterized by internal

inflammation affecting the uveal tract (uveitis/iritis). Ex.2085 (Murray 2016).

For these reasons, I understand PsA to require attention to distinct disease activity assessments and tailored treatment measures.

2. Treatments for RA and PsA Are Different

41. 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 slowing radiographic disease progression, with MTX emerging as the anchor drug in most DMARD regimens. Ex.2101 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” – e.g., anakinra) receptors, T-cells (abatacept), CD20 (rituximab), IL-6 receptors (tocilizumab), and Janus kinase (“JAK” – e.g., tofacitinib). These products demonstrated sustained inhibition of bone erosion and structural damage in RA patients.

42. A growing consensus within the rheumatology and dermatology communities recognized that therapeutic strategies for PsA warranted independent development rather than assumptions from treatment paradigms established for RA. *See* Ex.2072 at 34-35 (Gladman 2003). PsA treatment development started with a long period in which the only systemic options were corticosteroids, followed by the first targeted biologic approvals beginning in

2002 with TNF inhibitors. Thereafter, PsA development broadened into mechanisms tied more closely to psoriatic-disease biology, including IL-12/23 inhibition in 2013 and IL-17A inhibition in 2016 and 2017, all of which were not effective in RA. PsA also saw JAK-inhibitor therapy later than RA.

43. I approach treatment evidence in RA and PsA as disease-specific, not as automatically transferable evidence. The reason is straightforward: RA and PsA differ in immunopathogenesis, tissue involvement, clinical assessment, and patient characteristics. Just one example is the lack of efficacy in RA of IL-12/23 and IL-17A inhibitors.

44. The clinical endpoints in PsA reflect the broader disease phenotype. Treatment strategies for PsA must account not only for joint pain and swelling but also for skin disease, enthesitis, dactylitis, axial disease, and structural damage (or new bone formation). Ex.2072 at 29, 31-34 (Gladman 2003); Ex.2091 at 3 (Schett 2011). The total modified vdH-S score reflects this disease-specific assessment framework by expanding the joints evaluated, including distal interphalangeal joints, compared with its RA predecessor. Ex.2097 at ii63 (van der Heijde 2005). In my view, a PsA-specific assessment framework is clinically appropriate because PsA manifestations include inflammatory, skin, and structural changes that are not captured by RA-focused treatment paradigms.

45. Treatment administration and immunogenicity also differ. That difference is consistent with the different use of concomitant MTX in the two diseases: all RA patients must receive concomitant MTX with Simponi, while the same is not required in administering Simponi for PsA. Ex.1015 at 1 (PI2015-Simponi). Use of MTX in RA had been shown to prolong treatment efficacy, which had not been shown in PsA. Ex.2088 at S-31 (Ruderman 2013); Ex.2072 (Abstract) (Gladman 2003). Literature on these treatments confirms that extrapolation from RA to PsA is limited. Early conventional agents used to treat RA, such as MTX, were described as having adverse effects that often led to discontinuation and as not always effective in reducing symptoms or radiographic progression in PsA. Ex.2072 (Abstract) (Gladman 2003).

46. Developments in biologic treatments show the same disease-specific patterns. It is not the case that effective treatment in RA necessarily implies that a clinician could use the same dosage regimen to treat a patient with PsA. For example, infliximab was approved to treat RA with a dose of 3 mg/kg, but requires a dose of 5 mg/kg to treat PsA. Ex.2062 at 1 (Remicade Label). Also, while tocilizumab and rituximab were approved to treat RA, neither received approval for PsA. *See* Ex.2061 at 1 (Actemra Label); Ex.2083 (Mease 2012).

D. Antibodies

47. 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."

48. Typically, in terms of antigen binding, the definitive part of the antibody is the variable domains, and in particular, the six individual regions known as complementarity determining regions ("CDRs"). *See* Ex.2075 at 1-2 (Janeway 2001).

E. IV and SC Formulations Have Different Pharmacokinetic Profiles

49. Pharmacokinetic and pharmacodynamic ("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.2084 at 1 (Mould 2013). PD describes what the drug does to the body. Ex.2096 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.

50. During the development of IV golimumab for RA, the FDA raised two significant concerns about Janssen's proposal to submit a supplemental biologics licensing 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.*

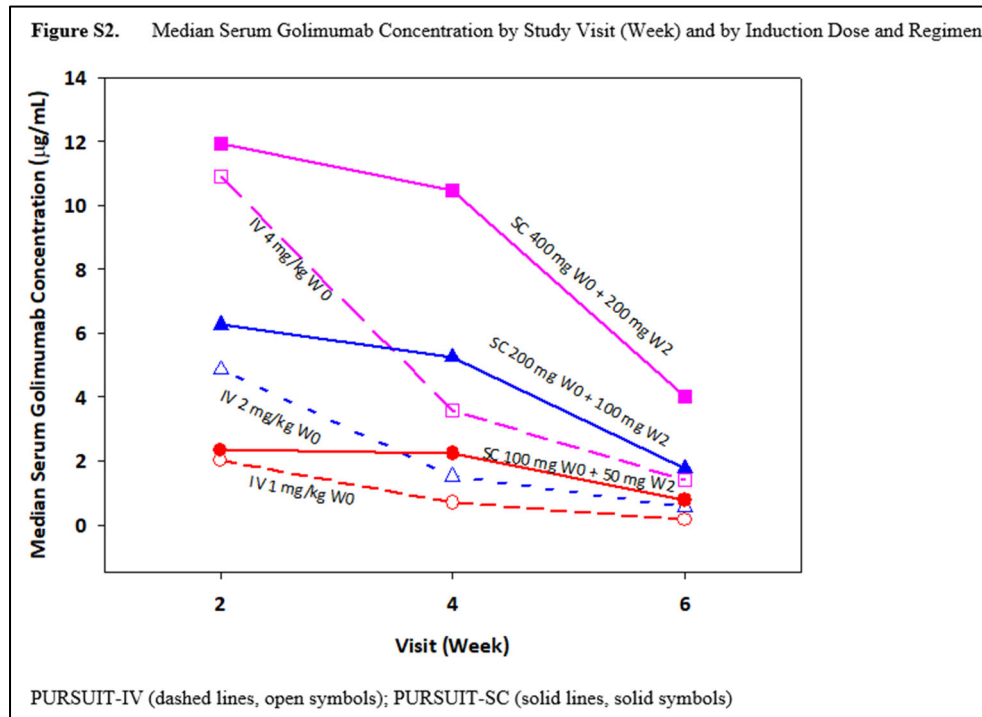
51. Other regulatory authorities shared these concerns. In 2013, the European Medicines Agency ("EMA") denied approval for Simponi IV because of the threat that the PK/PD profile posed to patient safety. Ex.2052 at 59 (EMA Simponi Withdrawal Assessment). The EMA withdrawal report stated the "Cmax that 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.*

52. 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 POA independent concerns about whether the IV formulation could maintain sustained therapeutic exposures necessary for effective treatment. *See* Ex.2090 at 13 (Fig. S2) (Rutgeerts Supplemental Appendix). 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.*

53. 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.2089 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.2086 at 332 (Naganuma 2016).

54. Rutgeerts et al. studied three dose levels in each of SC and IV.

Ex.2089 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.2090 at 13 (Fig. S2) (Rutgeerts Supplemental Appendix). 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.

55. Thus, the clinical results did not support continuing to pursue approval, and therefore the Phase III study was terminated. Ex.2089 at 510 (Rutgeerts 2015); Ex.2058 (NCT774 ClinicalTrials.gov). 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.2089 at 510 (Rutgeerts 2015). 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 PsA clinical trials.

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

VIII. The '020 Patent (Ex.1001)

57. The '020 Patent is titled “Methods for the Treatment of Active Psoriatic Arthritis.” Ex.1001 (Title) ('020 Patent). It teaches and claims “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 Psoriatic Arthritis.” *Id.* (Abstract). SEQ ID NOS: 36 and 37 correspond to golimumab. *Id.* at 85:6-7.

58. The '020 Patent describes a clinical study performed to show that golimumab is effective to treat PsA when administered intravenously, with or without MTX. *Id.* at 78:62-120:51 (Example 9) ('020 Patent). For example, the clinical study demonstrated that, 14 weeks after the start of treatment, PsA patients receiving 2 mg/kg IV golimumab at weeks 0, 4, and every 8 weeks thereafter, achieved improvements in several criteria, including ACR20. *Id.* at 116:29-117:48 (Tables 8-9). Some patients in the study continued treatment with stable doses of MTX, while others did not. *Id.* at 98:41-67.

59. The '020 Patent has three independent claims. Independent claim 1 of the '020 Patent recites:

1. A method for treating a tumor necrosis factor alpha (TNF- α) related condition, wherein the TNF- α related condition is active psoriatic arthritis, the method comprising: administering to a subject having active psoriatic arthritis a composition comprising a safe and effective

amount of at least one isolated mammalian anti-TNF- α antibody having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) comprising SEQ ID NO:37, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via intravenous (IV) infusion, and wherein at week 14 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in one or more criteria selected from the group consisting of: Health Assessment Questionnaire Disability Index score (HAQ-DI)=-0.60 $\pm$ 0.53 SD, enthesitis=-1.87 $\pm$ 1.75 SD, dactylitis=-7.8 $\pm$ 8.57 SD, 36-item Short-Form Health Survey Physical Component Summary score (SF-36 MCS)=8.65 $\pm$ 7.60 SD, and 36-item Short-Form Health Survey Mental Component Summary score (SF-36 MCS)=5.33 $\pm$ 9.95 SD.

Ex.1001 at 141:40-60 (claim 1) ('020 Patent).

60. Independent claim 4 of the '020 Patent recites:

4. A method for treating a TNF- α related condition, wherein the TNF- α related condition is active psoriatic arthritis, the method comprising: administering to a subject having active psoriatic arthritis a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF- α antibody having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) comprising SEQ ID NO:37, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via IV infusion, and wherein at week 24 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in van der Heijde-Sharp score (vdH-S)=-0.36 $\pm$ 0.144 SE.

Id. at 142:39-51 (claim 4).

61. Independent claim 7 of the '020 Patent recites:

7. A method for treating a TNF- α related condition, wherein the TNF- α related condition is active psoriatic arthritis, the method comprising: administering to a subject having active psoriatic arthritis a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF- α antibody having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) comprising SEQ ID NO:37, wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion, and wherein $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment.

Id. at 142:60-143:3 (claim 7).

62. I understand that during prosecution of the '020 Patent, the Examiner rejected the pending claims as anticipated by Inman (Ex.1016) and obvious over Inman and Doyle (Ex.1035), Ex.2001 at -237-240 ('020 Patent File History), but later the Examiner withdrew these rejections because of surprising clinical endpoints described in the '020 Patent. *Id.* at -299.

IX. Summary of the Art

A. NCT02181673 (“NCT673-V23”) (Ex.1011)

63. NCT673-V23 is a summary of a clinical trial protocol called “A Study of Golimumab in Participants With Active Psoriatic Arthritis.” The protocol discusses administering IV golimumab to PsA patients.

64. NCT673-V23 is missing several parameters found in the '020 Patent claims and specification that a POSA would understand to impact the likelihood of the study achieving the claimed clinical endpoints. Key differences include patient population criteria, concurrent treatment requirements, and study design.

65. The '020 Patent specification requires the study subjects meet classification criteria for PsA (“CASPAR”) at screening. *See* Ex.1001 at 80:4-7, 88:20-24, 90:28-30 ('020 Patent). CASPAR is a PsA-specific, data-driven classification system of PsA that had been shown to have high sensitivity and specificity. Ex.2065 at 305 (Congi 2010). CASPAR requires patients to demonstrate inflammatory articular disease evidence, including psoriasis, psoriatic nail dystrophy, rheumatoid-factor negativity, dactylitis, and radiological evidence of new bone formation. *Id.* at 306 (Table I).

66. However, NCT673-V23 is silent regarding CASPAR requirements. Based on NCT673-V23 alone, the study does not require the subject population to meet CASPAR criteria at screening. Alternative methods of PsA classification existed by the priority date. *Id.* For example, other pre-priority studies relied on the Moll and Wright classification criteria instead, which examine a different set of disease characteristics. *Id.*; Ex.2092 (Schett 2012). Different baseline CASPAR levels may reflect different severity of disease and may therefore also affect whether patients meet the other claimed clinical endpoints, as well.

Ex.2094 at 2665-66 (Taylor 2006). “Variability in case definition is problematic” as “[h]eterogeneous study populations confound clinical research.” *Id.* at 2666. Without the CASPAR requirement, the study population encompasses patients based on any classification method, which directly impacts the likelihood of the patients achieving the claimed clinical endpoints.

67. The '020 Patent specification also requires the study subjects “[h]ave at least 1 of the PsA subsets: DIP joint involvement, polyarticular arthritis with absence of rheumatoid nodules, arthritis mutilans, asymmetric peripheral arthritis, or spondylitis with peripheral arthritis.” Ex.1001 at 90:36-39 ('020 Patent). As explained above in Section VII.C, these subsets (particularly arthritis mutilans) indicate advanced forms of the disease.

68. NCT673-V23 makes no mention of PsA subset inclusion criteria. It could therefore have included no patients with arthritis mutilans or employed different definitions of the subsets. Ex.2074 at 1 (Jadon 2015). Patients with arthritis mutilans have severe inflammatory arthritis that can lead to irreversible joint deformity. For example, a study on etanercept demonstrated no improvement in scores pertaining to structural damage of patients with arthritis mutilans. *Id.* at 7. Including such patients in the study population could dilute the measurable treatment effect on functional endpoints, such as HAQ-DI.

NCT673-V23 therefore cannot ensure that the claimed clinical endpoints would be achieved.

69. The '020 Patent claims methods of treating active PsA “with or without [MTX].” Ex.1001 at 141:65-67, 142:57-59, 143:12-14 (claims 3, 6, and 10) ('020 Patent). The specification further requires subjects using MTX to have started at least 3 months prior to first administration of study agent with dose stability at least 4 weeks prior. *Id.* at 92:5-13, 98:41-54. NCT673-V23 includes no inclusion or exclusion criteria based on these requirements, and a POSA could not have knowledge of the study design.

70. For example, a POSA would know that other studies had required longer prior usage of MTX and longer-established stable dosage to avoid potential confounding. Ex.2092 at 3157 (Schett 2012) (inclusion criteria of at least 24 weeks MTX use and at least 8 weeks of stable dose). Studies have shown the impact that MTX can have on efficacy endpoints, including Kavanaugh 2014 (Ex.1044), which reported worse progression and vdH-S scores without MTX. Ex.1044 at 1690 (Kavanaugh 2014).

71. Concurrent DMARD therapy can significantly influence the immunogenicity and efficacy of anti-TNF biologics. A requisite stability period also influences the likely impact of the concurrent treatment on the patient's likelihood of achieving the claimed endpoints, as a fluctuating MTX dose may

confound the clinical endpoints. By not specifying whether such concomitant medications are permitted or excluded, NCT673-V23 allows for uncertainty regarding whether the study population exhibits confounding characteristics, and thus whether the clinical endpoints would be comparable.

72. The '020 Patent specification restricts the study population's use of topical treatments or ultraviolet ("UV") exposure. Ex.1001 at 92:26-27, 100:39-62 ('020 Patent). Subjects may not use UV or topical therapy for psoriasis and must avoid any prolonged UV exposure. *Id.* NCT673-V23 does not place any restrictions on patients' use of these therapies.

73. A POSA would know that other studies could employ different levels of restrictions. *See* Ex.2082 at 2265 (Mease 2004) (permitting topical therapies on the scalp, axillae, and groin only). Given the benefits of topical and UV treatment on psoriatic skin lesions and other conditions in the joints, Ex.2066 at 357 (Farid 2020), a study population without access to these options may yield different clinical endpoints than one with access. Ex.2078 (Abstract) (Koek 2009).

74. The '020 Patent specification details the study's early escape processes and population set analysis, whereas NCT673-V23 is silent. Ex.1001 at 82:37-40, 82:44-50, 98:1-18 ('020 Patent). There are two ways to calculate efficacy analyses—as an intent-to-treat population or per-protocol population.

See Ex.2076 at 1021 (Kavanaugh 2014). The '020 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. A POSA would understand that a protocol silent on the employed analysis does not necessarily disclose the same efficacy analysis framework used in the '020 Patent, which could impact the likelihood of achieving the claimed clinical endpoints. Ex.2063 (Abstract) (Bai 2021).

75. The '020 Patent specification explains that participants with <5% improvement from baseline in both tender and swollen joint counts at Week 16 will enter early escape, a protocol permitting new or increased “concomitant medication interventions.” Ex.1001 at 98:1-18 ('020 Patent). There is no standard definition or timepoint for early escape that would give a POSA sufficient knowledge to predict this design from NCT673-V23’s silence. In fact, a POSA would know many clinical trials with different thresholds (up to < 20%), timing, interventions, and analytic penalties for early escape. Ex.2081 at 2 (McInnes 2015). Kavanaugh 2012 (Ex.1042), using a different early escape definition, identified “changes in dose regimens via placebo crossover to active treatment and/or early escape” as a major limitation to its efficacy analysis. Ex.1042 at 2516 (Kavanaugh 2012).

76. Thus, NCT673-V23 does not provide when and how patients should be withdrawn from the study for safety or lack of efficacy, how or when early escape is conducted, or how impacted subjects are considered in the endpoint analysis. As a result, the claimed clinical endpoints may not be achieved depending on how non-responders or patients with adverse events are assessed, leaving the outcome uncertain rather than assured.

77. As a result, NCT673-V23 allows an enrolled population that may not respond to treatment in a manner consistent with the claimed clinical endpoints, since uncontrolled variability in these factors could significantly alter the endpoints.

B. PI2015-Simponi (Ex.1015)

78. PI2015-Simponi is a version of the prescribing information for Simponi, Janssen's SC formulation of golimumab. PI2015-Simponi describes SC administration of golimumab to treat PsA, but it does not disclose the claimed administration route, many of the '020 Patent's claimed endpoints, or meeting any of the claimed clinical endpoints. It notes that "[t]here was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg)." Ex.1015 at 26 (PI2015-Simponi).

C. PI2013-Aria (Ex.1032)

79. 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. Ex.1032 (PI2013-Aria).

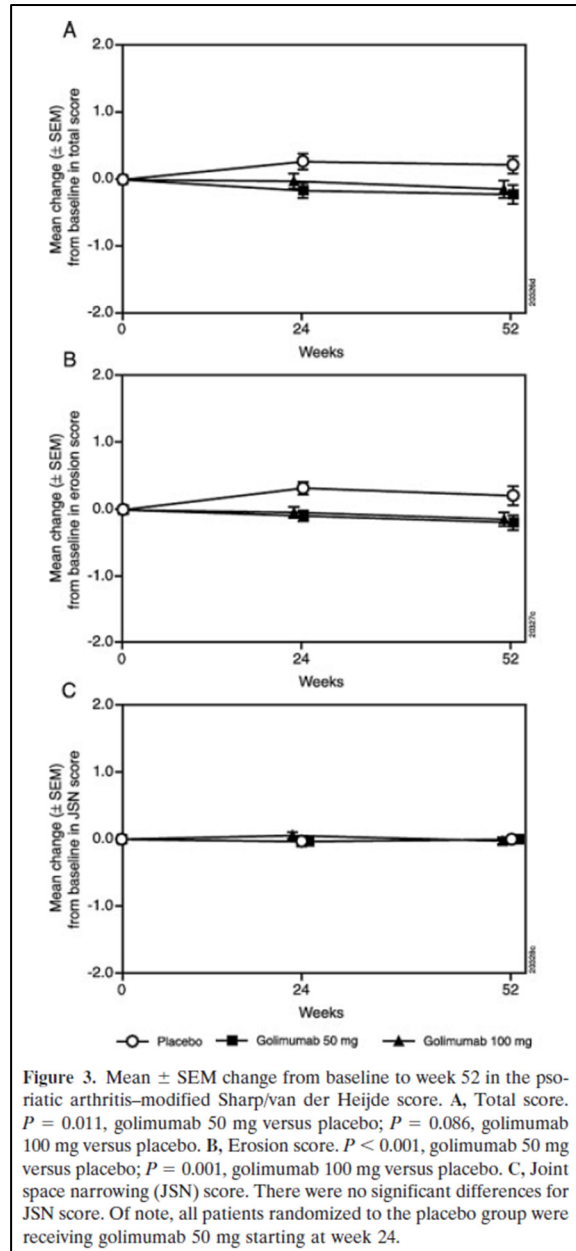
80. PI2013-Aria does not disclose any claimed clinical endpoints for PsA, nor does it describe meeting any of the claimed clinical endpoints used to assess treatment of PsA. It is directed exclusively to RA, a disease known by the priority date to have a different pathology, affected tissues, and patient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

D. “GO-REVEAL” (Exs.1041-1044)

81. GO-REVEAL was a Phase III clinical trial evaluating 50 mg and 100 mg golimumab by SC injections every four weeks (“q4w”). Four publications describe the results obtained in this study.

82. Kavanaugh 2009 describes the 24-week trial results that SC golimumab was effective in treating active PsA compared to placebo. Ex.1041 at 984 (Kavanaugh 2009). Kavanaugh 2012 reports the one-year results. Ex.1042 at 2504 (Kavanaugh 2012). Kavanaugh 2013 and 2014 report two- and five-year findings, respectively. Ex.1043 at 1666 (Kavanaugh 2013); Ex.1044 at 1689 (Kavanaugh 2014). All four publications report data on both doses studied, and Kavanaugh 2012 noted that “[g]olimumab efficacy was not substantially different

between patients receiving 50 mg and those receiving 100 mg” through the first year. Ex.1042 at 2516 (Kavanaugh 2012). Kavanaugh 2012 Table 2 and Figure 3 provide examples of the similar efficacy between the two doses. *Id.* at 2508-09 (Table 2), 2513 (Fig. 3). In some instances, the 50 mg dose had numerically better response (e.g., ACR70 and DAS28-CRP reduction). *Id.* at 2508-09 (Table 2). Figure 3 provides a visual of the scores:



Id. at 2513 (Fig. 3).

E. WO 2008/063213 (“WO213”) (Ex.1025)

83. WO213 is an international application publication titled “Uses and Compositions for Treatment of Psoriatic Arthritis.” Ex.1025 (Title) (WO213). WO213 discusses studies on SC adalimumab for treatment of PsA.

84. WO213 notes that its studies on adalimumab are meant to be representative of TNF inhibitors, *see, e.g., id.* at 31:34-35, 80:14-18, and that IV could be used, *see, e.g., id.* at 58:10-14. Nonetheless, all examples and outcomes relate to the use of SC adalimumab. *Id.*

X. Claim Construction

85. Petitioners have presented the following claim constructions for terms in the '020 Patent independent claims.

A. “Administering to a Subject” Is Not Limited to “a Single Subject”

86. I understand that Petitioners argue that a POSA would have understood that administering to “a subject” encompasses administering to a single subject or a single patient. In my opinion, this interpretation is incorrect and incompatible with how a clinician would read the claims. The '020 Patent claims describe a method of treatment whose scope is delineated by both the requirement of a “safe and effective” treatment and the population-level efficacy outcomes.

87. Moreover, a POSA reading the claims would note its use of “patients” in the plural form in describing the levels of efficacy achieved by the anti-TNF antibody. Ex.1001 at 141:50-51, 142:48-49, 143:1-2 (independent claims 1, 4, and 7) ('020 Patent). The claim language is consistent with a POSA’s understanding of how clinical trial data relates to patient treatment and

the reality of clinical medicine: clinicians select treatments for patients based on population-level evidence of safety and efficacy. These efficacy endpoints constitute the primary basis for treatment guidelines, formulary decisions, and clinical decision-making. Thus, Petitioners’ proposed construction that limits the treatment to a single patient is not supported by a POSA’s knowledge of PsA treatment.

B. “Treating” Active PsA in the Preamble Is Limiting

88. 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.” Petition at 37-39. In my opinion, this construction is inconsistent with a POSA’s reading of the claims.

89. A POSA would understand “treating” to require that administration be carried out with therapeutic intent and that it actually constitutes treatment of active PsA, 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 PsA, Ex.1001 at 78:62-120:51 (Example 9) (’020 Patent), while the claims recite

specific PsA-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.

C. Claimed Clinical Endpoints are Limiting

90. 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. Petition at 39-41.

91. 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: NCT673-V23 Does Not Anticipate the '020 Patent Claims³

92. In my opinion, NCT673-V23 does not anticipate the claims of the '020 Patent. At this stage, I have been asked to focus on the independent claims of the '020 Patent. I reserve the right to provide further opinions should the inter partes review proceed.

93. The clinical trial protocol does not disclose at least the following claim limitations:

- “at least one pharmaceutically acceptable carrier or diluent” (claims 1, 4);
- “at week 14 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in one or more criteria selected from the group consisting of: Health Assessment Questionnaire Disability Index score (HAQ-DI)= -0.60 ± 0.53 SD, enthesitis= -1.87 ± 1.75 SD, dactylitis= -7.8 ± 8.57 SD, 36-item Short-Form Health Survey Physical Component Summary score (SF-36

³ My opinions regarding Ground 1 apply to Ground 2 as well.

MCS)= 8.65 ± 7.60 SD, and 36-item Short-Form Health Survey Mental Component Summary score (SF-36 MCS)= 5.33 ± 9.95 SD” (claim 1);

- “at week 24 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in van der Heijde-Sharp score (vdH-S)= -0.36 ± 0.144 SE” (claim 4);
- “ $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment” (claim 7).

94. Petitioners admit that NCT673-V23 does not provide any outcome from the clinical trial. Petition at 51. Thus, I understand that Petitioners must 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 NCT673-V23, and not just probable or possible.

95. 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 NCT673-V23. Having a study plan established does not ensure that any level of efficacy will be achieved. It is common knowledge

to a POSA that studies on various therapies in treating PsA have failed, so a POSA would not have an expectation of success at the outset of such a trial.

96. For example, before 2012, it was believed that MTX should be used to treat active PsA. Ex.2077 at 1368 (Kingsley 2012). In search of supporting evidence for this belief, a group conducted the MTX in PsA (“MIPA”) randomized placebo-controlled trial. *Id.* at 1369. However, the outcome was not favorable. “MIPA found no statistically significant evidence that 6 months of MTX treatment was more likely than placebo to improve any rheumatology-related global response index in PsA.” *Id.* at 1372. A cornerstone treatment option that had been assumed an effective treatment for PsA did not show “true disease-modifying effect” when analyzed in a clinical trial. Similarly, the study of IV golimumab in UC failed despite researchers’ reliance on knowledge of SC golimumab. Ex.2089 at 509-10 (Rutgeerts 2015); Ex.2058 (NCT774 ClinicalTrials.gov). Thus, a POSA would know that the initiation of a clinical trial does not guarantee efficacy.

97. In my opinion, the claimed clinical endpoints would not necessarily be met by the study protocol described in NCT673-V23. As discussed above in Section IX.A, many important factors of the clinical trial described in the ’020 Patent are missing from the protocol version selected by Petitioners. Indeed, Example 9 describes many important procedures followed in the Phase III trial

that impact the likelihood of success. 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 NCT673-V23's discussion of administering golimumab.

98. 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 discussed above in Section IX.A, NCT673-V23 provides an incomplete picture of the study population described in the claimed invention.

99. For example, the '020 Patent specification requires that patients meet CASPAR criteria at screening. *See* Ex.1001 at 80:4-7, 88:20-24, 90:28-30 ('020 Patent). These patient selection criteria would not have been known to a POSA from NCT673-V23 alone and bear directly on whether NCT673-V23 would meet the claimed clinical endpoints.

100. Without these key details, NCT673-V23 does not ensure the claimed clinical endpoints would be necessarily met.

XII. Ground 3: NCT673-V23, PI2013-Aria, PI2015-Simponi, GO-REVEAL, and WO213 Do Not Render the '020 Patent Claims Obvious

101. My opinions regarding Grounds 1 also apply to Ground 3.⁴ A POSA would not understand the asserted combination of NCT673-V23, PI2013-Aria, PI2015-Simponi, GO-REVEAL, and WO213 to render the '020 Patent claims obvious.

A. NCT673-V23, PI2013-Aria, PI2015-Simponi, GO-REVEAL, and WO213 Do Not Disclose the Claimed Clinical Endpoints

102. In my opinion, the data relied on by Petitioners from the SC golimumab clinical trial reported in Kavanaugh 2009 and Kavanaugh 2012, along with the SC adalimumab trial reported in WO213, do not disclose achieving the clinical endpoint limitations as recited in independent claims 1, 4, and 7 of the '020 Patent.

⁴ As such, my earlier discussions regarding NCT673-V23, PI2015-Simponi, and PI2013-Aria, including their failure to disclose all limitations of the independent claims, apply accordingly to Ground 3.

1. **“at week 14 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in one or more criteria selected from the group consisting of: Health Assessment Questionnaire Disability Index score (HAQ-DI)=-0.60 $\pm$ 0.53 SD” (claim 1)**

103. I understand that Petitioners rely on a statement in Kavanaugh 2009 that patients in the GO-REVEAL study “had significant improvement in physical function and health-related quality of life, as measured by the HAQ and the SF-36, and also had significant improvement in enthesitis,” Ex.1041 at 984 (Kavanaugh 2009), as disclosure of the claimed HAQ-DI clinical endpoint. Petition at 54. A qualitative statement describing “significant improvement” does not disclose the specific quantitative magnitude of change (HAQ-DI=-0.60 $\pm$ 0.53 SD) required by the claim, because statistical significance in a comparison to placebo does not inform a POSA of the actual mean value or the variability of the treatment effect within the patient population.

104. Kavanaugh 2009 reports “HAQ scores at week 24 . . . with a mean $\pm$ SD change from baseline of 0.33 $\pm$ 0.55 and 0.39 $\pm$ 0.50 for golimumab 50 mg and golimumab 100 mg, respectively.” Ex.1041 at 980 (Kavanaugh 2009); Petition at 55. Based on these values, measured at week 24 with SC golimumab, a POSA would not have predicted the much higher claimed HAQ-DI clinical endpoint (-0.60 $\pm$ 0.53 SD at a much earlier timepoint of week 14 with IV golimumab), due to differences in the route of administration at an earlier

timepoint. Such extrapolation could not be made without impermissible assumptions about transferability across routes of administration, dosing regimens, and assessment timing.

105. In addition, a POSA would understand it to be impermissible to extrapolate from a different biologic therapy via a different route of administration at a different timepoint. Example 11 of WO213 reports a HAQ-DI score of -0.3 ± 0.5 SD from SC adalimumab at week 12. This cannot be compared to the claimed HAQ-DI mean and standard deviation of -0.60 ± 0.53 in a different study at week 14 of IV golimumab. Ex.1025 at 117-18 (WO213); Petition at 56. Based on these differences, a POSA would not have been able to predict the claimed clinical endpoint achieved by IV golimumab.

106. Additionally, a POSA would not understand the HAQ-DI data in Kavanaugh 2009 or WO213 to disclose the claimed clinical endpoint, nor would any alleged “overlap” cause a POSA to conflate Kavanaugh 2009 or WO213 with the claimed clinical endpoint. *See* Petition at 56. Thus, in my opinion, neither Kavanaugh 2009 nor WO213 discloses the claimed HAQ-DI clinical endpoint.

2. “enthesitis= -1.87 ± 1.75 SD” (claim 1)

107. I understand that Petitioners rely on a statement in Kavanaugh 2009 that patients in the GO-REVEAL study “had significant improvement in physical function and health-related quality of life, as measured by the HAQ and the SF-

36, and also had significant improvement in enthesitis,” Ex.1041 at 984 (Kavanaugh 2009), as disclosure of the claimed enthesitis endpoint. Petition at 54. As explained above, statements about “significant improvement” are insufficient to teach a POSA that IV golimumab would achieve the claimed enthesitis clinical endpoint.

3. “36-item Short-Form Health Survey Physical Component Summary score (SF-36 MCS)=8.65±7.60 SD” (claim 1)

108. I understand that Petitioners rely on a statement in Kavanaugh 2009 that patients in the GO-REVEAL study “had significant improvement in physical function and health-related quality of life, as measured by the HAQ and the SF-36, and also had significant improvement in enthesitis,” Ex.1041 at 984 (Kavanaugh 2009), as disclosure of the claimed SF-36 clinical endpoint. Petition at 54. As explained above, statements about “significant improvement” are insufficient to teach a POSA that IV golimumab would achieve the claimed SF-36 PCS clinical endpoint.

109. I understand that Petitioners rely on Kavanaugh 2009, which reports SF-36 PCS scores of 6.53 ± 8.88 and 7.85 ± 9.55 at week 14. Ex.1041 at 980 (Kavanaugh 2009); Petition at 55. Kavanaugh 2009’s SF-36 PCS mean values (6.53 and 7.85) from SC golimumab at week 14 are lower than the claimed mean (8.65). Kavanaugh 2009 also reports a broader SD (± 8.88 and ± 9.55) than the claimed value (± 7.60). A POSA could not reliably predict that a different route

of administration would yield the precise claimed improvement, particularly given the variability inherent in patient-reported quality-of-life outcomes.

4. “36-item Short-Form Health Survey Mental Component Summary score (SF-36 MCS)= 5.33 ± 9.95 SD” (claim 1)

110. I understand that Petitioners rely on a statement in Kavanaugh 2009 that patients in the GO-REVEAL study “had significant improvement in physical function and health-related quality of life, as measured by the HAQ and the SF-36, and also had significant improvement in enthesitis,” Ex.1041 at 984, as disclosure of the claimed SF-36 clinical endpoint. Petition at 54. As explained above, statements about “significant improvement” are insufficient to teach a POSA that IV golimumab would achieve the claimed SF-36 MCS clinical endpoint.

5. “at week 24 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in van der Heijde-Sharp score (vdH-S)= -0.36 ± 0.144 SE” (claim 4)

111. I understand that Petitioners rely on Kavanaugh 2012 for reporting PsA-modified Sharp/van der Heijde scores (“SHS”)⁵ for groups receiving MTX, at week 24, of -0.34 ± 1.10 and -0.16 ± 1.36 . Petition at 59-60. This reference fails to disclose the claimed total modified vdH-S endpoint.

⁵ SHS and vdH-S are both used to refer to the total modified van der Heijde-Sharp assessment tool for PsA.

112. Preliminarily, Petitioners provide an incomplete picture of the data available in Kavanaugh 2012. The values reported as the co-primary endpoint results of the study are not the values provided by Petitioners. Instead, “[f]or the coprimary end point of change from baseline in PsA-modified SHS at week 24, the mean±SD change from baseline indicated significantly less radiographic progression in patients receiving golimumab 50 mg (-0.16±1.31) than placebo (0.27±1.26) (P = 0.011) (Table 2). The difference between the golimumab 100 mg group (-0.02±1.32) and the placebo group at week 24 approached statistical significance (P = 0.086).” Ex.1042 at 2509 (Kavanaugh 2012). All scores reported are found in Tables 2 and 3, reproduced in relevant part here:

Table 2. Summary of radiographic and clinical efficacy findings by randomized treatment group*				
	Placebo (n = 113)†	Golimumab 50 mg (n = 146)†	Golimumab 100 mg (n = 146)	Golimumab combined (n = 292)
Change in PsA-modified SHS, baseline to week 24‡				
Total score§				
n	113	146	146	292
Mean ± SD	0.27 ± 1.26	-0.16 ± 1.31	-0.02 ± 1.32	-0.09 ± 1.32
P vs. placebo		0.011	0.086	0.015

Id. at 2508 (Table 2).

Table 3. Summary of radiographic findings by randomized treatment group and baseline MTX use*				
	Placebo (n = 113)†	Golimumab 50 mg (n = 146)†	Golimumab 100 mg (n = 146)	Golimumab combined (n = 292)
Change in PsA-modified SHS, baseline to week 24‡				
Total score§				
MTX at baseline				
n	55	71	71	142
Mean ± SD	0.22 ± 1.25	-0.34 ± 1.10	-0.16 ± 1.36	-0.25 ± 1.23
P vs. placebo		0.003	0.098	0.007
No MTX at baseline				
n	58	75	75	150
Mean ± SD	0.31 ± 1.28	0.01 ± 1.47	0.11 ± 1.28	0.06 ± 1.38
P vs. placebo		0.495	0.340	0.350

Id. at 2510 (Table 3).

113. Nonetheless, all three sets of SHS scores reported by Kavanaugh 2012 fail to disclose the claimed vdH-S clinical endpoint -0.36±0.144 SE. As

described above, a POSA would not consider it methodologically sound to compare any of these outcomes in the way Petitioners do, and, even so, none of them reach the achievement of a mean 0.36 reduction in vdH-S score from baseline. All SHS scores reported by Kavanaugh have lower means than the vdH-S clinical endpoint claimed in the '020 Patent. Further, Kavanaugh 2012 discloses SD values, while the claim requires a standard error ("SE") value. Simply, the reference's worse mean values and silence as to SE do not disclose the claimed total modified vdH-S endpoint.

114. I understand that Petitioners also rely on WO213's Example 12, which Petitioners assert reported mean change in mTSS as "-0.2 for adalimumab" at week 24. Petition at 60; Ex.1025 at 127-28 (WO213). Again, WO213 uses a different biologic therapy, in a different route of administration. Moreover, Example 12 failed to achieve the mean change from baseline in vdH-S score claimed in the '020 Patent. WO213 provides no SE for this value, which is a required component of the clinical endpoint as recited in claim 4.

115. Thus, the asserted references would only teach a POSA that the vdH-S clinical endpoint recited in the '020 Patent had not been achieved. Any other takeaway is unsupported speculation.

6. “ $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment” (claim 7)

116. I understand that Petitioners rely on Kavanaugh 2009 for disclosing GO-REVEAL’s outcome that 51% of the PsA patients who received 50 mg golimumab achieved ACR20 at week 14. Ex.1041 at 979 (Kavanaugh 2009); Petition at 62; *see* Ex.1025 at 133 (WO213). 51% is less than 65%, and the claims require $\geq 65\%$ of patients achieve ACR20. Thus, Kavanaugh 2009 does not disclose the ACR20 endpoint as recited in claim 7.

117. Petitioners also rely on results from Example 13 of WO213 that SC adalimumab achieved ACR20 of 72% at week 12. Petition at 62; Ex.1025 at 133 (WO213). However, a POSA would not have speculated that IV golimumab administered to PsA patients would achieve the same or better ACR20 at week 14 response as SC adalimumab at week 12, because the Example 13 data involves a different anti-TNF antibody (adalimumab), a different route of administration (SC), a different timepoint (week 12), and an open-label clinical practice setting rather than a randomized controlled trial. Extrapolating from this data to predict that $\geq 65\%$ of patients would achieve ACR20 at week 14 would require multiple unfounded assumptions that a POSA would not make.

118. Again, Kavanaugh 2009 and WO213 only confirm that the claimed ACR20 clinical endpoint had not been achieved by SC golimumab.

* * *

119. In conclusion, it is my opinion that Petitioners have not identified any prior art data sufficient to render the claimed clinical endpoints obvious to a POSA.

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

120. 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 PsA and RA, a POSA would be unlikely to arrive at this combination of references.

121. In my opinion, a POSA would not have had motivation to combine NCT673-V23 and PI2013-Aria. While both documents concern golimumab, they concern different diseases. NCT673-V23 is directed to PsA, and PI2013-Aria is directed to RA. Because a POSA would have known of the stark differences in disease pathogenesis, presentations, and treatment strategies between PsA and RA, a POSA would be unlikely to arrive at this combination of references.

122. A POSA would not have been motivated to combine references directed to RA and PsA because the state of the art as of the priority date clearly indicated that RA and PsA are pathologically and immunologically distinct diseases. Although both conditions are TNF-mediated inflammatory diseases,

they differ fundamentally in their underlying mechanisms: RA is predominantly associated with adaptive immune inflammation, whereas PsA is predominantly characterized by innate immune system involvement. Moreover, RA primarily affects synovial tissue and peripheral joints, resulting in progressive bone erosion and cartilage destruction, whereas PsA presents in a broad array of symptoms, including skin lesions, inflammation in the distal interphalangeal joints, and new bone formation. In my opinion, these substantial pathologic differences highlight that treatment outcomes observed in RA cannot be assumed to predict outcomes in PsA. Accordingly, a POSA would have had no motivation to combine references relating to these distinct disease indications.

123. Moreover, during the relevant time, Simponi Aria was approved only for RA, not PsA. In my experience, clinicians were not relying on the information found in PI2013-Aria to treat PsA with Simponi Aria “off label.” Accordingly, a POSA would not have been motivated to rely on PI2013-Aria as a basis for treating PsA patients.

124. 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 PsA and RA patient populations—PsA patients are characteristically younger and present with distinct disease duration and baseline characteristics compared to RA patients, as described above. Therefore, the shared active ingredient, dosing, and sponsor between the two studies would not have been enough to motivate a POSA to combine NCT673-V23 and PI2013-Aria, as a POSA would recognize them to concern totally distinct patient populations.

125. Also, 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.

126. 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 PsA (NCT673-V23), prescribing information for IV golimumab in RA (PI2013-Aria), prescribing information for SC golimumab across multiple indications (PI2015-Simponi), SC golimumab efficacy data in PsA (GO-REVEAL), *and* SC adalimumab efficacy data in PsA (WO213). This combination would require a POSA to bridge across

formulations with fundamentally different PK profiles (IV versus SC), distinct disease pathologies (PsA versus RA), wholly different treatments (golimumab versus adalimumab), and disparate patient populations (across studies), 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

127. I have been informed by counsel that to show obviousness, 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. In my opinion, Petitioners' assertion that a POSA would have had a reasonable expectation that the invented method would have achieved the claimed clinical endpoints because of "the higher drug exposure of the IV versus SC formulation" is incorrect for multiple reasons. Petition at 61, 63.

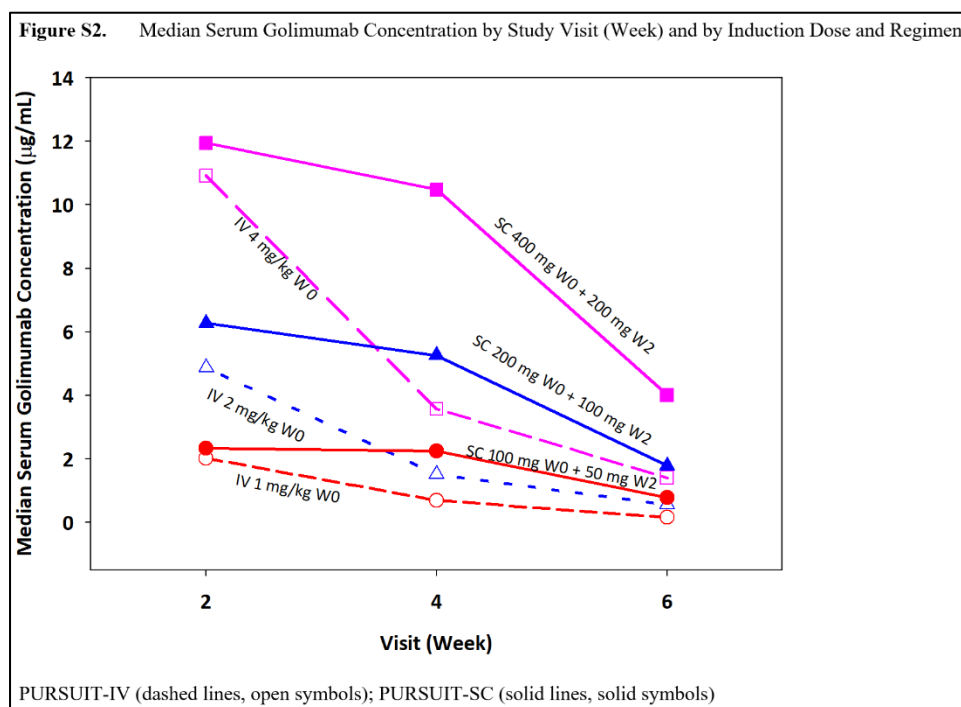
128. As of the priority date, a POSA would not have had a reasonable expectation of success. Rather, they would have been aware that an analogous extrapolation strategy (from SC to IV golimumab) had failed for UC. By the priority date, it was known in the art that Janssen attempted to develop Simponi

Aria for treating UC, an indication already approved for Simponi, Janssen's SC golimumab formulation.

129. 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.2089 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 PsA could be inferred from SC golimumab data for PsA.

130. The substantial pharmacokinetic differences between IV and SC administration, as I described in Section VII.E, would have precluded a POSA's expectation of success in IV based on SC data. IV administration produces higher peak concentrations, greater total exposure, faster clearance, and lower troughs than SC administration. Ex.1038 at 84 (Table II) (Zhuang); Ex.1015 at 19 (PI2015-Simponi); Ex.2090 at 13 (Rutgeerts Supplemental Appendix). In contrast to Petitioners' assertion regarding bioavailability, the available data suggest otherwise. For instance, Janssen's UC study included three comparisons

between IV and SC administration, as shown in Figure S2 of the Supplemental Appendix:



Ex.2090 at 13 (Rutgeerts Supplemental Appendix).

131. Further, the data reported by Petitioners' asserted references PI2013-Aria and WO213 stray even further from the SC golimumab data. PI2013-Aria reports data related to a different disease (RA), on which a POSA would not base a reasonable expectation of success in PsA, as explained above in Section VII.C.1 and 2. WO213 not only describes results from SC administration but also reports on the efficacy of a different anti-TNF antibody (adalimumab). As explained above in Section VII.B, the various TNF inhibitors available by the priority date were understood to bind to TNF differently, therefore exhibiting

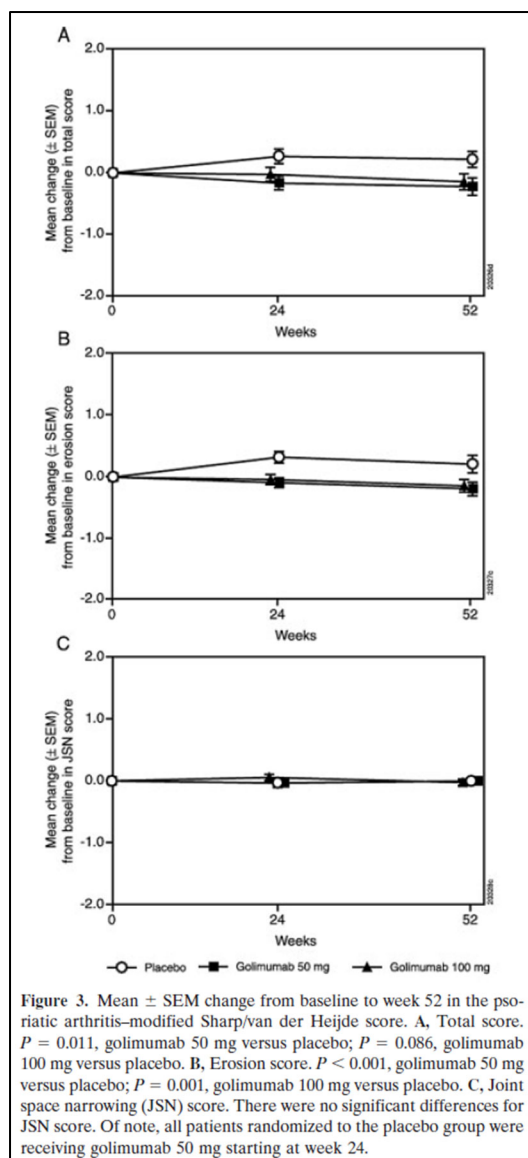
different levels of efficacy. A POSA would not have been able to expect IV golimumab to achieve the claimed clinical endpoints from data resulting from a distinct product in a different formulation.

132. A POSA would have recognized that actions taken by the FDA and other regulatory health agencies reflected and informed the perspective of POSAs themselves. As of the priority date, these regulatory agencies had taken actions that conflict with the 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.*

133. 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 (EMA Simponi Withdrawal Assessment). Accordingly, a POSA would have understood that higher drug exposure could lead to increased immunosuppression or adverse events that

interfere with achieving the claimed efficacy. Thus, a POSA would have shared these concerns and would not have considered IV golimumab treatment for PsA to be “safe and effective” as claimed by the ’020 Patent.

134. Critically, the asserted references do not support the assumption that higher exposure or bioavailability necessarily leads to greater 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), pre-priority date analyses of SC golimumab data demonstrated a plateau or saturation in efficacy between the 50 mg and 100 mg doses. *See* Ex.1042 at 2513 (Fig. 3) (Kavanaugh 2012); Ex.1016 at 3406 (Figs. 2-3) (Inman); Ex.1033 at 1099 (Fig. 1) (van der Heijde 2014). Petitioners’ asserted reference Kavanaugh 2012 provides a visual demonstrating comparable results in the two analyzed doses:



Ex.1042 at 2153 (Fig. 3) (Kavanaugh 2012). The Simponi label states that “[t]here was no clear evidence of improved ACR response with the higher SIMPONI dose group (100 mg) compared to the lower SIMPONI dose group (50 mg).” Ex.1015 at 26 (PI2015-Simponi). Indeed, the clinical trial data on IV golimumab in UC specifically indicated that “peak serum concentration is not a dominant driver of efficacy.” Ex.2089 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 PsA with a level of efficacy required to meet the claimed clinical endpoints.

135. Moreover, achieving the claimed clinical endpoints at specific timepoints is not merely a difference in degree. Rather, they represent qualitatively different therapeutic profiles that a POSA would not have predicted from the prior art. For example, achieving HAQ-DI score -0.60 ± 0.53 SD at week 14 of IV treatment is clinically significant given that SC data shows only approximately 0.33 to 0.39 mean change from baseline much later, at 24 weeks. Ex.1041 at 980 (Kavanaugh 2009). Reaching the claimed level of HAQ-DI achievement cannot be reliably extrapolated from data concerning a different dosage form at a much later timepoint. Similarly, because response rates may fluctuate over time, a POSA could not reliably extrapolate from week 24 SC data to predict week 14 IV clinical outcome within the range claimed.

136. 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 and therapies. As a

result, a POSA would not have had a reasonable expectation that IV golimumab in PsA would achieve the clinical endpoints recited in the '020 Patent.

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