

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

IPR2026-00256, IPR2026-00258, IPR2026-00259

Patents No. 11,014,982, 12,122,824, and 12,291,566

Title: ANTI-TNF ANTIBODIES, COMPOSITIONS, AND METHODS FOR
THE TREATMENT OF ACTIVE ANKYLOSING SPONDYLITIS

IPR2026-00257,

Patent No. 11,041,020

Title: METHODS FOR THE TREATMENT OF ACTIVE PSORIATIC
ARTHRITIS

**DECLARATION OF DR. ROY M. FLEISCHMANN IN SUPPORT OF
ACCORD'S PETITION FOR INTER PARTES REVIEW OF U.S. PATENTS
NO. 11,041,020, 11,014,982, 12,122,824, AND 12,291,566**

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I, Roy M. Fleischmann, declare and state as follows:

I. INTRODUCTION AND SUMMARY

1. I have been retained by Accord BioPharma, Inc., Intas Pharmaceuticals Ltd., and Bio-Thera Solutions, Ltd. (“Petitioner” or “Accord”) as a technical expert in connection with the above-identified proceedings. I have been asked to provide my opinions regarding the “novelty” and “obviousness” of: (a) claims 1-10 of U.S. Patent No. 11,041,020 (“*US020*”, EX1001); (b) claims 1-10 of U.S. Patent No. 11,014,982 (“*US982*”, EX1002); (c) claims 1-7 of U.S. Patent No. 12,122,824 (“*US824*”, EX1003); and (d) claims 1-7 of U.S. Patent No. 12,291,566 (“*US566*”, EX1004). *US020* and *US982* relate to methods of treating active psoriatic arthritis (“PsA”). *US824* and *US566* relate to methods of treating active ankylosing spondylitis (“AS”).

2. I understand that my declaration will be submitted in support of Accord’s Petitions for Inter Partes Review of *US020*, *US982*, *US824*, and *US566* against Janssen Biotech, Inc. (“Janssen” or “Patent Owner”).

3. My opinions in this declaration are based on my review of *US020*, *US982*, *US824*, and *US566* (collectively “the Janssen Patents”) and their respective prosecution histories (excerpts at EX1007-1010), the relevant prior art that I have identified and of which I have been informed, other documents referred to in this declaration, and my many years of experience as a practicing rheumatologist

treating auto-immune diseases, such as rheumatoid arthritis (“RA”), PsA, and AS, including during the relevant time period for the questions I have been asked to consider. The opinions I offer are made to a reasonable degree of scientific certainty.

4. I am being compensated for my time at my usual consulting rate of \$800 per hour, and I am being compensated at a rate of \$1,200 per hour for deposition testimony. I am also being reimbursed for reasonable travel expenses related to my consultation. I do not have a personal or financial interest in the outcome of this proceeding nor is my compensation affected by its outcome.

5. The opinions in this declaration are based on my review of the patent, its file history, the prior art, and the materials cited in this declaration, as well as my many years of experience as a practicing physician in the field of rheumatology who attends the annual meetings of the American College of Rheumatology and the European League Against Rheumatology (“EULAR”) / European Alliance of Associations for Rheumatology and who keeps up to date on the latest scientific literature and developments. I have also been involved in the design of many regulatory Phase 3 studies for all five approved tumor necrosis factor (“TNF”) inhibitors and conducted and reported the results of these pivotal trials.

II. BACKGROUND AND QUALIFICATIONS

6. I am currently the Medical Director, Metroplex Clinical Research Center, in Dallas. I am also an adjunct clinical professor in internal medicine at the University of Texas Southwestern Medical Center at Dallas.

7. I have a Bachelor of Arts in Zoology from Columbia College and a Doctor of Medicine (“MD”) from the State University of New York, Downstate Medical Center.

8. After earning my MD in 1969, I was a medical intern and a 1st year resident in internal medicine at Maimonides Medical Center in New York City from 1969-1971. I then was a 2nd year resident in internal medicine at Mt. Sinai Hospital in New York City from 1971-1972. I then was a fellow in rheumatology in the department of medicine, Division of Rheumatology at the College of Physicians and Surgeons of Columbia University in New York City from 1972-1974. From 1974-1975 I was an attending physician and an instructor of Medicine at the College of Physicians and Surgeons of Columbia University in New York City. I was recruited to the Department of Rheumatology in the Division of Medicine at the University of Texas Southwestern Medical Center at Dallas in 1975 where I have held the positions of clinical instructor in medicine, clinical assistant professor of medicine, and clinical associate professor of medicine from 1975-1984, 1984-1985, and 1986-2000, respectively. I was a Clinical Professor of

Medicine at the University of Texas Southwestern Medical Center from 2001-2025 and have been an Adjunct Professor of Medicine at the University of TEXAS Southwestern Medical Center since 2025. I was also the Director, Division of Rheumatology, at St. Paul University Hospital, from 1978-2009 (when the hospital closed), and the Medical Director, Osteoporosis Center, at St. Paul University Hospital, from 1984-2003. I was also the Co-Director, Division of Rheumatology, THR Presbyterian Hospital, Dallas, from 2010-2015.

9. I also hold, and have held, many editorial positions on prestigious journals. As examples, I have been the Editor-in-Chief of Rheumatology and Therapy since 2015. I have also been on the editorial board of Expert Opinion on Drug Safety since 2011, and the editorial boards of Annals of Rheumatic Disease and RMD Open since 2017. I previously served 5-year terms on the Editorial Boards of the Journal of Rheumatology and Rheumatology (Oxford). I have also been a reviewer for many prestigious journals including the New England Journal of Medicine, Lancet, Lancet Rheumatology, the American Journal of Medicine, Arthritis and Rheumatology (for which I am in the top 5% of all reviewers), and the Annals of Rheumatic Disease. A more complete list of my editorial positions and refereeing roles is provided in my CV (EX1006).

10. I have served on multiple committees including Abstract Review Committee ACR annual meeting (2008 – present), Abstract Review Committee

EULAR annual meeting (2010 – present), International Advisory Committee Member- Japanese College of Rheumatology (2012 – present), Medical and Scientific Committee, Arthritis Foundation, North Texas Chapter (1975-2009), Graduate Training Committee, St. Paul Medical Center (1979 1991), President, Texas Rheumatism Society (1983-1984), Finance Committee, American College of Rheumatology (1997- 2000).

11. I have also consulted, spoken, and published extensively in the field of rheumatology. For example, my CV (EX1006) lists the companies for which I have consulted during the last 2 years (over 30), the companies for which I serve on their advisory boards, peer speaking engagements since 2015 (over 100), book chapters (6), papers I have authored or co-authored in peer reviewed journals (over 300), and abstracts I have authored or co-authored presented at the annual meetings of the American College of Rheumatology and EULAR (over 500). Included among these are multiple papers reporting on the results of Phase 1-4 trials of all five approved TNF inhibitors and how they should be utilized in practice. Examples are: (1) M.E. Weinblatt, J.M. Kremer, A.D. Bankhurst, K.J. Bulpitt, R.M. Fleischmann, R.I. Fox, C.G. Jackson, M. Lange, D.J. Burge, *A Trial of Etanercept, a Recombinant Tumor Necrosis Factor Receptor: Fc Fusion Protein, in Patients with Rheumatoid Arthritis Receiving Methotrexate*, New England Journal of Medicine, 1999; 340(4)253-259; (2) RM Fleischmann,

Examining the Efficacy of Biologic Therapy: Are There Real Differences?, The Journal of Rheumatology. September 2002. 29 (S65) 27-32; (3) Fleischmann RM, Cohen SB, Moreland LW, Schiff M, Mease PJ, Smith DB, Keenan G, Kremer JM and the iRAMT Study Group, *Methotrexate Dosage Reduction in Patients with Rheumatoid Arthritis Beginning Therapy with Infliximab*, Curr Med Res and Opin 2005, 21(8):1181-1190; (4) Zhou H, Jang H, Fleischmann RM, Bouman-Thio E, Xu Z, Marini JC, Pendley C, Jiao Q, Shankar G, Marciniak SJ, Cohen SB, Rahman MU, Baker D, Mascelli MA, Davis HM, Everitt DE, *Pharmacokinetics and Safety of Golimumab, a fully human anti-TNF- α Monoclonal Antibody, in Subjects with Rheumatoid Arthritis*, Journal of Clinical Pharmacology 2007 47: 383-396; (5) Fleischmann RM, Vencovsky J, van Vollenhoven R, Borenstein D, Box J, Coteur G, Goel N, Brezinschek HP, Innes A, Strand V., *Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study*, Ann Rheum Dis; 2009;68(6):805-811; and (6) Fleischmann R, Blanco R, Hall S, Thomson G, Van den Bosch F, Zerbini C, Bessette L, Enejosa J, Li Y, Song Y, DeMasi R, Song I., *Switching between Janus kinase inhibitor upadacitinib and adalimumab following insufficient response: efficacy and safety in patients with rheumatoid arthritis*, Ann.Rheum.Dis.2021. 80(4):432-439.

12. I have also received several honors during my career, including becoming a Master of the American College of Rheumatology, being named a “World Expert” by Expertscape for being within the top 0.1% of scholars writing about RA over the past 10 years, and achieving an h-index of 96. I am a past President of the Dallas-Fort Worth and State of Texas Rheumatology Association. My CV (EX1006) includes a more complete list of the honors I have received.

13. As the Medical Director of the Metroplex Clinical Research Center, I have been a principal investigator in multiple Phase 1-4 clinical trials of the five approved TNF inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol) as well as other approved biologics, including abatacept, tocilizumab, sarilumab, and rituximab. Most of these trials were in rheumatoid arthritis (“RA”), but a significant number were in patients with psoriatic arthritis (“PsA”) and ankylosing spondylitis (“AS”). As seen in my CV, I reported the results of many of these trials in peer reviewed journals as well as the major rheumatology meetings world-wide. I have also written extensively and lectured on the appropriate use of these molecules.

14. I am the Editor in Chief of Rheumatology and Therapy, and on the editorial boards of the Annals of Rheumatic Disease, RMD Open, Expert Opinion on Drug Safety, and Drugs. I was previously Co-Editor in Chief of Rheumatology (Oxford), and on the Editorial Board of the Journal of Rheumatology.

15. A full list of my publications, qualifications, and appointments can be found in my CV, EX1006.

III. LEGAL BACKGROUND

16. I do not hold any legal qualifications; however, Accord's counsel has informed me of a number of legal principles to consider when formulating my opinions relating to the validity of *US020*, *US982*, *US824*, and *US566*. These principles are set forth below.

A. Claim Construction

17. I understand that in an *inter partes* review ("IPR") proceeding, the terms in a patent claim are generally given their ordinary and customary meaning as understood by a person of ordinary skill in the art ("POSA") in the context of the entire patent disclosure. If, however, an inventor defines a claim term in the patent disclosure, then the inventor's definition applies. If the inventor chooses to define a claim term, however, the inventor must do so with reasonable clarity, deliberateness, and precision.

18. I further understand that claims can be "independent" or "dependent." An independent claim does not refer to or incorporate the elements of any other claim. A dependent claim refers to another claim and includes all of its limitations, while also adding additional limitation(s). I further understand that a dependent claim can have multiple dependencies, wherein it refers to more than one claim

and includes the limitations of each claim to which it refers. *US020* contains three independent claims, claims 1, 4, and 7, with the remaining claims dependent on these claims. *US982* contains three independent claims, claims 1, 4, and 7, with the remaining claims dependent on these claims. *US824* contains three independent claims, claims 1, 3, and 5, with the remaining claims dependent on these claims. *US566* contains three independent claims, claims 1, 3, and 5 with the remaining claims dependent on these claims.

B. Burden of Proof

19. I understand that in an IPR, a claim is not patentable if a “preponderance of the evidence” establishes that the claim is anticipated by, or rendered obvious by, the prior art. I understand that “a preponderance of the evidence” means “more likely than not.”

C. Prior Art and Earliest Possible Effective Filing Date

20. With respect to *US020* and *US824*, I have been informed that the earliest possible effective filing date is January 30, 2017. I have been asked to assume that any printed publication published prior to January 30, 2017 (*i.e.*, what I have been asked to assume is the earliest possible effective filing date for these patents) should be considered “prior art” to *US020* and *US824*.

21. With respect to *US982* and *US566*, I have been informed that the earliest possible effective filing date is February 7, 2017. I have been asked to

assume that any printed publication published prior to February 7, 2017 (*i.e.*, what I have been asked to assume is the earliest possible effective filing date for these patents) should be considered “prior art” to *US982* and *US566*.

22. I further understand that a document is considered a “printed publication” if it was published or otherwise made available such that a POSA exercising reasonable diligence could have located it.

D. Anticipation

23. I have been informed that for a claimed invention to be patentable, it must be new, or “novel” over the prior art.

24. I have been informed that a patent claim is “anticipated” if a single prior art reference discloses to a POSA every element of the claim arranged as in the claim.

25. I have been informed that a member of a genus, that is, a species, anticipates a genus.

26. I have been informed that if a claim uses the word “or” to present alternative limitations, if any of the alternatives in a claim are anticipated by the prior art, then the claim is anticipated. Put another way, I have been informed that even if only one such alternative in a claim is anticipated by the prior art, then the claim as a whole is anticipated.

27. I have also been informed that if a claim describes a functional result, it is considered the natural result flowing from the prior art if the patent teaches that the only steps required to achieve the claimed result are the same as those disclosed in the prior art. In other words, when the patent does not itself disclose any more than what is in the prior art regarding how to achieve a claimed functional result, then the functional result is considered the natural result of those steps.

28. I also understand that prior art references are analyzed from the perspective and knowledge of a POSA, and that other art may be relied upon to show the general knowledge in the field that a POSA would have known, or to establish that a claimed feature is “enabled.”

29. I understand that a prior art publication must be “enabling” in order to anticipate a patent claim. Prior art is enabling if it describes the claimed invention sufficiently to allow a POSA to carry out the invention.

30. I have been informed and understand that, in an anticipation analysis, there is no need to consider secondary considerations.

E. Obviousness

31. I have been informed by counsel that, for a patent claim to be patentable, it must be “non-obvious” over the prior art.

32. I understand that a patent claim is obvious if the differences between the claims and the prior art are such that the subject matter as a whole would have been obvious to a POSA at the time the invention was made. For purposes of my analysis, I have been asked to assume a date of invention of January 30, 2017, for *US020* and *US824*, and a date of invention of February 7, 2017, for *US982* and *US566*.

33. I understand that when assessing whether a claim is obvious, I should consider: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between what is claimed and the prior art; and (4) any evidence of “secondary considerations” that may indicate that the claims are not obvious.

34. I understand that a claimed invention may be obvious when, for example, there is some teaching, suggestion, or motivation that would have led a POSA to modify a prior art reference or to combine prior art teachings to arrive at the claimed invention.

35. I also understand that in combining or modifying prior art references to arrive at the claimed invention, the POSA must have a reasonable expectation of success, given their general knowledge and what has been disclosed in the prior art. I understand that this success need only be reasonably expected, and does not need to be guaranteed or proven.

36. I understand further that if a member of a genus, that is, a species, is obvious, then the genus is also obvious.

37. I have been informed that if a claim uses the word “or” to present alternative limitations, if any of the alternatives in a claim are rendered obvious by the prior art, then the claim is rendered obvious. Put another way, I have been informed that even if only one such alternative in a claim is rendered obvious by the prior art, then the claim as a whole is rendered obvious.

38. I understand that evidence of “secondary considerations” may weigh against a finding that a claimed invention would have been obvious. Such secondary evidence may include: (1) commercial success of a product due to the merits of what is provided in the patent claim; (2) a long-felt but unsolved need for the solution provided by the patent claim; (3) unsuccessful attempts by others to find the solution provided; or (4) unexpected results of the claimed invention compared to the closest prior art. I understand such “secondary considerations” of non-obviousness must have a “nexus” to the claimed invention over what was known in the prior art.

F. The POSA

39. I understand that claim construction, anticipation and obviousness must be judged from the perspective of the POSA to which the patent is directed. I

understand that the POSA is a hypothetical person that is presumed to have a perfect knowledge of all of the relevant prior art.

40. I understand that in determining who a POSA is the following may be considered: (1) the educational level of the inventor(s); (2) the type of problems encountered in the relevant technical field; (3) prior-art solutions to those problems; (4) rapidity with which innovations are made; and (5) the sophistication of the technology and educational level of active workers in the field.

41. Here, *US824* and *US020* concern methods of treating PsA by intravenously administering golimumab, and *US982* and *US566* concern methods of treating AS by intravenously administering golimumab. Based on my extensive experience in the clinic treating patients, in academia, and as a consultant to the biopharmaceutical industry, I believe the POSA would have been a medical doctor and/or clinical researcher with a Ph.D. and significant experience treating and/or researching inflammatory diseases, such as RA, PsA, and AS. The POSA may collaborate with others, including scientists skilled in related fields typically employed in pharmaceutical development, such as pharmacokineticists and formulators.

42. Even if a different definition of POSA is adopted, that POSA would have had access to individuals skilled in clinical medicine, pharmacokinetics and formulation.

IV. SCIENTIFIC BACKGROUND

43. RA, PsA, and AS are rheumatic diseases characterized by immune system dysregulation that usually leads to joint inflammation, pain, and systemic complications. EX1027, 27.

44. RA is “a chronic and progressive systemic inflammatory disease characterized by chronic synovial inflammation that results in cartilage damage, progressive bone erosion, and functional decline.” EX1026, 160.

45. PsA is a systemic inflammatory disease occurring in patients with psoriasis (a chronic skin inflammation) that is characterized by chronic skin, synovial, and enthesial inflammation, which can also affect multiple domains, including joints, tendons, skin, nails, and the spine. EX1022, 113. The effects of the disease vary between individuals and over time, but patients with PsA “suffer from diminished quality of life (QoL) and functional impairment and have a significant escalation in mortality compared to the general population.” *Id.*

46. AS is a systemic inflammatory disease occurring in patients with “spondyloarthropathy characterized by enthesial and axial skeletal inflammation that results in syndesmophyte formation with spinal fusion and progressive functional decline,” as well as systemic complications. EX1026, 160.

47. Before the introduction of TNF inhibitors, treatment options for rheumatic diseases, such as RA, PsA, and AS, were limited to medications that

partially relieved inflammation and pain, and patients with these diseases had a significantly decreased quality of life and life expectancy. EX1029, 1.

48. The use of TNF inhibitors has “clinically demonstrated the dominant role played by TNF in IMID [immune-mediated inflammatory diseases]” such as RA, PsA, and AS and has “significantly improved outcome of patients affected by these disorders.” EX1027, 27.

A. TNF α Inhibitors as Therapeutic Agents

49. TNF is a member of a family of structurally related cytokines that play a pivotal role in various immune and inflammatory processes. EX1027, 27.

50. More specifically, TNF α is a cytokine protein, elevated levels of which have been implicated in the pathophysiology of chronic inflammatory diseases such as RA, PsA, and AS. EX1015, 18.

51. The scientific literature uses the terms “TNF” and “TNF α ” to refer to the same tumor necrosis factor protein. *US020*, *US982*, *US824*, and *US566* use the terms “TNF antibody,” TNF α antibody,” “anti-TNF antibody,” and “anti-TNF α antibody” interchangeably, and this declaration does as well. EX1001, 42:3-15, 14:10; EX1002, 42:17-29, 14:45; EX1003, 41:45-57, 14:15; EX1004, 42:36-48, 14:51.

52. As of 2010, many anti-TNF products existed, including Remicade (infliximab), Humira (adalimumab), Simponi (golimumab), Cimzia (certolizumab

pegol), and Enbrel (etanercept). EX1028, 540. The primary mechanism of action of TNF inhibitors is as competitive antagonists that block the binding of soluble and membrane TNF to its receptor. EX1027, 34. Blocking the binding of TNF to its receptor diminishes the TNF signaling cascade, thereby inhibiting the inflammatory response. *Id.*

53. According to *Shim*, in 2010 TNF α was “the single most successful antibody target molecule, worth more than 15 billion USD in combined worldwide sales in 2010 alone.” EX1028, 540.

54. The development of TNF inhibitors were a major advance in the treatment of RA, PsA, and AS, because they were proven to significantly decrease not only the inflammatory activity of RA but also to inhibit radiographic progression/joint destruction. EX1029, 1; EX1026, 160. TNF inhibitors suppress and control the inflammation driving these diseases and thereby inhibit irreversible tissue damage, systemic complications, and disability. EX1029, 1. In addition, TNF inhibitors, including golimumab, demonstrate clear efficacy in AS compared to placebo, with marked improvements in pain, functional ability, and inflammatory markers such as C-reactive protein. EX1030, 38.

55. In 2009 and earlier, available TNF inhibitors could be administered either intravenously or subcutaneously, depending on the molecule, and golimumab was intended for both routes of administration. EX1026, 161 (“GLM

[golimumab] is intended for both subcutaneous (SC) and intravenous (IV) administration.”).

56. As of 2015, it was well known that TNF α has the same mechanism of action in RA, PsA, and AS:

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF α . This interaction prevents the binding of TNF α to its receptors, thereby inhibiting the biological activity of TNF α (a cytokine protein).

Elevated TNF α levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic inflammatory diseases such as rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. TNF α is an important mediator of the articular inflammation that is characteristic of these diseases. ... Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

EX1015, 18.

57. As of at least 2015, it was known that when subcutaneously administering the TNF inhibitor golimumab for the treatment of RA, PsA, or AS, the same dose and dosing schedule was employed: 50 mg administered once per month. *Id.*, 1, 4.

58. According to *PI2015-Simponi*, TNF α has the same mechanism of action in RA, AS, and PsA (EX1015, 18), and when golimumab is administered subcutaneously, the same dose is effective at treating AS, RA, and PsA: 50 mg administered once per month (*Id.*, 1, 4).

B. Golimumab Was Proven to be Safe and Effective When Administered Subcutaneously or Intravenously for Treating Rheumatic Diseases

59. Golimumab is a human monoclonal antibody (IgG1 κ) that binds to both the soluble and transmembrane forms of human TNF, preventing its binding. EX1015, 18; EX1013, 285. Golimumab has a “high affinity and specificity for human TNF- α and can neutralize TNF- α bioactivity in vitro.” EX1026, 161.

60. Golimumab (under the brand name Simponi) was first approved by the FDA in 2009 for subcutaneous (“SC”) administration for the treatment of RA, PsA and AS. EX1018, 1. All three indications were approved with the same dosage, 50 mg once a month administered subcutaneously, in combination with MTX for RA, and with optional MTX for PsA and AS. *See* EX1015, 4.

61. In addition, Golimumab (under the brand name Simponi Aria) was first approved by the FDA in 2013 for intravenous (“IV”) infusions for the treatment of RA. EX1019, 1, 7.

62. Accordingly, golimumab was approved as safe and effective for treating RA, PsA, and AS long before the earliest possible effective filing date of *US020/US982* (January 30, 2017) and *US824/US566* (February 7, 2017).

63. Long before the earliest possible effective filing dates of the Janssen PsA and AS patents, it had been reported that the “efficacy and safety profile of golimumab in RA, PsA, and AS appears to be similar to other anti-TNF agents.” EX1026, 159.

64. A POSA also would have been aware that golimumab was intended for both subcutaneous and IV administration. *Id.* (golimumab “has the potential advantage of once monthly subcutaneous administration and the possibility of both subcutaneous and intravenous administration”); *see also id.*, 161 (“GLM [golimumab] is intended for both subcutaneous (SC) and intravenous (IV) administration.”).

65. Additional prior art taught that TNF inhibitors, including golimumab, could be administered intravenously. For example, *Wong* taught a method for treating AS by administering TNF α inhibitors, including golimumab. EX1024 ¶¶6, 81. *Wong* taught that, in a preferred embodiment, the TNF α inhibitor is administered intravenously. *Id.*, ¶199. Similarly, *WO213* taught a method for treating PsA by administering TNF α inhibitors, including golimumab, and taught

intravenous administration of the TNF α inhibitor. EX1025, 2:29-38, 31:34-35, 58:10-13.

66. *Rossini* reviewed studies looking at the efficacy, safety, and pharmacokinetics of treatment of various RA, PsA, and AS with golimumab. EX1013, 285.

67. *Rossini* teaches that golimumab is a human IgG1 κ monoclonal antibody that binds both the soluble and transmembrane bioactive forms of human TNF α , preventing it from binding to its receptors. *Id.*

68. *Rossini* reports that golimumab demonstrates dose-dependent pharmacokinetics with both IV and SC administration, with steady-state concentration reached at twelve weeks. When MTX is added to a SC dose of 50 mg, it increases the mean trough serum concentration in patients with PsA. Clearance of golimumab is dependent on body weight. *Id.*, 285-286.

69. *Rossini* provided the following table of Phase-III studies of golimumab in RA, PsA, and AS:

Table I - Summary of main phase-III studies on the use of golimumab in psoriatic arthritis (PsA), ankylosing spondylitis (AS) and rheumatoid arthritis (RA).

Study	Study design	Number of patients	Target Population
GO-REVEAL (15-18)	Multicenter randomized placebo-controlled double-blind phase III trial	405	Adult patients with at least a 6 month history of moderate/severe active PsA, negative RF and presence of plaque psoriasis with one qualifying lesion of at least 2 cm in diameter
GO-RAISE (22-28)	International multicenter randomized placebo-controlled double-blind phase III study	356	Adults patients with active AS despite current or previous therapy with DMARDs or NSAIDs for at least 3 months
GO-AFTER (30-33)	Prospective multicenter randomized placebo-controlled double-blind phase III trial	461	Adult patients with moderate/severe active RA previously treated with one or more doses of a biologic anti-TNF without severe adverse reactions
GO-MORE (34-37)	International multicenter prospective open-label study	3280	Patients naïve to biologic therapy with active RA despite DMARD treatment
GO-BEFORE (38-41)	52 week randomized placebo-controlled double-blind phase III trial	637	Patients RA with naïve to MTX
GO-FORWARD (42-45)	Multicenter randomized placebo-controlled double-blind phase III trial	444	Adult patients with moderate/severe active RA currently treated with MTX and without previous treatment with other drugs

Id., 287. The above table demonstrates the large number of patients to whom golimumab was administered long before the earliest possible effective filing date of the Janssen PsA or AS patents.

70. With regard to PsA patients, Rossini notes that treatment guidance recommends using a TNF α inhibitor (preferably with a DMARD) to treat PsA patients who are not responsive to DMARDs (disease-modifying anti-rheumatic drugs) or NSAIDs (non-steroidal anti-inflammatory drugs), or have active enthesitis and/or dactylitis. *Id.*, 286-87.

71. The pivotal clinical trial for treating PsA with SC golimumab, the “GO-REVEAL” Trial, “assessed the efficacy and safety of golimumab in patients naïve to biologically derived treatments, affected by active PsA despite therapy with DMARDs or NSAIDs.” *Id.*, 287.

72. The GO-REVEAL Trial included three groups: 50 mg/month (n=146) SC golimumab; 100 mg/month (n=146) SC golimumab; and SC placebo (n=113). *Id.* The primary endpoint was the percentage of patients achieving ACR20 at week 14. *Id.* Secondary endpoints included: proportion of patients achieving ACR20 at week 24; PASI75 (Psoriasis Area and Severity Index) response at week 14 in patients with $\geq 3\%$ of body surface area involved by psoriasis at baseline; improvement in NAPSI (Nail Psoriasis Severity Index) score for fingernail lesions, evaluation of dactylitis, enthesitis (MASES, Maastricht Ankylosing Spondylitis Enthesitis Score) and morning stiffness; improvement in HAQ-DI (Health Assessment Questionnaire Disability Index) scores and variations in the scores for the physical component summary (PCS) of the SF-36 (Short-Form 36) questionnaire between baseline and weeks 14 and 24. *Id.*

73. *Rossini* reports that at week 14, 48% of patients (140 of 292 in both golimumab groups) achieved an ACR20 response, compared to 9% of patients treated with placebo, with 51% and 45% of patients in the 50 mg and 100 mg groups, respectively, achieving ACR20 at 14 weeks regardless of MTX use compared to placebo ($P < 0.001$). *Id.*, 287-88.

74. *Rossini* also reports that “patients treated with golimumab showed a significant improvement ($p < 0.001$) in the HAQ-DI score at 24 weeks and in the

physical component of the SF-36 questionnaire at 14 weeks, compared with the placebo group.” *Id.*, 288.

75. With regard to AS patients, Rossini states that treatment guidance recommends use of TNF inhibitors “in patients with persistently high disease activity despite conventional treatments, without obligatory use of a DMARD before or simultaneously to the anti-TNF agent in patients with axial disease.” *Id.*, 290. *Rossini* further states that “there is no evidence to support the superior efficacy of any one TNF inhibitor in axial disease and in articular/enthesial disease manifestations.” *Id.*

76. The pivotal clinical trial for treating AS with SC golimumab is the “GO-RAISE” Trial. *Rossini* reports that the GO-RAISE Trial “evaluated the efficacy and safety of golimumab in 356 adults patients naïve to biologic therapy, with a diagnosis of active AS ... despite current or previous therapy with DMARDs or NSAIDs for at least 3 months.” *Id.*

77. The GO-RAISE Trial included three groups: 50 mg/month (n=138) SC golimumab; 100 mg/month (n=140) SC golimumab; and placebo (n=70). *Id.* The primary endpoint was the percentage of patients achieving ASAS20 response at week 14. *Id.* Secondary endpoints included: “ASAS20 response at week 24, ASAS40 response, the BASDAI for disease activity, VAS score of back pain and night pain, the patient’s global assessment, the BASFI (Bath Ankylosing

Spondylitis Functional Index) for physical function, the BASMI (Bath Ankylosing Spondylitis Metrology Index) for range of motion, the SF-36 Health Survey for quality of life, and the JSEQ (Jenkins Sleep Evaluation Questionnaire) for sleep disturbance.” *Id.*

78. *Rossini* reports that at 14 weeks, significantly more patients receiving 50 mg golimumab, 59.4%, achieved an ASAS20 response compared to 21.8% of patients receiving placebo ($P < 0.001$), and that at 24 weeks, 43.5%, 54.3%, and 15.4% of patients treated with golimumab 50 mg, 100 mg, and placebo, respectively, achieved an ASAS40 response. *Id.*

79. *Rossini* also reports that “[a]s for the BASMI scores, a significantly greater number of patients treated with golimumab 50 mg and 100 mg showed an improvement from baseline ≥ 1 unit at week 14” and that “[t]he overall scores for the physical and mental components of the SF-36 improved significantly ($P < 0.05$) from baseline to weeks 14 and 24 in all golimumab treated patients.” *Id.*

C. Golimumab Was Administered Intravenously for Years Before the Earliest Possible Effective Filing Dates of the Janssen Patents

80. The Center for Drug Evaluation and Research (“CDER”) Administrative and Correspondence Documents for Janssen’s Simponi Aria BLA (“CDER Review”) was published in September 2013. EX1034, 2; *see* Paragraph 242. The Clinical Pharmacology Review section included Table 1, which shows the list of five “studies with IV dose that have been submitted during the original

golimumab application (BLA125289) for its SC dosing regimen and the current golimumab application (BLA125433) for its IV dosing regimen.” *Id.*, 179.

Table 1. Listing of Golimumab Clinical Studies with IV Component

Study ID/Subject Population/Phase	Location of CSR in eCTD	Dose Regimen ^a	Route of Administration ^b	Number of PK Subjects ^c	Sampling Scheme ^d
C0466T01/RA Phase 1	24-Week SC submission, BLA, Sequence 0000	IV: 0.1, 0.3, 1.0, 3.0, 6.0 or 10.0 mg/kg single dose	IV	26	Intensive
C0524T14/RA Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 2 mg/kg Days 1 and 85 SC: 100 mg q4w through Week 20	IV/SC*	16*	Intensive
C0524T15/HS Phase 1	52-Week/104-Week SC submission, sBLA, Sequence 0069	IV: 100 mg single dose or SC: 100 mg single dose	IV/SC*	22*	Intensive
C0524T12/RA Phase 3	Current	IV: 2 mg/kg and 4 mg/kg q12w	IV	642	Sparse
CNT0148ART30 01/RA Phase 3	Current	IV: 2 mg/kg at Weeks 0, 4, and q8w thereafter	IV	463	Sparse

^a q12w = every 12 weeks, q8w = every 8 weeks

^b IV = intravenous

^c PK subjects (Non-compartmental analyses [NCA] for Phase 1, Population PK for Phase 3)

^d Intensive sampling schemes enable determination of the full PK profile using a non-compartmental analysis. Sparse sampling schemes require a model-based approach to characterize the pharmacokinetics adequately.

* Although both IV and SC administrations were studied in C0524T14 and C0524T15, only IV data are presented in this document

Abbreviations: HS = healthy subjects; RA = subjects with active rheumatoid arthritis; PK = pharmacokinetics; BLA = biologics license

Studies C0524T14 and C0524T15 included both IV and SC administrations and were submitted under BLA125289, in which PK exposures can be directly compared within a study.

81. *Weinblatt* reviewed the results of the Phase 3 GO-FURTHER Trial which evaluated the efficacy of IV golimumab, 2 mg/kg, with MTX in patients with active RA compared to patients receiving placebo and MTX. EX1012, 381.

82. The Phase 3 GO-FURTHER trial included 592 patients with active disease randomized 2:1 to receive IV golimumab or placebo, both with MTX, at weeks 0 and 4, and then every 8 weeks. *Id.*

83. Supplemental materials that accompanied *Weinblatt* provided the following rationale for the dosing regimen used in the GO-FURTHER study:

Data derived from the golimumab clinical development program indicated that maintaining drug levels close to or above the trough serum golimumab concentrations resulting from subcutaneous golimumab 50 mg every 4 weeks are important for robust and sustained ACR responses. Also using data from the golimumab program, results of simulations indicated that intravenous golimumab 2 mg/kg+MTX every 8 weeks would be anticipated to yield trough steady-state concentrations (0.28 µg/mL) comparable to subcutaneous golimumab 50 mg every 4 weeks (0.30 µg/mL). Thus, golimumab 2 mg/kg+MTX every 8 weeks was chosen as the dosing regimen for the current GO-FURTHER trial.

Id., Supplemental Online Text, 1.

84. *Weinblatt* taught that the golimumab used in the trial “was supplied in 4 ml vials of 12.5 mg/ml (50 mg/vial) and associated excipients” and that the IV golimumab was infused over 30±10 minutes. *Id.*, 382.

85. *Weinblatt* indicated that data was collected at visits scheduled for weeks 0, 2, 4, 8, 12, 14, 16, 20, and 24. *Id.*

86. *Weinblatt* stated that “[r]esponse to golimumab was rapid” and that by week 2, there were “statistically significant treatment group differences in ACR20, ACR50, HAQ and DAS28-CRP responses” and that after week 4, there were statistically significant treatment group differences in ACR70 response. *Id.*, 388; *see also id.*, 385, Figure 2.

87. *Weinblatt* stated that “[a] significant difference in ACR20 response was observed as early as week 2 (33.2% (131/395) vs 11.7% (23/197); [($p < 0.001$ not corrected for multiplicity).” *Id.*, 383; *see also id.*, 385, Figure 2, panel A. *Weinblatt* further states that “[a]t week 2, DAS28-CRP response rates were 65.1% for golimumab+MTX and 19.3% for placebo+MTX ($p < 0.001$ not corrected for multiplicity).” *Id.*, 383. *Weinblatt* also stated that 65% of patients achieved a EULAR (European League Against Rheumatism) response by week 2. *Id.*, 388. EULAR response is a measure of clinical response. *Id.*, 382.

88. The authors concluded that “[t]he addition of intravenous golimumab rapidly and significantly improved signs and symptoms in patients with active RA despite ongoing MTX, in some patients by week 2.” *Id.*, Abstract.

89. *PI2013-Aria* taught that the approved dosage of “2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks,” was safe and effective for the treatment of RA. EX1032, 1; *see also id.*, 3.

90. *Wong* also taught IV administration of TNF α inhibitors, including golimumab, to treat AS. *See* EX1024, ¶¶6, 81, 199.

91. *Rossini* taught that golimumab exhibits dose-dependent pharmacokinetics after both IV and subcutaneous administration, “with a steady-state concentration being reached within 12 weeks.” EX1013, 285.

D. The Pharmacokinetics of IV Golimumab Compared to SC Golimumab Were Well Known

92. The pharmacokinetics of IV golimumab versus SC golimumab were well known long before the earliest possible effective filing date of either set of Janssen Patents (*i.e.*, *US020*, *US982*, *US824*, and *US566*).

93. *PI2015-Simponi* taught that “the absolute bioavailability of subcutaneous SIMPONI was estimated to be approximately 53%.” EX1015, 19. A POSA would have understood that this meant that due to absorption barriers and first-pass metabolism, only about 53% of subcutaneously administered golimumab reaches the bloodstream. Such absorption barriers, especially for large molecules like proteins, can include extracellular matrix barriers, the limited vascularization of SC tissue, enzymatic degradation in the SC tissue, and the like. In contrast, 100% of IV golimumab reaches the bloodstream, because it is injected directly into the systemic circulation and therefore bypasses such absorption barriers and first-pass metabolism.

94. *Zhuang* (EX1038) assessed the pharmacokinetics of IV and SC golimumab after multiple administrations of each. EX1038, Abstract. Subcutaneous golimumab, 100 mg, was administered every four weeks through week 20 to 33 patients with RA. *Id.* Intravenous golimumab, 2 mg/kg, was administered at weeks 0 and 12 to 16 patients with RA. *Id.* The pharmacokinetic results were reported in Table II, reproduced below.

Table II. Summary of golimumab pharmacokinetic parameters.

Parameter	Group I (SC)		Group II (IV)	
	First Dose (n = 32)	Last Dose (n = 29)	First Dose (n = 16)	Last Dose (n = 16)
C_{max} , $\mu\text{g/mL}$				
Mean (SD)	5.1 (3.0)	6.1 (3.7)	44.4 (11.3)	45.7 (16.1)
Median (range)	4.6 (0.5–12.1)	5.0 (1.8–15.3)	43.9 (22.4–65.6)	43.1 (26.3–90.3)
T_{max} , d				
Median (range)	3.5 (2.0–7.1)	3.0 (1.0–15.1)	NA	NA
AUC_{0-28d} or AUC_{0-84d} , $\mu\text{g}\cdot\text{day/mL}^*$				
Mean (SD)	70.5 (41.0)	89.1 (53.3)	276.8 (65.0)	303.4 (121.9)
Median (range)	55.7 (8.9–139.4)	69.1 (20.6–216.8)	281.5 (161.1–391.1)	285.1 (155.8–591.5)
$t_{1/2}$, d				
Mean (SD)	NA	13.1 (5.0)	NA	13.2 (2.9)
Median (range)	NA	12.5 (2.9–25.3)	NA	14.8 (7.6–16.9)
CL, mL/d/kg [†]				
Mean (SD)	NA	19.7 (10.4)	NA	7.5 (2.6)
Median (range)	NA	17.8 (6.2–44.6)	NA	7.3 (3.5–12.8)
V_{ss} , mL/kg [†]				
Mean (SD)	NA	352.3 (216.0)	NA	98.8 (36.3)
Median (range)	NA	285.2 (95.2–1015.4)	NA	99.1 (46.5–182.0)
$R_{AUC(0-28d)}$ or $R_{AUC(0-84d)}^*$				
Mean (SD)	NA	1.3 (0.7)	NA	1.0 (0.3)
Median (range)	NA	1.2 (0.5–3.7)	NA	0.9 (0.7–1.8)
$R_{C_{max}}$				
Mean (SD)	NA	1.4 (0.9)	NA	1.1 (0.3)
Median (range)	NA	1.3 (0.3–4.7)	NA	0.9 (0.7–1.7)

CL = clearance; NA = not applicable; R_{AUC} = accumulation ratio for $AUC_{t_{1-42}}$ after multiple doses; $R_{C_{max}}$ = accumulation ratio for C_{max} after multiple doses; V_{ss} , volume of distribution at steady state.

* AUC_{0-28d} for Group I and AUC_{0-84d} for Group II.

[†]Apparent clearance (CL/F) and apparent volume of distribution (V_d/F) for Group I.

Id., 84.

95. As reported in Table II, the IV golimumab results in a maximum serum concentration (C_{max}) of about 45 $\mu\text{g/mL}$, more than seven-fold greater than the C_{max} of about 6 $\mu\text{g/mL}$ for 100 mg of golimumab administered SC once every four weeks. *Id.*

96. Table II also indicated that IV golimumab results in an area under the curve (AUC_{0-84d}) of over 300 $\mu\text{g}\cdot\text{day/mL}$, more than three-fold greater than the

AUC_{0-28d} of about 90 µg·day/mL observed when subcutaneously administering 100 mg golimumab once every four weeks. *Id.*

E. Other Prior Art Teachings

97. *Wong* taught administering a TNFα inhibitor to achieve a therapeutic goal, including “improvement in ASAS domains, induction of partial remission, ASAS20, ASAS50, ASAS70 response, improvement in BASDAI score, and/or maintenance of a positive PASS response.” EX1024 ¶224.

98. *Wong* also taught that commonly used measurements of AS symptoms include “the Assessment in Ankylosing Spondylitis (ASAS), the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) ..., the Bath Ankylosing Spondylitis Metrology Index (BASMI) ..., the Patient Acceptable Symptom State (PASS), and the Bath Ankylosing Spondylitis Functional Index (BASFI).” *Id.*, ¶258.

99. In addition, *Wong* claimed using golimumab to treat AS. *See id.*, claim 48, which depends from claim 31 or 33 (“The method of claim 31 or 33, wherein the human TNFα antibody, or antigen-binding portion thereof, is golimumab.”).

100. *PI2013-Aria* taught a golimumab composition comprising a pharmaceutically acceptable carrier/diluent: “[d]ilution of supplied SIMPONI

ARIA solution with 0.9% w/v sodium chloride is required prior to administration.”

EX1032, 1; *see also id.*, 3.

F. Measures of Efficacy in RA, PsA, and/or AS

101. The prior art relevant to the Janssen PsA and AS patents mentions several standard measures of efficacy, some of which I describe below.

102. **ACR20/50/70:** *US020* states that ACR20 is the proportion of subjects who achieve a 20% improvement from baseline in the American College of Rheumatology criteria at Week 14. EX1001, 79:35-38. An ACR20 response is defined as follows:

1. $\geq 20\%$ improvement from baseline in both swollen joint count (66 joints) and tender joint count (68 joints),

AND

2. $\geq 20\%$ improvement from baseline in 3 of the following 5 assessments:
Patient’s assessment of pain (VAS)
Patient’s Global Assessment of Disease Activity (VAS)
Physician’s Global Assessment of Disease Activity (VAS)
Patient’s assessment of physical function as measured by
HAQ-DI
CRP

EX1001, 103:35-44. VAS is the acronym for “Visual Analogue Scale” (*id.*, 84:64) and CRP is the acronym for “C-reactive protein” (*id.*, 83:58).

“ACR50 and ACR70 are similarly defined, except they look at 50 and 70% improvement from baseline, respectively. *Id.*, 103:47-49.

103. **ASAS20:** Refers to a 20% improvement in AS response according to the criteria of the ASAS International Working Group, which *US566* defines as:

1. An improvement of $\geq 20\%$ from baseline and absolute improvement from baseline of at least 1 on a 0 to 10 cm scale in at least 3 of the following 4 domains:
 - i. patient global;
 - ii. Total back pain;
 - iii. Function (BASFI), and
 - iv. Inflammation (average of the last 2 questions of the BASDAI concerning morning stiffness).
2. Absence of deterioration from baseline ($\geq 20\%$ and worsening of at least 1 on a 0 to 10 cm scale) in the potential remaining domain.

EX1004, 99:18-33.

104. **ASDAS:** ASDAS is an Ankylosing Spondylitis (AS) Disease Activity Score (DAS) developed by the Assessment of SpondyloArthritis International Society. EX1004, 99:48-51. *US566* applied the following formula for calculating the ASDAS score:

$$\text{ASDAS} = 0.121 \times \text{Total back pain} + 0.058 \times \text{Duration of morning stiffness} + 0.110 \times \text{Patient global assessment} + 0.073 \times \text{Peripheral pain/swelling} + 0.579 \times \ln(\text{CRP (mg/L)} + 1).$$

EX1004, 99:53-55. *US566* defines a clinically important improvement in ASDAS as a decrease of ≥ 1.1 , defines a major improvement in ASDAS as a decrease of ≥ 2.0 , and defines inactive disease as an ASDAS score of < 1.3 . *Id.*, 99:56-59.

105. **ASQoL:** ASQoL is an acronym for Ankylosing Spondylitis Quality of Life. EX1004, 46:9-10. *US566* states that “Ankylosing spondylitis quality of

life is a self-administered patient-reported outcomes instrument. It consists of 18 questions requesting a Yes or No response to questions related to the impact of pain on sleep, mood, motivation, ability to cope, activities of daily living, independence, relationships, and social life. A score of 1 is given to a response of 'YES' on each item and all item scores are summed to a total score with a range of 0-18. Higher scores indicate worse health related quality of life. Subjects can complete the instrument in less than four minutes." EX1004, 101:3-12 (footnote omitted).

106. **BASFI:** BASFI is an acronym for Bath Ankylosing Spondylitis Functional Index. EX1004, 83:24. *US566* states that "[t]he BASFI is a subject's self-assessment represented as a mean (VAS; 0 to 10 cm) of 10 questions, 8 of which relate to the subject's functional anatomy and 2 of which relate to a subject's ability to cope with everyday life. An increase along the scale indicates a worsening condition." EX1004, 98:5-9 (footnote omitted).

107. **BASMI:** BASMI is an acronym for Bath Ankylosing Spondylitis Metrology Index. EX1004, 83:25. *US566* states that "[t]he BASMI is represented as an aggregate score of 5 components (ranging from 0 to 10) and will be calculated using the van der Heijde calculation as shown in Table 6.

TABLE 6

Equations proposed for the conversion of the assessments (A) into scores (S) for the five components of the BASMI _{lin}			
	S = 0 if:	Between 0 and 10:	S = 10 if:
Lateral lumbar flexion* (cm)	$A \geq 21.1$	$S = (21.1 - A)/2.1$	$A \leq 0.1$
Tragus-to-wall distance* (cm)	$A \leq 8$	$S = (A - 8)/3$	$A \geq 38$
Lumbar flexion (modified Schober) (cm)	$A \geq 7.4$	$S = (7.4 - A)/0.7$	$A \leq 0.4$

TABLE 6-continued

Equations proposed for the conversion of the assessments (A) into scores (S) for the five components of the BASMI _{lin}			
	S = 0 if:	Between 0 and 10:	S = 10 if:
Intermalleolar distance (cm)	$A \geq 124.5$	$S = (124.5 - A)/10$	$A \leq 24.5$
Cervical rotation angle* (°)	$A \geq 89.3$	$S = (89.3 - A)/8.5$	$A \leq 4.3$

*For lateral lumbar flexion, tragus-to-wall distance, and cervical rotation the average of right and left should be taken. If a score lies beyond the range 0-10, the values 0 or 10 have to be used, respectively.

The BASMI_{lin} is the mean of the five S scores.” EX1004, 98:53–99:12 (footnote omitted).

108. **BASDAI:** BASDAI is an acronym for Bath Ankylosing Spondylitis Disease Activity Index. EX1004, 83:23. *US566* states that the BASDAI is defined as follows:

Subject self-assessment using a VAS (0 to 10 cm) on the following criteria:

- A. Fatigue
- B. Spinal pain
- C. Joint pain
- D. Enthesitis
- E. Qualitative morning stiffness
- F. Quantitative morning stiffness

The BASDAI=0.2 (A+B+C+D+0.5[E+F]).

EX1004, 97:61-98:3.

109. **Dactylitis:** *US020* states that “[d]actylitis can be assessed for presence and severity in both hands and both feet.” EX1001, 45:48-50.

110. **Enthesitis:** *US020* states that “[e]nthesitis can be assessed by evaluating the presence or absence of pain by applying local pressure to entheses including, e.g., the left and right lateral elbow epicondyle, the left and right medial femoral condyle, and the left and right Achilles tendon insertion.” *Id.*, 45:44-48.

111. **HAQ-DI:** HAQ-DI is an acronym for the Health Assessment Questionnaire Disability Index score. *Id.*, 45:35-36. As explained in *US020*, HAQ-DI is a “20-question instrument that assesses the degree of difficulty a person has in accomplishing tasks in 8 functional areas (dressing, arising, eating, walking, hygiene, reaching, gripping, and activities of daily living).” *Id.*, 45:40-44.

112. **mTSS:** mTSS is an acronym for modified Total Sharp Score. It is a modification of the Sharp score originally designed for RA, adapted to better capture the unique changes seen in PsA, including the distal interphalangeal (DIP) joints. The mTSS is also known as the Van der Heijde-Sharpe score.

113. **SF-36:** SF-36 stands for Short-Form Health Survey 36 and refers to the Medical Outcome Study health measure SF-36 questionnaire, which is a questionnaire consisting of 8 multi-item scales that are scored. The scales are

scored from 0 to 100 with higher scores indicating better health. *Id.*, 45:50-51, 105:14-32.

114. **SF-36 PCS:** SF-36 PCS (Physical Component Summary) uses the SF-36 responses to calculate a physical component summary, in which higher scores indicate better physical health. EX1001, 45:50-54, 105:32-39.

115. **SF-36 MCS:** SF-36 MCS (Mental Component Summary) uses the SF-36 responses to calculate a mental component summary, in which higher scores indicate better mental health. EX1001, 45:50-54, 105:32-39.

116. **vdH-S:** vdH-S is an acronym for the Van der Heijde-Sharp score. The Van der Heijde-Sharp score is used to quantify structural joint damage. In RA, the score ranges from 0-448 and in PsA from 0-528. The mTSS is also known as the Van der Heijde-Sharpe score.

G. Pertinent Statistics Concepts

117. Clinical trial results are often presented with an associated standard deviation (“SD”) or with an associated standard error (“SE”).

118. A POSA would have understood that a standard deviation is the average distance between each data point and the mean of a dataset. It is calculated using the following formula:

$$SD = \sqrt{[\sum(x-\mu)^2 / N]}$$

where x is each measured value, μ is the mean, and N is the total number of measured values. EX1017, 2.¹

119. The standard error is a measure of the precision of a sample statistic, such as the standard deviation. It can be calculated as follows:

$$SE = SD/\sqrt{n}$$

where SD is the standard deviation of the sample and n is the sample size. *Id.*, 3.

Thus, while SD measures the variability within a dataset, SE estimates the precision of a sample statistic. *Id.*

120. As an example, in a study of the height of adults, a mean height of 170 cm with a standard deviation of 10 cm would mean that approximately 68% of adults would fall within one standard deviation of the mean, *i.e.*, approximately 68% of adults would fall within 160 cm and 180 cm (170 ± 10 cm). *Id.*

¹ *SixSigma* (EX1017), to which I refer, is dated September 25, 2024, but the concepts it discusses are well-known statistical concepts that have not changed since long before the earliest possible effective filing date of *US020* (or the remainder of the Janssen PsA and AS patents).

V. OVERVIEW OF THE JANSSEN PSA AND AS PATENTS

A. The PsA Patents: *US020* and *US824*

1. The Specification of *US020* and *US824*

121. *US020*, titled “Methods for the Treatment of Active Psoriatic Arthritis,” issued on June 22, 2021. EX1001, 1. I have been informed that the earliest possible effective filing date is January 30, 2017.

122. *US824*, titled “Anti-TNF Antibodies, Compositions, and Methods for the Treatment of Active Ankylosing Spondylitis,” issued on October 22, 2024. EX1003, 1. I have been informed that the earliest possible effective filing date is January 30, 2017.

123. The application that issued as *US824* is a continuation of the application that issued as *US020*. See EX1003, 1. I have been informed that as a continuation application, the specification of *US824* is the same as the specification of *US020*.

124. *US020* and *US824* state that biologic treatments targeting TNF, including golimumab, have been shown to have an acceptable safety profile and induce rapid and significant improvement in subjects with PsA:

Biologic treatments targeting TNF, including infliximab, SC golimumab, adalimumab, and certolizumab pegol, have been shown to induce rapid and significant improvement of arthritis and psoriasis in subjects with active PsA while maintaining an acceptable safety profile. Etanercept, adalimumab, and certolizumab pegol are administered twice weekly, weekly, or every 2 to 4 weeks by SC injection. Golimumab is administered monthly by SC injection.

Infliximab is administered as an IV infusion in an office-based setting at Weeks 0, 2, 6, and every 8 weeks thereafter.

EX1001, 86:8-17; EX1003, 83:58-67.

125. According to *US020* and *US824*, while the precise role of TNF α in PsA is unknown, “there is already a large and mounting body of evidence that TNF α inhibition is of major therapeutic benefit in this disease.” EX1001, 86:40-43; EX1003, 84:24-26.

126. *US020* and *US824* describe the binding properties of the anti-TNF α inhibitor broadly, stating that the antibody that can bind “one TNF, or specified portions, variants, or domains thereof.” EX1001, 12:54-57; EX1003, 12:59-62.

127. *US020* and *US824* also describe the effects of the anti-TNF α inhibitor broadly, stating that it can optionally affect “at least one of TNF activity or function, such as but not limited to, RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.” EX1001, 12:57-62; EX1003, 12:63-67.

128. *US020* and *US824* broadly describe the uses for anti-TNF α antibodies “to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one TNF condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease” (EX1001, 14:34-43; EX1003, 14:38-47), and defines immune diseases as including, among

other things, RA, juvenile, systemic onset juvenile rheumatoid arthritis, PsA, and AS (EX1001, 38:33-39:33; EX1003, 38:10-39:9).

129. *US020* and *US824* teach a wide variety of compositions and excipients that may be used, but do not disclose any specific formulations for a golimumab composition to be administered to a human. *See* EX1001, 31:59-36:33; EX1003, 31:43-36:14. Accordingly, a POSA would have understood that the safety and efficacy of golimumab depended on the dose and dosing regimen, not the excipients used in the specific formulation or composition.

130. *US020* and *US824* also teach a broad array of known routes of administration for the disclosed anti-TNF α antibodies, including the following:

parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar [sic], intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means.

EX1001, 47:44-54; EX1003, 47:19-30.

131. As an example, *US020* and *US824* teach that for parental administration, the anti-TNF α inhibitor can be formulated, among other things, as a solution, suspension, powder, or an emulsion, and may be provided with a

pharmaceutically acceptable carrier, such as water or saline, among other things.

EX1001, 46:61-47:7; EX1003, 46:37-50.

132. *US020* and *US824* acknowledge that IV golimumab, 2 mg/kg administered infused over 30 minutes at Weeks 0, 4, and every 8 weeks thereafter, was definitively studied in a Phase 3 clinical trial:

Intravenous (IV) golimumab has been definitively studied in a Phase 3 study in RA (CNTO148ART3001) that formed the basis of approval for golimumab IV for the treatment of RA. The CNTO148ART3001 study was a randomized, double-blind, placebo-controlled, multicenter, 2-arm study of the efficacy and safety of IV administration of golimumab 2 mg/kg infusions administered over a period of 30±10 minutes at Weeks 0, 4, and q8w thereafter in subjects with active RA despite concurrent MTX therapy. Subjects with active RA despite MTX were randomized to receive either placebo infusions (with MTX) or IV golimumab administered 2 mg/kg at Weeks 0, 4, and q8w (with MTX) through Week 24. Starting at Week 24, all subjects were dosed with IV golimumab through Week 100. It was demonstrated that IV golimumab provided substantial benefits in improving RA signs and symptoms, physical function, and health related quality of life, as well as inhibiting the progression of structural damage.

EX1001, 86:52-87:3; EX1003, 84:35-53.

133. The specifications of *US020* and *US824* have nine Examples. Example 9 of each specification describes a planned multicenter, randomized, double-blind, placebo-controlled trial of golimumab for the treatment of PsA and its initial results. EX1001, 78:62-117:45; EX1003, 76:45-115:18.

134. *US020* and *US824* describe golimumab as having a heavy chain of SEQ ID NO: 36, a light chain of SEQ ID NO: 37, as binding to human TNF α with

high affinity and specificity, and as neutralizing TNF α activity. EX1001, 79:3-11; EX1003, 76:53-61.

135. The specifications of *US020* and *US824* hypothesize that IV golimumab could prove to be safe and effective based on its safety and efficacy when administered subcutaneously: “Given the safety and efficacy of SC golimumab, it was hypothesized that IV golimumab could prove efficacious with an acceptable safety profile consistent with other anti-TNF α agents.” EX1001, 86:49-52; EX1003, 84:32-35. In relation to this hypothesis, the specifications note that 2 mg/kg of IV golimumab administered at weeks 0, 4, and every 8 weeks thereafter provided substantial benefits in improving RA. EX1001, 86:52-87:3; EX1003, 84:35-53.

136. In the Phase 3 clinical study on PsA described in the *US020* and *US824* specifications, biologic-naïve subject with PsA were randomized into two groups, one receiving placebo and the other receiving 2 mg/kg golimumab at weeks 0, 4, and every 8 weeks thereafter, with the placebo group crossing over at week 24. EX1001, 114:62-115:2; EX1003, 113:4-11. This is the same dosing regimen as was approved for RA.

137. *US020* and *US824* provide preliminary efficacy and safety results through week 24 of the study. EX1001, 114:58-117:45; EX1003, 113:1-115:18. The inventors concluded that IV golimumab resulted in clinically meaningful

improvements in “disease activity and physical function, skin psoriasis clearance, reduction in dactylitis and enthesitis, HRQoL and inhibition of structural progression. Golimumab was also well-tolerated through wk24 and the safety profile was consistent with other anti-TNF therapies, including SC golimumab.” EX1001, 116:19-27; EX1003, 113:60-67.

2. The Claims of *US020*

138. *US020* issued with independent claims 1, 4, and 7 and dependent claims 2, 3, 5, 6, 8, 9, and 10. Claims 1-10 are reproduced below:

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.

2. The method according to claim 1, wherein said composition is administered such that said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter.

3. The method according to any one of claims 1-2, further comprising administering said composition with or without methotrexate (MTX).

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 intravenous (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.

5. The method according to claim 4, wherein said composition is administered such that said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter.

6. The method according to any one of claims 4-5, further comprising administering said composition with or without methotrexate (MTX).

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.

8. The method according to claim 7, wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.

9. The method according to any of claims 7-8, wherein said antibody is administered at a dose of 2 mg/kg, over 30±10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter.

10. The method according to any one of claims 7-8, wherein said antibody is administered with or without methotrexate (MTX).

3. The Claims of *US824*

139. *US824* issued with independent claims 1, 3, and 5, and dependent claims 2, 4, 6, and 7. Claims 1-7 are reproduced below:

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 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 intravenous (IV) infusion, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, 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, Short-Form Health Survey Physical Summary score (SF-36-PCS)=8.65 $\pm$ 7.60 SD, and Short-Form Health Survey Mental Component Summary score (SF-36 MCS)=5.33 $\pm$ 9.95 SD.
2. The method according to claim 1, further comprising administering said composition with or without methotrexate (MTX).
 3. 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 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, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, and wherein at week 24 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in total modified van der Heijde-Sharp score (vdH-S) = -0.36 ± 0.144 SE.
4. The method according to claim 3, further comprising administering said composition with or without methotrexate (MTX).
5. 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 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, wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion, wherein said antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter, and wherein $\geq$ 65% of patients receiving the treatment achieve ACR20 at week 14 of treatment.
6. The method according to claim 5, wherein said $\geq$ 65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.
7. The method according to claim 5, wherein said antibody is administered with or without methotrexate (MTX).

B. The AS Patents

1. The Specifications of *US982* and *US566*

140. *US982*, titled “Anti-TNF Antibodies, Composition, and Methods for the Treatment of Active Ankylosing Spondylitis,” issued on May 25, 2021. *See*

EX1002, 1. I have been informed that the earliest possible effective filing date is February 7, 2017.

141. *US566*, titled “Anti-TNF Antibodies, Composition, and Methods for the Treatment of Active Ankylosing Spondylitis,” issued on May 6, 2025. *See* EX1004, 1. I have been informed that the earliest possible effective filing date is February 7, 2017.

142. The application that issued as *US566* is a continuation of the application that issued as *US982*. *See* EX1004, 1. I have been informed that as a continuation application, the specification of *US566* is the same as the specification of *US982*.

143. *US982* and *US566* state the following regarding clinical trials showing the efficacy of subcutaneously administered TNF α inhibitors for treating AS: “Tumor necrosis factor α inhibition in AS using subcutaneous (SC) drugs, including etanercept, adalimumab, golimumab, and certolizumab, also has been shown to be efficacious in randomized, placebo-controlled trials.” EX1002, 85:60-63; EX1004, 85:56-59.

144. *US982* and *US566* further state (as known in the prior art) that IV golimumab was being studied for the treatment of AS: “[t]he IV route of administration [of golimumab] in subjects with AS is being evaluated since currently available IV anti-TNF α agents have limitations with respect to

immunogenicity and infusion reactions, and have longer infusion times (60 to 120 minutes) compared with the proposed 30 ± 10 minute infusions with IV golimumab.” EX1002, 86:56-62; EX1004, 86:53-59.

145. Regarding IV administration of golimumab, *US982* and *US566* further state that “IV golimumab may be an important addition to the currently available treatment options” because “[p]atients may also prefer the maintenance dosage schedule of q8w IV golimumab rather than more frequent administrations compared with SC agents.” EX1002, 86:63-67; EX1004, 86:60-64.

146. *US982* and *US566* provide the following rational for expecting IV golimumab to be as safe and effective as other anti-TNF α inhibitors: “[g]iven the known safety and efficacy of SC golimumab, it was anticipated that IV golimumab would prove efficacious with an acceptable safety profile consistent with other anti-TNF α agents in rheumatologic diseases such as RA, PsA, and AS.” EX1002, 86:29-33; EX1004, 86:25-29. In that regard, *US982* and *US566* note that IV administration of golimumab 2 mg/kg infusions administered over a period of 30 ± 10 minutes at Weeks 0, 4, and every 8 weeks (q8w) thereafter provided substantial benefits in improving RA. EX1002, 86:35-50; EX1004, 86:31-47.

147. *US982* and *US566* explain that “[e]levated expression of TNF α has been linked to chronic inflammatory diseases such as rheumatoid arthritis (RA), as well as spondyloarthropathies such as psoriatic arthritis (PsA) and ankylosing

spondylitis (AS), and is an important mediator of the articular inflammation and structural damage that are characteristic of these diseases.” EX1002, 84:42-48; EX1004, 84:39-45.

148. *US982* and *US566* broadly describe anti- α -TNF antibodies and their use in treating TNF disorders such as ankylosing spondylitis (“AS”). *E.g.*, EX1002, 2:56-64; EX1004, 2:61-3:2.

149. With respect to TNF α inhibitors, *US982* and *US566* describe the binding properties of the anti-TNF α inhibitor broadly, stating that the antibody that can bind “one TNF, or specified portions, variants, or domains thereof.” EX1002, 13:22-25; EX1004, 13:28-31.

150. *US982* and *US566* also describe the effects of the anti-TNF α inhibitor broadly, stating that it can optionally affect “at least one of TNF activity or function, such as but not limited to, RNA, DNA or protein synthesis, TNF release, TNF receptor signaling, membrane TNF cleavage, TNF activity, TNF production and/or synthesis.” EX1002, 13:25-30; EX1004, 13:31-36.

151. *US982* and *US566* also broadly describe the uses of the antibody: “to diagnose, monitor, modulate, treat, alleviate, help prevent the incidence of, or reduce the symptoms of, at least one TNF condition, selected from, but not limited to, at least one of an immune disorder or disease, a cardiovascular disorder or disease, an infectious, malignant, and/or neurologic disorder or disease.” EX1002,

15:2-11; EX1004, 15:7-16. As to the referenced immune diseases, *US982* and *US566* indicate that they include, among others, RA, juvenile, systemic onset juvenile RA, and AS. EX1002, 38:49–39:48; EX1004, 39:1-67.

152. *US982* and *US566* describe a broad array of known/developed routes of administration (EX1002, 47:34-37; EX1004, 47:53-57), including the following:

parenteral, subcutaneous, intramuscular, intravenous, intrarticular, intrabronchial, intraabdominal, intracapsular, intracartilaginous, intracavitary, intracelial, intracelebellar [sic], intracerebroventricular, intracolic, intracervical, intragastric, intrahepatic, intramyocardial, intraosteal, intrapelvic, intrapericardiac, intraperitoneal, intrapleural, intraprostatic, intrapulmonary, intrarectal, intrarenal, intraretinal, intraspinal, intrasynovial, intrathoracic, intrauterine, intravesical, bolus, vaginal, rectal, buccal, sublingual, intranasal, or transdermal means.”

EX1002, 48:2-12; EX1004, 48:21-32; *see also* EX1002, 47:19-23; EX1004, 47:39-44 (for parental administration, the antibody can be formulated, among other things, as a solution, suspension, powder, or an emulsion, and may be provided with a pharmaceutically acceptable carrier, such as water or saline, among other things). *US982* and *US566* teach a wide variety of compositions and excipients that may be used, but do not disclose any specific formulations for a golimumab composition to be administered to a human. *See* EX1002:32:8-36:49; EX1004, 32:32-37:3. Accordingly, a POSA would have understood that the safety and

efficacy of golimumab depended on the dose and dosing regimen, not the excipients used in the specific formulation or composition.

153. With respect to IV administration, the specifications of *US982* and *US566* acknowledge:

Intravenous golimumab has been definitively studied in a Phase 3 study in RA (CNT0148ART3001) that formed the basis of approval for the treatment of RA. The CNT0148ART3001 study was a randomized, double-blind, placebo-controlled, multicenter, 2-arm study of the efficacy and safety of IV administration of golimumab 2 mg/kg infusions administered over a period of 30±10 minutes at Weeks 0, 4, and every 8 weeks (q8w) thereafter in subjects with active RA despite concurrent methotrexate (MTX) therapy. Subjects with active RA despite MTX were randomized to receive either placebo infusions or IV golimumab administered 2 mg/kg at Weeks 0, 4, and every 8 weeks through Week 24. Starting at Week 24, all subjects were treated with IV golimumab through Week 100. It was demonstrated that IV golimumab provided substantial benefits in improving RA signs and symptoms, physical function, and health related quality of life, as well as inhibiting the progression of structural damage.

EX1002, 86:33-50; EX1004, 86:29-47.

154. *US982* and *US566* each have nine Examples. Example 9 of each patent describes a planned multicenter, randomized, double-blind, placebo-controlled trial of golimumab for the treatment of AS and its initial results.

EX1002, 78:62-110:39; EX1004, 78:60-110:47.

155. According to *US982* and *US566*, golimumab has a heavy chain of SEQ ID NO: 36 and a light chain of SEQ ID NO: 37, binds to human TNF α with

high affinity and specificity, and neutralizes TNF α activity. EX1002, 79:3-7; EX1004, 79:4-9.

156. With respect to the dosing regimen used in the clinical trial described in Example 9, *US982* and *US566* state that “[p]atients were randomized (1:1) to IV golimumab 2 mg/kg at weeks (wks) 0, 4, and every 8 wks or placebo at wks 0, 4, and 12, with crossover to golimumab at wk 16.” EX1002, 105:12-14; EX1004, 105:38-40.

157. *US982* and *US566* also present preliminary efficacy and safety results through week 28. EX1002, 106:7–107:30; EX1004, 106:22–107:40. Applicants concluded that “IV golimumab 2 mg/kg was efficacious in reducing signs and symptoms of AS compared with placebo. Golimumab was well-tolerated through wk28 and the safety profile was consistent with other anti-TNFs, including SC golimumab.” EX1002, 106:6-10; EX1004, 106:20-25.

158. The clinical trial data provided in *US982* and *US566* indicates that <10% and <15% of golimumab treated subjects achieved the claimed Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at weeks 2 and 4, respectively. EX1002, Table 9; EX1004, Table 9.

2. The Claims of *US982*

159. *US982* issued with independent claims 1, 4, and 7, and dependent claims 2, 3, 5, 6, and 8-10. Claims 1-10 are reproduced below:

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 having a heavy chain (HC) comprising the amino acid sequence set forth in SEQ ID NO:36 and a light chain (LC) comprising the amino acid sequence set forth in SEQ ID NO:37, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via IV infusion, 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.

2. The method according to claim 1, wherein said composition is administered such that said anti-TNF antibody is administered at a dose of 2 mg/kg, administered over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

3. The method according to any one of claims 1-2, further comprising administering said composition with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

4. 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 having a heavy chain (HC) comprising the amino acid sequence set forth in SEQ ID NO:36 and a light chain (LC) comprising the amino acid sequence set forth in 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 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.

5. The method according to claim 4, wherein said composition is administered such that said anti-TNF antibody is administered at a dose of 2 mg/kg, administered over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

6. The method according to any one of claims 4-5, further comprising administering said composition with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

7. 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 having a heavy chain (HC) comprising the amino acid sequence set forth in SEQ ID NO:36 and a light chain (LC) comprising the amino acid sequence set forth in SEQ ID NO:37, and at least one pharmaceutically acceptable carrier or diluent, wherein said composition is administered via IV infusion, and wherein $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.

8. The method according to claim 7, wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.

9. The method according to any of claims 7-8, wherein said antibody is administered at a dose of 2 mg/kg, administered over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

10. The method according to any one of claims 7-8, wherein said antibody is administered with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

3. The Claims of *US566*

160. *US566* issued with independent claims 1, 3, and 5, and dependent claims 2, 4, 6, and 7. Claims 1-7 are reproduced below:

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.

2. The method according to claim 1, further comprising administering said composition with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

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.

4. The method according to claim 3, further comprising administering said composition with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

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 anti- 20 body 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, 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 $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.

6. The method according to claim 5, wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.

7. The method according to claim 5, wherein said antibody is administered with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).

VI. THE PRIOR ART

A. NCT02181673 (“NCT673-V23”) (EX1011)

161. NCT02181673 is a clinical trial protocol sponsored by Janssen Research and Development LLC, titled “A Study of Golimumab in Participants with Active Psoriatic Arthritis” obtained from clinicaltrials.gov. EX1011, 1; available at <https://clinicaltrials.gov/study/NCT02181673?>. I have verified that a POSA searching for studies on “golimumab” and “psoriatic arthritis” would have readily found, among other studies, NCT02181673. In this declaration I rely on Version 23 of the clinical trial, *NCT673-V23*, which was published on ClinicalTrials.gov on January 8, 2016 (*id.*, 2) and therefore was a printed

publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*. I was aware of ClinicalTrials.gov in the relevant time frame and had used it, in 2015 and earlier, to search for and locate clinical trial records. Moreover, NIH, which launched ClinicalTrials.gov in 2000, described it as “a consumer-friendly database ... with information on more than 4,000 federal and private medical studies involving patients and others at more than 47,000 locations nationwide” and stated that ClinicalTrials.gov “provides patients, families and members of the public easy access to information about the location of clinical trials, their design and purpose, criteria for participation, and, in many cases, further information about the disease and treatment under study.” EX1052, 1. In 2015 and earlier, ClinicalTrials.gov was well-known and POSAs routinely visited ClinicalTrials.gov to discover information about new therapies being investigated in clinical trials.

162. *NCT673-V23* teaches that the purpose of the clinical trial was “to evaluate the efficacy of intravenously (administration of a fluid into the vein) administered golimumab 2 milligram per kilogram (mg/kg) in participants with active psoriatic arthritis (a chronic inflammatory arthritis that is associated with psoriasis).” EX1011, 3.

163. According to *NCT673-V23*:

Eligible Participants will be randomly assigned to either Treatment Group 1: Placebo or Treatment Group 2: Golimumab. Participants randomized to

Placebo Group, will receive intravenous infusions of placebo at Weeks 0, 4, 12 and 20. At Week 24, all participants receiving placebo will begin receiving intravenous infusions of golimumab (2 mg/kg) at Week 24, 28 and thereafter every 8 weeks up to Week 52. Participants randomized to Golimumab Group, will receive intravenous infusions of golimumab 2 mg/kg at Week 0, 4 and thereafter every 8 weeks up to Week 52. At Week 24, participants randomized to golimumab Group will receive a placebo infusion to maintain the blind. The efficacy will be assessed primarily by measuring percentage of participants who achieve a 20 percent improvement from baseline in the assessment used in active psoriatic arthritis at Week 14. Participants' safety will be monitored throughout the study.

Id.

164. A POSA would have understood that golimumab is a protein that is solid when isolated, and that to administer it intravenously it would necessarily be in a carrier or diluent.

165. A POSA also would have understood that because *NCT673-V23* was a double-blind study, the drug and placebo would both have to be diluted in the same volume of diluent and infused at the same rate so that investigators would not know the difference between the two.

166. A POSA also would have been aware of *PI2013-Aria*, the label for Janssen's IV golimumab product for treating RA, which states that golimumab is diluted with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent, prior to infusion. EX1032, 1. A POSA therefore would have understood that the golimumab to be used in *NCT673-V23* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

167. A POSA also would have been aware of *PI2013-Aria*, Janssen's FDA-approved label for IV golimumab, directed that IV golimumab be infused over a period of approximately 30 minutes. EX1032, 1. A POSA would have understood that the same dose of IV golimumab in *NCT673-V23* would be administered using the same infusion time as in the FDA-approved label.

168. *NCT673-V23* discloses the following primary and secondary outcome measures:

- Primary outcome measure: the percentage of patients achieving ACR20 response at week 14.
- Secondary outcome measures: change from baseline in the HAQ-DI score at week 14; percentage of participants who achieve ACR50 at week 14; percentage of participants achieving Psoriatic Area and Severity Index (PASI) 75 response at week 14; change from baseline in the vdH-S score at week 24; and change from baseline in the SF-36 PCS at week 14.

EX1011, 4.

B. NCT02186873 (“*NCT873-V24*”) (EX1014)

169. NCT02186873 is a clinical trial protocol sponsored by Janssen Research and Development LLC, titled “A Study of Golimumab in Participants with Active Ankylosing Spondylitis,” obtained from clinicaltrials.gov. EX1014, 1; available at <https://clinicaltrials.gov/study/NCT02186873?>. I have verified that a POSA searching for studies on “golimumab” and “ankylosing spondylitis” would have readily found, among other studies, NCT02186873. In this declaration I rely on Version 24 of the clinical trial, *NCT873-V24*, which was published on

ClinicalTrials.gov on October 27, 2015 (*id.*, 4) and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*. As I indicated in Paragraph 161, I was aware of ClinicalTrials.gov in the relevant time frame and had used it, in 2015 and earlier, to search for and locate clinical trial records, which was its intended purpose when launched by NIH. EX1052, 1. As I indicated in Paragraph 161, in 2015 and earlier, ClinicalTrials.gov was well-known and POSAs routinely visited ClinicalTrials.gov to discover information about new therapies being investigated in clinical trials.

170. The purpose of the study reported by *NCT873-V24* “is to evaluate the efficacy of intravenously (administration of a fluid into the vein) administered golimumab 2 milligram per kilogram (mg/kg) in participants with active ankylosing spondylitis (a chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, and often the axial skeleton, entheses, and peripheral joints).” EX1014, 5.

171. According to *NCT873-V24*:

Eligible Participants will be randomly assigned to either Treatment group 1: Placebo or Treatment group 2: Golimumab. Participants randomized to Placebo group, will receive intravenous infusions of placebo at Weeks 0, 4 and 12. At Week 16, all participants receiving placebo will begin receiving intravenous infusions of golimumab (2 mg/kg) at Weeks 16, 20 and thereafter every 8 weeks up to Week 52. Participants randomized to Golimumab group, will receive intravenous infusions of golimumab 2 mg/kg at Weeks 0, 4 and

thereafter every 8 weeks up to Week 52. At Week 16, participants randomized to golimumab group will receive a placebo infusion to maintain the blind. The efficacy will be assessed primarily by measuring percentage of participants who achieve a 20 percent improvement from baseline in the assessment in ankylosing spondylitis (ASAS) at Week 16. Participant's safety will be monitored throughout the study.

Id., 6.

172. A POSA would have understood that golimumab is a protein that is solid when isolated, and that to administer it intravenously it would necessarily be in a carrier or diluent.

173. A POSA also would have understood that because *NCT873-V24* was a double-blind study, the drug and placebo would both have to be diluted in the same volume of diluent and infused at the same rate so that investigators would not know the difference between the two.

174. A POSA also would have been aware of *PI2013-Aria*, the label for Janssen's IV golimumab product for treating RA, which states that golimumab is diluted with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent, prior to infusion. EX1032, 1. A POSA therefore would have understood that the golimumab to be used in *NCT873-V24* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

175. A POSA also would have been aware of *PI2013-Aria*, Janssen's FDA-approved label for IV golimumab, directed that IV golimumab be infused

over a period of approximately 30 minutes. EX1032, 1. 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.

176. *NCT873-V24* discloses the following primary outcome measure:

“Percentage of Participants Achieving a 20 Percent Improvement in Assessment in Ankylosing Spondylitis (ASAS 20) at Week 16.” EX1015, 7.

177. *NCT873-V24* discloses the following secondary outcome measures:

- “1. Percentage of Participants Achieving a 40 Percent Improvement in Assessment in Ankylosing Spondylitis (ASAS 40) at Week 16”;
- “2. Percentage of Participants With at Least 50 Percent Improvement From Baseline in Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 16”; and
- “3. Change From Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) Score at Week 16.”

Id., 7-8.

178. A POSA would have been aware of both the *NCT673-V23* and the *NCT873-V24* studies, and would have also understood that both studies use the same dose and dosing schedule as Janssen’s FDA-approved label for IV golimumab, *PI2013-Aria*.

C. GO-REVEAL (EX1041-1044)

179. GO-REVEAL is the acronym for Janssen’s golimumab PsA clinical trial titled: “Golimumab—A Randomized Evaluation of Safety and Efficacy in

Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody.”

See EX1041, 977. The following series of publications authored by Kavanaugh et al., which I refer to as “*GO-REVEAL*”, report on the results of the GO-REVEAL study at different timepoints.

- A. Kavanaugh, et al., *Golimumab, a New Human Tumor Necrosis Factor α Antibody, Administered Every Four Weeks as a Subcutaneous Injection in Psoriatic Arthritis*, 60 ARTHRITIS & RHEUMATISM 4, 976-986 (Apr. 2009) (“*Kavanaugh 2009*”) (EX1041), which published in 2009;
- A. Kavanaugh, et al., *Golimumab in Psoriatic Arthritis, One-Year Clinical Efficacy, Radiographic, and Safety Results From a Phase III, Randomized, Placebo-Controlled Trial*, 64 ARTHRITIS & RHEUMATISM 8, 2504-2517 (2012) (“*Kavanaugh 2012*”) (EX1042), which published in 2012;
- A. Kavanaugh, et al., *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*, 65 ARTHRITIS CARE & RESEARCH 10, 1666-73 (Oct. 2013) (“*Kavanaugh 2013*”) (EX1043), which published in 2013; and

- A. Kavanaugh, et al., *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)*, 73 ANN. RHEUM. DIS. 1689-1694 (Apr. 19, 2014) (“Kavanaugh 2014”) (EX1044), which published in 2014.

Based on their publication dates, *Kavanaugh 2009*, *Kavanaugh 2012*, *Kavanaugh 2013*, and *Kavanaugh 2014*, were printed publications available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

a. *Kavanaugh 2009* (EX1041)

180. *Kavanaugh 2009* provides 24-week efficacy and safety results from the GO-REVEAL study. EX1041, 977.

181. As explained in *Kavanaugh 2009*, GO-REVEAL was a PHASE-III, multicenter, randomized, double-blind, placebo controlled, study of the safety and efficacy of SC golimumab, 50 mg or 100 mg, administered every 4 weeks for the treatment of PsA. EX1041, 977. When it was conducted, the study was the “largest of its kind yet completed with a biologic agent in PsA.” *Id.*

182. The primary end point of the GO-REVEAL study was ACR20 at week 14, “and at least 3 of the following 5 assessments: patient’s assessment of

pain, patient's global assessment of disease activity, physician's global assessment of disease activity, patient's assessment of physical function using the Health Assessment Questionnaire (HAQ), and the C-reactive protein (CRP) level." *Id.* (citation omitted).

183. With respect to the primary endpoint of ACR20 at week 14, 48% of all patients receiving golimumab (either 50mg or 100mg of golimumab) achieved ACR20 at week 14 compared to 9% of patients receiving placebo. *Id.*, 979. When broken down by dose, 51% of patients receiving 50 mg achieved ACR20, and 45% of patients receiving 100 mg achieved ACR20. *Id.*, 976, 984.

184. *Kavanaugh 2009* reports that patients in both the 50 mg and 100 mg groups "had significantly improved HAQ scores at week 24 (major secondary end point), with a mean $\pm$ SD change from baseline of 0.33 ± 0.55 and 0.39 ± 0.50 for golimumab 50 mg and golimumab 100 mg, respectively, versus -0.01 ± 0.49 for patients in the placebo group ($P < 0.001$ for both comparisons)." EX1041, 980.

185. With regard to other psoriatic arthritis and assessments of enthesitis and dactylitis, *Kavanaugh 2009* reported:

Significantly greater improvement from baseline to weeks 14 and 24 was generally observed in each golimumab dose group versus placebo for each supportive arthritis efficacy parameter, including the PsARC, the European League Against Rheumatism (EULAR) response, change in the DAS28-CRP, and assessments of enthesitis and morning stiffness (Table 2). No significant difference between placebo and golimumab was seen in the proportion of patients with dactylitis at week 14 or week 24; however, there was significantly greater

improvement in the dactylitis severity score at both time points with golimumab 100 mg. Significantly smaller proportions of patients in the golimumab 50 mg and 100 mg groups had enthesitis at week 24 compared with patients in the placebo group (Table 2), and significantly greater improvement in the PsA-modified MASES enthesitis score was observed in the golimumab 50 mg and 100 mg groups compared with the placebo group at weeks 14 and 24.

Id.

186. The *Kavanaugh 2009* authors concluded that “[g]olimumab, a human monoclonal antibody against TNF α , was demonstrated to be efficacious and generally well tolerated when administered subcutaneously every 4 weeks during 24 weeks of treatment.” *Id.*, 984. Based on the results in *GO-REVEAL*, FDA approved SIMPONI as safe and effective for the treatment of active PsA. EX1015, 1, 11, 25-28; EX1041, 979, 984

b. *Kavanaugh 2012* (EX1042)

187. *Kavanaugh 2012* reported on the one-year clinical efficacy, radiographic, and safety results of the GO-REVEAL study. EX1042, 2504.

188. *Kavanaugh 2012* reported changes compared to baseline in the second of two coprimary endpoints: “change from baseline to week 24 in PsA-modified Sharp/van der Heijde score [SHS]” (brackets in original). EX1042, 2504-05. Radiographs were obtained at baseline, week 24, and week 52, or when golimumab was discontinued. *Id.*, 2505. The authors concluded that “[t]reatment of PsA with

golimumab inhibited structural damage progression and demonstrated continued clinical efficacy and safety through 1 year.” *Id.*, 2505.

189. *Kavanaugh 2012* reported the following: “In analyses that assessed changes from baseline to week 24 in the PsA-modified SHS by baseline MTX use, changes in scores indicated less radiographic progression for both golimumab doses (-0.34 ± 1.10 for 50 mg and -0.16 ± 1.36 for 100 mg) versus placebo (0.22 ± 1.25) within the subgroup of patients receiving MTX at baseline than in patients receiving golimumab alone (0.01 ± 1.47 for 50 mg and 0.11 ± 1.28 for 100 mg versus 0.31 ± 1.28 for placebo).” EX1042, 2509.

190. *Kavanaugh 2012* also reported that “significantly more patients in the golimumab 50 mg or 100 mg groups had no progression in radiographic scores, defined by change from baseline in the total PsA-modified SHS ≤ 0 , versus placebo.” *Id.*, 2512.

191. The authors also noted that “[g]olimumab efficacy was not substantially different between patients receiving 50 mg and those receiving 100 mg and was comparable to that observed with other commercially available anti-TNF agents.” *Id.*, 2516.

c. *Kavanaugh 2013* (EX1043)

192. *Kavanaugh 2013* reported on the findings through two years of the GO-REVEAL study. EX1043, 1666.

193. *Kavanaugh 2013* states that patients with PsA exhibit degrees of impaired physical function and health-related quality of life similar to patients with RA. *Kavanaugh 2013* further compared to RA patients, PsA patients are more commonly younger and male, and have constraints on productivity similar to or worse than RA patients. EX1043, 1667.

194. *Kavanaugh 2013* concludes that “[g]olimumab-treated patients had significant improvements in physical function, HRQOL, and productivity through week 24” and that “these improvements correlated with clinical improvement in signs and symptoms of peripheral arthritis and were sustained through 2 years.” EX1043, 1666.

d. *Kavanaugh 2014* (EX1044)

195. *Kavanaugh 2014* reported on the clinical efficacy, radiographic, and safety findings through 5 years of SC golimumab treatment in patients with active PsA, providing results from a long-term extension of the GO-REVEAL study. EX1044, 1689.

196. *Kavanaugh 2014* concluded that “[l]ong-term golimumab safety/efficacy in PsA was demonstrated through 5 years.” *Id.*

D. WO 2008/063213 (“WO213”; EX1025)

197. International publication number WO 2008/063213 (“WO213”) is the publication of international application number PCT/US2007/008820 to Medich et al. WO213, titled “Uses and Composition for Treatment of Psoriatic Arthritis,” published May 29, 2008 (EX1025, cover page), and therefore was a printed publication available more than one year before the earliest possible effective priority date of US020, US824, US982, and US566.

198. WO213 is directed to methods and composition for treating PsA using a TNF α inhibitor, such as a TNF α antibody, and that the antibody may be golimumab. EX1025, 1:24-25, 30-31; 31:34-35.

199. WO213 taught that the TNF α antibody can be administered in many standard ways, including parenteral and oral, such as SC delivery. *Id.*, 59:8-60:8. WO213 taught that in a preferred embodiment, the TNF α inhibitor is administered intravenously. *Id.*, 59:3-7. Similarly, WO2013 taught a method for treating PsA using TNF α inhibitors, including golimumab, and taught IV administration of the TNF α inhibitor. EX1025, 2:22-3:8, 31:34-35, 58:10-13.

200. WO213 taught that the TNF α inhibitor, in embodiments of the invention, achieves an ACR20 response in at least about 59% to 75% as an effective treatment for PsA. *Id.*, 2:22-3:8.

201. *WO213* provides examples using adalimumab, which the applicants describe as “representative of a TNF α inhibitor.” *Id.*, 80:14-15. *WO2013* further teaches that the Examples may be “used as a guideline for determining the efficacy of a TNF α inhibitor.” *Id.*, 80:15-20. *WO213* discloses that by week 24, adalimumab had significantly reduced the overall amount of radiographic progression vs. placebo, with the mean change in the modified version of the total Sharp Score from baseline to week 24 being 1.0 for placebo (n=152), and -0.2 for adalimumab (n=144) (p<0.001 vs. placebo for the ADA group). EX1025, 127:8-11; *see also* EX1042, 2516 (noting that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents.).

202. In Example 1, subjects received placebo or 40 mg adalimumab administered subcutaneously every other week. EX1025, 81:16-82:16. At 24 weeks, the adalimumab group had an ACR20 of 57% versus 15% for placebo. *Id.*, 82:22-25. Applicants concluded that “adalimumab is efficacious for skin and joint disease in patients with PsA.” *Id.*, 84:20-21.

203. Example 5 describes an open label extension of Example 1 to determine the 24- and 48-week efficacy of adalimumab for arthritis and disability. EX1025, 89:20-26. Table 11, reproduced below, shows the arthritis related outcomes by the duration of time the subject had PsA:

	PsA duration, years (N)			
	<2 (26)	2-5 (29)	5-10 (35)	≥10 (61)
ACR 20/50/70	46*/38/23†	66/52/28	54/34*/23†	59/36/20†
Baseline HAQ	0.8	0.9	1.0	1.0
Mean Δ HAQ	-0.3*	-0.5	-0.3†	-0.4
Baseline DAS28	4.7	4.6	4.8	4.9
Mean Δ DAS28	-1.5	-1.7	-1.5	-1.8

* $p < 0.05$, † $p < 0.01$, ‡not significant; all other results $p < 0.001$; ada vs. pbo (pbo data not shown)

Id., 90:25-28.

204. Table 11, above, shows that subject responses may change based on characteristics of the patient population, including how long the subject has had PsA, baseline HAQ score, and baseline DAS28. The HAQ score was originally developed for RA, with lower HAQ scores being predictive of better RA outcomes. EX1025, 78:25-31.

205. Applicants concluded that adalimumab was efficacious regardless of the duration of PsA of the subject. *Id.*, 95:10-13.

206. Example 6 assessed whether 40mg of adalimumab administered subcutaneously every other week provided “complete resolution of loss of physical function in patients with PsA versus those on placebo.” *Id.*, 95:24-26. Physical function was assessed using HAQ DI, in which scores range from 0 to 3, with lower scores indicating less functional loss. *Id.*, 95:30-33.

207. *WO213* reported the following results:

At weeks 12 and 24, significantly more patients in the adalimumab group had no functional loss (HAQ DI=0) versus those

treated with placebo. At week 12, 34% of adalimumab group patients had an HAQ DI=0, whereas only 14% of the placebo group had such a score. At week 24, 34% of adalimumab group patients had an HAQ DI=0, whereas only 14% of the placebo group had such a score.

EX1025, 96:11-15.

208. *WO213* Example 12 was a subanalysis study of the results of Example 1 in which data from subjects that had evaluable radiographs at baseline and week 24 were used to assess radiographic efficacy. *Id.*, 126: Example 12.

209. With respect to the results of the subanalysis, *WO213* found that adalimumab significantly reduced radiographic progression compared to placebo:

By Week 24, adalimumab had significantly reduced the overall amount of radiographic progression vs. placebo. Specifically, the mean change in mTSS from baseline to Week 24 was 1.0 for placebo (n=152), and -0.2 for ADA (n=144)(p<0.001 vs. placebo for the ADA group). For all demographic subgroups with an adequate number of patients, the mean Δ mTSS at Week 24 with adalimumab was ≤ 0 and was significantly lower with than with placebo (Table 44).

Id., 127:8-13.

210. Example 13 assessed adalimumab in clinical practice, with the following ACR results at week 12:

Table 49. ACR Responses Up to Week 12

	Week 2	Week 6	Week 12
ACR20 (% Patients)	38	60	72
ACR50 (% Patients)	14	35	49
ACR70 (% Patients)	2	13	27

EX1025, 134, Table 49. These results show that the adalimumab was effective.

E. *PI2013-Aria* (EX1032)

211. *PI2013-Aria* is the July 2013 revision of the prescribing information for Simponi Aria (EX1032, 1; https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125433s0001bledt.pdf), available at <https://www.fda.gov/drugsatfda>, and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

212. *PI2013-Aria* disclosed the following FDA-approved safe and effective dosing regimen for rheumatoid arthritis: “2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks.” EX1032, 1; *see also id.*, 3. *PI2013-Aria* further disclosed that the solution needs to be diluted with 0.9% w/v sodium chloride prior to administration. *Id.*, 1.

213. *PI2013-Aria* further disclosed that “[e]ach 4 mL vial of SIMPONI ARIA contains 50 mg golimumab, 9.5 mM histidine, 4.5% (w/v) sorbitol, and 0.015% (w/v) polysorbate 80.” *Id.*, 15.

214. *PI2013-Aria* stated that “[f]ollowing a single intravenous administration of 2 mg/kg SIMPONI ARIA, a mean $C_{\max}$ of 44.4 ± 11.3 $\mu\text{g/ml}$ was observed in patients with RA” and that “data directly comparing 2 mg/kg

intravenous administration and 50 mg subcutaneous administration are not available.” EX1032, 15.

215. *PI2013-Aria* further stated that “[w]ith concomitant use of MTX, treatment with 2 mg/kg golimumab every 8 weeks resulted in a mean steady-state trough serum concentration of approximately 0.4 ± 0.4 $\mu\text{g/ml}$ in patients with active RA despite MTX therapy.” *Id.*, 16.

216. *PI2013-Aria* taught the following regarding the mechanism of action of golimumab: “[golimumab] binds to both the soluble and transmembrane bioactive forms of human $\text{TNF}\alpha$ ” and thereby “prevents the binding of $\text{TNF}\alpha$ to its receptors, thereby inhibiting the biological activity of $\text{TNF}\alpha$ (a cytokine protein).” EX1032, 15.

217. *PI2013-Aria* taught that in a clinical trial, 59% of patients treated with golimumab and methotrexate achieved ACR20 at 14 weeks compared to 25% for placebo and methotrexate. *Id.*, 17-18.

218. *PI2013-Aria* also taught that golimumab resulted in significantly less radiographic change than placebo, with patients receiving golimumab and methotrexate having a total change in vdH-S score of 0.03 compared to 1.1 for placebo plus methotrexate. EX1032, 19.

219. *PI2013-Aria* also taught that golimumab resulted in a significantly greater mean improvement in the HAQ-DI, with patients receiving golimumab and

methotrexate having an improvement in HAQ-DI of 0.5 compared to 0.2 for placebo plus methotrexate, with a 95% confidence interval for that difference. *Id.*, 19-20.

F. *PI2015-Simponi* (EX1015)

220. *PI2015-Simponi* is the June 2015 revision of the prescribing information for Simponi (EX1015, 1; https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125289s024lbl.pdf), available at <https://www.fda.gov/drugsatfda>, and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

221. *PI2015-Simponi* taught that golimumab is a human IgG1 κ monoclonal antibody that binds both the soluble and transmembrane bioactive forms of human TNF α , preventing it from binding to its receptors. *Id.*, 18.

222. *PI2015-Simponi* disclosed that RA, PsA, and AS are associated with elevated levels of TNF α :

Golimumab is a human monoclonal antibody that binds to both the soluble and transmembrane bioactive forms of human TNF α . This interaction prevents the binding of TNF α to its receptors, thereby inhibiting the biological activity of TNF α (a cytokine protein).

Elevated TNF α levels in the blood, synovium, and joints have been implicated in the pathophysiology of several chronic

inflammatory diseases such as rheumatoid arthritis. TNF α is an important mediator of the articular inflammation that is characteristic of these diseases.... Golimumab modulated the *in vitro* biological effects mediated by TNF in several bioassays, including the expression of adhesion proteins responsible for leukocyte infiltration (E-selectin, ICAM-1 and VCAM-1) and the secretion of proinflammatory cytokines (IL-6, IL-8, G-CSF and GM-CSF).

EX1015, 18-19.

223. *PI2015-Simponi* presented prescribing information for subcutaneous golimumab. EX1015, 1. The prescribing information for RA, PsA, and AS is the same, that is, administration 50 mg by SC injection once a month. *Id.*, 4. For patients with RA, the golimumab should be given in conjunction with MTX, whereas the use of MTX in the treatment of PsA and AS is optional. *Id.*

224. *PI2015-Simponi* also disclosed that golimumab for SC administration was effective at treating RA, PsA, and AS using the same dose and dosing schedule: 50 mg administered SC once per month. EX1015, 1, 4. The label reported the following results for the RA trial using those doses:

	Trial RA-1 Active RA previously treated with one or more doses of TNF-blockers		Trial RA-2 Active RA, despite MTX		Trial RA-3 Active RA, MTX Naïve	
	Placebo ± DMARDs ^b	SIMPONI 50 mg ± DMARDs ^b	Background MTX	SIMPONI 50 mg + Background MTX	MTX	SIMPONI 50 mg + MTX
N ^c	150	147	133	89	160	159
ACR 20						
Week 14	18%	35%	33%	55%	NA ^e	NA ^e
Week 24	16%	31%	28%	60%	49%	62%

Id., 23.

225. *PI2015-Simponi* presented data from a clinical trial in which golimumab, 50 mg, was administered subcutaneously every four weeks to adult patients with active ankylosing spondylitis. EX1015, 28. Figure 3 shows the Percent of AS patients achieving ASAS20 response by visit, and indicates that at the four week visit, about 48% of golimumab patients achieved ASAS20, while only about 12 percent of placebo patients achieved ASAS20. *Id.*, 30, Figure 3.

G. *Inman* (EX1016)

226. R. D. Inman, et al., *Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis*, 58 ARTHRITIS & RHEUMATISM 11:3402-3412 (Nov. 2008) (“*Inman*”), titled “Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis” was published in November 2008 (EX1016, 3402), and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

227. *Inman* described the results of a randomized, double-blind, placebo-controlled, phase II trial of golimumab, 50 mg or 100 mg, administered SC every four weeks to subjects with AS. EX1016, 3402. According to *Inman*, “[g]reater proportions of patients in the golimumab groups achieved an ASAS20 response at the first assessment, 4 weeks after the first injection.” *Id.*, 3406, Figure 3A.

228. *Inman* reported that 59.4% and 60% of patients receiving SC doses of 50 mg and 100 mg of golimumab, respectively, achieved ASAS20 at week 14,

compared to 21.8% for subjects receiving placebo, and that this result was significant ($P < 0.001$). *Id.*, Abstract.

229. *Inman* provided the following figure, Figure 3, which shows the 3, 8, 12, 14, 16, 20, and 24 week ASAS20 (Figure 3A), mean BASDAI (Figure 3B), and mean BASFI (Figure 3C) results observed for patients receiving SC golimumab, 50 or 100 mg, every four weeks, or placebo.

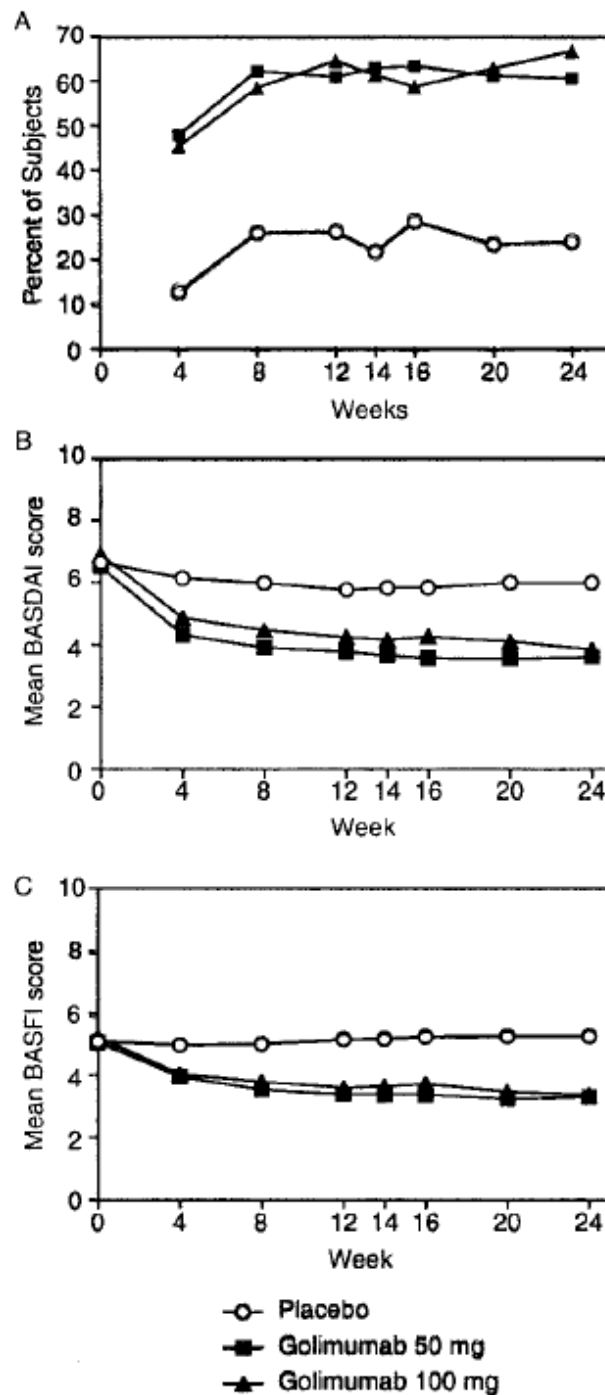


Figure 3. A, Proportion of patients achieving a 20% improvement in the ASsessment in Ankylosing Spondylitis International Working Group criteria through week 24. B, Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score through week 24. C, Mean Bath Ankylosing Spondylitis Functional Index (BASFI) score through week 24.

EX1016, 3406.

230. Based on Figure 3B, at 4 weeks, patients on golimumab saw improvement compared to those on placebo, with the patients receiving SC golimumab, 50 or 100 mg, having BASDAI scores of about 4.2 and 4.5, respectively, compared to 6.2 for subjects receiving placebo. *See* EX1016, Figure 3B. A lower BASDAI score reflects lesser AS symptoms than a higher BASDAI score.

231. Based on Figure 3C, at 4 weeks, patients on golimumab saw improvement compared to those on placebo, with the patients receiving SC golimumab, 50 or 100 mg, having BASFI scores of about 4.0 compared to 6.2 for subjects receiving placebo. *See id.*, Figure 3C. A lower BASFI score reflects lesser AS symptoms than a higher BASFI score.

232. Based on these results, a POSA would have understood that SC golimumab can rapidly provide improvement in AS symptoms.

H. *Van der Heijde* (EX1033)

233. D. Van der Heijde, et al., *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*, 41 THE JOURNAL OF RHEUMATOLOGY 6:1095-1103 (2014) (“*Van der Heijde*”), titled “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” (EX1033, 1095), was published in 2014 and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

234. *Van der Heijde* evaluated the effect of golimumab therapy, 50 mg or 100 mg SC every four weeks, on achieving inactive disease or major improvement in AS through two years as measured by ASDAS or improvements in health-related quality of life and productivity. EX1033, Abstract.

235. *Van der Heijde* concluded that “[g]reater proportions of golimumab-treated patients achieved ASDAS major improvement or inactive disease and improved HRQOL versus placebo. *Id.*

236. *Van der Heijde* reported that “significantly greater proportions of patients in Groups 2 and 3 [*i.e.*, receiving golimumab] had ASDAS inactive disease at weeks 14 and 24 (Figure 1).” EX1033, 1097.

237. Figure 1 of *Van der Heijde*, reproduced below, reported ASDAS inactive disease results.

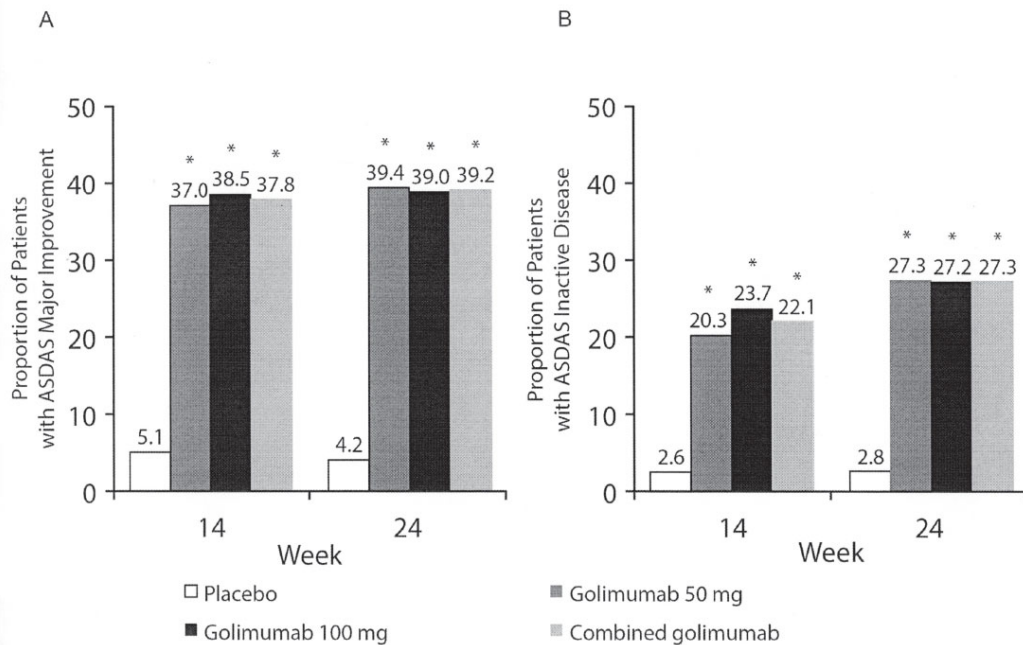


Figure 1. Proportions of patients with ASDAS major improvement (A) or inactive disease (B) at weeks 14 and 24. *p < 0.001. ASDAS: Ankylosing Spondylitis Disease Activity Score.

EX1033, Figure 1.

238. The data in Figure 1 showed that at week 14, 20.3% and 23.7% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive disease compared to 2.6% of patients on placebo ($p < 0.001$). *Id.*, 1099, Figure 1. These results are very similar to the 12 week results reported in *US982* and *US566*, wherein 19.0% of subjects treated with IV golimumab, 2 mg/kg at week 0, 4, and every 8 weeks thereafter, achieved ASDAS inactive disease. *See* EX1002, Table 9; EX1004, Table 9.

239. The data in Figure 1 shows that at week 24, 27.3% and 27.2% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive disease compared to 2.8% of patients on placebo ($p < 0.001$). EX1033,

1099, Figure 1. These results are very similar to the 20 week (28.6%) and 28 week (29.5%) ASDAS inactive disease results reported in *US982* and *US566*. EX1002, Table 9; EX1004, Table 9.

240. *Van der Heijde* reported that at week 14, the average change from baseline in SF-36 PCS (0-100; normal ≥ 50) for subjects receiving 50 mg and 100 mg golimumab were 8.8 ± 9.6 and 8.9 ± 9.8 , respectively ($p < 0.001$ for both measures). EX1033, 1098, Table 2.

241. *Van der Heijde* reported that at week 14, the average change from baseline in SF-36 MCS (100 point scale) for subjects receiving 50 mg and 100 mg golimumab were 2.6 ± 8.5 and 4.8 ± 10.4 , respectively ($p < 0.001$ for both measures). *Id.*, 1098, Table 2.

I. CDER Review (EX1034)

242. *CDER Review* is a publicly available compilation of administrative and correspondence documents compiled by FDA related to Application Number 125433, the BLA for Janssen Biotech's Simponi Aria golimumab product, that can be obtained from the FDA website:

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125433review.pdf.

EX1034, 1-2. *CDER Review* was publicly available on September 30, 2013, which can be confirmed using the Drugs@FDA Data Files. *See*

43330 3 125433 ORIG 1 0 http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125433review.pdf 2013-09-30 00:00:00

Based on its publication date, *CDER Review* was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*.

243. In a Clinical Pharmacology Review, FDA included Table 1, which “shows the list of studies with IV dose that have been submitted during the original golimumab application (BLA125289) for its SC dosing regimen and the current golimumab application (BLA125433) for its IV dosing regimen.” *Id.*, 179.

244. FDA’s statistical review and evaluation of Janssen’s clinical studies including Table 8 titled: “Major Secondary Efficacy Analysis: Change from Baseline in vdH-S at week 24.” EX1034, 593. Table 8 notes that Simponi Aria had a mean change from baseline in vdH-S score at week 24 of 0.04 ± 1.9 SD. *Id.*

245. Despite the above studies, Janssen does not appear to have conducted a head-to-head comparative study of SC and IV golimumab. In a November 30, 2012 communication, FDA stated:

As discussed at the Pre-BLA filing meeting on October 3, 2011, we require independent substantiation of efficacy for IV golimumab. The adequacy of your proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons will be a review issue, but determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen.

EX1034, 114; *see also id.*, 127, 128, 607.

246. From this passage, I understand that Janssen proposed using SC golimumab data to help support its IV BLA, and that FDA indicated that doing so is made more difficult because of the lack of a direct comparison of IV and SC golimumab. Janssen did not do “head-to-head comparison of the IV and SC formulations that would enable a descriptive clinical comparison” for its RA study or any other study. EX1034, 114; *see also* EX1032, 15 (“Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.”)

247. Janssen does not appear to have conducted a head-to-head study of SC and IV golimumab, which is the only way of conclusively determining whether differences between clinical trials of two different treatments are clinically significant. The FDA pointed this out in the CDER Review: “In general, two adequate and well-controlled superiority trials are needed to support a comparative efficacy claim.” EX1034 at 134; *see also id.* at 283 (“However, CNTO148ART3001 [RA study] was not powered to specifically determine safety risk and the comparison to the SC formulation is based on cross-study comparisons, not head-to-head data.”)

248. Such studies are required by FDA regulations and FDA Guidance before comparative efficacy claims can be made. *See* 21 C.F.R. §21.202.1(e)(6)(ii); *see also* EX1051, *Industry Guidance*, 3.

J. CATH (EX1050)

249. *CATH* is titled “Appendix 6 Summary of Comparators” and is attached to the publication titled “Golimumab (Simponi) IV: In Combination with Methotrexate (MTX) for the Treatment of Adult Patients with Moderately to Severely Active Rheumatoid Arthritis,” published July 2015 on the NCBI Bookshelf, a free online resource managed by the National Center for Biotechnology Information (“NCBI”), which is part of the National Library of Medicine, Golimumab (Simponi) IV (EX1050, 1) and therefore was a printed publication available more than one year before the earliest possible effective priority date of *US020*, *US824*, *US982*, and *US566*. This resource is something that a POSA would have been aware of and would have relied upon.

250. Although Janssen does not appear to have conducted a head-to-head study of SC and IV golimumab, Janssen did do a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. *US1050*, 1.

251. The purpose of the meta-analysis was to “summarize the methods and results, and to conduct a critical appraisal of the manufacturer-submitted network meta-analysis (NMA) comparing the efficacy and safety of intravenous (IV) golimumab (Simponi IV) with other IV biologic response modifiers (BRMs), specifically IV infliximab and IV abatacept, as well as subcutaneous

(SC) golimumab in patients with moderate to severe rheumatoid arthritis (RA) with inadequate response to methotrexate.” EX1050, 1 (Objective).

252. According to *CADTH*, a comparative study had not been done and Janssen needed comparative data for economic analysis:

The manufacturer indicated that the systematic review and NMA were undertaken because the comparative efficacy and safety of the IV golimumab formulation versus other biologics, in particular IV biologics such as IV infliximab and IV abatacept, have yet to be established from identified randomized controlled trials (RCTs). Comparative data were needed in order to inform the economic analysis.

Id., 1 (Rationale).

253. The meta-analysis compared the reported clinical results for ACR 20, ACR 50, ACR 70, DAS 28 (Disease Activity Score in 28 joints), and HAQ-DI. EX1050, 2-4.

254. For ACR 20, the meta-analysis reports that “[t]here was no significant difference between IV golimumab versus IV infliximab, or between IV golimumab versus SC golimumab at Week 2 and Week 4. At Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.” EX1050, 3.

255. For ACR 50, the meta-analysis reports that “[a]t Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.” *Id.*, 4.

256. For ACR 70, the meta-analysis reports that “[a]t Weeks 12–16 and Weeks 24–26, no differences were seen between IV golimumab and its active comparators, namely IV infliximab, IV abatacept, and SC golimumab.”

EX1050, 4.

257. For DAS 28, the meta-analysis reports that “[a]t Weeks 12 to 16, no data were available for IV abatacept or IV infliximab, and no difference was seen between IV golimumab and SC golimumab. At Weeks 24 to 26, there were no differences between IV golimumab and its active comparators, namely IV infliximab, IV abatacept and SC golimumab.” *Id.*

258. For HAQ-DI, the meta-analysis reports that “[t]here was no statistically significant difference between IV golimumab and IV infliximab (mean difference [MD] = 0.00; 95% CrI, –0.15 to 0.15) or between IV golimumab and SC golimumab (MD = –0.06; 95% CrI, –0.22 to 0.09). No statistically significant difference was found between IV golimumab and IV tocilizumab (MD = –0.01; 95% CrI, –0.14 to 0.12), between IV golimumab and SC adalimumab (MD = –0.03; 95% CrI, –0.18 to 0.12), or between IV

golimumab and SC certolizumab pegol (MD = -0.02; 95% CrI, -0.13 to 0.17).”

EX1050, 4.

259. Regarding adverse events, “[n]o differences were seen between IV golimumab and its active comparators for discontinuations due to AEs.”

EX1050, 5.

260. In summary, the meta-analysis concluded that these therapies had no statistically significant differences in efficacy:

Without head-to-head trial data for IV golimumab versus other IV biologic comparators, the manufacturer conducted a Bayesian NMA based on RCTs to compare IV golimumab with IV infliximab, abatacept, and SC golimumab. Overall, the NMA showed no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26. There were no differences between IV golimumab and its comparators with respect to WDAEs. NMA methodology was well detailed and appropriate. The NMA is limited by variable baseline methotrexate dose across the studies and the lack of long-term comparative data for selected outcomes.

EX1050, 9 (Summary).

VII. DETAILED OPINIONS REGARDING *US020*

A. The Claims of *US020* and Their Construction

261. *US020* issued with 10 claims. Claims 1, 4, and 7 are independent claims, and claims 2, 3, 5, 6, and 8-10 are dependent claims. EX1001, 141-143.

262. In conducting my analysis, I applied the following claim constructions.

1. “Administering to a Subject”

263. Independent claims 1, 4, and 7 all recite “administering to a subject having active psoriatic arthritis.” A POSA would have understood that administering to “a subject” encompasses administering to a single subject, i.e., a single patient.

2. “Treating” (Claims 1, 4, and 7)

264. Claims 1, 4, and 7 have an introductory phrase, “a method of treating a [tumor necrosis factor alpha (TNF- α) / TNF- α] related condition in a patient.”

265. In my view, a POSA would not view the term “treating” as limiting because it does not change how the actual steps of the method of treating are performed.

266. A POSA would have understood that the only required active step is “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) SEQ ID NO: 37.” While claims 1, 4, and 7 do not specify that safe and effective amount, the only safe and effective amount disclosed in *US020* for treating PsA in humans is 2 mg/kg administered IV over 30 $\pm$ 10 minutes at week 0,

4, and every 8 weeks thereafter. EX1001, 3-8. Moreover, claim 2, which is dependent on claim 1, recites the use of that precise dosing regimen.

267. In my opinion, in view of the language of the claims and the disclosures in the specification, the term “treating” does not in any way limit how a POSA would practice the active steps of claimed methods because it does not modify the safe and effective amount of the anti-TNF antibody or how it is administered to a subject having active psoriatic arthritis.

268. Moreover, to the extent that the term “treating” is deemed to limit the claims in any way, a POSA would have understood the term “treating” means to administer the claimed dosage to a patient regardless of the clinical outcome, because *US020* teaches that not all golimumab treated patients with active PsA experience a clinical benefit. For example, claim 7 acknowledges that as many as 35% of patients may not achieve an ACR20 at week 14. Moreover, when treating a particular patient with active PsA, it cannot be predicted whether that particular patient will respond to the treatment.

3. Claimed Results Do Not Limit Claimed Method of Treatment

269. Independent claims 1, 4, and 7 recite the following clinical outcomes:

- Claim 1: “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 PCS)= 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 4: “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 ± 0.144 SE”;
- Claim 7: “wherein $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment.”

270. In addition, claim 8, which depends on claim 7, adds the following: “wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%.”

271. These claimed results appear to be the clinical responses reported in Table 8 of Example 9 in *US020. EX1001*, 116-117. Many of the claimed results pertain to a mean change from baseline and a statistical analysis obtained from a cohort of patients as opposed to a single patient. For example, the claimed results include mean changes from baseline (claims 1 and 4), standard deviations/SD (claim 1), and standard error/SE (claim 4). *EX1001*, claims 1, 4.

272. As an initial matter, as explained above in Paragraph 263, the claims expressly encompass administering the anti-TNF α antibody to a patient, *i.e.*, a single patient. Yet the recited results pertain to mean changes from baseline and other statistics that could only be obtained from analysis of a larger cohort of subjects, treated for at least 14 weeks, with data then collected and analyzed, such

as in this case, the subjects in the clinical trial described in Example 9. These statistical results in the claims appear to come from the clinical trial described in the specification, in which 239 subjects received placebo and 241 subjects received 2 mg/kg golimumab. EX1001, 116:Table 8. A POSA would have understood that the clinical result of treating a single patient does not provide a mean, cannot be used to determine a standard deviation or standard error, and is therefore not applicable to the claimed results.

273. A POSA also would have understood that when treating a particular patient with a biologic, such as golimumab, one cannot predict how that particular patient with active PsA will respond to the treatment. The claims of *US020* acknowledge as much. For example, claim 7 recites that “ $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment.” EX1001, claim 7. That means that at week 14, as many as 35% of patients receiving the treatment will not achieve ACR20. For any particular patient, before as many as 14 weeks of treatment, it would not be known whether that patient would achieve the claimed ACR20. Accordingly, a POSA would have understood that the claimed results do not limit the claimed treatment of “a subject.”

274. In addition, *US020* does not provide an explanation of how to determine the standard deviation or standard error in claims 1 and 4, respectively. In the absence of such an explanation, a POSA would have understood that the

terms have their typical statistical meanings. Thus, a POSA would have understood that a standard deviation is the average distance between each data point and the mean of a dataset. It is calculated using the following formula:

$$SD = \sqrt{[\sum(x-\mu)^2 / N]}$$

where x is each measured value, μ is the mean, and N is the total number of measured values. The standard error is a measure of the precision of a sample statistic, such as the standard deviation. It can be calculated as follows:

$$SE = SD/\sqrt{n}$$

where SD is the standard deviation of the sample and n is the sample size.

EX1017, 2-3.² Thus, while SD measures the variability within a dataset, SE estimates the precision of a sample statistic. *Id.*, 3.

275. As an example, in a study of adult heights, a mean height of 170cm with a standard deviation of 10 cm would mean that approximately 68% of adults would fall within one standard deviation of the mean, i.e., approximately 68% of adults would fall within 160 cm and 180 cm (170 ± 10 cm).

276. The intention of administering the antibody to a patient is to improve their condition, but a POSA would not know whether, for example, that patient

² *SixSigma* (EX1017), to which I refer, is dated September 25, 2024, but the concepts it discusses are well-known statistical concepts that have not changes since long before the earliest possible effective filing date of *US020* (or the remainder of the Janssen PsA and AS patents).

would be in the at least 65% that achieves ACR20 at week 14 of treatment or in the almost 35% of patients that do not meet that metric until those results are measured and analyzed, weeks after the treatment occurs.

277. In addition, a POSA would have known that the effect of administering golimumab, including the percentage of subjects achieving ACR20, may depend on the demographics of the patient population. For example, Example 5 in *WO213* reports that 46% of adalimumab treated subjects with PsA for less than 2 years achieved ACR20 at week 24 of treatment, while 66% of subjects with PsA from 2-5 years achieved ACR20. EX1025, 90:Table 11.

4. The Term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed Sequences]” Encompasses Golimumab

278. Independent claims 1, 4, and 7 include the term “at least one isolated mammalian anti-TNF antibody having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) comprising SEQ ID NO:37.” *US020* defines SEQ ID NOs 36 and 37 as the “Golimumab Heavy Chain (HC)” and “Golimumab Light Chain (LC),” respectively. EX1001, 137-142. SEQ ID NO 36 has the claimed heavy chain sequence and SEQ ID NO 37 has the claimed light chain sequence. *See id.* Accordingly, a POSA would have known that the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed Sequences]” encompasses golimumab.

5. “Administered with or without methotrexate”

279. Dependent claims 3, 6, and 10 add that the anti-TNF- α antibody is “administered with or without methotrexate.” A POSA would have understood that there are only two options for how the patient is treated with respect to methotrexate – either methotrexate is administered to the patient or it is not. This phrase also fails to limit independent claims 1, 4, and 7, as the word “or” causes the methotrexate to be optional. Therefore, a POSA would have understood that this phrase does not limit independent claims 1, 4, and 7 in any way.

B. *NCT673-V23* Anticipates Claims 1-10

280. Independent claims 1, 4, and 7, all claim a method of treating a subject with active PsA, a TNF- α related condition. Each of the independent claims recites essentially the same method of administering an anti-TNF- α antibody, differing only in the recited results of such administration. As explained below, *NCT673-V23* discloses all of the steps of the claimed method arranged as they are arranged in the claims.

1. Claims 1, 4, 7, and 8

- a. Claims 1, 4, and 7: “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”**

281. As explained above in Paragraph 265-268, in my opinion, the term “treating” does not add any additional steps to the step of administering the

golimumab. Regardless, *NCT673-V23* discloses “a method for treating a tumor necrosis factor alpha (TNF- α) related condition, wherein the TNF- α related condition is active psoriatic arthritis.”

282. *NCT673-V23* is the study record of a clinical study where subjects with active PsA were intravenously administered 2 mg/kg IV of golimumab. The title of the study indicates that it is a study of golimumab for treating patients with active PsA: “A Study of Golimumab in Participants with Active Psoriatic Arthritis.” EX1011, 1.

283. In addition, *NCT673-V23* disclosed the following primary purpose: “to evaluate the efficacy of intravenously (administration of a fluid into the vein) administered golimumab 2 milligram per kilogram (mg/kg) in participants with active psoriatic arthritis (a chronic inflammatory arthritis that is associated with psoriasis). EX1011, 3. The primary endpoint of the study was the “Percentage of Participants who Achieve an American College of Rheumatology (ACR) 20 Response at Week 14,” which is a particular degree of efficacy in treating PsA in the study subjects. *Id.*, 4.

284. A POSA would have understood that the administration of golimumab to patients as described in *NCT673-V23* is “a method for treating a tumor necrosis factor alpha (TNF- α) related condition, wherein the TNF- α related condition is active psoriatic arthritis.”

- b. Claims 1 and 4: “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 [the Claimed Sequences], and at least one pharmaceutically acceptable carrier or diluent”**

Claim 7: “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 [the Claimed Sequences]”

285. As explained above in Paragraphs 162-163, *NCT673-V23* is the study record of a clinical trial evaluating IV administration of golimumab in patients with active PsA. As explained above in Paragraph 278, a POSA would have understood that golimumab has the Claimed Sequences. EX1001, 137-142.

286. As explained above in Paragraph 266, the specification of *US020* only discloses treatment of humans via IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter. In addition, claims 2, 5, and 9 of *US020* each further limit the safe and effective amount of golimumab to 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter. I have been informed that because claims 2, 5, and 9 depend from claims 1, 4, and 7-8, claims 1, 4, and 7-8 encompass administering 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter. Accordingly, a POSA would have understood that the claimed safe and effective amount in claim 1 (and claims 4 and 7-8) encompasses IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter.

287. *NCT673-V23* evaluates the efficacy of the IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter in patients with active PsA, and therefore discloses use of that dose. EX1011, 3-4. Therefore, *NCT673-V23* discloses administration of a safe and effective amount of golimumab.

288. In addition, a POSA would have understood that because the golimumab described in *NCT673-V23* was for IV administration, it would have to be administered in a carrier or diluent. As I discuss above in Paragraph 164, golimumab is isolated as a solid. As is also well-known and is stated in *NCT673-V23*, IV administration involves administering a fluid to a vein. EX1011, 3. In addition, *NCT673-V23* disclosed infusing a placebo, which would be a pharmaceutically acceptable carrier or diluent without golimumab. *Id.*, 3, 4. A POSA would have further understood that as a double-blind study (*id.*), the golimumab and placebo would have to look the same, meaning that the golimumab and placebo would have to be in the same volume and infused at the same rate.

289. A POSA also would have been aware that *PI2013-Aria* discloses an FDA approved dosing regimen for the treatment of RA that is the same as the dosing regimen disclosed in *NCT673-V23*. EX1032, 1 (“2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks (2.1).”). *PI2013-Aria* teaches that prior to infusion, the golimumab is diluted with 0.9% w/v sodium

chloride, a pharmaceutically acceptable carrier or diluent. EX1032, 1 (“Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration (2.3).” A POSA reading *NCT673-V23* therefore would have likewise understood that the golimumab used in *NCT673-V23* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

290. Accordingly, *NCT673-V23* discloses this element of claims 1, 4, and 7.

c. Claims 1 and 4: “wherein said composition is administered via intravenous (IV) [IV] infusion”

Claim 7: “wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion”

291. As discussed above in Paragraph 162-163, *NCT673-V23* evaluated the efficacy of 2 mg/kg of golimumab administered IV to patients with active PsA, and therefore discloses IV administration of golimumab. EX1011, 3.

- d. **Claim 1: “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 PCS)=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”;**

Claim 4: “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 $\pm$ 0.144SE”;

Claim 7: “and wherein $\geq$ 65% of patients receiving the treatment achieve ACR20 at week 14 of treatment.”

292. As discussed above in Paragraphs 271-273, in my opinion, the clinical results recited in claims 1, 4, and 7 do not separately limit the steps required by the claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT673-V23*, i.e., 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter.

293. The claimed clinical results appear to be taken from the results of the clinical trial described in Example 9 of *US020*. EX1001, 116-117:Table 8. If IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as required in claims 1, 3, and 5 and as used in the clinical trial in Example 9 produces the claimed efficacy, then IV administration of 2 mg/kg of golimumab at

weeks 0 and 4, and then every 8 weeks as reported in *NCT673-V23* must also produce the claimed efficacy. Put another way, practicing the same method should give the same results.

e. Claim 8

294. Claim 8 depends from claim 7 and further recites: “wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%.” EX1001, 143:3-6.

295. Like claim 7, the clinical result recited in claim 8 does not change the active step of the claim. As explained above, that active step encompasses IV administration of 2 mg/kg of golimumab to patients with active PsA at weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

296. Accordingly, for the reasons set forth above with respect to claim 7, in my opinion *NCT673-V23* discloses all of the steps of the method of claim 8 arranged as they are arranged in claim 8.

f. *NCT673-V23* Anticipates Claims 1, 4, 7, and 8

297. For the reasons set forth in Paragraphs 281-296, above, in my opinion *NCT673-V23* discloses all of the steps of the methods of claims 1, 4, 7, and 8, arranged as they are arranged in the claims.

2. Claims 2, 5, and 9

298. Claims 2, 5, and 9 depend from claims 1, 4, and any one of claims 7-8, respectively, and add that “said composition is administered such that said anti-

TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter,” or that “said antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter,” EX1001, 141:61-64, 142:53-56, 143:8-11.

299. *NCT673-V23* discloses IV infusion of golimumab, 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter. EX1011, 3. *NCT673-V23* does not, however, expressly state that the golimumab was administered over 30 $\pm$ 10 minutes

300. In my opinion, a POSA would have been aware of *PI2013-Aria* and its disclosure that IV golimumab for treating RA is also administered 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter, and is infused “over 30 minutes.”

EX1032, 1. With this awareness in mind, a POSA reading *NCT673-V23* would have understood that the 2 mg/kg dose, infused at weeks 0, 4, and every 8 weeks thereafter, described in *NCT673-V23* also would have been infused over a period of approximately 30 minutes.

301. For this reason and the reasons above with respect to claims 1, 4, and 7-8, in my opinion a POSA would have viewed *NCT673-V23* as disclosing all of the elements of claims 2, 5, and 9.

3. Claims 3, 6, and 10

302. Claims 3, 6, and 10 depend from claims 1, 4, and 7, respectively, and further recite administering the composition (claims 3, 6) or antibody (claim 10)

“with or without methotrexate (MTX).” EX1001, 141:65-67, 142:56-58, 143:12-14.

303. *NCT673-V23* does not require MTX and thus discloses administration “without” MTX.

C. Claims 1-10 are Obvious Over *NCT673-V23* and *PI2013-Aria*

304. As explained above in Paragraphs 281-303, in my opinion, *NCT673-V23* discloses each of the limitations of claims 1-10 as arranged in those claims and therefore anticipates those claims. To the extent that a POSA would not have understood when reading *NCT673-V23* that the golimumab is dispersed in a pharmaceutically acceptable carrier or diluent as required by independent claims 1 and 4, that dispersion would have been obvious.

305. As explained below, when the recited clinical results are not treated as limiting the claimed method (because they do not impact the active method steps), a POSA would have been motivated to combine the teachings of *NCT673-V23* and *PI2013-Aria* to practice the subject matter of claims 1-10, and would have had a reasonable expectation of success when doing so.

306. A POSA would have understood that solid golimumab could not be infused intravenously without first being dissolved or dispersed within a liquid carrier or diluent. Further, *PI2013-Aria*, which is drawn to treating patients with the same IV dose of golimumab, teaches that prior to administration, the

golimumab solution must be diluted with a 0.9% w/v sodium chloride solution, a pharmaceutically acceptable IV diluent. EX1032, 1.

307. A POSA would have used the diluent of *PI2013-Aria* when administering the IV golimumab dose in *NCT673-V23*, and would have reasonably expected success, because (1) IV dosing requires a liquid carrier or diluent, (2) *PI2013-Aria* describes the same IV dose of golimumab used for the same purpose—to treat a TNF α related disease in humans, (3) *PI2013-Aria* is the FDA-approved prescribing information that informs doctors of the safe way to administer SIMPONI ARIA; (4) *NCT673-V23* and *PI2013-Aria* are both Janssen publications, and (5) 0.9% w/v sodium chloride solution, known as “normal saline,” was the most commonly-used human IV diluent at the time. Claims 7 and 8 do not recite this limitation and are obvious based on *NCT673-V23* alone or in combination with *PI2013-Aria*.

1. Claims 1, 4, and 7

- a. Claims 1, 4, and 7: “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”**

308. *NCT673-V23* taught a method for treating a TNF α related condition, wherein the TNF related condition is active PsA. More specifically, *NCT673-V23* taught that Janssen had sponsored a clinical trial titled “A Study of Golimumab in Participants with Active Psoriatic Arthritis” in which the purpose of the study was

to evaluate the efficacy of golimumab administered IV at a dose of 2 mg/kg in subjects with active PsA. EX1011, 1, 3.

- b. **Claims 1 and 4: “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 [the Claimed Sequences], and at least one pharmaceutically acceptable carrier or diluent”**

Claim 7: “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 [the Claimed Sequences]”

309. As explained above, *NCT673-V23* taught administering golimumab intravenously at a dose 2 mg/kg administered at week 0, 4, and then every 8 weeks thereafter. EX1011, 3.

310. As explained in Paragraphs 278 above, the Claimed Sequences encompass golimumab, because golimumab has those sequences.

311. With respect to a safe and effective amount, claims 2, 5, and 9 recite administering IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter, meaning that this is a safe and effective amount. This is also the dose and dosing schedule used in Example 9 of *US020*. Moreover, *NCT673-V23* taught Janssen’s intent to treat PsA by administering the same amount on the same dosing schedule. EX1011, 4. *NCT673-V23* also used the same dose and dosing schedule as Janssen’s FDA-approved label for IV golimumab, *PI2013-Aria*. EX1011, 3-4.

312. A POSA would have been motivated to use this dosing regimen as a treatment for active PsA with a reasonable expectation of this being a safe and effective amount because: (a) it is the dosing regimen taught in Janssen's *NCT673-V23*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US020* (EX1011, 2-3); and (b) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

313. With respect to the recited "at least one pharmaceutically acceptable carrier or diluent," while *NCT673-V23* does not expressly state that the IV golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, it taught that IV administration is the administration of a fluid to a vein, and that the placebo would be an infusion (EX1014, 5, 6-7), which a POSA would have understood is a pharmaceutically acceptable carrier or diluent without golimumab. Based on these teachings, a POSA would have understood that to administer golimumab as an IV infusion, the golimumab would also have been dispersed in a pharmaceutically acceptable carrier or diluent.

314. A POSA also would have known from *PI2013-Aria* that the same IV concentration of golimumab, 2 mg/kg, had been approved for the treatment of RA wherein the prescribing information requires dilution of the golimumab with 0.9% w/v sodium chloride: "Dilution of supplied SIMPONI ARIA solution with 0.9%

w/v sodium chloride is required prior to administration.” EX1032, 1. Moreover, a POSA would have known that 0.9% sodium chloride, known as “normal saline,” was a commonly used diluent at the time.

315. It would have been obvious to a POSA to use the 0.9% w/v sodium chloride carrier taught in *PI2013-Aria* as the carrier for a golimumab composition for IV administration for the treatment of PsA, as taught in *NCT673-V23*, because *PI2013-Aria* and *NCT673-V23* are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or PsA, respectively).

316. A POSA would have used the diluent of *PI2013-Aria* in the clinical protocol of *NCT673-V23* with a reasonable expectation of success for the same reason, *i.e.*, because they are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (PsA or RA, respectively). EX1011, 3, 4; EX1032, 1, 3.

317. For the above reasons, based on the teachings of *NCT673-V23* and *PI2013-Aria*, a POSA would have found it apparent to administer a composition

comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising the Claimed CDR Sequences, such as golimumab, and at least one pharmaceutically acceptable carrier or diluent.

c. Claims 1 and 4: “wherein said composition is administered via intravenous (IV) [IV] infusion”

Claim 7: “wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion”

318. As discussed above, *NCT673-V23* evaluated the efficacy of 2 mg/kg of golimumab administered IV to patients with active PsA, and therefore discloses IV administration of golimumab. EX1011, 3.

d. Claim 1: “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 PCS)=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”;

Claim 4: “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 $\pm$ 0.144SE”;

Claim 7: “and wherein $\geq$ 65% of patients receiving the treatment achieve ACR20 at week 14 of treatment.”

319. As discussed above in Paragraphs 271-273, in my opinion, the clinical results recited in claims 1, 4, and 7 do not separately limit the steps required by the

claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT673-V23*, *i.e.*, 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter, which is encompassed by claims 1, 4, and 7. Accordingly, those clinical results do not impact my obviousness analysis.

320. Moreover, in my opinion, there is nothing in the active steps of the claims when administering golimumab, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter, that would give a different result than practicing the method taught in *NCT673-V23*, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter.

321. For the above reasons, the combined teachings of *NCT673-V23* and *PI2013-Aria* would have motivated a POSA to practice the subject matter of claims 1, 4, and 7 with a reasonable expectation of success. Thus, claims 1, 4, and 7 would have been obvious.

2. Claim 8

322. Claim 8 depends from claim 7 and further recites: “wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment have a treatment with a difference (improvement compared to placebo) of about 50%.”

323. Claim 8 is obvious for the same reasons as set forth above for claim 7.

3. Claims 2, 5, and 9

324. Claims 2, 5, and 9 depend from claims 1, 4, and any one of 7-8, respectively, and further recite that the composition (claims 2 and 5) or the anti-TNF- α antibody (claim 9) is administered such that said anti-TNF- α antibody “is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at weeks 0 and 4, then every 8 weeks (q8w) thereafter.” *PI2013-Aria* teaches that dosing regimen. As explained above, *NCT673-V23* and *PI2013-Aria* are both Janssen publications and teach administration of the same anti-TNF drug (golimumab), with the same route of administration (IV), dosage (2 mg/kg), and dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter) to treat a TNF α related condition. EX1011, 3, 4; EX1032, 1, 3. *PI2013-Aria* also expressly teaches that the golimumab is infused over 30 minutes. EX1032, 1, 3, 4.

325. A POSA would have been motivated to use this dosing regimen, including the 30-minute infusion time, as a treatment for active AS with a reasonable expectation of this being a safe and effective amount because: (1) it is the dosing regimen taught in Janssen’s *NCT673-V23*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US020* (EX1011, 2-3);

and (2) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

326. For the above reasons and the reasons set forth in Paragraphs 304-323, the combined teachings of *NCT673-V23* and *PI2013-Aria* would have motivated a POSA to practice the subject matter of claims 2, 5, and 9 with a reasonable expectation of success. Thus, claims 2, 5, and 9 would have been obvious.

4. Claims 3, 6, and 10

327. Claim 3 depends from claims 1-2, claim 6 depends from claims 4-5, and claim 10 depends from claims 7-8. Claims 3, 6, and 10 add the limitation that the anti-TNF- α antibody is “administered with or without methotrexate (MTX).” This added recitation provides two options, that the anti-TNF α antibody is administered with MTX or that it is administered without MTX. As explained in Paragraph 279, the optional choice of administering MTX does not limit the claims.

328. Also, as explained above with respect to claims 1, 4, and 7, treatment without MTX would have been obvious to a POSA because *NCT673-V23* does not require MTX, and thus teaches administration “without” MTX.

329. For the above reasons and the reasons given above with respect to claims 1-2, 4-5, and 7-8, the subject matter of claims 3, 6, and 10 would have been

obvious to a POSA in view of the combined teachings *NCT673-V23* and *PI2013-Aria*.

D. Claims 1-10 are Obvious Over the Combination of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*

330. In my opinion, if the clinical results recited in claims 1, 4, 7, and 8 were treated as limitations, even though they do not impact any of the active method steps in the claims, claims 1-10 would have been obvious over the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*.

331. In Paragraphs 281-303, I explained why *NCT673-V23* anticipates claims 1-10.

332. In Paragraphs 304-329, above, I explained why, when the recited clinical results are not treated as limitations, claims 1-10 would have been obvious to a POSA in view of the combined *NCT673-V23* and *PI2013-Aria*.

333. Below I explain why the recited results in claims 1-10 would have been obvious over to a POSA the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*, thus rendering obvious claims 1-10 of *US020*.

1. **Claim 1: 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 PCS)=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”**

334. Claim 1 recites achieving, at week 14 of treatment with the claimed anti-TNF- α antibody, a recited mean change from baseline in one or more of HAQ-DI, enthesitis, dactylitis, SF-36 PCS, and SF-36 MCS. Each recited mean change is presented with an associated standard deviation.

335. The fact that the claims recite a mean change from baseline would have indicated to a POSA that the claims recite clinical results from a population of patients, not just one patient. The fact that the mean change from baseline is recited with a standard deviation claims also would have indicated to a POSA that the claims recite clinical results from a population of patients, not just one patient.

336. The mean change from baseline results recited in claim 1, and their associated standard deviations, indicate that the results cover a range of mean changes, not just a single value. As explained in paragraphs above, based on general statistical principles, the standard deviation indicates that about 68% of subjects would fall within one standard deviation of the specified mean.

337. Applying these general statistical principles to the recited mean change in HAQ-DI and its standard deviations results in the following, which is further evidence there are no clinically meaningful differences between the efficacy data in GO-REVEAL for SIMPONI and the claimed regimen:

- HAQ-DI = -0.6 ± 0.53 actually means that 68% of subjects in the given cohort have a change from baseline in HAQ-DI that ranges from -1.13 to -0.07, which is calculated by subtracting 0.53 from -0.6 ($-0.6 - 0.53 = -1.13$) and adding 0.53 to -0.6 ($-0.6 + 0.53 = -0.07$).

338. Using the same methodology with the remaining mean changes recited in claim 1 results in the following:

- Enthesitis = -1.87 ± 1.75 actually means that 68% of subjects in the given cohort have a change from baseline in enthesitis that ranges from -3.62 to -0.12;
- Dactylitis = -7.8 ± 8.57 actually means that 68% of subjects in the given cohort have a change from baseline in dactylitis that ranges from -16.37 to 0.77;
- SF-36 PCS = 8.65 ± 7.6 actually means that 68% of subjects in the given cohort have a change from baseline in SF-36 PCS that ranges from 1.05 to 16.25; and
- SF-36 MCS = 5.33 ± 9.95 actually means that 68% of subjects in the given cohort have a change from baseline in SF-36 MCS that ranges from -4.62 to 15.28.

339. While *NCT673-V23* does not report the results recited in claim 1, it teaches that such results will be determined as part of the clinical study. More specifically, *NCT673-V23* teaches secondary outcome measures include the

following: (1) change from baseline in HAQ-DI at week 15; and (2) change from baseline in SF-36 PCS at week 14. EX1011, 4. That teaching would have motivated a POSA to assess the efficacy of the claimed method using the parameters recited by claim 1.

340. The recited parameters are standard clinical endpoints that are assessed when looking at the efficacy of TNF α therapies, such as treatment with golimumab.

341. *WO213* taught measures of efficacy of TNF α inhibitors using standard parameters, including HAQ-DI, dactylitis score, enthesitis score, and a modified version of the total Sharp Score. *See, e.g.*, EX1025, 62:6-63:24; 119:4-11; 126:21-28.

342. Moreover, a POSA would also have expected the clinical protocol described in *NCT673-V23* to achieve the efficacy of SC and IV golimumab as reported in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*.

343. For example, *GO-REVEAL* reported the results of treating patients with active PsA with 50 mg or 100 mg SC golimumab. Patients who received either dose of SC golimumab received benefit at week 14. *GO-REVEAL* concluded that patients “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.” EX1041, 984. The patients also had “significantly improved active PsA and associated skin disease.” *Id.*

344. Patients in *GO-REVEAL* demonstrated improvements in two of the claimed clinical results:

Patients in both golimumab groups had significantly improved HAQ scores at week 24 (major secondary end point), with a mean±SD change from baseline of 0.33 ± 0.55 and 0.39 ± 0.50 for golimumab 50 mg and golimumab 100 mg, respectively, versus -0.01 ± 0.49 for patients in the placebo group ($P < 0.001$ for both comparisons). Patients in the golimumab 50 mg group and patients in the golimumab 100 mg group also had significant improvement in the PCS component of the SF-36 at week 14 (major secondary end point) ($P < 0.001$), with respective mean±SD changes of 6.53 ± 8.88 and 7.85 ± 9.55 versus 0.63 ± 7.68 for placebo.

EX1041, 980.

345. In my opinion, the results reported in *GO-REVEAL* are not different from the claimed results in any clinically meaningful way. Based on these results, FDA approved SIMPONI as safe and effective for the treatment of active PsA. EX1015, 1; EX1041, 979, 984.

346. It was also understood that IV SIMPONI ARIA, which has the same dose and dosing schedule as *NCT673-V23* and the claims, had a similar efficacy of SIMPONI, is delivered subcutaneously. EX1032, 1; EX1050, 4; *see also* EX1014 (clinical trial for the treatment of AS using the same dose and dosing schedule for IV golimumab). Because Janssen designed the IV dosing regimen to produce

minimum trough levels of golimumab that are similar or higher than SIMPONI, to ensure equivalent efficacy, it is not unexpected that SC and IV golimumab have similar efficacies. EX1012, Supplemental Online Text, 1. Accordingly, it is my opinion a POSA would have expected that SIMPONI ARIA would also be effective at treating PsA.

347. A POSA would have also known that other anti-TNF α therapies for the treatment of PsA also achieved similar clinical results. *WO213* notes that anti-TNF α antibody therapies generally met or exceeded claimed efficacy parameters. *E.g.*, EX1025, 71:28-72:8.

348. Example 11 of *WO213* studied the safety and efficacy of adalimumab, a TNF α antibody, in the treatment of patients with PsA who had failed disease-modifying antirheumatic drug therapy. EX1025, 111:23-126:4.

349. Table 42 of Example 11 of *WO213* reports several measures of efficacy, including mean change from baseline at week 12 in HAQ-DI, SF-36 PCS (on a 0-100 scale) and SF-36 MCS (on a 0-100 scale). EX1025, 117-118, Table 42. Table 42 reports the following changes from baseline at week 12:

- HAQ-DI: -0.3 ± 0.5 SD
- SF-36 PCS (0-100): 5.7 ± 8.5
- SF-36 MCS (0-100): 1.1 ± 7.4 . *Id.*

Id., 119:8-11.

350. The HAQ-D1 clinical score of -0.3 ± 0.5 SD overlaps with the claimed efficacy of -0.6 ± 0.53 SD. *Id.*, 117-118.

351. *WO213* noted that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents, including adalimumab. EX1025, 44:37-45:10.

352. In addition, a POSA would not have considered small differences between the claimed parameters and the clinical data reported for prior-art golimumab treatment as being clinically significant.

353. As I discuss above in Paragraph 245-247, Janssen does not appear to have conducted a head-to-head study of SC and IV golimumab. A POSA would have understood that a head-to-head study is the only way of conclusively determining whether differences between clinical trials of two different treatments are clinically significant. EX1034, 114; EX1051, 3 (*Industry Guidance*); EX1034, 134 (“In general, two adequate and well-controlled superiority trials are needed to support a comparative efficacy claim.”)

354. As I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. That analysis supports my view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy, stating that there were “no statistical differences in efficacy

between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” EX1050, 6.

355. Further, as I discuss in Paragraphs 93-96, a POSA would have understood that the claimed IV dose would produce an average drug exposure—*i.e.*, bioavailability, $C_{\max}$ and AUC—significantly greater than that of SC golimumab. Thus, it would not have been unexpected to a POSA that administering golimumab intravenously would result in a somewhat better clinical outcome in some patients.

356. For the above reasons, and the reasons provided in Paragraphs 304-321, the subject matter of claim 1, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*. Claims 2 and 3, which depend from claim 1, do not recite any additional clinical results, and therefore would have been obvious to a POSA for the same reasons as claim 1.

2. Claim 4: “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”

357. For the same reasons as explained with respect to claim 1 in Paragraphs 334-339, because claim 4 recites mean results and a standard error, it means that the results are from many patients, not just one. The recited mean

change from baseline in vdH-S at week 24 of 0.36 ± 0.144 SE would include a range of mean changes from 0.216 to 0.504.

358. While *NCT673-V23* does not report a mean change from baseline in vdH-S at week 24, it teaches that change in baseline in total modified vdH-S score at week 24 will be determined as part of the clinical study as a secondary outcome measure. EX1011, 4. A POSA would have thus been motivated to measure the resulting van der Hejde-Sharp score.

359. *GO-REVEAL* reported modified Sharp/van der Heijde score [“SHS”] radiographic progression results, at week 24, for patients in the 50mg, 100mg, and placebo groups receiving methotrexate at baseline, at week 24, $-0.34 \pm 1.10\%$, $-0.16 \pm 1.36\%$, and $0.22 \pm 1.25\%$ of patients, respectively. EX1042, 2504-05. According to *GO-REVEAL*, “significantly more patients in the golimumab 50 mg or 100 mg groups had no progression in radiographic scores, defined by change from baseline in the total PsA-modified SHS ≤ 0 , versus placebo.” *Id.*, 2512.

360. In addition, Example 12 of *WO213* reports a mean change from baseline in the modified version of the total Sharp Score (“mTSS”) at week 24: 1.0 for placebo (n=152), and -0.2 for adalimumab (n=144) ($p < 0.001$). EX1025, 127:8-11.

361. Given the efficacy reported in the prior art, it is my opinion that a POSA would have reasonably expected that the claimed dosing regimen would be

effective and would achieve mean changes from baseline in vdH-S at week 24 similar to the claimed “mean change from baseline in van der Hejde-Sharp score (vdH-S)=-0.36±0.144 SE.”

362. As discussed above as to the analysis of claim 1, a POSA would not regard the small differences between the mean changes in van der Hejde-Sharp score in the claims and the score reported in *GO-REVEAL* as being clinically meaningful as the claimed score is not the product of a head-to-head study of SIMPONI versus SIMPONI ARIA for PsA. Thus, a POSA reviewing the data in *GO-REVEAL* and *WO213* would have expected the clinical efficacy to be similar to that of claim 4. In addition, as also described above as to claim 1, because of the higher drug exposure of the IV versus SC formulation, it is my opinion that a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy from the IV formulation than the SC.

363. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. Although it does not discuss the Van der Hejde-Sharp score, it still confirmed that SC and IV therapies had equivalent efficacy, as there was no statistically significant differences with the other parameters reported. EX1050, 4.

364. For the above reasons, and the reasons provided in Paragraphs 304-321, the subject matter of claim 4, including the recited result, would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*. Claims 5 and 6, which depend from claim 4, do not recite any clinical results, and therefore would have been obvious to a POSA for the same reasons as claim 4.

3. Claim 7: “wherein $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment”

Claim 8: “The method according to claim 7, wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.”

365. While *NCT673-V23* does not report the percentage of patients achieving ACR20 at week 14 of treatment, it teaches that the percentage of participants who achieve ACR20 at week 14 will be determined as part of the clinical study, as the primary outcome measure. EX1011, 4.

366. *NCT673-V23* would have motivated a POSA to apply the claimed dosing regimen to patients with active PsA, and to measure the resulting ACR20 score in accord with the claims. A POSA would have been motivated to consider the results in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*, because they all concern golimumab and other TNF- α antibodies. The data in those references would have caused the POSA to expect the clinical efficacy to be similar to the claimed parameter.

367. As discussed above in Paragraph 183, *GO-REVEAL* disclosed that 51% of the PsA patients administered 50 mg golimumab obtained an ACR20 score at week 14, compared to only 9% of subjects administered placebo, which is a difference of 42%. EX1041, 979.

368. As also discussed above in Paragraph 203, Example 5 of *WO213* teaches that 66% of subjects who had PsA for 2-5 years and were treated with adalimumab achieved ACR20 at week 24. EX1025, 90:Table 11.

369. Example 13 of *WO213* reports preliminary results of a study in real-life clinical practice, of the safety and efficacy of adalimumab in subjects with active PsA. *Id.*, 131-132. Table 48 of Example 13 reports that 72% of subjects achieved ACR20 at week 12. *Id.*, 133.

370. *WO213* also teaches that the TNF α inhibitor achieves an ACR20 response from 59% to 75% for PsA. *Id.*, 2:22-3:8.

371. *PI2015-Simponi* discloses that TNF α has the same mechanism of action in RA, AS, and PsA (EX1015, 18), and that when golimumab is administered subcutaneously, the same dose is effective at treating AS, RA, and PsA: 50 mg administered once per month. *Id.*, 1, 4.

372. In view of the above TNF α inhibitor teachings and results, it would have been obvious to a POSA that $\geq 65\%$ of patients would achieve ACR20 at week 14 of treatment with golimumab. Accordingly, the subject matter of claim 7 would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213*.

373. As explained above, Example 13 of *WO213*, which taught that 72% of subjects in actual clinical practices achieved ACR20 at 12 weeks, does not include

a placebo comparison, which is not surprising because the subjects were already receiving treatment in the clinic. EX1025, 131-133, Table 48. In view of 72% of subjects achieving ACR20 at week 12, and *WO213* having taught that adalimumab is effective as a TNF α inhibitor for the treatment of active PsA, it would have been obvious to a POSA that a TNF α inhibitor, such as golimumab, could result in $\geq 65\%$ of subjects achieving ACR20 at week 14, with a treatment difference/improvement compared to placebo of about 50%.

374. Given this reported efficacy, a POSA would have reasonably expected that the claimed dosing regimen would be effective and would achieve ACR20 scores at week 14 similar to the claimed “ $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%.” In my view, a POSA would not regard the small differences between the week-14 ACR20 scores in the claims and those reported in *GO-REVEAL* as being clinically meaningful, since the claimed scores are not the product of a head-to-head study of SIMPONI versus SIMPONI ARIA for PsA. Further, given the higher drug exposure of the IV versus SC formulation (*see* Paragraphs 93-96), a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy from the IV formulation than the SC.

375. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. The meta-analysis states that there were “no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” *Id.*, 6. That analysis supports my view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy.

376. A POSA would have combined the teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213*, and had a reasonable expectation of success for the same reasons as provided in Paragraphs 334-355, above.

377. For the above reasons, and the reasons provided in Paragraphs 304-323, the subject matter of claims 7 and 8, including the recited result, would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213*. Claims 9 and 10, which depend from “any one of claims 7-8,” do not recite any clinical results, and therefore would have been obvious to a POSA for the same reasons as claims 7 and 8.

E. Secondary Considerations

378. During prosecution, Applicant argued that the claimed invention yielded surprising and unexpected results. EX1007, 32. As explained below, in my opinion, the results were not surprising or unexpected.

379. Applicant stated the following during prosecution: “it is demonstrated in the present application that IV golimumab demonstrated clinically meaningful and surprisingly significant improvements of disease activity and physical function, skin psoriasis clearance, reduction in dactylitis and enthesitis, HRQoL and inhibition of structural progression.” *Id.* In support of this allegation, applicant pointed to data in Table 8 of *US020*. *Id.*; EX1001, Table 8.

380. The data in Table 8, to which applicants pointed, was generated in the clinical trial of Example 9, which assessed the effect of IV administration of golimumab 2 mg/kg in subjects with active PsA. EX1007, 32; EX1001, Table 8.

381. Citing Table 8 and paragraph [324] (which corresponds to *US020* 84:1-22), Janssen argued that at week 14, 75.1% of subjects receiving IV golimumab achieved ACR20 by 14 weeks compared to only 51% of subjects receiving SC golimumab. EX1007, 32-33; EX1001, Table 8, 86:18-39.

382. Based on this data, Janssen argued to the patent office that the results achieved by the claimed method could not have been expected based on the

teachings of the *Inman* and *Doyle* references upon which the examiner's obviousness arguments had relied. EX1007, 33.

383. I have been informed that to demonstrate unexpected results, the applicant is supposed to compare the results achieved by the claimed subject matter to the closest prior art. In my opinion, the closest prior art is *NCT673-V23*, which used the same 2 mg/kg IV golimumab dose and frequency as claimed in *US020* and indicated that many of the clinical outcomes claimed in *US020* would be measured during the clinical trial. EX1011, 4.

384. Janssen compared its results to the teachings of *Inman* and *Doyle*. Those are not the closest prior art because, unlike *NCT673-V23*, neither *Inman* nor *Doyle* assessed administration of the same 2 mg/kg IV golimumab dose and frequency as claimed in *US020*. Both *Inman* and *Doyle* report on studies in which SC golimumab is administered. EX1016, 3403; EX1035, 1214-1215.

385. In addition, during prosecution, Janssen argued that IV golimumab provided surprising results relative to SC golimumab. EX1007, 32-33 (Office Action response dated Nov. 5, 2020). That argument is not consistent with Janssen's dealings with FDA while seeking approval for Simponi Aria for treating RA.

386. During review of the Simponi Aria BLA, FDA raised concerns about the adequacy of the data Janssen submitted for its IV golimumab. EX1034, 114.

According to FDA, Janssen “proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons.” *Id.* The FDA responded that “determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen.” *Id.* As demonstrated by FDA’s statements in *CDER Review* (*see* Paragraphs 242-248), it appears that Janssen never directly compared SC administration to IV administration. EX1034, 114; *see also* EX1032, 15 (“Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.”) As shown in *WO213*, the results obtained in clinical trials can vary based on, for example, the patient population or the length of time a subject has had active PsA. EX1025, 90:25-28, Table 11 (reporting that 46% of subjects with PsA for less than 2 years achieved ACR20, while 66% subjects with PsA from 2-5 years achieved ACR20).

387. It is inconsistent for Janssen to propose reliance on SC efficacy data when seeking FDA approval for IV golimumab, but then argue that the results obtained with IV golimumab are unexpectedly superior to SC golimumab. Without a head-to-head study, Janssen’s argument regarding unexpected superiority is not supported.

388. I reserve the right to respond to any allegations that secondary considerations support the validity of the challenged claims.

VIII. DETAILED OPINIONS REGARDING *US824*

A. The Claims of *US824*

389. *US824* issued with 7 claims. Claims 1, 3, and 5 are independent claims, and claims 2, 4, and 6-7 are dependent claims.

390. In conducting my analysis, I applied the following claim constructions.

1. “Treating” (Claims 1, 3, and 5)

391. Claims 1, 3, and 5 have an introductory phrase, “[a] method for treating a [tumor necrosis factor alpha (TNF- α) / TNF- α] related condition.”

392. In my view, a POSA would not view the term “treating” as limiting because it does not change how the actual steps of the method of treating are performed.

393. A POSA would have understood that the only active steps recited in the independent claims are “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 comprising [the Claimed CDR Sequences] wherein said composition is administered via intravenous (IV) infusion [and] wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter.” Thus, the independent claims require administering a safe and effective amount and then

recite that amount, *i.e.*, 2 mg/kg administered IV over 30±10 minutes at week 0, 4, and every 8 weeks thereafter. In addition, 2 mg/kg administered IV over 30±10 minutes at week 0, 4, and every 8 weeks thereafter is the only dosing regimen disclosed in *US824* for treating humans. EX1003, 3-8 and Example 9.

394. In my opinion, in view of the language of the claims and the disclosures in the specification, the term “treating” does not in any way limit how a POSA would practice the active steps of claimed methods because it does not modify the safe and effective amount of the anti-TNF α antibody or how it is administered.

395. Moreover, to the extent that the term “treating” is deemed to limit the claims in any way, a POSA would have understood the term “treating” means to administer the claimed dosage to a patient regardless of the clinical outcome, because *US824* teaches that not all golimumab treated patients with active PsA experience a clinical benefit. For example, claim 5 acknowledges that as many as 35% of patients may not achieve an ACR20 at week 14. Moreover, when treating a particular patient with active PsA, it cannot be predicted how that particular patient will respond to the treatment.

2. “Administering to a subject”

396. Independent claims 1, 3, and 5 all recite “administering to a subject having active psoriatic arthritis.” A POSA would have understood that

administering to “a subject” encompasses administering to a single subject, i.e., a single patient.

3. Claimed Results Do Not Limit Claimed Method of Treatment

397. Independent claims 1, 3, and 5 recite the following clinical outcomes:

- Claim 1: “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 PCS)=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”;
- Claim 3: “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”;
- Claim 5: “wherein $\geq$ 65% of patients receiving the treatment achieve ACR20 at week 14 of treatment.”

398. In addition, claim 6, which depends on claim 5, adds the following:

“wherein said $\geq$ 65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%.”

399. These claimed results appear to be the clinical responses reported in Table 8 of Example 9 in *US824, EX1003*, 114.

400. Many of the claimed results pertain to a mean change from baseline and a statistical analysis obtained from a cohort of patients as opposed to a single

patient. For example, the claimed results include mean changes from baseline (claims 1 and 3), standard deviations/SD (claim 1), and standard error/SE (claim 3). EX1003, claim 1, 3.

401. As an initial matter, as explained above, the claims expressly encompass administering the anti-TNF α antibody to a patient, *i.e.*, a single patient. Yet the recited results pertain to mean changes from baseline and other statistics that could only be obtained from analysis of a larger cohort of subjects, treated for at least 14 weeks, with data then collected and analyzed, such as in this case, the subjects in the clinical trial described in Example 9. These statistical results in the claims appear to come from the clinical trial described in the specification, in which 239 subjects received placebo and 241 subjects received 2 mg/kg golimumab. EX1001, 114:Table 8. A POSA would have understood that the clinical result of treating a single patient does not provide a mean, cannot be used to determine a standard deviation or standard error, and is therefore not applicable to the claimed results.

402. A POSA also would have understood that when treating a particular patient with a new biologic such as golimumab, one cannot predict how that particular patient with active PsA will respond to the treatment. The claims of *US824* acknowledge as much. For example, claim 5 recites that “ $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment.” EX1003, claim

5. That means that at week 14, as many as 35% of patients receiving the treatment will not achieve ACR20 at week 14. For any particular patient, before as many as 14 weeks of treatment, it would not be known whether that patient would achieve the claimed ACR20. Accordingly, a POSA would have understood that the claimed results do not limit the claimed treatment of “a subject.”

403. In addition, *US824* does not provide an explanation of how to determine the standard deviation or standard error in claims 1 and 3, respectively. In the absence of such an explanation, a POSA would have understood that the terms have their typical statistical meanings. *See, e.g.*, Paragraphs 117-120.

404. In addition, a POSA would have known that the effect of administering golimumab, including the percentage of subjects achieving ACR20, may depend on the demographics of the patient population. For example, Example 5 in *WO213* reports that 46% of adalimumab treated subjects with PsA for less than 2 years achieved ACR20 at week 24 of treatment, while 66% of subjects with PsA from 2-5 years achieved ACR20. EX1025, 90:Table 11.

4. The Term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences]” Encompasses Golimumab

405. Independent claims 1, 3, and 5 include the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences].”

US824 defines SEQ ID NOs 36 and 37 as the “Golimumab Heavy Chain (HC)”

and “Golimumab Light Chain (LC),” respectively. EX1003, 135-140. SEQ ID NO 36 encompasses the claimed heavy chain CDR sequences and SEQ ID NO 37 encompasses the claimed light CDR chain sequences. *See id.* Accordingly, a POSA would have known that the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences]” encompasses golimumab but does not exclude other antibodies.

5. Administered “with or without methotrexate”

406. Dependent claims 2, 4, and 7 add that the anti-TNF- α antibody is “administered with or without methotrexate.” A POSA would have understood that there are only two options for how the patient is treated with respect to methotrexate – either methotrexate is administered to the patient or it is not. This phrase also fails to limit independent claims 1, 3, and 5, as the word “or” causes the methotrexate to be optional. Therefore, a POSA would have understood that this phrase does not limit independent claims 1, 3, and 5 in any way.

B. *NCT673-V23* Anticipates Claims 1-7

407. As explained below, in my opinion *NCT673-V23* anticipates claims 1-7 because it discloses all of the steps required by the recited method, arranged as in the claim.

1. Claims 1, 3, and 5

- a. Claim 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”**

Claims 3 and 5: “A method for treating a TNF- α related condition, wherein the TNF- α related condition is active psoriatic arthritis, the method comprising”

408. As explained above in Paragraph 392-395, in my opinion, the term “treating” does not add any additional steps to the step of administering the golimumab. Regardless, *NCT673-V23* discloses “a method for treating a TNF related condition, wherein the TNF related condition is active psoriatic arthritis.”

409. *NCT673-V23* is the study record of a clinical study where subjects with active PsA were intravenously administered 2 mg/kg IV of golimumab. The title of the study indicates that it is a study of golimumab for treating patients with active PsA. For example, *NCT673-V23* is titled “A Study of Golimumab in Participants with Active Psoriatic Arthritis.” EX1011, 1.

410. In addition, *NCT673-V23* disclosed the following primary purpose: “to evaluate the efficacy of intravenously (administration of a fluid into the vein)

administered golimumab 2 milligram per kilogram (mg/kg) in participants with active psoriatic arthritis (a chronic inflammatory arthritis that is associated with psoriasis). EX1011, 3. The primary endpoint of the study was the “Percentage of Participants who Achieve an American College of Rheumatology (ACR) 20 Response at Week 14,” which is a particular degree of efficacy in treating PsA in the study subjects. EX1011, 4.

411. A POSA would have understood that the administration of golimumab to patients as described in *NCT673-V23* is “a method for treating a TNF related condition, wherein the TNF related condition is active psoriatic arthritis.”

b. Claims 1 and 3: “administering ... a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences], and at least one pharmaceutically acceptable carrier or diluent”

Claim 5: “administering ... a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences]”

412. *NCT673-V23* studied the efficacy of IV administration of 2 mg/kg of golimumab, which has the Claimed CDR Sequences (*see* Paragraphs 162-163) in patients with active PsA.

413. As to the claimed “safe and effective amount,” claims 1, 3, and 5 identify IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter. *NCT673-V23* disclosed that PsA patients would receive “intravenous

infusions of golimumab 2mg/kg at Weeks 0, 4, and thereafter every 8 weeks” (EX1011, 3, 4), and therefore disclosed a safe and effective amount.

414. Independent claims 1 and 3 require “at least one pharmaceutically acceptable carrier or diluent.” As I discuss above in Paragraphs 162-163, *NCT673-V23* studied the efficacy of IV golimumab. EX1011, 3. While *NCT673-V23* does not expressly state that the golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, a POSA would have known that IV administration is administration of a fluid to a vein and would require a carrier. Indeed, *NCT673-V23* disclosed the administration of a placebo infusion, which a POSA would have understood is a pharmaceutically acceptable carrier or diluent without golimumab. *Id.*, 4. A POSA would have further understood that as a double-blind study, the golimumab and placebo would have to look the same, meaning that the golimumab and placebo would have to be in the same volume and infused at the same rate.

415. A POSA also would have been aware that *PI2013-Aria* discloses an FDA approved dosing regimen for the treatment of RA that is the same as the dosing regimen disclosed in *NCT673-V23*. EX1032, 1. *PI2013-Aria* teaches that prior to infusion, the golimumab is diluted with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent. EX1032, 1. A POSA reading *NCT673-V23* therefore would have likewise understood that the golimumab used

in *NCT673-V23* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

416. Accordingly, *NCT673-V23* discloses this element of claims 1, 3, and 5.

c. **Claim 1: “wherein said composition is administered via intravenous (IV) infusion, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter”**

Claim 3: “wherein said composition is administered via IV infusion, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter”

Claim 5: “wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion, wherein said antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter”

417. *NCT673-V23* discloses IV infusion of golimumab, 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter. EX1011, 3, 4. *NCT873-V24* does not, however, expressly state that the golimumab was administered over 30 $\pm$ 10 minutes

418. In my opinion, a POSA would have been aware of *PI2013-Aria* and its disclosure that IV golimumab for treating RA is also administered 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter, and is infused over a period of approximately 30 minutes. EX1032, 1. With this awareness in mind, a POSA

reading *NCT673-V23* would have understood that the 2 mg/kg dose, infused at weeks 0, 4, and every 8 weeks thereafter, described in *NCT673-V23* also would have been infused over a period of approximately 30 minutes.

d. The Clinical Results

419. As discussed above in Paragraphs 399-402, in my opinion, the clinical results recited in claims 1, 3, and 5 do not separately limit the steps required by the claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT673-V23*, *i.e.*, 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter.

420. The claimed clinical results appear to be taken from the results of the clinical trial described Example 9 of *US824*. If IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as required in claims 1, 3, and 5 and as used in the clinical trial in Example 9 produces the claimed efficacy, then IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as reported in *NCT873-V24* must also produce the claimed efficacy. Put another way, practicing the same method should give the same results.

2. Claim 6

421. Claim 6 depends from claim 5 and adds the following limitation: “said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.” EX1003, 141:7-10.

422. In my opinion, *NCT673-V23* discloses this limitation for the same reasons as set forth above with respect to claim 5.

3. Claims 2, 4, and 7

423. Claims 2, 4, and 7 depend from claims 1, 3, and 5 respectively, and further recite that the composition (claims 1 and 3) or antibody (claim 5) is administered “with or without methotrexate (MTX).”

424. *NCT673-V23* does not require MTX and thus discloses administration “without” MTX.

C. Claims 1-7 Would have been Obvious to a POSA in View of the Combined Teachings of *NCT673-V23* and *PI2013-Aria*

425. As explained above in Paragraphs 408-424, in my opinion, *NCT673-V23* discloses each of the limitations of claims 1-7 as arranged in those claims and therefore anticipates those claims. As explained below, when the recited clinical results are not treated as limiting the claimed method (because they do not impact the active method steps), a POSA would have been motivated to combine the teachings of *NCT673-V23* and *PI2013-Aria* to practice the subject matter of claims 1-7, and would have had a reasonable expectation of success when doing so.

426. In summary, *NCT673-V23* teaches all of the elements of claims 1-7 other than explicitly teaching the use of a pharmaceutically acceptable carrier or diluent (claims 1-4), and also fails to explicitly teach the infusion time. EX1011, 1, 3, 4. *PI2013-Aria* teaches administration of the same drug as *NCT673-V23*

(golimumab), with the same route of administration (IV), dosage (2 mg/kg), and dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter), for treatment of the TNF α related condition of active RA. EX1011, 4; EX 1032, 1. *PI2013-Aria* also expressly teaches: (a) diluting the golimumab solution, prior to administration, with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent; and (b) infusing golimumab over 30 minutes. EX1032, 1.

427. A POSA would have been motivated to combine the teachings of *NCT673-V23* and *PI2013-Aria* with a reasonable expectation of success because both are Janssen publications that, as explained above, relate to treating a TNF α related condition (PsA or RA, respectively) by administering the same TNF α inhibitor (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg), and with the same dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter). EX1011, 3, 4; EX1032, 1.

1. **Claims 1, 3, and 5**

- a. **Claim 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”**

Claims 3 and 5: “A method for treating a TNF- α related condition, wherein the TNF- α related condition is active psoriatic arthritis, the method comprising”

428. *NCT673-V23* taught a method for treating a TNF related condition, wherein the TNF related condition is active PsA. More specifically, *NCT673-V23* taught that Janssen had sponsored a clinical trial titled “A Study of Golimumab in Participants with Active Psoriatic Arthritis” in which the purpose of the study was to evaluate the efficacy of golimumab administered IV at a dose of 2 mg/kg in subjects with active PsA. EX1011, 1, 3.

- b. **Claims 1 and 3: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences], and at least one pharmaceutically acceptable carrier or diluent”**

Claim 5: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences]”

429. As explained above, *NCT673-V23* taught administering golimumab intravenously at a dose 2 mg/kg administered at week 0, 4, and then every 8 weeks thereafter. EX1011, 4.

430. As explained in Paragraph 405, the Claimed CDR Sequences encompass golimumab, because golimumab has those sequences.

431. With respect to a safe and effective amount, claims 1, 3, and 5 recite administering IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter, meaning that this is a safe and effective amount. This is also the dose and dosing schedule used in Example 9 of *US824*. Moreover, *NCT673-V23* taught Janssen's intent to treat PsA by administering the same amount on the same dosing schedule. EX1011, 4. *NCT673-V23* also used the same dose and dosing schedule as Janssen's FDA-approved label for IV golimumab, *PI2013-Aria*. EX1011, 3-4.

432. A POSA would have been motivated to use this dosing regimen as a treatment for active PsA with a reasonable expectation of this being a safe and effective amount because: (1) it is the dosing regimen taught in Janssen's *NCT673-V23*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US824* (EX1011, 2); and (2) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

433. With respect to the recited "at least one pharmaceutically acceptable carrier or diluent," while *NCT673-V23* does not expressly state that the IV golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, it taught that IV administration is the administration of a fluid to a vein, and that the

placebo would be an infusion, which a POSA would have understood is a pharmaceutically acceptable carrier or diluent without golimumab. EX1011, 3, 4.

434. There is no way to administer golimumab intravenously without mixing it with some kind of carrier such as water for injection or a saline solution.

435. Based on these teachings, a POSA would have understood that to administer golimumab as an IV infusion, the golimumab would also have been dispersed in a pharmaceutically acceptable carrier or diluent.

436. A POSA also would have known from *PI2013-Aria* that the same IV concentration of golimumab, 2 mg/kg, had been approved for the treatment of RA wherein the prescribing information requires dilution of the golimumab with 0.9% w/v sodium chloride: “Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration.” EX1032, 1. Moreover, a POSA would have known that 0.9% sodium chloride, known as “normal saline,” was the most used carrier or diluent for IV infusion before the filing date of *US824*.

437. It would have been obvious to a POSA to use the 0.9% w/v sodium chloride carrier taught in *PI2013-Aria* as the carrier for a golimumab composition for IV administration for the treatment of AS, as taught in *NCT673-V23*, because *PI2013-Aria* and *NCT673-V23* are both Janssen publications and teach administration of the same drug (golimumab), with the same route of

administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or PsA, respectively).

438. A POSA would have used the diluent of PI2013-Aria in the clinical protocol of *NCT673-V23* with a reasonable expectation of success for the same reason, *i.e.*, because they are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or PsA, respectively). EX1011, 4; EX1032, 1, 3.

439. For the above reasons, based on the teachings of *NCT673-V23* and *PI2013-Aria*, a POSA would have found it apparent to administer a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising the Claimed CDR Sequences, such as golimumab, and at least one pharmaceutically acceptable carrier or diluent.

- c. **Claims 1: “wherein said composition is administered via intravenous (IV) infusion, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter”**

Claim 3: “wherein said composition is administered via IV infusion, wherein said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter”

Claim 5: “wherein said anti-TNF- α antibody is administered via intravenous (IV) infusion, wherein said antibody is administered at a dose of 2 mg/kg, over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter”

440. *NCT673-V23*, a Janssen publication, taught a dosing regimen for IV administration of golimumab to treat active PsA: IV infusions of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter (EX1011, 4), but did not expressly disclose an infusion time.

441. *PI2013-Aria*, another Janssen publication, taught the same golimumab IV dosing regimen as *NCT873-V24* for treating another TNF α medication condition, RA, and taught an infusion time of 30 minutes: “The SIMPONI ARIA dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.” EX1032, 1, 3.

442. A POSA would have been motivated to administer the 2 mg/kg IV dose of golimumab taught by *NCT673-V23* over the 30 minutes taught by *PI2013-*

Aria, with a reasonable expectation of success, because they are both Janssen publications and both teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or PsA, respectively). EX1011, 4; EX1032, 1, 3.

443. For the above reasons, based on the teachings of *NCT673-V23* and *PI2013-Aria*, a POSA would have found it apparent to administer golimumab via IV infusion at a dose of 2 mg/kg administered over 30 $\pm$ 10 minutes at Weeks 0 and 4, and then every 8 weeks (q8W) thereafter.

- d. **Claim 1: “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 ± 0.53 SD, enthesitis= -1.87 ± 1.75 SD, dactylitis= -7.8 ± 8.57 SD, Short-Form Health Survey Physical Summary score (SF-36 PCS)= 8.65 ± 7.60 SD, and Short-Form Health Survey Mental Component Summary score (SF-36 MCS)= 5.33 ± 9.95 SD”**

Claim 3: “wherein at week 24 of treatment patients treated with the anti-TNF- α antibody achieve a mean change from baseline in total modified van der Heijde-Sharp score (vdH-S)= -0.36 ± 0.144 SE”

Claim 5: “wherein $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment”

444. As discussed above in Paragraph 399-402, in my opinion the results recited in claims 1, 3, and 5 do not in any way modify the active steps in the

claimed methods of treatment, and the claims do not recite steps of measuring or determining the clinical endpoints. Accordingly, those clinical results do not impact my obviousness analysis.

445. Moreover, in my opinion, there is nothing in the active steps of the claims when administering golimumab, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter, that would give a different result than practicing the method taught in *NCT673-V23*, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter.

446. For all of the above reasons, the combined teachings of *NCT673-V23* and *PI2013-Aria* would have rendered claims 1, 3, and 5 obvious to a POSA.

2. Claim 6

447. Claim 6 depends from claim 5, and further recites that “said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.” Thus, claim 6 merely recites another aspect of the clinical response, again without impacting an active method step. Put another way, the recited result in claim 6 does not affect the active steps of the claim, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter. Accordingly, those clinical results do not impact my obviousness analysis.

448. For the above reasons, the subject matter of claim 6 would have been obvious to a POSA in view of the combined teachings *NCT673-V23* and *PI2013-Aria* for the same reason as claim 5.

3. Claims 2, 4, and 7

449. Claims 2, 4, and 7 depend from claims 1, 3, and 5 respectively, and further recite that the composition (claims 1 and 3) or antibody (claim 5) is administered “with or without methotrexate (MTX).” This added recitation provides two options, that the anti-TNF antibody is administered with MTX, or that the anti-TNF antibody is administered without MTX.

450. As explained above with respect to claims 1, 3, and 5, treatment without MTX would have been obvious to a POSA because *NCT673-V23* does not require MTX and thus teaches administration “without” MTX. As explained in Paragraph 406, the optional choice of administering MTX does not limit the claims.

451. Moreover, a POSA would have known that subcutaneous administration of golimumab was FDA approved for the treatment of active PsA with or without MTX. EX1015, 1, 4 (“SIMPONI, alone or in combination with methotrexate, is indicated for the treatment of adult patients with active psoriatic arthritis.”).

452. For the above reasons and the reasons given above with respect to claims 1, 3, and 5, the subject matter of claims 2, 4, and 7 would have been obvious to a POSA in view of the combined teachings *NCT373-V23* and *PI2013-Aria*.

D. Claims 1-7 Would have been Obvious to a POSA in View of the Combined Teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*

453. In Paragraphs 408-424, I explained why *NCT673-V23* anticipates claims 1-7. In Paragraphs 426-452, above, I explained why, when the recited clinical results are not treated as limitations, a POSA would have found claims 1-7 obvious over the combined teachings of *NCT673-V23* and *PI2013-Aria*. Below I explain why even if the recited results are treated as limitations, claims 1-7 would have been obvious over the combined teachings of *NCT673-V23*, *PI2013-Aria*, and *WO213*. Since I already addressed all of the elements of claims 1-7 other than the clinical outcomes, I only address the clinical results below.

1. **Claim 1: 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 PCS)=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”**

454. Claim 1 recites achieving, at week 14 of treatment with the claimed anti-TNF- α antibody, a recited mean change from baseline in one or more of HAQ-DI, enthesitis, dactylitis, SF-36 PCS, and SF-36 MCS. Each recited mean change is presented with an associated standard deviation.

455. The fact that the claims recite a mean change from baseline would have indicated to a POSA that the claims recite clinical results from a population of patients, not just one patient. The fact that the mean change from baseline is recited with a standard deviation claims also would have indicated to a POSA that the claims recite clinical results from a population of patients, not just one patient.

456. The mean change from baseline results recited in claim 1, and their associated standard deviations, indicate that the results cover a range of mean changes, not just a single value. As explained in Paragraph 117-120, above, based on general statistical principles, the standard deviation indicates that about 68% of subjects would fall within one standard deviation of the specified mean.

457. Applying these general statistical principles to the recited mean change in HAQ-DI and its standard deviations results in the following, which is further evidence there are no clinically meaningful differences between the efficacy data in GO-REVEAL for SIMPONI and the claimed regimen:

- HAQ-DI = -0.6 ± 0.53 actually means that 68% of subjects have a change from baseline in HAQ-DI that ranges from -1.13 to -0.07, which is calculated by subtracting 0.53 from -0.6 ($-0.6 - 0.53 = -1.13$) and adding 0.53 to -0.6 ($-0.6 + 0.53 = -0.07$).

458. Using the same methodology with the remaining mean changes recited in claim 1 results in the following:

- Enthesitis = -1.87 ± 1.75 actually means that 68% of subjects have a change from baseline in enthesitis that ranges from -3.62 to -0.12;
- Dactylitis = -7.8 ± 8.57 actually means that 68% of subjects have a change from baseline in dactylitis that ranges from -16.37 to 0.77;
- SF-36 PCS = 8.65 ± 7.6 actually means that 68% of subjects have a change from baseline in SF-36 PCS that ranges from 1.05 to 16.25; and
- SF-36 MCS = 5.33 ± 9.95 actually means that 68% of subjects have a change from baseline in SF-36 MCS that ranges from -4.62 to 15.28.

459. While *NCT673-V23* does not report the results recited in claim 1, it teaches that such results will be determined as part of the clinical study. More specifically, *NCT673-V23* teaches secondary outcome measures include the following: (1) change from baseline in HAQ-DI at week 15; and (2) change from baseline in SF-36 PCS at week 14. EX1011, 4. That teaching would have

motivated a POSA to assess the efficacy of the claimed method using the parameters recited by claim 1.

460. The recited parameters are standard clinical endpoints that are assessed when looking at the efficacy of TNF α therapies, such as treatment with golimumab.

461. *WO213* taught measures of efficacy of TNF α inhibitors using standard parameters, including HAQ-DI, dactylitis score, enthesitis score, and a modified version of the total Sharp Score. *See, e.g.*, EX1025, 62:6-63:24; 119:4-11; 126:21-28.

462. Moreover, a POSA would also have expected the clinical protocol described in *NCT673-V23* to achieve the efficacy of SC and IV golimumab as reported in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*.

463. For example, *GO-REVEAL* reported the results of treating patients with active PsA with 50 mg or 100 mg SC golimumab. Patients who received either dose of SC golimumab received benefit at week 14. *GO-REVEAL* concluded that patients “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.” EX1041, 984. The patients also had “significantly improved active PsA and associated skin disease.” *Id.*

464. Patients in *GO-REVEAL* demonstrated improvements in two of the claimed clinical results:

Patients in both golimumab groups had significantly improved HAQ scores at week 24 (major secondary end point), with a mean±SD change from baseline of 0.33±0.55 and 0.39±0.50 for golimumab 50 mg and golimumab 100 mg, respectively, versus -0.01±0.49 for patients in the placebo group ($P<0.001$ for both comparisons). Patients in the golimumab 50 mg group and patients in the golimumab 100 mg group also had significant improvement in the PCS component of the SF-36 at week 14 (major secondary end point) ($P<0.001$), with respective mean±SD changes of 6.53±8.88 and 7.85±9.55 versus 0.63±7.68 for placebo.

EX1041, 980.

465. In my opinion, the results reported in *GO-REVEAL* are not different from the claimed results in any clinically meaningful way. Based on these results, FDA approved SIMPONI as safe and effective for the treatment of active PsA.

EX1015, 1; EX1041, 979, 984.

466. It was also understood that IV SIMPONI ARIA, which has the same dose and dosing schedule as *NCT673-V23* and the claims, had a similar efficacy of SIMPONI, is delivered subcutaneously. EX1032, 1; EX1050, 4; see also EX1014, 1, 4-6 (clinical trial for the treatment of AS using the same dose and dosing schedule for IV golimumab). Because Janssen designed the IV dosing regimen to produce minimum trough levels of golimumab that are similar or higher than SIMPONI, to ensure equivalent efficacy, it is not unexpected that SC and IV

golimumab have similar efficacies. EX1012, Supplemental Online Text, 1.

Accordingly, it is my opinion a POSA would have expected that SIMPONI ARIA would also be effective at treating PsA.

467. A POSA would have also known that other anti-TNF α therapies for the treatment of PsA also achieved similar clinical results. *WO213* notes that anti-TNF α antibody therapies generally met or exceeded the claimed efficacy parameters. *E.g.*, EX1025, 71:28-72:8.

468. Example 11 of *WO213* studied the safety and efficacy of adalimumab, a TNF α antibody, in the treatment of patients with PsA who had failed disease-modifying antirheumatic drug therapy. EX1025, 111.

469. Table 42 of Example 11 of *WO213* reports several measures of efficacy, including mean change from baseline at week 12 in HAQ-DI, SF-36 PCS (on a 0-100 scale) and SF-36 MCS (on a 0-100 scale). EX1025, 117-118, Table 42. Table 42 reports the following changes from baseline at week 12:

- HAQ-DI: -0.3 ± 0.5 SD
- SF-36 PCS (0-100): 5.7 ± 8.5
- SF-36 MCS (0-100): 1.1 ± 7.4 . *Id.*

Id., 119:8-11.

470. The HAQ-DI clinical score of -0.3 ± 0.5 SD overlaps with the claimed efficacy of -0.6 ± 0.53 SD. *Id.*, 117-118; EX1042, 2516.

471. *WO213* noted that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents, including adalimumab. EX1025, 44:37-45:10.

472. In addition, a POSA would not have considered small differences between the claimed parameters and the clinical data reported for prior-art golimumab treatment as being clinically significant.

473. As I discuss above in Paragraph 245-247, Janssen does not appear to have conducted a head-to-head study of SC and IV golimumab. A POSA would have understood that a head-to-head study is the only way of conclusively determining whether differences between clinical trials of two different treatments are clinically significant. EX1034, 114; EX1051, 3; EX1034, 134 (“In general, two adequate and well-controlled superiority trials are needed to support a comparative efficacy claim.”)

474. As I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. The meta-analysis states that there were “no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” *Id.*, 6. That analysis supports my

view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy.

475. Further, as I discuss in Paragraphs 93-96, a POSA would have understood that the claimed IV dose would produce an average drug exposure—*i.e.*, bioavailability, $C_{\max}$ and AUC—significantly greater than that of SC golimumab. Thus, it would not have been unexpected to a POSA that administering golimumab intravenously would result in a somewhat better clinical outcome in some patients.

476. For the above reasons, and the reasons provided in Paragraphs 425-446, the subject matter of claim 1, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*. Claims 2 and 3, which depend from claim 1, do not recite any additional clinical results, and therefore would have been obvious to a POSA for the same reasons as claim 1.

2. Claim 3: “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”

477. For the same reasons as explained with respect to claim 1 in Paragraphs 400-403, because claim 3 recites mean results and a standard error, it means that the results are from many patients, not just one. The recited mean

change from baseline in vdH-S at week 24 of 0.36 ± 0.144 SE would include a range of mean changes from 0.216 to 0.504.

478. While *NCT673-V23* does not report a mean change from baseline in vdH-S at week 24, it teaches that change in baseline in total modified vdH-S score at week 24 will be determined as part of the clinical study as a secondary outcome measure. EX1011, 4. A POSA would have thus been motivated to measure the resulting Van der Hejde-Sharp score.

479. *GO-REVEAL* reported modified Sharp/van der Heijde score [“SHS”] radiographic progression results, at week 24, for patients in the 50mg, 100mg, and placebo groups receiving methotrexate at baseline, at week 24, $-0.34 \pm 1.10\%$, $-0.16 \pm 1.36\%$, and $0.22 \pm 1.25\%$ of patients, respectively. EX1042, 2510. According to *GO-REVEAL*, the “subjects receiving 50 mg or 100 mg golimumab had no progression in radiographic scores, defined by change from baseline in the total PsA-modified SHS ≤ 0 , versus placebo.” *Id.*, 2512.

480. In addition, Example 12 of *WO213* reports a mean change from baseline in the modified version of the total Sharp Score (“mTSS”) at week 24: 1.0 for placebo (n=152), and -0.2 for adalimumab (n=144) ($p < 0.001$). EX1025, 127:8-11.

481. Given the efficacy reported in the prior art, it is my opinion that a POSA would have reasonably expected that the claimed dosing regimen would be

effective and would achieve mean changes from baseline in vdH-S at week 24 similar to the claimed “mean change from baseline in van der Hejde-Sharp score (vdH-S)= -0.36 ± 0.144 SE.”

482. As discussed above as to the analysis of claim 1, a POSA would not regard the small differences between the mean changes in van der Hejde-Sharp score in the claims and the score reported in *GO-REVEAL* as being clinically meaningful as the claimed score is not the product of a head-to-head study of SIMPONI versus SIMPONI ARIA for PsA. Thus, a POSA reviewing the data in *GO-REVEAL* and *WO213* would have expected the clinical efficacy to be similar to that of claim 3. In addition, as also described above as to claim 1, because of the higher drug exposure of the IV versus SC formulation, it is my opinion that a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy from the IV formulation than the SC.

483. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. Although it does not discuss the van der Hejde-Sharp score, it still confirmed that SC and IV therapies had equivalent therapy, as there was no statistically significant differences with the other parameters reported. EX1050, 4.

484. For the above reasons, and the reasons provided in Paragraphs 428-446, the subject matter of claim 3, including the recited result, would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*. Claim 4, which depends from claim 3, does not recite any clinical results, and therefore would have been obvious to a POSA for the same reasons.

3. **Claim 5: “wherein $\geq 65\%$ of patients receiving the treatment achieve ACR20 at week 14 of treatment”**

Claim 6: “The method according to claim 7, wherein said $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.”

485. While *NCT673-V23* does not report the percentage of patients achieving ACR20 at week 14 of treatment, it teaches that the percentage of participants who achieve ACR20 at week 14 will be determined as part of the clinical study, as the primary outcome measure. EX1011, 4.

486. *NCT673-V23* would have motivated a POSA to apply the claimed dosing regimen to patients with active PsA, and to measure the resulting ACR20 score in accord with the claims. A POSA would have been motivated to consider the results in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*, because they all concern golimumab and other TNF- α antibodies. The data in those

references would have caused the POSA to expect the clinical efficacy to be similar to the claimed parameter.

487. As discussed above in Paragraph 183, *GO-REVEAL* disclosed that 51% of the PsA patients administered 50 mg golimumab obtained an ACR20 score at week 14, compared to only 9% of subjects administered placebo, which is a difference of 42%. EX1041, 979.

488. As also discussed above in Paragraph 203, Example 5 of *WO213* teaches that 66% of subjects who had PsA for 2-5 years and were treated with adalimumab achieved ACR20 at week 24. EX1025, 90:Table 11.

489. Example 13 of *WO213* reports preliminary results of a study in real-life clinical practice, of the safety and efficacy of adalimumab in subjects with active PsA. *Id.*, 131-132. Table 48 of Example 13 reports that 72% of subjects achieved ACR20 at week 12. *Id.*, 133.

490. *WO213* also teaches that the TNF α inhibitor achieves an ACR20 response from 59% to 75% for PsA. *Id.*, 2:22-3:8.

491. *PI2015-Simponi* discloses that TNF α has the same mechanism of action in RA, PsA, and AS (EX1015, 18), and that when golimumab is administered subcutaneously, the same dose is effective at treating PsA, RA, and AS: 50 mg administered once per month. *Id.*, 4.

492. In view of the above TNF α inhibitor teachings and results, it would have been obvious to a POSA that $\geq 65\%$ of patients would achieve ACR20 at week 14 of treatment with golimumab. Accordingly, the subject matter of claim 5 would have been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213*.

493. As explained above, Example 13 of *WO213*, which taught that 72% of subjects in actual clinical practices achieved ACR20 at 12 weeks, does not include a placebo comparison, which is not surprising because the subjects were already receiving treatment in the clinic. EX1025, 131-133, Table 48. In view of 72% of subjects achieving ACR20 at week 12, and *WO213* having taught that adalimumab is effective as a TNF α inhibitor for the treatment of active PsA, it would have been obvious to a POSA that a TNF α inhibitor, such as golimumab, could result in $>65\%$ of subjects achieving ACR20 at week 14, with a treatment difference/improvement compared to placebo of about 50%.

494. Given this reported efficacy, a POSA would have reasonably expected that the claimed dosing regimen would be effective and would achieve ACR20 scores at week 14 similar to the claimed “ $\geq 65\%$ of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%.” In my view, a POSA would not regard the small differences between the week-14 ACR20 scores in the claims and those reported in

GO-REVEAL as being clinically meaningful, since the claimed scores are not the product of a head-to-head study of SIMPONI versus SIMPONI ARIA for PsA. Further, given the higher drug exposure of the IV versus SC formulation (Paragraphs 93-96), a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy from the IV formulation than the SC.

495. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. The meta-analysis states that there were “no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” *Id.*, 6. That analysis supports my view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy.

496. A POSA would have combined the teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213* and had a reasonable expectation of success for the same reasons as provided in Paragraphs 428-446, above.

497. For the above reasons, and the reasons provided in Paragraphs 425-452, the subject matter of claims 5 and 6, including the recited result, would have

been obvious to a POSA in view of the combined teachings of *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, and *WO213*. Claim 7, which depends from claim 5, does not recite any clinical results, and therefore would have been obvious to a POSA for the same reasons.

E. Secondary Considerations

498. During prosecution, Applicant argued that the claimed invention yielded surprising and unexpected results. EX1009, 41-42. As explained below, in my opinion, the results were not surprising or unexpected.

499. Applicant stated the following during prosecution: “IV golimumab demonstrated clinically meaningful and surprisingly significant improvements of disease activity and physical function, skin psoriasis clearance, reduction in dactylitis and enthesitis, HRQoL and inhibition of structural progression.” *Id.*, 42. In support of this allegation, applicant pointed to data in Table 8 of *US824*. *Id.*; EX1003, Table 8.

500. The data in Table 8, to which applicants pointed, was generated in the clinical trial of Example 9, which assessed the effect of IV administration of golimumab 2 mg/kg in subjects with active PsA. EX1003, Table 8.

501. Citing Table 8 and paragraph [324] (which corresponds to *US824*, 84:1-22), Janssen argued that at week 14, 75.1% of subjects receiving IV

golimumab achieved ACR20 by 14 weeks compared to only 51% of subjects receiving SC golimumab. EX1009, 42; EX1003, Table 8, 84:1-22.

502. Based on this data, Janssen argued to the patent office that the results achieved by the claimed method could not have been expected based on the teachings of the *Inman* and *Doyle* references upon which the examiner's obviousness arguments had relied. EX1009, 42.

503. I have been informed that to demonstrate unexpected results, the applicant is supposed to compare the results achieved by the claimed subject matter to the closest prior art. In my opinion, the closest prior art is *NCT673-V23*, which used the same 2 mg/kg IV golimumab dose and frequency as claimed in *US824* and indicated that many of the clinical outcomes claimed in *US824* would be measured during the clinical trial. EX1011, 3, 4.

504. Janssen compared its results to the teachings of *Inman* and *Doyle*. Those are not the closest prior art because, unlike *NCT673-V23*, neither *Inman* nor *Doyle* assessed administration of the same 2 mg/kg IV golimumab dose and frequency as claimed in *US824*. *Inman* reports data for studies in which adalimumab was administered SC and *Doyle* report on studies in which SC golimumab is administered. EX1016, 3403; EX1035, 1214-1215.

505. In addition, during prosecution, Janssen argued that IV golimumab provided surprising results relative to SC golimumab. EX1009, 42 (Office Action

response dated Aug. 15, 2023). That argument is not consistent with Janssen's dealings with FDA while seeking approval for Simponi Aria for treating RA.

506. During review of the Simponi Aria BLA, FDA raised concerns about the adequacy of the data Janssen submitted for its IV golimumab. EX1034, 114. According to FDA, Janssen "proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons." *Id.* The FDA responded that "determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen." *Id.* As demonstrated by FDA's statements in *CDER Review* (see Paragraphs 242-248), it appears that Janssen never directly compared SC administration to IV administration. EX1034, 114; *see also* EX1032, 15 ("Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.") As shown in *WO213*, the results obtained in clinical trials can vary based on, for example, the patient population or the length of time a subject has had active PsA. EX1025, 90:25-28, Table 11 (reporting that 46% of subjects with PsA for less than 2 years achieved ACR20, while 66% subjects with PsA from 2-5 years achieved ACR20).

507. It is inconsistent for Janssen to propose reliance on SC efficacy data when seeking FDA approval for IV golimumab, but then argue that the results obtained with IV golimumab are unexpectedly superior to SC golimumab.

Without a head-to-head study, Janssen’s argument regarding unexpected superiority is not supported.

508. In addition, while claims 1-7 encompass administering golimumab, they are not limited to administering golimumab. The only evidence of alleged unexpected results offered by patentees, however, relates to the results of administering golimumab. Applicants offered no evidence of how any other TNF inhibitor within the scope of the claims would perform.

509. I reserve the right to respond to any allegations that objective indicia support the validity of the challenged claims.

IX. DETAILED OPINIONS REGARDING *US982*

A. The Claims of *US982*

510. *US982* issued with 10 claims. Claims 1, 4, and 7 are independent claims, and claims 2, 3, 5, 6, and 8-10 are dependent claims.

511. In conducting my analysis, I applied the following claim constructions.

B. *US982* - Claim Construction

1. “Treating” (Claims 1, 4, and 7)

512. Claims 1, 4, and 7 recite “[a] method for treating a TNF related condition.”

513. In my view, a POSA would not view the term “treating” in claims 1, 4, and 7 as limiting because it does not change how the actual steps of the method of treating are performed.

514. A POSA would have understood that the only active step recited in the independent claims is “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody having a heavy chain (HC) comprising SEQ ID NO: 36 and a light chain (LC) comprising the amino acid sequence set forth in SEQ ID NO: 37.” While claims 1, 4, and 7 do not specify the safe and effective amount, the only safe and effective amount disclosed in *US982* for treating AS in humans is 2 mg/kg administered IV over 30±10 minutes at week 0, 4, and every 8 weeks thereafter. Moreover, claim 2, which is dependent on claim 1, recites the use of that precise dosing regimen.

515. In my opinion, in view of the language of the claims and the disclosures in the specification, the term “treating” does not in any way limit how a POSA would practice the active steps of claimed methods because it does not modify the safe and effective amount of the anti-TNF antibody or how it is administered.

516. Moreover, to the extent that the term “treating” is deemed to limit the claims in any way, a POSA would have understood the term “treating” means to administer the claimed dosage to a patient regardless of the clinical outcome,

because *US982* teaches that not all golimumab treated patients with active AS experience a clinical benefit. For example, claim 7 acknowledges that as many as 35% of patients may not achieve an ASAS20 at week 16, and Table 9 reports that as of week 28, fewer than 30% of patients achieve ASDAS inactive disease. EX1004, Table 9. Moreover, when treating a particular patient with active AS, it cannot be predicted how that particular patient will respond to the treatment.

2. Claimed Results Do Not Limit Claimed Method of Treatment

517. Independent claims 1, 4, and 7 recite the following clinical outcomes:

- Claim 1: “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.”;
- Claim 4: 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) = 5.5 ± 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.”;
- Claim 7: “wherein $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”

518. In addition, claim 8, which depends on claim 7, adds the following: “wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 14 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.”

519. These claimed results appear to be the clinical responses reported in Tables 8 and 9 of Example 9 in *US982*. EX1002, Table 8, Table 9.

520. The results recited in claims 4 and 7 pertain to a mean change from baseline and a statistical analysis obtained from a cohort of patients as opposed to a single patient. For example, the claimed results include mean changes from baseline and standard deviations/SD (claim 4). EX1002, claim 4. These statistical results in the claims appear to come from the clinical trial described in the specification, in which 103 subjects received placebo and 105 subjects received 2 mg/kg golimumab. EX1002, 106:Table 8. A POSA would have understood that the clinical result of treating a single patient does not provide a mean, cannot be used to determine a standard deviation, and is therefore not applicable to the claimed results.

521. A POSA also would have understood that when treating a particular patient with a new biologic such as golimumab, one cannot predict how that particular patient with active AS will respond to the treatment. The claims of *US982* acknowledge as much. For example, claim 7 recites that “ $\geq 65\%$ of patients receiving the treatment achieve Assessment of Ankylosing Spondylitis 20

(ASAS20) at week 16 of treatment.” EX1002, claim 7. That means that at week 16, as many as 35% of patients receiving the treatment will not achieve ASAS20 at week 16. For any particular patient, before as many as 16 weeks of treatment, it would not be known whether that patient would achieve the claimed ASAS20 at week 16.

522. In addition, *US982* does not provide an explanation of how to determine the standard deviation or standard error in claim 3. In the absence of such an explanation, a POSA would have understood that the terms have their typical statistical meanings. *See, e.g.*, Paragraphs 117-120.

523. In addition, a POSA would have known that the effect of administering golimumab, including the percentage of subjects achieving any given clinical result, may depend on the demographics of the patient population. The claims do not, however, require any baseline characteristic other than having active AS. Thus, the claims encompass treating a patient with a baseline ASDAS of, for example, 2.1, who would be likely to achieve ASDAS inactive disease faster than a subject with a baseline ASDAS of 4.5. Example 5 in *WO213* reports a similar impact of demographic differences in the context of PsA, reporting that 46% of adalimumab treated subjects with PsA for less than 2 years achieved ACR20 at week 24 of treatment, while 66% of subjects with PsA from 2-5 years achieved ACR20. EX1025, 90:Table 11.

3. “at least one isolated mammalian anti-TNF antibody comprising [the Claimed Sequences]”

524. Independent claims 1, 4, and 7 include the term “at least one isolated mammalian anti-TNF antibody having [the Claimed Sequences].” *US982* defines SEQ ID NOs 36 and 37 as the “Golimumab Heavy Chain (HC)” and “Golimumab Light Chain (LC),” respectively. *EX1002*, col. 127-131. SEQ ID NO 36 encompasses the claimed heavy chain CDR sequences and SEQ ID NO 37 encompasses the claimed light chain CDR sequences. *See id.* Accordingly, a POSA would have known that the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed Sequences]” encompasses golimumab.

4. Administering “with or without Methotrexate (MTX), Sulfasalazine (SSZ) or Hydroxychloroquine (HCQ)”

525. Dependent claims 3, 6, and 10 add that the anti-TNF- α antibody is administered “with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).” A POSA would have understood that there are only two options for how the patient is treated with respect to MTX, SSZ, and HCQ, either MTX, SSZ, or HCQ is administered to the patient or it is not. This phrase also fails to limit independent claims 1, 4, and 7, as the term “or” in the phrase “with or without” makes administration of MTX, SSZ, or HCQ optional. Therefore, a POSA would have understood that this phrase does not limit independent claims 1, 4, and 7 in any way.

C. NCT873-V24 Anticipates Claims 1-10

526. Independent claims 1, 4, and 7, all claim a method of treating active ankylosing spondylitis, a TNF related condition. Each of the independent claims recites essentially the same method of administering an anti-TNF α antibody, differing only in the recited results of such administration. As explained below, *NCT873-V24* discloses all of the steps of the claimed method arranged as they are arranged in the claims.

1. Claims 1, 4, 7, and 8

- a. Claims 1, 4, and 7: “A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising”**

527. As explained above Paragraph 513-516, in my opinion, the term “treating” does not add any additional steps to the step of administering the golimumab. Regardless, *NCT873-V24* discloses “a method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis.”

528. *NCT673-V24* is the study record of a clinical study where subjects with active AS were intravenously administered 2 mg/kg IV of golimumab. The title of the study indicates that it is a study of golimumab for treating patients with active AS: “A Study of Golimumab in Participants with Active Ankylosing Spondylitis.” EX1014, 1.

529. In addition, *NCT873-V24* disclosed the following primary purpose: “to evaluate the efficacy of intravenously (administration of a fluid into the vein) administered golimumab 2 milligram per kilogram (mg/kg) in participants with active ankylosing spondylitis (chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, and often the axial skeleton, entheses, and peripheral joints). EX1014, 5. The primary endpoint of the study was the “Percentage of Participants Achieving a 20 Percent Improvement in Assessment in Ankylosing Spondylitis at Week 16,” which is a particular degree of efficacy in treating AS in the study subjects. *Id.*, 7.

530. A POSA would have understood that the administration of golimumab to patients as described in *NCT873-V24* is “a method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis.”

b. Claims 1 and 4: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody having [the Claimed Sequences], and at least one pharmaceutically acceptable carrier or diluent,”

Claim 7: “administering a safe and effective amount of at least one isolated mammalian anti-TNF antibody having [the Claimed Sequences]”

531. As explained above, *NCT873-V24* is the study record of a clinical trial evaluating IV administration of golimumab in patients with active AS. As

explained in Paragraph 524, above, A POSA would have understood that golimumab has the Claimed CDR Sequences. EX1002, 127-132.

532. As explained above in Paragraph 514, the specification of *US982* only discloses treatment of humans via IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter. In addition, claims 2, 5, and 9 of *US982* each further limit the safe and effective amount of golimumab to 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter. I have been informed that because claims 2, 5, and 9 depend from claims 1, 4, and 7-8, claims 1, 4, and 7-8 encompass administering 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter. Accordingly, a POSA would have understood that the claimed safe and effective amount in claim 1 (and claims 4 and 7-8) encompasses IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter

533. *NCT673-V23* evaluates the efficacy of the IV administration of 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter in patients with active PsA, and therefore discloses use of that dose. EX1011, 3-4. Therefore, *NCT673-V23* discloses administration of a safe and effective amount of golimumab.

534. In addition, a POSA would have understood that because the golimumab described in *NCT873-V24* was for IV administration, it would have to be administered in a carrier or diluent. As I discuss above in Paragraph 172,

golimumab is isolated as a solid. As is also well-known and is stated in *NCT873-V24*, IV administration involves administering a fluid to a vein. EX1014, 5. In addition, *NCT873-V24* disclosed infusing a placebo, which would be a pharmaceutically acceptable carrier or diluent without golimumab. *Id.*, 6. A POSA would have further understood that as a double-blind study, the golimumab and placebo would have to look the same, meaning that the golimumab and placebo would have to be in the same volume and infused at the same rate.

535. A POSA also would have been aware that *PI2013-Aria* discloses an FDA approved dosing regimen for the treatment of RA that is the same as the dosing regimen disclosed in *NCT873-V24*. EX1032, 1. *PI2013-Aria* teaches that prior to infusion, the golimumab is diluted with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent. *Id.* A POSA reading *NCT873-V24* therefore would have likewise understood that the golimumab used in *NCT873-V24* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

536. Accordingly, *NCT873-V24* discloses this element of claims 1, 4, and 7.

c. **Claims 1 and 4: “wherein said composition is administered via IV infusion”**

Claim 7: “wherein said anti-TNF antibody is administered via intravenous (IV) infusion”

537. As discussed above, *NCT873-V24* evaluated the efficacy of 2 mg/kg of golimumab administered IV to patients with active AS, and therefore discloses IV administration of golimumab. EX1014, 5, 7.

- d. **Claim 1: “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”;**

Claim 4: “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”;

Claim 7: “wherein $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”

538. As discussed above in Paragraphs 519-521, in my opinion, the clinical results recited in claims 1, 4, and 7 do not separately limit the steps required by the claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT873-V24*, i.e., 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter.

539. The claimed clinical results appear to be taken from the results of the clinical trial described Example 9 of *US982*. EX1002, 78:Example 9. If IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as required in claims 1, 3, and 5 and as used in the clinical trial in Example 9 produces the claimed efficacy, then IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as reported in *NCT873-V24* must also produce the claimed efficacy. Put another way, practicing the same method should give the same results.

e. Claim 8

540. Claim 8 depends on claim 7 and further recites: “wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.”

541. Like claim 7, the clinical result recited in claim 8 does not affect the active step of the claim. As explained above, that active step encompasses IV administration of 2 mg/kg of golimumab to patients with active PsA at weeks 0 and 4, and then every 8 weeks (q8w) thereafter.

542. Accordingly, for the reasons set forth above with respect to claim 7, in my opinion *NCT873-V24* discloses all of the steps of the method of claim 8 arranged as they are arranged in claim 8.

f. NCT873-V24 Anticipates Claims 1, 4, 7, and 8

543. For the reasons set forth in Paragraphs 527-542, above, in my opinion *NCT873-V24* discloses all of the steps of the methods of claims 1, 4, 7, and 8, arranged as they are arranged in the claims.

2. Claims 2, 5, and 9

544. Claims 2, 5, and 9 depend from claims 1, 4, and any of 7-8, respectively, and further recite that the composition or antibody is administered such that “said anti-TNF- α antibody is administered at a dose of 2 mg/kg, over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.”

545. *NCT873-V24* discloses IV infusion of golimumab, 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter. EX1014, 6-7. *NCT873-V24* does not, however, expressly state that the golimumab was administered over 30 ± 10 minutes.

546. In my opinion, a POSA would have been aware of *PI2013-Aria* and its disclosure that IV golimumab for treating RA is also administered 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter, and is infused over a period of approximately 30 minutes. EX1032, 1. With this awareness in mind, a POSA reading *NCT873-V24* would have understood that the 2 mg/kg dose, infused at weeks 0, 4, and every 8 weeks thereafter, described in *NCT873-V24* also would have been infused over a period of approximately 30 minutes.

547. For this reason and the reasons above with respect to claims 1, 4, and 7-8, in my opinion a POSA would have viewed *NCT673-V23* as disclosing all of the elements of claims 2, 5, and 9.

3. Claims 3, 6, and 10

548. Claims 3, 6, and 10 depend from claims 1, 4, and 7, respectively, and further recite administering the composition (claims 3 and 6) or antibody (claim 10) “with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).”

549. *NCT873-V24* does not require MTX, SSX, or HCQ, and thus discloses administration “without” MTX, SSX, or HCQ.

D. Claims 1-10 are Obvious Over *NCT873-V24* and *PI2013-Aria*

550. As explained above in Paragraph 527-549, in my opinion, *NCT873-V24* discloses each of the limitations of claims 1-10 as arranged in those claims and therefore anticipates those claims.

551. As explained below, when the recited clinical results are not treated as limiting the claimed method (because they do not impact the active method steps), a POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* to practice the subject matter of claims 1-10, and would have had a reasonable expectation of success when doing so.

552. In summary, *NCT873-V24* teaches all of the elements of claims 1-10 other than explicitly teaching the use of a pharmaceutically acceptable carrier or diluent (claims 1-4), and also fails to explicitly teach the infusion time. EX1014, 5-7. *PI2013-Aria* teaches administration of the same drug as *NCT873-V24* (golimumab), with the same route of administration (IV), dosage (2 mg/kg), and dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter), for treatment of the TNF α related condition of active RA. EX1014, 6-7; EX 1032, 1. *PI2013-Aria* also expressly teaches: (a) diluting the golimumab solution, prior to administration, with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent; and (b) infusing golimumab over 30 minutes. EX1032, 1.

553. A POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* with a reasonable expectation of success because both are Janssen publications that, as explained above in Paragraph 170-175 and 212, relate to treating a TNF α related condition (AS or RA, respectively) by administering the same TNF α inhibitor (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg), and with the same dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter).

1. Claims 1, 4, and 7

- a. Claims 1, 4, and 7: “A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising”**

554. *NCT873-V24* taught a method for treating a TNF related condition, wherein the TNF related condition is active AS. More specifically, *NCT873-V24* taught that Janssen had sponsored a clinical trial titled “A Study of Golimumab in Participants with Active Ankylosing Spondylitis” in which the purpose of the study was to evaluate the efficacy of golimumab administered IV at a dose of 2 mg/kg in subjects with active AS. EX1014, 1, 5.

- b. Claims 1 and 4: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody having [the Claimed Sequences], and at least one pharmaceutically acceptable carrier or diluent,”**

Claim 7: “administering a safe and effective amount of at least one isolated mammalian anti-TNF antibody having [the Claimed Sequences]”

555. As explained above, *NCT873-V24* taught administering golimumab intravenously at a dose 2 mg/kg administered at week 0, 4, and then every 8 weeks thereafter. EX1014, 6-7.

556. As explained in Paragraph 524, the Claimed Sequences encompass golimumab, because golimumab has those sequences.

557. With respect to a safe and effective amount, claims 2, 5, and 9 recite administering IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter, meaning that this is a safe and effective amount. This is also the dose and dosing schedule used in Example 9 of *US982*. Moreover, *NCT873-V24* taught Janssen's intent to treat AS by administering the same amount on the same dosing schedule. EX1014, 6-7. *NCT873-V24* also used the same dose and dosing schedule as Janssen's FDA-approved label for IV golimumab, *PI2013-Aria*. EX1014, 5-7.

558. A POSA would have been motivated to use this dosing regimen as a treatment for active AS with a reasonable expectation of this being a safe and effective amount because: (1) it is the dosing regimen taught in Janssen's *NCT873-V24*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US982* (EX1014, 4); and (2) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

559. With respect to the recited "at least one pharmaceutically acceptable carrier or diluent," while *NCT873-V24* does not expressly state that the IV golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, it taught that IV administration is the administration of a fluid to a vein, and that the placebo would be an infusion, which a POSA would have understood is a

pharmaceutically acceptable carrier or diluent without golimumab. EX1014, 5, 6-7. Based on these teachings, a POSA would have understood that to administer golimumab as an IV infusion, the golimumab would also have been dispersed in a pharmaceutically acceptable carrier or diluent.

560. There is no way to administer golimumab intravenously without mixing it with some kind of carrier such as water for injection or a saline solution.

561. A POSA also would have known from *PI2013-Aria* that the same IV concentration of golimumab, 2 mg/kg, had been approved for the treatment of RA wherein the prescribing information requires dilution of the golimumab with 0.9% w/v sodium chloride: “Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration.” EX1032, 1. Moreover, a POSA would have known that 0.9% sodium chloride, known as “normal saline,” was a commonly used diluent at the time.

562. It would have been obvious to a POSA to use the 0.9% w/v sodium chloride carrier taught in *PI2013-Aria* as the carrier for a golimumab composition for IV administration for the treatment of AS, as taught in *NCT873-V24*, because *PI2013-Aria* and *NCT873-V24* are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at

weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or AS, respectively).

563. A POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* with a reasonable expectation of success for the same reason, *i.e.*, because they are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (AS or RA, respectively). EX1014, 6-7; EX1032, 1, 3.

564. For the above reasons, based on the teachings of *NCT873-V24* and *PI2013-Aria*, a POSA would have found it apparent to administer a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising the Claimed CDR Sequences, such as golimumab, and at least one pharmaceutically acceptable carrier or diluent.

c. Claims 1 and 4: “wherein said composition is administered via IV infusion”

Claim 7: “wherein said anti-TNF antibody is administered via intravenous (IV) infusion”

565. As discussed above, *NCT873-V24* evaluated the efficacy of 2 mg/kg of golimumab administered IV to patients with active AS (EX1014, 5, 7), and therefore discloses IV administration of golimumab.

- d. **Claim 1: “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”;**

Claim 4: “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”;

Claim 7: “wherein $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”

566. As discussed above in Paragraphs 519-521, in my opinion, the clinical results recited in claims 1, 4, and 7 do not separately limit the steps required by the claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT873-V24*, i.e., 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter, which is encompassed by claims 1, 4, and 7. Accordingly, those clinical results do not impact my obviousness analysis.

567. Moreover, in my opinion, there is nothing in the active steps of the claims when administering golimumab, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter, that would give a different result than practicing the method taught in *NCT873-V24*, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter.

568. For the above reasons, the combined teachings of *NCT873-V24* and *PI2013-Aria* would have motivated a POSA to practice the subject matter of claims 2, 5, and 9 with a reasonable expectation of success.

569. For the reasons set forth above, claims 1, 4, and 7 would have been obvious to a POSA in view of the combined teachings of *NCT873-V24* and *PI2013-Aria*.

2. Claim 8

570. Claim 8 depends from claim 7 and further recites: “wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.”

Claim 8 is obvious for the same reasons as set forth above for claim 7.

3. Claims 2, 5, and 9

571. Claims 2, 5, and 9 depend from claims 1, 4, and any one of 7-8, respectively, and further recite that the composition (claims 2 and 5) or the anti-TNF antibody (claim 9) is administered such that said anti-TNF antibody “is

administered at a dose of 2 mg/kg, over 30±10 minutes, at weeks 0 and 4, then every 8 weeks (q8w) thereafter.” *PI2013-Aria* teaches that dosing regimen.

572. As explained above, *NCT873-V24* and *PI2013-Aria* are both Janssen publications and teach administration of the same anti-TNF drug (golimumab), with the same route of administration (IV), dosage (2 mg/kg), and dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter) to treat a TNF related condition (AS and RA, respectively). EX1014, 5-7; EX 1032, 1. *PI2013-Aria* also expressly teaches that the golimumab is infused over 30 minutes. EX1032, 1, 3, 4.

573. A POSA would have been motivated to use this dosing regimen, including the 30-minute infusion time, as a treatment for active AS with a reasonable expectation of this being a safe and effective amount because: (a) it is the dosing regimen taught in Janssen’s *NCT873-V24*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US982* (EX1014, 4); and (b) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

574. For the above reasons and the reasons set forth in Paragraphs 554-569, the combined teachings of *NCT873-V24* and *PI2013-Aria* would have motivated a POSA to practice the subject matter of claims 2, 5, and 9 with a reasonable expectation of success.

575. For the reasons set forth above, claims 2, 5, and 9 would have been obvious to a POSA in view of the combined teachings of *NCT873-V24* and *PI2013-Aria*.

4. Claims 3, 6, and 10

576. Claim 3 depends from claims 1-2, claim 6 depends from claims 4-5, and claim 10 depends from claims 7-8. Claims 3, 6, and 10 add the limitation that the anti-TNF- α antibody is administered “with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ). This added recitation provides two options, that the anti-TNF antibody is administered with MTX, SSX, or HCQ, or that the anti-TNF antibody is administered without MTX, SSX, or HCQ.

577. As explained above with respect to claims 1, 4, and 7, treatment without MTX, SSX, or HCQ would have been obvious to a POSA because *NCT873-V24* does not require MTX, SSX, or HCQ, and thus teaches administration “without” MTX, SSX, or HCQ. As explained in Paragraph 525, the optional choice of administering MTX, SSX, or HCQ does not limit the claims.

578. A POSA also would have known that the safety and efficacy of subcutaneously administered golimumab were evaluated in a clinical trial of patients with AS in which patients were allowed to continue stable doses of, among other things, concomitant MTX, SSZ, and/or HCQ. EX1015, 28.

579. For the above reasons and the reasons given above with respect to claims 1-2, 4-5, and 7-8, the subject matter of claims 3, 4, and 10 would have been obvious to a POSA in view of the combined teachings *NCT873-V24* and *PI2013-Aria*.

580. For the above reasons and the reasons given above with respect to claims 1-2, 4-5, and 7-8, set forth in Paragraphs 554-575, the subject matter of claims 3, 6, and 10 would have been obvious to a POSA in view of the combined teachings *NCT873-V24* and *PI2013-Aria*.

E. The Subject Matter of Claims 1-10 Would Have Been Obvious to a POSA in view of the Combined Teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*

581. In Paragraphs 527-549, I explain why *NCT873-V24* anticipates claims 1-10.

582. In Paragraphs 550-580, above, I explained why, when the recited clinical results are not treated as limitations, a POSA would have found claims 1-10 obvious over the combined teachings of *NCT873-V24* and *PI2013-Aria*. Below I explain why even if the recited results are deemed to be limitations, claims 1-10 would have been obvious over the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. Since I already addressed all of the elements of claims 1-10 other than the clinical outcomes in claim 1, I only address the clinical results below.

1. Claim 1: “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”

583. Claim 1 states the following result of the IV infusion of golimumab: “achiev[ing] an Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at 4 weeks of treatment or at 2 weeks of treatment.” Claim 2 depends from claim 1 and adds that “said composition is administered such that said anti-TNF antibody is administered at a dose of 2 mg/kg, administered over 30±10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.” I have been informed that because claim 2 depends from claim 1, claim 1 encompass administering 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter.

584. While neither *NCT873-V24* nor *PI2013-Aria* discloses the claimed ASDAS clinical outcome, that result is would have been apparent to a POSA in view of the teachings of *Van der Heijde* and *Inman*.

585. *Van der Heijde* describes the results of a phase 3 study of SC golimumab for the treatment of AS. *Van der Heijde*, when comparing the results of golimumab treatment to placebo, reported that “significantly greater proportions [of subjects receiving golimumab] had ASDAS inactive disease at weeks 14 and 24.” EX1033, 1097.

586. *Van der Heijde* reported that at week 14, 20.3% and 23.7% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive

disease compared to 2.6% of patients on placebo ($p < 0.001$). *Id.*, Figure 1. This is very similar to the 12 and 16 week results for IV golimumab reported in *US982*, wherein 19.0% and 27.6% of subjects, respectively, achieved ASDAS inactive disease. EX1002, 106-107:Table 9.

587. *Van der Heijde* reported that at week 24, 27.3% and 27.2% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive disease compared to 2.8% of patients on placebo ($p < 0.001$). EX1034, Figure 1. Again, this is very similar to the 20 and 28 week results for IV golimumab reported in *US982*, wherein 28.5% and 29.5% of subjects, respectively, achieved ASDAS inactive disease. EX1002, 106-107:Table 9.

588. *Inman*, which also reports the results of a phase III clinical trial of golimumab, 50 mg or 100 mg, administered SC every four weeks to subjects with AS, did not calculate ASDAS scores. EX1016, 3403. However, *Inman* observed rapid improvement in ASAS20. For example, *Inman* reported that at four weeks (the first assessment) golimumab outperformed placebo with respect to achieving ASAS20: “[g]reater proportions of patients in the golimumab groups achieved an ASAS20 response at the first assessment, 4 weeks after the first injection (Figure 3A).” *Id.*, 3406.

589. Figure 3A of *Inman*, reproduced below, likewise shows that patients receiving golimumab saw improvements, by four weeks, in ASAS40, BASDAI, and BASFI.

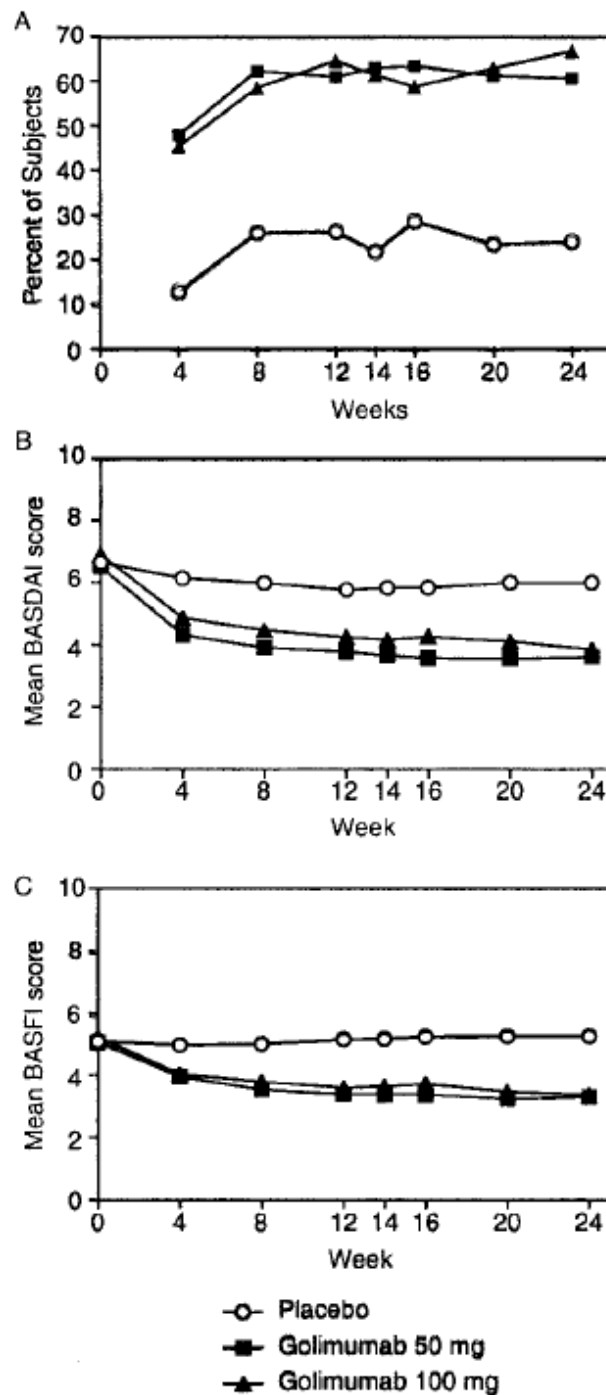


Figure 3. A, Proportion of patients achieving a 20% improvement in the ASsessment in Ankylosing Spondylitis International Working Group criteria through week 24. B, Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score through week 24. C, Mean Bath Ankylosing Spondylitis Functional Index (BASFI) score through week 24.

590. Based on Figure 3, by four weeks patients receiving SC golimumab, 50 or 100 mg every four weeks, saw improvements compared to placebo in ASAS20 (about 48%, 45%, and 12%, respectively), BASDAI score (about 4.2, 4.5, and 6.2, respectively), and mean BASFI score (about 4.0, 4.0, and 5.2, respectively). *Id.*, Figure 3A, 3B, 3C.

591. A POSA also would have been aware that IV golimumab administered for treating RA, at the same dose and frequency as taught in *NCT873-V24*, resulted in improvement in RA symptoms in as little as two weeks in some patients. EX1012, 381, Abstract. *Weinblatt* taught that by week 2, there were statistically significant treatment group differences in ACR20 (33.2% vs 11.7%), ACR50, HAQ and DAS28-CRP (65.1% vs 19.3%), and that by week 2, 65% of patients achieved a EULAR (European League Against Rheumatism) response. *Id.*, 382, 383; Figure 2, panel A, 388.

592. Claim 1 does not specify a percentage of patients that have to achieve ASDAS inactive disease at week 2 or 4. Instead, claim 1 only requires that “a patient treated with the [claimed] composition achieves” an ASDAS inactive disease at week 2 or 4 of treatment, which means that only one patient out of the number of patients treated must achieve ASDAS inactive disease at week 2 or 4. Consistent with this, Table 9 of Example 9 of *US982* reports that at two weeks under 10% of treated subjects achieved ASDAS inactive disease, and that at 4

weeks under 15 percent of subjects achieved ASDAS inactive disease. EX1002, 106-108, Table 9.

593. In my opinion, based on the ASDAS inactive disease results reported in *Van der Heijde* (>20% achieved inactive disease at week 14), the rapid results that *Inman* reports for the treatment of AS seen in *Inman* when treating AS with SC golimumab, and a POSA's knowledge (from *Weinblatt*) of the rapid results achieved in RA with IV golimumab given at the same dose and dosing schedule as taught in *NCT873-V24*, a POSA would have reasonably expected at least some patients receiving IV golimumab as taught in *NCT873-V24* would achieve ASDAS inactive disease by week 2 or week 4.

594. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *Van der Heijde*, and *Inman* because they all relate to using golimumab for the treatment of AS. A POSA would have been motivated to combine these teachings with *PI2013-Aria* because *NCT873-V24* and *PI2013-Aria* are both Janssen publications and teach administration of the same drug (golimumab), using the same route of administration (IV), at the same dose (2 mg/kg), and the same dosing regimen (at weeks 0 and 4 and then every 8 weeks thereafter) to treat a TNF α related condition (AS and RA, respectively). A POSA would have had a reasonable expectation of success because the prior art teaches that golimumab achieves results quickly, and in view of FDA's approval of

golimumab administered to treat RA, a related TNF α mediated condition, using the same dosing regimen as taught in *NCT873-V24*. *NCT673-V23* also used the same dose and dosing schedule as Janssen's FDA-approved label for IV golimumab, *PI2013-Aria*. EX1011, 3-4.

595. For the above reasons, to the extent that the results recited in claim 1 are limiting, the subject matter of claim 1, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. See also Paragraphs 550-580.

2. **Claim 4: “wherein at In addition, Van der Heijde, which reported on the results of a phase III clinical trial of golimumab, 50 mg or 100 mg, administered SC every four weeks to subjects with AS, reported changes in, among other things, SF-36 PCS compared to placebo at 14 and 24 weeks. EX1033, 1098, Table 2.**

596. Claim 4 states results of the IV infusion of golimumab. Claim 5 depends from claim 4 and adds that “said composition is administered such that said anti-TNF antibody is administered at a dose of 2 mg/kg, administered over 30 $\pm$ 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.” I have been informed that because claim 5 depends from claim 4, claim 4 encompass administering 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter.

597. While *NCT873-V24* does not disclose the results of the claims, those results are broadened by a recited standard deviation. For example, claim 3 recites

that the mean change from baseline in SF-36 PCS is 8.5 ± 7.5 SD, where SD is the standard deviation.

598. As explained above (Paragraph 522), *US982* does not explain how the SD is determined, so a POSA would have applied general statistics knowledge and would have understood that the standard deviation measures the spread of data points in a data set. Applying such general statistical knowledge, a mean change in SF-36 PCS of 8.5 ± 7.5 SD means that 68% of subjects would have a change in SF-36 PCS of 1.0 to 16.0.

599. *Van der Heijde* reports in Table 2 that at week 14, the mean change in SF-36 PCS in patients receiving 50 or 100 mg golimumab was 8.8 ± 9.6 SD and 8.9 ± 9.8 SD, respectively ($p < 0.001$). EX1033, 1098 (Table 2). *Van der Heijde* reports in Table 2 that at week 24, the mean change in SF-36 PCS in patients receiving 50 or 100 mg golimumab was 9.6 ± 10.6 SD and 9.2 ± 10.3 SD, respectively ($p < 0.001$). *Id.* Thus, patients treated with SC golimumab achieved the claimed results.

600. Although *Van der Heijde* reported results for SC administration of golimumab rather than the claimed IV administration, in view of the fact that golimumab has the same mechanism of action whether administered SC or IV, and that when administered IV, golimumab has a higher bioavailability, $C_{\max}$, and AUC than 100 mg SC golimumab and therefore should achieve the same or better results

than the SC golimumab, a POSA would have reasonably expected to see the same or better results for IV administration. A POSA likewise would not have expected to see material differences between the results at 14 weeks (*Van der Heijde*) and 16 weeks (*US566* claims).

601. Based on the SC results reported in *Van der Heijde*, a POSA would have reasonably expected that 2 mg/kg of IV golimumab administered at week 0, 4, and then every 8 weeks thereafter, would achieve a mean change in SF-36 PCS of 8.5 ± 7.5 SD.

602. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*, with a reasonable expectation of success, for the above reasons and the same reasons as set forth with regard to claim 1. *See* Paragraphs 552-553.

603. For the above reasons, to the extent that the results recited in claim 3 are limiting, the subject matter of claim 3, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. *See also* Paragraphs 550-580.

3. **Claim 7: “wherein >65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”**

Claim 8: “The method according to claim 5 wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$ ”

604. Claims 7 and 8 states results of the IV infusion of golimumab. Claim 9 depends from claims 7-8 and adds that “said antibody is administered at a dose of 2 mg/kg, administered over 30 ± 10 minutes, at Weeks 0 and 4, and then every 8 weeks (q8w) thereafter.” I have been informed that because claim 9 depends from claims 7-8, claims 7-8 encompass administering 2 mg/kg of golimumab at weeks 0, 4, and every 8 weeks thereafter.

605. While *NCT873-V24* does not provide results of the disclosed clinical trial, it does teach that the percentage of patients achieving ASAS20 at Week 16 is a primary endpoint. EX1014, 7. Thus, *NCT873-V24* would have motivated a POSA to assess the outcomes recited in claims 5 and 6. In addition, *Inman* reported determining the percentage of subjects achieving ASAS20 at week 14. It would have been obvious to a POSA to determine that outcome measure based on the above teachings of *NCT873-V24* and *Inman*.

606. Claim 7 recites that $\geq 65\%$ of patients receiving the treatment achieve ASA20 at week 16 of treatment, and claim 8 is dependent on claim 7, and specifies

that said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment achieve a treatment difference (improvement compared to placebo) of $\geq 45\%$.

607. *Inman* reported percentage of golimumab patients that achieved ASAS20 at week 14. EX1016, 3407, Table 2. *Inman* reported that for the 50 mg, 100 mg, and placebo groups, at week 14, 59.4%, 60%, and 21.8% of patients, respectively, achieved ASAS20 ($P < 0.001$). *Id.*, 3402, Abstract. Based on those results, *Inman* concluded that “Golimumab was effective and well tolerated in a large cohort of patients with AS.” *Id.*, 3402.

608. While *Inman* reports a lower percentage of patients achieving ASAS20 at week 14 for 50 mg SC golimumab that what is achieved with IV golimumab at week 16, both *Inman* and *PI2015-Simponi* teach that the SC dose was very effective for treating AS.

609. Moreover, a POSA would have known that determining the relative performance of SC and IV golimumab would require head-to-head clinical studies. In the absence of such head-to-head data, a POSA would not have viewed as clinically-meaningful the small differences between the results observed in the SC and IV studies, both of which satisfied their primary endpoints and therefore demonstrated efficacy.

610. In addition, a POSA would have been aware that 2 mg/kg of IV golimumab results in higher bioavailability, $C_{\max}$ and AUC than the SC golimumab

regimen used in *Inman* and *PI2015-Simponi*. A POSA therefore would not have been surprised if some additional individual patients treated with IV golimumab achieved ASAS20 at week 16 with a higher percentage showing improvement compared to placebo.

611. While the percentage of patients reported in *Inman* as achieving ASAS20 at week 14 for 50 mg SC golimumab is a lower number than the claimed percentage of patients achieving ASAS20 with IV golimumab at week 16, a POSA would have known that both *Inman* and *PI2015-Simponi* teach that the SC dose was very effective for treating AS.

612. Moreover, a POSA would have known that determining whether IV golimumab outperforms SC golimumab would require head-to-head clinical studies. In the absence of such head-to-head studies, a POSA would not have viewed as clinically-meaningful the small differences between the results observed in the SC and IV studies, both of which demonstrated efficacy by satisfying their primary endpoints.

613. A POSA also would have appreciated that 2 mg/kg of IV golimumab would produce greater average drug exposure—i.e., bioavailability, $C_{\max}$ and AUC—than SC golimumab. It therefore would not have surprised a POSA if some additional individual patients treated with IV golimumab achieved ASAS20 at week 16 with a higher percentage showing improvement compared to placebo.

614. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. The meta-analysis states that there were “no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16 weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” *Id.*, 6. That analysis supports my view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy.

615. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*, with a reasonable expectation of success, for the above reasons and the same reasons as set forth with regard to claim 1. *See* Paragraphs 552-553.

616. For the above reasons, to the extent that the results recited in claims 7 and 8 are deemed to be limiting, the subject matter of claims 7 and 8, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2015-Simponi*, *PI2013-Aria*, *Van der Heijde*, and *Inman*. *See also* Paragraphs 550-580.

4. Claims 2-3, 5-6, and 9-10

617. Claims 2-3, 5-6, and 9-10 depend from claims 1, 4, and 7-8, respectively. Claims 2-3, 5-6, and 9-10 do not recite any additional clinical responses. Therefore, for the same reasons as with respect to claims 1, 4, and 7, the subject matter of claims 2-3, 5-6, and 9-10 would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*.

F. Secondary Considerations

618. During prosecution, Applicant argued that the claimed invention yielded surprising and unexpected results. EX1008, 27-30. As explained below, in my opinion, the results were not surprising or unexpected.

619. Applicant stated the following during prosecution: “[e]ach of the clinical measures at 16 weeks post-IV golimumab was surprisingly and unexpectedly improved over the same clinical measures at 14 and 24 weeks post-subcutaneous golimumab as reported by Inman.” *Id.*, 29-30.

620. Janssen also represented that “[a]chieving an ASDAS inactive disease score (i.e. <1.3) after only 2 weeks or 4 weeks of IV golimumab treatment is a very surprising and unpredictable result that would not be obvious to a person skilled in the art.” *Id.*, 29.

621. The purported unexpected results correspond to the results reported in Tables 8 and 9 of Example 9 of *US982*, which assessed the effect of IV administration of golimumab 2 mg/kg in subjects with active AS. EX1002, Table 8, Table 9.

622. Based on this data, Janssen argued to the patent office that the results achieved by the claimed method could not have been expected based on the teachings of the *Inman* and *Doyle* references upon which the examiner's obviousness arguments had relied. EX1008, 29-30.

623. I have been informed that to demonstrate unexpected results, the applicant is supposed to compare the results achieved by the claimed subject matter to the closest prior art. In my opinion, the closest prior art is *NCT873-V24*, which used the same 2 mg/kg IV golimumab dose and frequency as claimed in *US982* and indicated that outcomes claimed in *US982* would be measured during the clinical trial. EX1014, 5, 7-8.

624. Janssen compared its results to the teachings of *Inman* and *Doyle*. Those are not the closest prior art because, unlike *NCT874-V24*, neither *Inman* nor *Doyle* assessed administration of the same 2 mg/kg IV golimumab dose and frequency as claimed in *US982*. Both *Inman* and *Doyle* report on studies in which SC golimumab is administered. EX1016, 3402; EX1035, 1214.

625. In addition, during prosecution, Janssen argued that IV golimumab provided surprising results relative to SC golimumab. EX1008, 29-30. But it appears that Janssen did not compare conduct a head-to-head clinical study comparing SC and IV golimumab. EX1034, 114.

626. During review of the Simponi Aria BLA, FDA raised concerns about the adequacy of the data Janssen submitted for its IV golimumab. EX1034, 114. According to FDA, Janssen “proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons.” *Id.* The FDA responded that “determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen.” *Id.* As demonstrated by FDA’s statements in *CDER Review* (*see* Paragraphs 242-248), it appears that Janssen never directly compared SC administration to IV administration. EX1034, 114; *see also* EX1032, 15 (“Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.”) As shown in *WO213*, the results obtained in clinical trials can vary based on, for example, the patient population or the length of time a subject has had active PsA. EX1025, 90:25-28, Table 11 (reporting that 46% of subjects with PsA for less than 2 years achieved ACR20, while 66% subjects with PsA from 2-5 years achieved ACR20).

627. It is inconsistent for Janssen to propose reliance on SC efficacy data when seeking FDA approval for IV golimumab, but then argue that the results obtained with IV golimumab are unexpectedly superior to SC golimumab. Without a head-to-head study, Janssen’s argument regarding unexpected superiority is not supported.

628. I reserve the right to respond to any allegations that objective indicia support the validity of the challenged claims.

X. DETAILED OPINIONS REGARDING *US566*

A. The Claims of *US566*

629. *US566* issued with 7 claims. Claims 1, 3, and 5 are independent claims, and claims 2, 4, and 6-7 are dependent claims.

630. In conducting my analysis, I applied the following claim constructions.

B. *US566* - Claim Construction

1. “Treating” (Claims 1, 3, and 5)

631. Claims 1, 3, and 5 have an introductory phrase, “a method for treating a TNF related condition.”

632. In my view, a POSA would not view the term “treating” as limiting because it does not change how the actual steps of the method of treating are performed.

633. A POSA would have understood that the only active steps of the independent claims are “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences]” and doing so 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.” Thus, the independent claims require administering a safe and effective amount and then recite that amount, *i.e.*, 2 mg/kg administered IV over 30 ± 10 minutes at week 0, 4, and every 8 weeks thereafter. In addition, 2 mg/kg administered IV over 30 ± 10 minutes at week 0, 4, and every 8 weeks thereafter is the only specific dosing regimen disclosed in *US566* for treating humans. EX1004, 3-8, Example 9.

634. In my opinion, in view of the language of the claims and the disclosures in the specification, the term “treating” does not in any way limit how a POSA would practice the active steps of claimed methods because it does not modify the safe and effective amount of the anti-TNF antibody or how it is administered.

635. Moreover, to the extent that the term “treating” is deemed to limit the claims in any way, a POSA would have understood that the term “treating” means to administer the claimed dosage to a patient regardless of the clinical outcome, because *US566* teaches that not all golimumab treated patients with active AS

experience a clinical benefit. For example, claim 5 acknowledges that as many as 35% of patients may not achieve ASAS20 at week 16 of treatment, and Table 9 of reports that as of week 28, fewer than 30% of patients achieve ASDAS inactive disease. EX1004, Table 9. Moreover, when treating a particular patient with active AS, it cannot be predicted how that particular patient will respond to the treatment.

2. The Claimed Results do Not Limit the Claimed Method of Treatment

636. Independent claims 1, 3, and 5 recite the following clinical outcomes:

- Claim 1: “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.”;
- Claim 3: 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.”;
- Claim 5: ““wherein $\geq 65\%$ of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”

637. In addition, claim 6, which depends on claim 5, adds the following: “wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.”

638. These claimed results appear to be the clinical responses reported in Tables 8 and 9 of Example 9 in *US566*. EX1004, 106-108.

639. The results recited in claims 3 and 5 pertain to a mean change from baseline and a statistical analysis obtained from a cohort of patients as opposed to a single patient. For example, the claimed results include mean changes from baseline and standard deviations/SD. EX1004, claim 3. These statistical results in the claims appear to come from the clinical trial described in the specification, in which 103 subjects received placebo and 105 subjects received 2 mg/kg golimumab. EX1004, 106:Table 8. A POSA would have understood that the clinical result of treating a single patient does not provide a mean, cannot be used to determine a standard deviation, and is therefore not applicable to the claimed results.

640. A POSA also would have understood that when treating a particular patient with a biologic, such as golimumab, one cannot predict how that particular patient with active AS will respond to the treatment. The claims of *US566* acknowledge as much. For example, claim 5 recites that “ $\geq 65\%$ of patients receiving the treatment achieve Assessment of Ankylosing Spondylitis 20

(ASAS20) at week 16 of treatment.” EX1004, claim 5. That means that at week 16, as many as 35% of patients receiving the treatment will not achieve ASAS20 at week 16. For any particular patient, before as many as 16 weeks of treatment, it would not be known whether that patient would achieve the claimed ASAS20 at week 16.

641. In addition, *US566* does not provide an explanation of how to determine the standard deviation in claim 3. In the absence of such an explanation, a POSA would have understood that the terms have their typical statistical meanings. *See, e.g.*, Paragraph 117-120.

642. In addition, a POSA would have known that the effect of administering golimumab, including the percentage of subjects achieving any given clinical result, may depend on the demographics of the patient population. The claims do not, however, require any baseline characteristic other than having active AS. Thus, the claims encompass treating a patient with a baseline ASDAS of, for example, 2.1, who would be likely to achieve ASDAS inactive disease faster than a subject with a baseline ASDAS of 4.5. Example 5 in *WO213* reports a similar impact of demographic different in the context of PsA, reporting that 46% of adalimumab treated subjects with PsA for less than 2 years achieved ACR20 at week 24 of treatment, while 66% of subjects with PsA from 2-5 years achieved ACR20. EX1025, 90:Table 11.

3. The Term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences]” Encompasses Golimumab

643. Independent claims 1, 3, and 5 include the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences].”

US566 defines SEQ ID NOs 36 and 37 as the “Golimumab Heavy Chain (HC)” and “Golimumab Light Chain (LC),” respectively. EX1004, 127-132. SEQ ID NO 36 encompasses the claimed heavy chain CDR sequences and SEQ ID NO 37 encompasses the claimed light chain CDR sequences. *See id.* Accordingly, a POSA would have known that the term “at least one isolated mammalian anti-TNF antibody comprising [the Claimed CDR Sequences]” encompasses golimumab but does not exclude other antibodies.

4. Administering “with or without Methotrexate (MTX), Sulfasalazine (SSZ) or Hydroxychloroquine (HCQ)”

644. Dependent claims 2, 4, and 7 add that the anti-TNF- α antibody is administered “with or without methotrexate (MTX), sulfasalazine (SSZ) or hydroxychloroquine (HCQ).” A POSA would have understood that there are only two options for how the patient is treated with respect to MTX, SSZ, and HCQ, either MTX, SSZ, or HCQ is administered to the patient, or it is not. This phrase also fails to limit independent claims 1, 4, and 7, as the term “or” in the phrase “with or without” makes administration of MTX, SSZ, or HCQ optional.

Therefore, a POSA would have understood that this phrase does not limit independent claims 1, 3, and 5 in any way.

C. *NCT873-V24* Anticipates Claims 1-7

645. As explained below, in my opinion *NCT873-V24* anticipates claims 1-7 because it discloses all of the steps required by the recited method, arranged as in the claim.

1. Claims 1, 3, and 5

a. Claims 1, 3, and 5: “A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising”

646. As explained above in Paragraph 632-634, in my opinion, the term “treating” does not add any additional steps to the step of administering the golimumab. Regardless, *NCT873-V24* discloses “a method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis.”

647. *NCT673-V24* is the study record of a clinical study where subjects with active AS were intravenously administered 2 mg/kg IV of golimumab. The title of the study indicates that it is a study of golimumab for treating patients with active AS: “A Study of Golimumab in Participants with Active Ankylosing Spondylitis.” EX1014, 1.

648. In addition, *NCT873-V24* disclosed the following primary purpose: “to evaluate the efficacy of intravenously (administration of a fluid into the vein) administered golimumab 2 milligram per kilogram (mg/kg) in participants with active ankylosing spondylitis (chronic inflammatory disease of unknown etiology that involves the sacroiliac joints, and often the axial skeleton, entheses, and peripheral joints).” EX1014, 5. The primary endpoint of the study was the “Percentage of Participants Achieving a 20 Percent Improvement in Assessment in Ankylosing Spondylitis at Week 16,” which is a measure of efficacy in treating AS in the study subjects. *Id.*, 7.

649. A POSA would have understood that the administration of golimumab to patients as described in *NCT873-V24* is “a method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis.”

b. Claims 1 and 3: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences], and at least one pharmaceutically acceptable carrier or diluent”

Claim 5: “administering a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences]”

650. *NCT873-V24* studied the efficacy of IV administration of 2 mg/kg of golimumab, which has the claimed CDR Sequences (*see* Paragraph 643) in patients with active AS.

651. As to the claimed “safe and effective amount,” claims 1, 3, and 5 identify IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter. *NCT873-V24* disclosed that AS patients would receive “intravenous infusions of golimumab 2mg/kg at Weeks 0, 4, and thereafter every 8 weeks” (EX1014, 6-7), and therefore disclosed a safe and effective amount.

652. Independent claims 1 and 3 require “at least one pharmaceutically acceptable carrier or diluent.” As noted above, *NCT873-V24* studied the efficacy of IV golimumab. EX1014, 5. While *NCT873-V24* does not expressly state that the golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, a POSA would have known that IV administration is administration of a fluid to a vein and would require a carrier. Indeed, *NCT873-V24* disclosed the administration of a placebo infusion, which a POSA would have understood is a pharmaceutically acceptable carrier or diluent without golimumab. *Id.*, 6-7. A POSA would have further understood that as a double-blind study, the golimumab and placebo would have to look the same, meaning that the golimumab and placebo would have to be in the same volume and infused at the same rate.

653. A POSA also would have been aware that *PI2013-Aria* discloses an FDA approved dosing regimen for the treatment of RA that is the same as the dosing regimen disclosed in *NCT873-V24*. EX1032, 1. *PI2013-Aria* teaches that prior to infusion, the golimumab is diluted with 0.9% w/v sodium chloride, a

pharmaceutically acceptable carrier or diluent. EX1032, 1. A POSA reading *NCT873-V24* therefore would have likewise understood that the golimumab used in *NCT873-V24* was dissolved or otherwise dispersed within a carrier or diluent suitable for human IV infusions.

654. Accordingly, *NCT873-V24* discloses this element of claims 1, 3, and 5.

c. **Claims 1 and 3: “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”**

Claim 5: “wherein said anti-TNF antibody 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”

655. *NCT873-V24* discloses IV infusion of golimumab, 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter. EX1014, 6-7. *NCT873-V24* does not, however, expressly state that the golimumab was administered over 30±10 minutes

656. In my opinion, a POSA would have been aware of *PI2013-Aria* and its disclosure that IV golimumab for treating RA is also administered 2 mg/kg, at weeks 0, 4, and every 8 weeks thereafter, and is infused over a period of approximately 30 minutes. EX1032, 1. With this awareness in mind, a POSA reading *NCT873-V24* would have understood that the 2 mg/kg dose, infused at

weeks 0, 4, and every 8 weeks thereafter, described in *NCT873-V24* also would have been infused over a period of approximately 30 minutes.

d. The Clinical Results

657. As discussed above in Paragraphs 638-640, in my opinion, the clinical results recited in claims 1, 3, and 5 do not separately limit the steps required by the claimed method because they merely describe the result of administering golimumab as expressly disclosed in *NCT873-V24*, *i.e.*, 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter.

658. The claimed clinical results appear to be taken from the results of the clinical trial described Example 9 of *US566*. EX1004, Example 9. If IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as required in claims 1, 3, and 5 and as used in the clinical trial in Example 9 produces the claimed efficacy, then IV administration of 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks as reported in *NCT873-V24* must also produce the claimed efficacy. Put another way, practicing the same method should give the same results.

2. Claim 6

659. Claim 6 depends from claim 5 and adds the following limitation: “wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.”

660. In my opinion, *NCT873-V24* discloses this limitation for the same reasons as set forth above with respect to claim 5.

3. Claims 2, 4, and 7

661. Claims 2, 4, and 7 depend from claims 1, 3, and 5, respectively, and further recite that the composition (claims 1 and 3) or antibody (claim 5) is administered “with or without methotrexate (MTX), sulfasalazine (SSX) or hydroxychloroquine (HCQ).”

662. *NCT873-V24* does not require MTX, SSX, or HCQ, and thus discloses administration “without” MTX, SSX, or HCQ.

D. Claims 1-7 Would Have Been Obvious To A POSA in View of the Combined Teachings of *NCT873-V24* and *PI2013-Aria*

663. As explained above in Paragraph 646-662, in my opinion, *NCT873-V24* discloses each of the limitations of claims 1-7 as arranged in those claims and therefore anticipates those claims. As explained below, when the recited clinical results are not treated as limiting the claimed method (because they do not impact the active method steps), a POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* to practice the subject matter of claims 1-7, and would have had a reasonable expectation of success when doing so.

664. In summary, *NCT873-V24* teaches all of the elements of claims 1-7 other than explicitly teaching the use of a pharmaceutically acceptable carrier or diluent (claims 1-4), and also fails to explicitly teach the infusion time. EX1014,

5-7. *PI2013-Aria* teaches administration of the same drug as *NCT873-V24* (golimumab), with the same route of administration (IV), dosage (2 mg/kg), and dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter), for treatment of the TNF α related condition of active RA. EX1014, 6-7; EX 1032, 1. *PI2013-Aria* also expressly teaches: (a) diluting the golimumab solution, prior to administration, with 0.9% w/v sodium chloride, a pharmaceutically acceptable carrier or diluent; and (b) infusing golimumab over 30 minutes. EX1032, 1.

665. A POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* with a reasonable expectation of success because both are Janssen publications that, as explained above, relate to treating a TNF α related condition (AS or RA, respectively) by administering the same TNF α inhibitor (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg), and with the same dosing schedule (at weeks 0 and 4, and then every 8 weeks thereafter).

1. Claims 1, 3, and 5

a. Claims 1, 3, and 5: “A method for treating a TNF related condition, wherein the TNF related condition is active ankylosing spondylitis, the method comprising”

666. *NCT873-V24* taught a method for treating a TNF related condition, wherein the TNF related condition is active AS. More specifically, *NCT873-V24* taught that Janssen had sponsored a clinical trial titled “A Study of Golimumab in

Participants with Active Ankylosing Spondylitis” in which the purpose of the study was to evaluate the efficacy of golimumab administered IV at a dose of 2 mg/kg in subjects with active AS. *Id.*, 1, 5.

- b. Claims 1 and 3: “administering a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences], and at least one pharmaceutically acceptable carrier or diluent”**

Claim 5: “administering a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising: [the Claimed CDR Sequences]”

667. As explained above, *NCT873-V24* taught administering golimumab intravenously at a dose 2 mg/kg administered at week 0, 4, and then every 8 weeks thereafter. EX1014, 6-7.

668. As explained in Paragraphs 643, the Claimed CDR Sequences encompass golimumab, because golimumab has those sequences.

669. With respect to a safe and effective amount, claims 1, 3, and 5 recite administering IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter, meaning that this is a safe and effective amount. This is also the dose and dosing schedule used in Example 9 of *US566*. EX1002, Example 9. Moreover, *NCT873-V24* taught Janssen’s intent to treat AS by administering the same amount on the same dosing schedule. EX1014, 6-7. *NCT873-V24* also used

the same dose and dosing schedule as Janssen's FDA-approved label for IV golimumab, *PI2013-Aria. Id.*, 5-7.

670. A POSA would have been motivated to use this dosing regimen as a treatment for active AS with a reasonable expectation of this being a safe and effective amount because: (1) it is the dosing regimen taught in Janssen's *NCT873-V24*, a clinical trial which had been ongoing for over a year as of the earliest filing date of *US566* (EX1014, 4); and (2) that dosing regimen was FDA approved as safe and effective for the treatment of a related TNF α mediated condition, RA (EX1032, 1).

671. With respect to the recited "at least one pharmaceutically acceptable carrier or diluent," while *NCT873-V24* does not expressly state that the IV golimumab was dispersed in a pharmaceutically acceptable carrier or diluent, it taught that IV administration is the administration of a fluid to a vein, and that the placebo would be an infusion, which a POSA would have understood is a pharmaceutically acceptable carrier or diluent without golimumab. EX1014, 5, 6-7. Based on these teachings, a POSA would have understood that to administer golimumab as an IV infusion, the golimumab would also have been dispersed in a pharmaceutically acceptable carrier or diluent.

672. There is no way to administer golimumab intravenously without mixing it with some kind of carrier such as water for injection or a saline solution.

673. A POSA also would have known from *PI2013-Aria* that the same IV concentration of golimumab, 2 mg/kg, had been approved for the treatment of RA wherein the prescribing information requires dilution of the golimumab with 0.9% w/v sodium chloride: “Dilution of supplied SIMPONI ARIA solution with 0.9% w/v sodium chloride is required prior to administration.” EX1032, 1. Moreover, a POSA would have known that 0.9% sodium chloride, known as “normal saline,” was a commonly used diluent at the time.

674. It would have been obvious to a POSA to use the 0.9% w/v sodium chloride carrier taught in *PI2013-Aria* as the carrier for a golimumab composition for IV administration for the treatment of AS, as taught in *NCT873-V24*, because *PI2013-Aria* and *NCT873-V24* are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or AS, respectively).

675. A POSA would have been motivated to combine the teachings of *NCT873-V24* and *PI2013-Aria* with a reasonable expectation of success for the same reason, *i.e.*, because they are both Janssen publications and teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at

weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or AS, respectively). EX1014, 6-7; EX1032, 1, 3.

676. For the above reasons, based on the teachings of *NCT873-V24* and *PI2013-Aria*, a POSA would have found it apparent to administer a composition comprising a safe and effective amount of at least one isolated mammalian anti-TNF antibody comprising the Claimed CDR Sequences, such as golimumab, and at least one pharmaceutically acceptable carrier or diluent.

c. Claims 1 and 3: “wherein said composition is administered via IV infusion at a dose of 2 mg/kg administered over 30 $\pm$ 10 minutes at Weeks 0 and 4, and then every 8 weeks (q8W) thereafter”

Claim 5: “wherein said anti-TNF antibody is administered via IV infusion at a dose of 2 mg/kg administered over 30 $\pm$ 10 minutes at Weeks 0 and 4, and then every 8 weeks (q8W) thereafter”

677. *NCT873-V24*, a Janssen publication, taught a dosing regimen for IV administration of golimumab to treat active AS: IV infusions of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter (EX1014, 1, 6-7), but did not expressly disclose an infusion time.

678. *PI2013-Aria*, another Janssen publication, taught the same golimumab IV dosing regimen as *NCT873-V24* for treating another TNF α medication condition, RA, and taught an infusion time of 30 minutes: “The SIMPONI ARIA

dosage regimen is 2 mg per kg given as an intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks thereafter.” EX1032, 3; *see also, id.*, 1.

679. A POSA would have been motivated to administer the 2 mg/kg IV dose of golimumab taught by *NCT873-V24* over the 30 minutes taught by *PI2013-Aria*, with a reasonable expectation of success, because they are both Janssen publications and both teach administration of the same drug (golimumab), with the same route of administration (IV), at the same dose (2 mg/kg) with the same dosing frequency (at weeks 0, 4, and every 8 weeks thereafter), for the treatment of a TNF α mediated condition (RA or AS, respectively). EX1014, 6-7; EX1032, 1, 3.

680. For the above reasons, based on the teachings of *NCT683-V24* and *PI2013-Aria*, a POSA would have found it apparent to administer golimumab via IV infusion at a dose of 2 mg/kg administered over 30 $\pm$ 10 minutes at Weeks 0 and 4, and then every 8 weeks (q8W) thereafter.

- d. **Claim 1: “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.”**

Claim 3: “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)=5.5±7.5 SD, 36-item Short-Form Health Survey Mental Component Summary (SF-36 MCS)=6.5±9.1 SD, and Ankylosing Spondylitis Quality of Life questionnaire (ASQoL)=-5.4±5.0 SD.”

Claim 5: “wherein >65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”

681. As discussed above in Paragraph 638-640, in my opinion the results recited in claims 1, 3, and 5 do not in any way modify the active steps in the claimed methods of treatment, and the claims do not recite steps of measuring or determining the clinical endpoints. Accordingly, those clinical results do not impact my obviousness analysis.

682. Moreover, in my opinion, there is nothing in the active steps of the claims when administering golimumab, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter, that

would give a different result than practicing the method taught in *NCT873-V24*, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter.

683. For all of the above reasons, the combined teachings of *NCT873-V24* and *PI2013-Aria* would have rendered claims 1, 3, and 5 obvious to a POSA.

2. Claim 6

684. Claim 6 depends from claim 5, and further recites that “said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$.” Thus, claim 6 merely recites another aspect of the clinical response, again without impacting an active method step. Put another way, the recited result in claim 6 does not affect the active steps of the claim, *i.e.*, IV administration of golimumab at a dose of 2 mg/kg over 30 minutes at weeks 0, 4, and every 8 weeks thereafter. Accordingly, those clinical results do not impact my obviousness analysis.

685. For the above reasons, the subject matter of claim 6 would have been obvious to a POSA in view of the combined teachings *NCT873-V24* and *PI2013-Aria* for the same reason as claim 5.

3. Claims 2, 4, and 7

686. Claims 2, 4, and 7 depend from claims 1, 3, and 5 respectively, and further recite that the composition (claims 1 and 3) or antibody (claim 5) is administered “with or without methotrexate (MTX), sulfasalazine (SSX) or hydroxychloroquine (HCQ).” This added recitation provides two options, that the anti-TNF antibody is administered with MTX, SSX, or HCQ, or that the anti-TNF antibody is administered without MTX, SSX, or HCQ.

687. As explained above with respect to claims 1, 3, and 5, treatment without MTX, SSX, or HCQ would have been obvious to a POSA because *NCT873-V24* does not require MTX, SSX, or HCQ, and thus teaches administration “without” MTX, SSX, or HCQ. As explained in Paragraph 644, the optional choice of administering MTX, SSX, or HCQ does not limit the claims.

688. A POSA also would have known that the safety and efficacy of subcutaneously administered golimumab were evaluated in a clinical trial of patients with AS in which patients were allowed to continue stable doses of, among other things, concomitant MTX, SSZ, and/or HCQ. EX1015, 28.

689. For the above reasons and the reasons given above with respect to claims 1, 3, and 5, the subject matter of claims 2, 4, and 7 would have been obvious to a POSA in view of the combined teachings *NCT873-V24* and *PI2013-Aria*.

E. Claims 1-7 Would Have Been Obvious to a POSA in View of the Combined Teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*

690. In Paragraphs 646-662, I explain why *NCT873-V24* anticipates claims 1-7.

691. In Paragraphs 663-689, above, I explained why, when the recited clinical results are not treated as limitations, a POSA would have found claims 1-7 obvious over the combined teachings of *NCT873-V24* and *PI2013-Aria*. Below I explain why even if the recited results are deemed to be limitations, claims 1-7 would have been obvious to a POSA over the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. Since I already addressed all of the elements of claims 1-7 other than the clinical outcomes in claims 1, 3, and 5-6, I only address the clinical results below.

1. Claim 1: “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”

692. Claim 1 states the following result of the IV infusion of golimumab, 2 mg/kg, over 30±10 minutes at weeks 0, 4, and every 8 weeks thereafter: “achiev[ing] an Ankylosing Spondylitis Disease Activity Score (ASDAS) inactive disease (<1.3) at 4 weeks of treatment or at 2 weeks of treatment.”

693. While neither *NCT873-V24* nor *PI2013-Aria* discloses the claimed ASDAS clinical outcome, that result is would have been apparent to a POSA in view of the teachings of *Van der Heijde* and *Inman*.

694. *Van der Heijde* describes the results of a phase 3 study of SC golimumab for the treatment of AS. *Van der Heijde*, when comparing the results of golimumab treatment to placebo, reported that “significantly greater proportions [of subjects receiving golimumab] had ASDAS inactive disease at weeks 14 and 24.” EX1033, 1097.

695. *Van der Heijde* reported that at week 14, 20.3% and 23.7% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive disease compared to 2.6% of patients on placebo ($p < 0.001$). *Id.*, Figure 1. This is very similar to the 12 and 16 week results for IV golimumab reported in *US566*, wherein 19.0% and 27.6% of subjects, respectively, achieved ASDAS inactive disease. EX1004, Table 9.

696. *Van der Heijde* reported that at week 24, 27.3% and 27.2% of patients receiving 50 and 100 mg golimumab, respectively, achieved ASDAS inactive disease compared to 2.8% of patients on placebo ($p < 0.001$). EX1033, Figure 1. Again, this is very similar to the 20 and 28 week results for IV golimumab reported in *US566*, wherein 28.6% and 29.5% of subjects, respectively, achieved ASDAS inactive disease. EX1004, Table 9.

697. *Inman*, which also reports the results of a phase III clinical trial of golimumab, 50 mg or 100 mg, administered SC every four weeks to subjects with AS, did not calculate ASDAS scores. EX1016, 3403. However, *Inman* observed rapid improvement in ASAS20. For example, *Inman* reported that at four weeks (the first assessment) golimumab outperformed placebo with respect to achieving ASAS20: “[g]reater proportions of patients in the golimumab groups achieved an ASAS20 response at the first assessment, 4 weeks after the first injection (Figure 3A).” *Id.*, 3406.

698. Figure 3A of *Inman*, reproduced below, likewise shows that patients receiving golimumab saw improvements, by four weeks, in ASAS40, BASDAI, and BASFI.

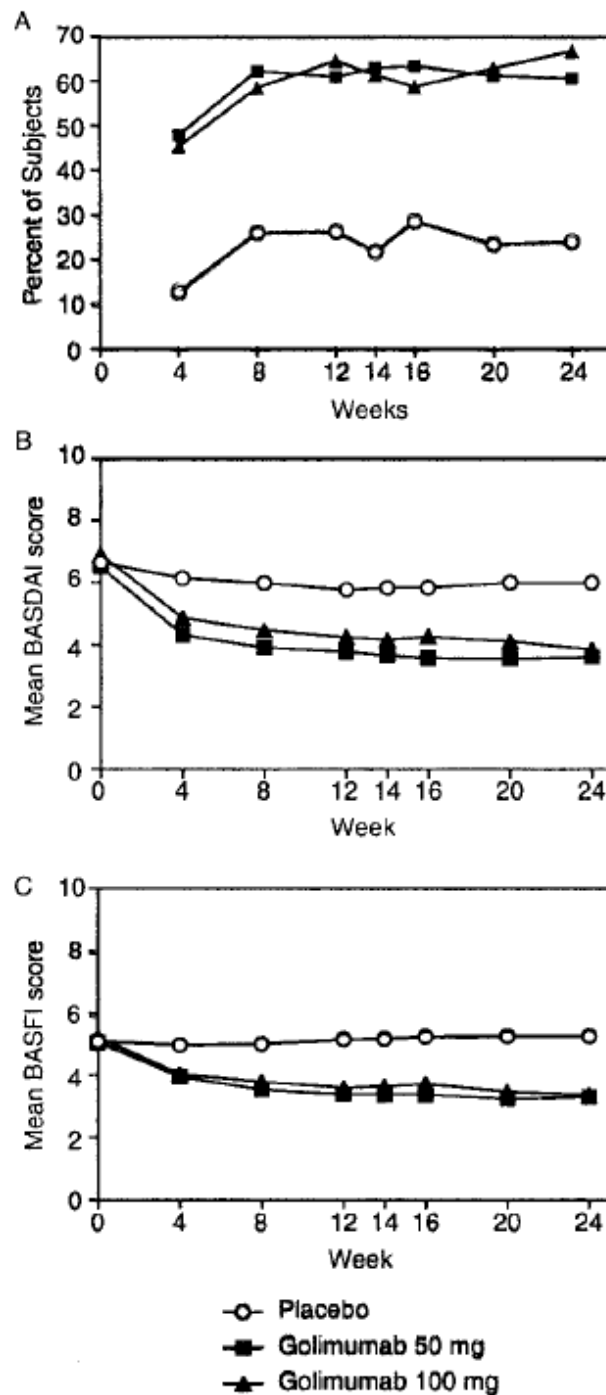


Figure 3. A, Proportion of patients achieving a 20% improvement in the ASsessment in Ankylosing Spondylitis International Working Group criteria through week 24. B, Mean Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score through week 24. C, Mean Bath Ankylosing Spondylitis Functional Index (BASFI) score through week 24.

699. Based on Figure 3, by four weeks patients receiving SC golimumab, 50 or 100 mg every four weeks, saw improvements compared to placebo in ASAS20 (about 48%, 45%, and 12%, respectively), BASDAI score (about 4.2, 4.5, and 6.2, respectively), and mean BASFI score (about 4.0, 4.0, and 5.2, respectively). *Id.*, Figure 3A, 3B, 3C.

700. A POSA also would have been aware that IV golimumab administered for treating RA, at the same dose and frequency as taught in *NCT873-V24*, resulted in improvement in RA symptoms in as little as two weeks in some patients. EX1012, 1, Abstract. *Weinblatt* taught that by week 2, there were statistically significant treatment group differences in ACR20 (33.2% vs 11.7%), ACR50, HAQ and DAS28-CRP (65.1% vs 19.3%), and that by week 2, 65% of patients achieved a EULAR (European League Against Rheumatism) response. *Id.*, 382, 383; Figure 2, panel A, 388.

701. Claim 1 does not specify a percentage of patients that have to achieve ASDAS inactive disease at week 2 or 4. Instead, claim 1 only requires that “a patient treated with the [claimed] composition achieves” an ASDAS inactive disease at week 2 or 4 of treatment, which means that only one patient out of the number of patients treated must achieve ASDAS inactive disease at week 2 or 4. Consistent with this, Table 9 of Example 9 of *US566* reports that at two weeks under 10% of treated subjects achieved ASDAS inactive disease, and that at 4

weeks under 15 percent of subjects achieved ASDAS inactive disease. EX1004, 107:Table 9.

702. Moreover, as explained above in Paragraphs 642, a POSA would have known that the effect of administering golimumab, including extent and rapidity of response, may depend on the demographics of the patient population. But the claims do not require any baseline characteristic other than having active AS. Therefore, the claims encompass treating a patient with a baseline ASDAS of, for example, 2.1, who would be likely to achieve ASDAS inactive disease faster than a subject with a baseline ASDAS of 4.5.

703. In my opinion, based on the ASDAS inactive disease results reported in *Van der Heijde* (>20% achieved inactive disease at week 14), the rapid results that *Inman* reports for the treatment of AS seen in *Inman* when treating AS with SC golimumab, and a POSA's knowledge (from *Weinblatt*) of the rapid results achieved in RA with IV golimumab given at the same dose and dosing schedule as taught in *NCT873-V24*, a POSA would have reasonably expected at least some patients receiving IV golimumab as taught in *NCT873-V24* would achieve ASDAS inactive disease by week 2 or week 4.

704. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *PI2015-Simponi*, *Van der Heijde*, and *Inman* because they all relate to using golimumab for the treatment of AS. A POSA would have been motivated

to combine these teachings with *PI2013-Aria* because *NCT873-V24* and *PI2013-Aria* are both Janssen publications and teach administration of the same drug (golimumab), using the same route of administration (IV), at the same dose (2 mg/kg), and the same dosing regimen (at weeks 0 and 4 and then every 8 weeks thereafter) to treat a TNF α related condition (AS and RA, respectively). A POSA would have had a reasonable expectation of success because the prior art teaches that golimumab achieves results quickly, and in view of FDA's approval of golimumab administered to treat RA, a related TNF α mediated condition, using the same dosing regimen as taught in *NCT873-V24*. *NCT673-V23* also used the same dose and dosing schedule as Janssen's FDA-approved label for IV golimumab, *PI2013-Aria*. EX1011, 3-4.

705. For the above reasons, to the extent that the results recited in claim 1 are limiting, the subject matter of claim 1, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. See also Paragraphs 663-689.

1. **Claim 3: “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 Quality of Life questionnaire (ASQoL)=-5.4±5.0 SD.”**

706. *NCT873-V24* teaches that BASFI scores at Week 16 (one of the clinical outcomes recited in claim 3) are a secondary endpoint (EX1014, 8), but does not report the actual results. As in my analysis of claim 1, it would have been obvious to a POSA to determine that clinical outcome based on the above teachings of *NCT873-V24*.

707. In addition, *Van der Heijde*, which reported on the results of a phase III clinical trial of golimumab, 50 mg or 100 mg, administered SC every four weeks to subjects with AS, reported changes in, among other things, SF-36 PCS compared to placebo at 14 and 24 weeks. EX1033, 1098 (Table 2).

708. While *NCT873-V24* does not disclose the results of the claims, those results are broadened by a recited standard deviation. For example, claim 3 recites that the mean change from baseline in SF-36 PCS is 8.5±7.5 SD, where SD is the standard deviation.

709. As explained above (Paragraph 641), *US566* does not explain how the SD is determined, so a POSA would have applied general statistics knowledge and would have understood that the standard deviation measures the spread of data points in a data set. Applying such general statistical knowledge, a mean change in SF-36 PCS of 8.5 ± 7.5 SD means that 68% of subjects would have a change in SF-36 PCS of 1.0 to 16.0.

710. *Van der Heijde* reports in Table 2 that at week 14, the mean change in SF-36 PCS in patients receiving 50 or 100 mg golimumab was 8.8 ± 9.6 SD and 8.9 ± 9.8 SD, respectively ($p < 0.001$). EX1033, 1098 (Table 2). *Van der Heijde* reports in Table 2 that at week 24, the mean change in SF-36 PCS in patients receiving 50 or 100 mg golimumab was 9.6 ± 10.6 SD and 9.2 ± 10.3 SD, respectively ($p < 0.001$). *Id.* Thus, patients treated with SC golimumab achieved the claimed results.

711. Although *Van der Heijde* reported results for SC administration of golimumab rather than the claimed IV administration, in view of the fact that golimumab has the same mechanism of action whether administered SC or IV, and that when administered IV, golimumab has a higher bioavailability, $C_{\max}$, and AUC than 100 mg SC golimumab and therefore should achieve the same or better results than the SC golimumab, a POSA would have reasonably expected to see the same or better results for IV administration. A POSA likewise would not have expected

to see material differences between the results at 14 weeks (*Van der Heijde*) and 16 weeks (*US566* claims).

712. Based on the SC results reported in *Van der Heijde*, a POSA would have reasonably expected that 2 mg/kg of IV golimumab administered at week 0, 4, and then every 8 weeks thereafter, would achieve a mean change in SF-36 PCS of 8.5 ± 7.5 SD.

713. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*, with a reasonable expectation of success, for the above reasons and the same reasons as set forth with regard to claim 1. *See* Paragraph 704.

714. For the above reasons, to the extent that the results recited in claim 3 are limiting, the subject matter of claim 3, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. *See also* Paragraphs 663-689.

2. **Claim 5: “wherein >65% of patients receiving the treatment achieve Assessment in Ankylosing Spondylitis 20 (ASAS20) at week 16 of treatment.”**

Claim 6: “The method according to claim 5 wherein said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment have a treatment difference (improvement compared to placebo) of $\geq 45\%$ ”

715. While *NCT873-V24* does not provide results of the disclosed clinical trial, it does teach that the percentage of patients achieving ASAS20 at Week 16 is a primary endpoint. EX1014, 7. Thus, as in my analysis of claims 1 and 3, *NCT873-V24* would have motivated a POSA to assess the outcomes recited in claims 5 and 6. In addition, *Inman* reported determining the percentage of subjects achieving ASAS20 at week 14. It would have been obvious to a POSA to determine that outcome measure based on the above teachings of *NCT873-V24* and *Inman*.

716. Claim 5 recites that $\geq 65\%$ of patients receiving the treatment achieve ASA20 at week 16 of treatment, and claim 6 is dependent on claim 5, and specifies that said $\geq 65\%$ of patients that achieve ASAS20 at week 16 of treatment achieve a treatment difference (improvement compared to placebo) of $\geq 45\%$.

717. *Inman* reported the percentage of golimumab patients that achieved ASAS20 at week 14. EX1016, 3407, Table 2. *Inman* reported that for the 50 mg, 100 mg, and placebo groups, at week 14, 59.4%, 60%, and 21.8% of patients, respectively, achieved ASAS20 ($P < 0.001$). *Id.*, 3402, Abstract. Based on those

results, *Inman* concluded that “Golimumab was effective and well tolerated in a large cohort of patients with AS.” *Id.*, 3402.

718. While *Inman* reports a lower percentage of patients achieving ASAS20 at week 14 for 50 mg SC golimumab than what is achieved with IV golimumab at week 16, both *Inman* and *PI2015-Simponi* teach that the SC dose was very effective for treating AS.

719. Moreover, a POSA would have known that determining the relative performance of SC and IV golimumab would require head-to-head clinical studies. In the absence of such head-to-head data, a POSA would not have viewed as clinically-meaningful the small differences between the results observed in the SC and IV studies, both of which satisfied their primary endpoints and therefore demonstrated efficacy.

720. In addition, a POSA would have been aware that 2 mg/kg of IV golimumab results in higher bioavailability, $C_{\max}$ and AUC than the SC golimumab regimen used in *Inman* and *PI2015-Simponi*. A POSA therefore would not have been surprised if some additional individual patients treated with IV golimumab achieved ASAS20 at week 16 with a higher percentage showing improvement compared to placebo.

721. While the percentage of patients reported in *Inman* as achieving ASAS20 at week 14 for 50 mg SC golimumab is a lower number than the claimed

percentage of patients achieving ASAS20 with IV golimumab at week 16, a POSA would have known that both *Inman* and *PI2015-Simponi* teach that the SC dose was very effective for treating AS.

722. Moreover, a POSA would have known that determining whether IV golimumab outperforms SC golimumab would require head-to-head clinical studies. In the absence of such head-to-head studies, a POSA would not have viewed as clinically-meaningful the small differences between the results observed in the SC and IV studies, both of which demonstrated efficacy by satisfying their primary endpoints.

723. A POSA also would have appreciated that 2 mg/kg of IV golimumab would produce greater average drug exposure—i.e., bioavailability, $C_{\max}$ and AUC—than SC golimumab. It therefore would not have surprised a POSA if some additional individual patients treated with IV golimumab achieved ASAS20 at week 16 with a higher percentage showing improvement compared to placebo.

724. In addition, as I discuss above in Paragraphs 249-260, Janssen did a meta-analysis comparing the efficacy and safety of IV golimumab with other biologics, as well as SC golimumab in patients with RA. EX1050, 1. The meta-analysis states that there were “no statistical differences in efficacy between IV golimumab and IV infliximab, abatacept, or SC golimumab in terms of ACR 20, ACR 50, and ACR 70 at Weeks 12 to 16 and Weeks 24 to 26, HAQ-DI at 12–16

weeks, and DAS 28 at Weeks 12 to 16 and Weeks 24–26.” *Id.*, 6. That analysis supports my view that a POSA would have regarded the SC and IV therapies as having equivalent efficacy.

725. A POSA would have been motivated to combine the teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*, with a reasonable expectation of success, for the above reasons and the same reasons as set forth with regard to claim 1. *See* Paragraph 704.

726. For the above reasons, to the extent that the results recited in claims 5 and 6 are deemed to be limiting, the subject matter of claims 5 and 6, including the recited results, would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*. *See also* Paragraphs 663-689.

3. Claim 2, 4, and 7

727. Claims 2, 4, and 7 depend from claims 1, 3, and 5, respectively. Claims 2, 4, and 7 do not recite any additional clinical responses. Therefore, for the same reasons as with respect to claims 1, 3, and 5, the subject matter of claims 2, 4, and 7 would have been obvious to a POSA in view of the combined teachings of *NCT873-V24*, *PI2013-Aria*, *PI2015-Simponi*, *Van der Heijde*, and *Inman*.

F. Secondary Considerations

728. During prosecution, Applicant argued that the claimed invention yielded surprising and unexpected results. EX1010, 36-38, 66, 145-146 (Office Action Responses dated January 20, 2023, July 5, 2023, and November 4, 2024, respectively). As explained below, in my opinion, the results were not surprising or unexpected.

729. Applicant stated the following during prosecution: “[a]chieving an ASDAS inactive disease score (i.e. <1.3) after only 2 weeks or 4 weeks of IV golimumab treatment is a very surprising and unpredictable result” and achieving the claimed ASAS20 results was unexpected and surprising. *Id.* The purported unexpected results correspond to the results reported in Example 9 of *US566*, which assessed the effect of IV administration of golimumab 2 mg/kg in subjects with active AS. EX1004, 79:12-15. Janssen argued that these purported unexpected results could not have been expected based on the references cited by the examiner, including *Wong*, *Le*, and *Zhuang*.

730. I have been informed that to demonstrate unexpected results, the applicant is supposed to compare the results achieved by the claimed subject matter to the closest prior art. In my opinion, the closest prior art is *NCT873-V24*, which used the same 2 mg/kg IV golimumab dose and frequency as claimed in

US566 and indicated that clinical outcomes claimed in *US566* would be measured during the clinical trial. EX1014, 5, 6, 7-8.

731. Janssen compared its results to the teachings of *Wong*, *Le*, and *Zhuang*. Those are not the closest prior art for the following reasons.

732. *Wong* is not the closest prior art because *Wong* does not teach the 2 mg/kg IV administration of golimumab that is expressly taught in *NCT873-V24* and claimed in *US566*.

733. *Le* is not the closest prior art because unlike *NCT873-V24*, *Le* does not relate to treatment of AS and does not teach the 2 mg/kg IV administration of golimumab that is expressly taught in *NCT873-V24* and claimed in *US566*.

734. *Zhuang* is not the closest prior art because unlike *NCT873-V24*, it does not teach IV administration of 2 mg/kg at week 0, 4, and every 8 weeks thereafter as expressly taught in *NCT873-V24* and claimed in *US566*.

735. In addition, during prosecution, Janssen argued that IV golimumab provided surprising results relative to SC golimumab. EX1010, 36-37 (Office Action response dated Nov. 5, 2020). But it appears that Janssen did not compare conduct a head-to-head clinical study comparing SC and IV golimumab. EX1034, 114.

736. During review of the Simponi Aria BLA, FDA raised concerns about the adequacy of the data Janssen submitted for its IV golimumab. EX1034, 114.

According to FDA, Janssen “proposed bridging to efficacy data for subcutaneous (SC) golimumab on the basis of pharmacokinetic comparisons.” *Id.* The FDA responded that “determination is made more difficult by a lack of data derived from a direct comparison of the to-be-marketed IV dose regimen and the SC regimen.” *Id.* As demonstrated by FDA’s statements in *CDER Review* (see Paragraphs 242-248), it appears that Janssen never directly compared SC administration to IV administration. EX1034, 114; *see also* EX1032, 15 (“Data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available.”) As shown in *WO213*, the results obtained in clinical trials can vary based on, for example, the patient population or the length of time a subject has had active PsA. EX1025, 90:25-28, Table 11 (reporting that 46% of subjects with PsA for less than 2 years achieved ACR20, while 66% subjects with PsA from 2-5 years achieved ACR20).

737. It is inconsistent for Janssen to propose reliance on SC efficacy data when seeking FDA approval for IV golimumab, but then argue that the results obtained with IV golimumab are unexpectedly superior to SC golimumab. Without a head-to-head study, Janssen’s argument regarding unexpected superiority is not supported.

738. In addition, while claims 1-7 encompass administering golimumab, they are not limited to administering golimumab. The only evidence of alleged

unexpected results offered by patentees, however, relates to the results of administering golimumab. Applicants offered no evidence of how any other TNF α inhibitor within the scope of the claims would perform.

739. I reserve the right to respond to any allegations that objective indicia support the validity of the challenged claims.

XI. CONCLUSION

740. For the foregoing reasons, claims 1-10 of *US020* are anticipated or obvious over the prior art.

741. For the foregoing reasons, claims 1-7 of *US824* are obvious over the prior art.

742. For the foregoing reasons, claims 1-10 of *US982* are anticipated or obvious over the prior art.

743. For the foregoing reasons, claims 1-7 of *US566* are obvious over the prior art.

744. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Respectfully Submitted,

Roy Fleischmann

Dated: March 9, 2026

APPENDIX 1: LIST OF EXHIBITS RELIED UPON

In preparing my declaration, I relied upon the exhibits cited below, and any other document cited in my declaration.

Exhibit No.	Description
1001	U.S. Patent No. 11,041,020 to Harrison et al. (June 22, 2021) (“US020”)
1002	U.S. Patent No. 11,014,982 to Harrison et al. (May 25, 2021) (“US982”)
1003	U.S. Patent No. 12,122,824 to Harrison et al. (Oct. 22, 2024) (“US824”)
1004	U.S. Patent No. 12,291,566 to Harrison et al. (May 6, 2025) (“US566”)
1005	Declaration of Dr. Roy M. Fleischmann in Support of IPR Petition
1006	Dr. Roy M. Fleischmann <i>curriculum vitae</i>
1007	Excerpts from prosecution history of U.S. Application No. 16/517,594, now U.S. Patent No. 11,041,020
1008	Excerpts from prosecution history of U.S. Application No. 16/517,592, now U.S. Patent No. 11,014,982
1009	Excerpts from prosecution history of U.S. Application No. 17/320,490, now U.S. Patent No. 12,122,824
1010	Excerpts from prosecution history of U.S. Application No. 17/237,650, now U.S. Patent No. 12,291,566
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”)
1012	M. E. Weinblatt, et al., <i>Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial</i> , 72 ANN RHEUM DIS 381-389 (2013) (“Weinblatt”)
1013	M. Rossini, et al., <i>Why golimumab in the treatment of psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis?</i> , 66 REUMATISMO 4:285-303 (Apr. 2014) (“Rossini”)

Exhibit No.	Description
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-Simoni”)
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”)
1017	<i>Understanding the Difference: Standard Error vs. Standard Deviations</i> , SIXSIGMA (September 25, 2024), available at https://www.6sigma.us/six-sigma-in-focus/standard-error-vs-standard-deviation/ (“SixSigma”)
1018	<i>BLA Approved re BLA 125289</i> , FOOD AND DRUG ADMINISTRATION (Apr. 24, 2009) (“2009 Approval”)
1019	<i>BLA Approved re BLA 125433</i> , FOOD AND DRUG ADMINISTRATION (July 18, 2013) (“2013 Approval”)
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