Filed on behalf of: Accord BioPharma, Inc.
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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.

Case No. IPR2026-00258
Patent No. 12,122,824

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 12,122,824

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I. INTRODUCTION

Accord BioPharma, Inc., Intas Pharmaceuticals Ltd., and Bio-Thera Solutions, Ltd. ("Petitioner" or "Accord") respectfully request *inter partes* review of claims 1-7 of US12,122,824 ("*US824*" EX1003), assigned to Janssen Biotech, Inc. ("Janssen" or "PO").

The challenged claims broadly cover a method of treating active psoriatic arthritis ("PsA") in which golimumab is administered intravenously ("IV") at a dose of 2 mg/kg at weeks 0 and 4, then every 8 weeks thereafter. This method is anticipated by a clinical trial sponsored by Janssen, NCT02181673 ("*NCT673-V23*") (EX1011), which disclosed the exact same IV dose and schedule for the treatment of active PsA. *NCT673-V23* was publicly available more than one year prior to the earliest possible effective filing date of *US824* and is prior art.

The claims issued only because Janssen failed to disclose *NCT673-V23* to the examiner, leading the examiner to erroneously conclude that the prior art did not teach administering golimumab to PsA patients intravenously. Had Janssen directed the examiner's attention to *NCT673-V23*—its own prior art—the examiner would have gleaned that it disclosed not only IV administration to PsA patients, but all the other steps of the claimed method, and *US824* never would have issued.

While the challenged claims also recite specific efficacy parameters the claimed method of treatment must achieve, these parameters merely describe the

results Janssen obtained when it treated PsA patients with the method disclosed in *NCT673-V23*. The parameters do not alter or modify the steps of the method and thus cannot distinguish it over Janssen's disclosure of the method in *NCT673-V23*. Moreover, the law is clear that an obvious method cannot be made non-obvious merely by claiming the results it produces. *Baxter Healthcare Corp. v. Millenium Biologix, LLC*, IPR2013-00590, Paper 49, at 7–8 (PTAB Mar. 18, 2015) (claim elements not entitled to patentable weight because they "list various intended results," "do not recite positive acts that are carried out as part of the claimed methods," "[n]or do they specify any limitation on the manner in which the [method] step is to be carried out"); *id*. at 10-11; *Fresenius-Kabi USA LLC v. Cubist Pharms., Inc.*, Case No. IPR2015-00227, Paper No. 13, at 5–7 (PTAB May 14, 2015) ("the requirement of 'minimiz[ing] skeletal muscle toxicity' would be understood as nothing more than the intended result or consequence of administering daptomycin at the specifically recited dosage interval" because it "does not require anything beyond administering daptomycin at the express dosage intervals recited in the claims").

While Janssen will no doubt attempt to save its obvious claims by alleging that the method produced better-than-expected efficacy, as it did during prosecution, this is not supported by the law or facts. At best for Janssen, the small alleged improvement in efficacy is a difference in degree, not kind. Such a

difference is entitled to little weight as secondary evidence of non-obviousness. *In re Huang,* 100 F.3d 135, 139 (Fed. Cir. 1996) (even modifications to the prior art that result in "great improvement and utility" are not patentable unless they "produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art").

Further, Janssen cannot marshal evidence sufficient to prove the claimed method produces improved efficacy over prior art golimumab treatments, *e.g.*, Janssen's subcutaneous golimumab treatment for PsA, because it did not conduct a head-to-head clinical trial. Such a trial would have been necessary to substantiate Janssen's allegation.

Finally, a person of ordinary skill in the art ("POSA") would have expected the claimed method to be very effective for treating PsA. Long before the earliest possible effective filing date of *US824*, it was well known that a cytokine (messaging protein) known as TNFα played a key role in the molecular etiology of RA, PsA, and ankylosing spondylitis ("AS"), which are closely related diseases characterized by chronic inflammation and the damage that accrues therefrom. Because of this common mechanism, TNFα inhibitors such as golimumab were known to be equally effective at treating all three diseases. Indeed, in 2009, long before the earliest possible effective filing date of *US824*, the U.S. Food & Drug Administration ("FDA") had approved Janssen's

subcutaneous golimumab product, marketed as SIMPONI, as an effective treatment for all three diseases. Moreover, *the same dose and dosing schedule were approved as effective for all three diseases*. In 2013, FDA also approved Janssen's SIMPONI ARIA golimumab product, a follow-on IV formulation of golimumab, as effective for treating RA, and Janssen was also testing the same dose and dosing schedule for AS.

Crucially, the approved dose of SIMPONI ARIA was 2 mg/kg of golimumab infused over 30 minutes at weeks 0 and 4, and then every 8 weeks thereafter, *which is identical to the method of the challenged claims*. Janssen published this dose and schedule were the product of pharmacokinetic modeling intended to produce sustained plasma levels that met or exceeded those produced by SIMPONI. Given the equivalent efficacy of SC and IV golimumab for RA, the efficacy of SC golimumab for PsA, and the data showing the IV dose produced the same or higher plasma levels as the SC dose, a POSA would have had far more than a reasonable expectation that SIMPONI ARIA would be very effective for PsA. Indeed, as explained in the accompanying declaration of Dr. Roy Fleischmann, a prominent rheumatologist with many decades of experience researching and prescribing golimumab and other TNFα inhibitors to treat RA, PsA, and AS, the skilled practitioner would only have been surprised if the claimed dosing regimen failed to effectively treat PsA.

US824 should be seen for what it is: the invalid fruit of Janssen's scheme to hide key prior art from the examiner in order to evergreen its patent protection for SIMPONI ARIA and frustrate competition by lower-cost biosimilar products. PTAB review is necessary to prevent the public from having to pay higher prices arising out of Janssen's gaming of the patent system.

For reasons as explained more fully below, *inter partes* review should be instituted, and claims 1-7 should be found unpatentable.

A. Overview of *US824*

US824, titled "Anti-TNF Antibodies, Compositions, and Methods for the Treatment of Active Ankylosing Spondylitis," issued on October 2, 2024. The earliest possible effective filing date is January 30, 2017. EX1003, 1.

Though its title is directed to AS, the claims of *US824* are directed to PsA. *See* EX1003, claims 1-7, Abstract ("safe and effective treatment of active Psoriatic Arthritis (PsA)"). Indeed, the disclosure of *US824* broadly describes use of anti-TNFα antibodies to treat a wide range of TNF disorders, including both AS and PsA. *Id*., 38:10-39:9.

According to *US824*:

> 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.

Id., 83:587-67. *US824* notes "there is already a large and mounting body of evidence that TNFα inhibition is of major therapeutic benefit in this disease." *Id.*, 84:24-26.

US824 broadly describes anti-αTNF antibodies[1] and their use in treating PsA. *E.g.*, *id*., 2:60-3:8. *US824* also broadly describes the antibody as one that can bind "at least one TNF, or specified portions, variants, or domains thereof," and can also 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

[1] The scientific literature uses the terms "TNF" and "TNFα" to refer to the same tumor necrosis factor protein. *US824* uses the terms "TNF antibody," TNFα antibody," "anti-TNF antibody," and "anti-TNFα antibody" interchangeably, and this petition does as well. EX1003, 41:45-57, 14:15; EX1005 ¶51.

synthesis." *Id.*, 12:61-67. The antibodies may be used "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." *Id.*, 14:42-47. Immune diseases include, *inter alia*, RA, PsA, and AS. *Id.*, 38-10-67.

US824 acknowledges that "[m]any known and developed modes of administration can be used according to the present invention for administering pharmaceutically effective amounts of at least one anti-TNF antibody according to the present invention." EX1003, 46:51-55. The disclosed methods include "parenteral, subcutaneous, intramuscular, intravenous, intraarticular, intrabronchial," and more than 30 others. *Id.*, 47:20-30. As an example, *US824* recognizes that for parental administration, anti-TNF antibodies 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. *Id.*, 47:7-10.

Regarding IV administration, the specification acknowledges that golimumab had already been successfully used to treat RA using the same dosing regimen:

> 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 60 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 though 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.

EX1003, 84:35-53.

Example 9 describes a planned multicenter, randomized, double-blind, placebo-controlled trial of golimumab for the treatment of PsA and its initial results. *Id.*, 76:45-67-113:67. Golimumab is described as having a heavy chain of SEQ ID NO: 36, a light chain of SEQ ID NO: 37, binding to human TNFα with

high affinity and specificity, and neutralizing TNFα bioactivity. *Id.*, 78:53-57. As the specification explains, "[g]iven 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-TNFα agents." *Id.*, 84:32-35. The specification notes that 2 mg/kg of IV golimumab administered at weeks 0, 4, and every 8 weeks thereafter provided substantial benefits in improving RA. *Id.*, 84:38-54.

US824 presents preliminary efficacy and safety results for the study through week 24. EX1003, 114:58-117:48. Biologic-naïve PsA patients were randomized into two groups, with one group receiving a placebo and the other receiving 2 mg/kg golimumab at weeks 0, 4, and every 8 weeks thereafter, with the placebo group crossing over to golimumab at week 24. *Id.*, 113:1-20. As the specification reports, IV golimumab produced 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." *Id.*, 113:62-67.

US824 has three independent claims: 1, 3, and 5. Claim 6 depends from claim 5. Claims 2, 4, and 7 depend from claims 1, 3, and 5, respectively, and

further specify that the claimed method can be performed with or without methotrexate ("MTX"). Claim 1 is representative and is 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±10 minutes, at Weeks 0 and 4, 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±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.

Every claim encompasses the use of an anti-TNFα antibody to achieve certain clinical results and is limited to the dosing schedule of 2mg/kg, infused over 30±10 minutes, at Weeks 0 and 4, then every 8 weeks thereafter. Every claim also includes, or depends from, a claim that includes, the HC CDR1, HC CDR2, HC DCR3, LC CDR1, LC CDR2, and LC CDR3 sequences recited in claim 1.

(hereafter referred to as "the Claimed Sequences)." EX1003; EX1005 ¶¶121-137, 139.

B. Prosecution History

US824 issued from U.S. Patent Application No. 17/320,490 ("the '490 Application"), filed on May 14, 2021, which is a continuation of U.S. Patent Application No. 16/517,594, filed on July 20, 2019, now U.S. Patent No. 11,041,020, which is a continuation of U.S. Patent Application No. 15/818,063, filed on November 20, 2017, now abandoned, which claims priority to and the benefit of U.S. Provisional Application No. 62/452,079, filed on January 30, 2017. EX1003, 1.

During prosecution, the pending claims were rejected as anticipated by *Hoffmann* (EX1036) and/or as obvious over *Hoffman* in view of *Doyle* (EX1035). EX1009, 12-17, 65-71.

In response, two of the three pending independent claims were amended to recite "wherein said anti-TNF-α 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." EX1009, 80-83. The third independent claim was similarly amended to recite "wherein said 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." *Id*., 83.

Based on these amendments, Applicant argued that "Hoffman does not teach the recited dosing regimen or any of the recited criteria … and therefore nothing in Hoffman provides a skilled artisan with any predictability that golimumab can be delivered by IV infusion at the recited dosing regimen to subjects with psoriatic arthritis wherein said treatment would achieve the recited criteria." EX1009, 88 (Office Action response of December 8, 2023). In response, the Examiner withdrew the rejections under 35 U.S.C. §102 and §103. *Id*., 96-97, 115-122.

C. Scope and Content of the Prior Art

1. Background

RA is a chronic and progressive systemic inflammatory disease characterized by chronic inflammation of the joints that results in cartilage damage, progressive bone erosion, and functional decline. EX1026, 160. PsA and AS are also systemic inflammatory diseases. PsA is characterized by the chronic inflammation of the skin, entheses (sites where tendons and ligaments connect to the bones) and joints. AS is characterized by the chronic inflammation of entheses and the joints of the spine, which results in the formation of bony outgrowths on the spine and progressive functional decline. *Id.*

TNFα is a member of a family of structurally related cytokines, playing a pivotal role in various inflammatory processes within the body. EX1027, 27. Elevated levels of TNFα play a key role in the pathophysiology of chronic

inflammatory diseases such as RA, PsA, and AS. EX1015, 18. TNFα is naturally present in the body in both soluble and membrane-bound forms. The binding of soluble or membrane-bound TNFα to the TNFα receptor is one step in the cascade of molecular interactions that cause the inflammation characteristic of RA, PsA and AS. TNFα inhibitors decrease inflammation by acting as competitive antagonists to block the binding of soluble and membrane-bound TNFα to the TNFα receptor. EX1027, 34. The efficacy of a wide variety of TNFα inhibitors in treating and preventing RA, PsA, and AS established the importance of TNFα in the pathology of these diseases. EX1027, 27; EX1005 ¶¶43-48.

a) TNFα Inhibitors as Therapeutic Agents

TNFα is the single most successful antibody target molecule. Approved therapies that block the activity of TNFα were worth more than $15 billion in combined worldwide sales in 2010 alone. EX1028, 540. Before the introduction of TNF inhibitors, few options existed for the treatment of inflammatory rheumatic diseases such as RA, and patients with RA had a significantly decreased life expectancy. EX1029, 1. Like RA, patients with PsA have impaired physical function and health-related quality of life, and since PsA patients are more commonly younger and male, they have constraints on productivity similar to or worse than patients with RA. EX1043, 1667. The development of TNF inhibitors changed the therapeutic landscape, as they were shown to significantly decrease

not only the inflammation characteristic of RA, PsA, and AS, but also the damage that the inflammation causes. EX1029, 1; EX1026, 160. TNF inhibitors "suppress and control the inflammation driving these diseases and thereby prevent irreversible tissue damage and disability." EX1029, 1. The TNF inhibitors available before the earliest possible effective filing date of *US824*, including golimumab, were administered by both IV and SC routes. EX1026, 161. Those TNF inhibitors, including golimumab, demonstrated clear efficacy as compared to placebo, providing striking improvements in pain, functional ability, and inflammatory markers such as C-reactive protein. EX1030, 38.

PI2015-Simponi disclosed that TNFα 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; EX1005 ¶¶49-58.

b) Golimumab Was Approved Long Ago for the Treatment of PsA

Golimumab is a human IgG1κ monoclonal antibody that binds the soluble and transmembrane bioactive forms of human TNFα, preventing it from binding to its receptors. EX1015, 18; EX1013, 285; EX1005 ¶59.

Golimumab was used to treat PsA, AS, and RA well before the earliest possible effective filing date of *US824*. EX1013, 285. SIMPONI, Janssen's SC presentation of golimumab, received FDA approval for the treatment of RA, PsA,

and AS in 2009, and SIMPONI ARIA, Janssen's IV presentation of golimumab, received FDA approval for the treatment of RA in 2013. EX1018, 1; EX1019, 1, 7. The efficacy and safety profile of golimumab in RA, PsA, and AS "appears to be similar to other anti-TNF agents." EX1026, 159. But golimumab was recognized as having "the potential advantage of once monthly subcutaneous administration and the possibility of both subcutaneous and intravenous administration." *Id.*, 159, 161; EX1005 ¶¶60-62.

For example, *Wong* taught a method for treating AS using TNFα inhibitors, including golimumab. EX1024 ¶¶6-8. *Wong* taught that in a preferred embodiment, the TNFα inhibitor is administered intravenously. *Id.* ¶199. Similarly, *WO2013* taught a method for treating PsA using TNFα inhibitors, including golimumab, and taught IV administration of the TNFα inhibitor. EX1025, 2:22-3:8, 31:34-35, 58:10-13; EX1005 ¶65.

As explained above, *PI2015-Simponi,* the prior art prescribing information for SIMPONI, disclosed that a 50 mg dose administered by SC infusion once per month was approved to treat RA, PsA, and AS. For patients with RA, methotrexate (MTX) is administered with the golimumab, whereas for patients with PsA and AS, MTX is optional. EX1015, 4; EX1005 ¶60.

Rossini reviews and updates studies looking at the efficacy, safety, and pharmacokinetics of treatment of various conditions, including PsA, with

golimumab. EX1013, 285. According to *Rossini*, golimumab demonstrates dose-dependent pharmacokinetics with both IV and SC administration, with steady-state concentration reached at twelve weeks. *Id.*, 285. Clearance of golimumab is dependent on body weight. *Id.*, 286.

Rossini summarizes the main phase-III studies on the use of golimumab: GO-REVEAL (PsA, 405 patients); GO-RAISE (AS, 356 patients); and GO-AFTER, GO-MORE, GO-BEFORE, and GO-FORWARD (RA, 461, 3280, 637, and 444 patients, respectively). EX1013, 287, Table 1. *Rossini* demonstrates the large number of patients, including PsA patients, to whom golimumab had been administered well before the earliest possible effective filing date of *US824*. With respect to PsA patients, *Rossini* notes that treatment guidance recommends that 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, be treated with a TNFα inhibitor, preferably in combination with a DMARD. *Id.*, 286-87.

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." EX1013, 287. The 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 with ACR20 (American College of Rheumatology) response at week 14. *Id.* Secondary endpoints included: proportion of patients with ACR20 response at week 24; PASI75 (Psoriasis Area and Severity Index) response at week 14 in a subset of patients with ≥3% of body surface area involved by psoriasis at baseline; improvement in the 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.*; EX1005 ¶¶101-16.

Rossini reports at week 14, 48% of patients receiving golimumab overall achieved an ACR20 response, compared to only 9% of patients receiving placebo. In the 50 and 100 mg groups, 51% and 45% of patients achieved ACR20, respectively, regardless of MTX use, and both were significant ($P<0.001$) compared to placebo. EX1013, 287-88; EX1005 ¶¶66-79.

c) Golimumab Had Long Been Administered Intravenously

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; EX1005 ¶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." EX1034, 179; EX1005 ¶¶80, 243-44.

Analyzing the results of the Phase 3 GO-FURTHER trial, one of the trials listed by *Rossini*, *Weinblatt* evaluated the efficacy of IV golimumab at a dose of 2 mg/kg in patients with active RA who were also receiving MTX. EX1012, 381. The Phase 3 GO-FURTHER trial included 592 patients with active RA, who were randomized 2:1 to receive IV golimumab or placebo at weeks 0 and 4, and then every 8 weeks. *Id.* *Weinblatt* taught that study agents were infused over 30±10 minutes. *Id.*, 382; EX1005 ¶¶81-82.

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.

Weinblatt disclosed "[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, 385, Figure 2, panel A. Moreover, "[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.* *Weinblatt* also stated that 65% of patients achieved a EULAR (European League Against Rheumatism) response by week 2. *Id.*, 388. Thus, according to the authors, the "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; EX1005 ¶¶83-91.

Based on these clinical trials, in 2013 FDA granted Janssen marketing approval for an IV formulation of golimumab, which Janssen marketed under the trade name SIMPONI ARIA, for the treatment of RA. *PI2013-Aria*, a version of the approved label (prescribing information) for SIMPONI ARIA published in

2013, more than one year before the earliest possible effective filing date of the challenged claims, disclosed the dosing regimen is "2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks." EX1032, 1, 3. *PI2013-Aria* further disclosed the golimumab solution must be diluted with 0.9% w/v sodium chloride prior to administration, and the infusion time is 30 minutes. *Id.*, 1; EX1005 ¶100.

The pharmacokinetics of IV versus SC golimumab were also known. For example, *PI2015-Simponi* taught "the absolute bioavailability of subcutaneous SIMPONI was estimated to be approximately 53%," while a POSA would have understood that IV administered golimumab has a bioavailability of 100% EX1015, 19; EX1005 ¶93. Moreover, *Zhuang* taught that 2 mg/kg IV golimumab, administered once every 12 weeks, results in a maximum serum concentration (C_{max}) of about 45 μg/ml compared to only about 6 μg/ml for 100 mg of golimumab administered SC once every four weeks. EX1038, 84, Table II. *Zhuang* also taught golimumab, administered once every 12 weeks, results in an area under the curve ($AUC_{0\text{-}84d}$) of over 300μg·day/ml, compared to an $AUC_{0\text{-}28d}$ of only about 90 μg·day/ml for SC golimumab administered once every four weeks. *Id.*; EX1005 ¶¶92-96.

2. Key Prior Art

a) NCT02181673-V23 ("NCT673-V23"; EX1011)

NCT673-V23 is version 23 of a clinical trial protocol sponsored by Janssen Research titled "A Study of Golimumab in Participants with Active Psoriatic Arthritis." It was publicly available on ClinicalTrials.gov on January 8, 2016. EX1005 ¶161. Since it published more than one year before the earliest possible effective filing date of the challenged claims, it is prior art under post-AIA 35 U.S.C. §102(a). *Celltrion, Inc. v. Chugai*, IPR2022-00578, Paper 78 at 27-28 (Aug. 29, 2023) (a clinical trial protocol published on ClinicalTrials.gov was a prior art printed publication). Neither *NCT673-V23* nor any other version of NCT02182673 appear on the face of *US824* and the examiner did not rely on any version of NCT02182673.

The purpose of the study reported by *NCT673-V23* 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; EX1005 ¶162.

Under the *NCT673-V23* protocol, the PsA patients were dosed according to the following schedule:

> 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.

EX1011, 3; EX1005 ¶ 163. In addition, Janssen tested the exact same IV dose and dosing schedule in a clinical trial to treat AS, NCT02186873 ("*NCT873-V24*"). EX1014, 5; EX1005 ¶170.

NCT673-V23 disclosed that the primary outcome measure of the study is the percentage of patients who achieve an ACR20 response at week 14. EX1011, 4.

Secondary outcomes include determining the change from baseline in the HAQ-DI score at week 14, the change from baseline in the vdH-S score at week 24, the change from baseline in the SF-36 PCS at week 14, and the change from baseline in the SF-36 PCS at week 14. *Id.*, 4; EX1005 ¶168.

Thus, *NCT673-V23* taught what the examiner found was missing from the prior art—IV administration of golimumab for the treatment of active PsA.

b) *PI2013-Aria* (EX1032)

PI2013-Aria is a version of the prescribing information for SIMPONI ARIA that was publicly available in 2013. EX1032, 1; EX1005 ¶211. Since it published more than one year before the earliest possible effective filing date of the challenged claims, it is prior art under post-AIA 35 U.S.C. §102(a). *PI2013-Aria* does not appear on the face of *US824* and the examiner did not rely on *PI2013-Aria*.

PI2013-Aria disclosed that FDA had approved the following golimumab dose and dosing schedule as effective for the treatment of RA: "2 mg/kg intravenous infusion over 30 minutes at weeks 0 and 4, then every 8 weeks." EX1032, 1, 3. *PI2013-Aria* further disclosed that the solution needs to be diluted with 0.9% w/v sodium chloride prior to administration. *Id.*, 1.

As in *PI2015-Simponi* (EX1015), *PI2013-Aria* also describes the mechanism of action of golimumab as preventing "the binding of TNFα to its receptors,

thereby inhibiting the biological activity of TNFα (a cytokine protein)." EX1032, 15. *PI2013-Aria* also presents the clinical results, such as ACR20 scores, obtained in Janssen's clinical trial of SIMPONI ARIA for the treatment of RA. *Id.*, 17. *PI2013-Simponi* further reports that "data directly comparing 2 mg/kg intravenous administration and 50 mg subcutaneous administration are not available." *Id.*, 15; EX1005 ¶¶212-219.

c) *PI2015-Simponi* (EX1015)

PI2015-Simponi is the approved label for SIMPONI that was publicly available in 2015. EX1015, 1; EX1005 ¶220. Since it published more than one year before the earliest possible effective filing date of *US824*, it is prior art under post-AIA §102(a). *PI2015-Simponi* does not appear on the face of *US824* and the examiner did not rely on *PI2015-Simponi.*

PI2015-Simponi disclosed TNFα 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 TNFα. This interaction prevents the binding of TNFα to its receptors, thereby inhibiting the biological activity of TNFα (a cytokine protein).

***

> Elevated TNFα 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. TNFα is an important mediator of the articular inflammation that is characteristic of these diseases.

EX1015, 18.

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. *Id.*, 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; EX1005 ¶¶221-225.

d) *GO-REVEAL* (EX1041-1044)

GO-REVEAL refers to four reports by Kavanaugh on Janssen's Phase III trial for SC golimumab in PsA, which were published in 2009, 2012, 2013, and

2014 and are prior art to *US020*. EX1005 ¶179. Since Go-REVEAL published more than one year before the earliest effective filing date of the challenged claims, it is prior art under post-AIA 35 U.S.C. §102(a).

Kavanaugh 2009 disclosed that GO-REVEAL was a PHASE-III, multicenter, randomized, double-blind, placebo-controlled study of the safety and efficacy of SC administered golimumab for the treatment of PsA, and the largest study of its kind. EX1041, 977. Subjects received SC injection of placebo, 50 mg of golimumab, or 100 mg of golimumab every 4 weeks. *Id.* The primary end point of the 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.* For the combined golimumab group (patients receiving both 50 mg and 100 mg of golimumab), 48% of subjects achieved ACR20 at week 14, compared to only 9% of subjects administered placebo. *Id.*, 979. In the group given 50 mg, 51% of patients achieved ACR20 at week 15, while 45% of patients in the group given 100 mg did. *Id.* Subjects in both 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)." *Id.*, 980.

Kavanaugh 2009 also taught that patients receiving golimumab achieved the following clinical results as well:

> 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.

In 2009, the authors concluded that "[g]olimumab, a human monoclonal antibody against TNFα, was demonstrated to be efficacious and generally well tolerated when administered subcutaneously every 4 weeks during 24 weeks of treatment." *Id.*, 984.

The *GO-REVEAL* study authors also looked at clinical, radiographic, and safety findings at 1 year, reporting the change from baseline to week 24 in PsA modified Sharp/Van der Heijde score [SHS]. EX1042, 2504-05. Radiographs were obtained at baseline, week 24, and week 52. *Id.*, 2505. "[C]hanges 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)." *Id.*, 2509. The authors also reported 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. The authors noted further 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; EX1005 ¶¶180-186, 187-196.

e) *WO213* (EX1025)

WO213 was published in 2007. EX1025; EX1005 ¶197. Since it published more than one year before the earliest effective filing date of the challenged claims, it is prior art under post-AIA 35 U.S.C. §102(a).

WO213 is directed to methods and composition for treating PsA using a TNFα inhibitor, such as a TNFα antibody, wherein the antibody may be golimumab. EX1025, 1:24-25, 30-31,32:34-35, 37:32-38:10. Like the *US824* specification, *WO213* taught multiple modes of administration, including parenteral, oral, and SC. *Id.*, 58:3-14. *WO213* also taught that in embodiments of the invention, the TNFα inhibitor achieves an ACR20 response from 59% to 75% as an effective treatment for PsA. *Id.*, 2:22-3:8. Although *WO213* uses adalimumab as an exemplary TNFα antibody, it also taught that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents, which includes adalimumab. EX1025, 44:37-45:10.

WO213 provides examples using the TNFα inhibitor adalimumab, which the inventors describe as "a representative of a TNFα inhibitor," and that the examples may be "used as a guideline for determining the efficacy of a TNFα inhibitor," providing specific efficacy outcomes. EX1025, 80:14-20. In Example 1, patients were given adalimumab, SC 40 mg, every other week or placebo. *Id.*, 81:6-82:16. At 24 weeks, 57% of the patients in the adalimumab group achieved ACR20

compared to 15% for placebo. *Id.*, 82:22-25. Example 5 describes an open label extension of Example 1 to determine the 24- and 48-week efficacy of adalimumab for arthritis and disability. *Id.*, 89:23-26. Although arthritis-related outcomes varied by the duration of time the subject had PsA at week 24, the inventors concluded that adalimumab was efficacious regardless of the time the subject had suffered with PsA. *Id.*, Table 11, 90:25-28; 95:10-13. Example 6 assessed physical function using HAQ DI, in which scores range from 0 to 3, with lower scores indicating less functional loss. *Id.*, 95:30-33. "At weeks 12 and 24, significantly more patients in the adalimumab group had no functional loss (HAQ DI=0) versus those treated with placebo." EX1025, 96:11-15. Example 12 looked at radiographic efficacy in a post-hac analysis of Example 1, using data from subjects that had evaluable radiographs at baseline and week 24. *Id.*, 126:17-30. 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 ("mTSS"), which is a different name for the Van der Heijde-Sharp score ("vdH-S") (EX1005 ¶112), from baseline to week 24 being 1.0 for placebo (n=152), and -0.2 for adalimumab (n=l44) ($p<0.001$ vs. placebo for the adalimumab group). EX1025, 127:29-38. Example 13 looked at the use of adalimumab in clinical practice. *Id.*, 131:17-18. Treatment was effective as shown by the ACR scores at week 12, wherein 72% of patients achieved an ACR20 of

72%. *Id.*, Table 49, 134. *WO213* concludes that "adalimumab is efficacious for skin and joint disease in patients with PsA." *Id.*, 84:20-21; EX1005 ¶¶198-210.

3. Level of Ordinary Skill in the Art

A 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 have collaborated with others, including scientists skilled in related fields typically employed in pharmaceutical development, such as pharmacokineticists and formulators. EX1005 ¶¶39-42.

II. GROUNDS FOR STANDING (37 C.F.R. §42.104(A))

Petitioner certifies that *US824* is available for IPR under 37 CFR §42.104(a) and that Petitioner is not barred or estopped from bringing this petition or challenging any claim of *US824* on the grounds identified herein. Petitioner has not filed a civil action challenging the validity of *US824*.

III. MANDATORY NOTICES UNDER 37 C.F.R. §42.8

The following mandatory notices are provided pursuant to 37 C.F.R. §§42.8(a)(1) and 42.8(b).

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

Accord BioPharma, Inc., Intas Pharmaceuticals Ltd., and Bio-Thera Solutions, Ltd., are the real parties in interest.

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

Petitioner is also filing on the same day as this petition:

IPR2026-00256, challenging US Patent No. 11,014,982 (method of treating AS);

IPR2026-00257, challenging US Patent No, 11,041,020; and (method of treating PsA)

IPR2026-00259, challenging US Patent No. 12,291,566 (method of treating AS).

US824, as well as the patents being challenged in the IPRs listed above, were asserted in *Janssen Biotech, Inc., et. al. v. Accord BioPharma, Inc., et al.*, No. 1:26-cv-00222 (D. Del. Mar. 3, 2026), but Janssen and Petitioner filed a stipulation dismissing them from the litigation without prejudice. *See Janssen Biotech, Inc., et. al. v. Accord BioPharma, Inc., et al.*, No. 1:26-cv-00222 (D. Del. Mar. 17, 18, 2026), D.I. 12, 13.

C. Lead and Back-Up Counsel and Service Information (37 C.F.R. §42.8(b)(3), (4))

Lead counsel is Lora M. Green (Reg. No. 43,541). Back-up counsel are:

- Robert Cerwinski (to be admitted *pro hac vice*)
- Keith A. Zullow (Reg. No. 37,975)
- Michael Cottler (Reg. No. 79,455)
- Michael W. Johnson (Reg. No. 63,731)
- Heather M. Schneider (Reg. No. 56,484)
- Yahn-Lin (Franklin) Chu (Reg. No. 75,946)

- Counsel associated with USPTO Customer Number 192101.

Petitioner hereby consents to electronic service. Please direct all correspondence to lead and back-up counsel at the contact information below. A power of attorney accompanies this petition.

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D. Payment of Fees Under 37 C.F.R. §42.15(a) and §42.103

The required fees are submitted herewith. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 604962.

IV. OVERVIEW OF CHALLENGE AND PRECISE RELIEF REQUESTED

A. Challenged Claims and Relief Requested

Petitioner requests institution of IPR against claims 1-7 of *US824* and cancellation of these claims as unpatentable.

B. Statutory Grounds of Challenge

Each of the following prior art references and/or combinations of references renders the challenged claims unpatentable:

Ground	Claims	35 U.S.C.	References
1	1-7	§102	*NCT673-V23* (EX1011)
2	1-7	§103	*NCT673-V23* and *PI2013-Aria* (EX1032)
3	1-7	§103	*NCT673-V23, PI2013-Aria*, *PI2015-Simponi (EX1015), GO-REVEAL* (EX1041-1044), and *WO2013* (EX1025)

Petitioner's full statement of the reasons for the relief requested is set forth in greater detail below, as supported by the declaration of Dr. Roy M. Fleischmann, M.D.. EX1005. Dr. Fleischmann has decades of experience as a practicing physician in the field of rheumatology, is a Master of the American College of Rheumatology, was named a "World Expert" based on the impact of his publications, and has also been a principal investigator in multiple Phase 1-4

clinical trials of the five approved TNFα inhibitors (etanercept, infliximab, adalimumab, golimumab and certolizumab pegol). EX1005 ¶¶6-15; EX1006.

V. CLAIM CONSTRUCTION

Claim terms should be given their ordinary and customary meaning they would have to a POSA, when read in light of the specification. 37 C.F.R. §42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312-13 (Fed. Cir. 2005) (*en banc*). Accordingly, the terms of the challenged claims should be given their plain and ordinary meaning. To avoid confusion, the plain and ordinary meaning of five claim terms are discussed below, none of which are defined in the patent.

A. "Administering to a Subject" Encompasses Administration to a Single Subject

The method of independent claims 1, 3, and 5 all recite "administering to a subject having active psoriatic arthritis." A POSA would understand that administering to "a subject" encompasses administration to a single subject. EX1005 ¶396.

B. "Treating" Should Not Be Construed as Limiting the Claimed Method

The preamble of the independent claims describes them as being drawn to "a method for treating a tumor necrosis factor alpha (TNFα) related condition wherein that TNFα related condition is active psoriatic arthritis." As discussed above, each

of the independent claims is narrowly drawn to a specific IV dosage, infusion time, and dosing frequency.

The term "treating" in the preamble should not be construed as limiting the claimed method because it does not limit how the actual steps of the claimed method are to be performed. *Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc.*, 246 F.3d 1368, 1376 (Fed. Cir. 2001) ("The expression does not result in a manipulative difference in the steps of the claim."); *In Re: Copaxone Consol. Cases*, 906 F.3d 1013, 1023 (Fed. Cir. 2018). The active step required by the independent claims 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 the Claimed Sequences and doing so via "a dose of 2 mg/kg, over 30±10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter," which is "a safe and effective amount." "Treating" does not add any step to, otherwise modify, the active step of "administering" a "safe and effective amount" of golimumab to "a subject having active psoriatic arthritis. EX1005 ¶¶391-94.

Even if "treating" were found to be a limitation, the claims and specification make clear that the term should be construed as referring to the act of administering the claimed dosing regimen to the patient, and not as requiring that the patient actually experience a clinical benefit from the treatment. For example,

independent claim 5 recites that only ≥65% of patients achieve an ACR20 at week 14 of treatment. That is, claim 5 acknowledges that not all patients achieve an ACR20 at week 14. Thus, "treating" as used in claims refers to the act of administering the claimed golimumab to the patient regardless of clinical benefit, since it encompasses administering golimumab to patients with active PsA that do not experience a clinical benefit. EX1005 ¶¶391-95.

Further, if the preamble required that a patient actually experience a clinical benefit before falling within the scope of the claims, a POSA would be unable to determine, prior to completing the claimed treatment, whether their activity fell within the claims or not. As Dr. Fleischmann explains, when treating a particular patient with active PsA, it cannot be predicted *a priori* whether that particular patient will respond to the treatment. *Id*.

C. The Claimed Clinical Results Do Not Limit the Methods of Treatment

Independent claims 1, 3, and 5 recite achieving the following clinical results:

- **Claim 1:** "wherein at week 14 of treatment patients treated with the anti-TNF-αantibody 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 ≥65% of patients receiving the treatment achieve ACR20 at week 14 of treatment."

In addition, dependent claim 6, which depends from claim 5, adds the following clinical result:

- **Claim 6:** wherein said ≥65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%.

EX1003, claims 1, 3, 5, and 6.

These claimed results are merely the clinical responses reported in Table 8 of Example 9 of *US824*, which reports the results of the clinical trial disclosed in *NCT673-V23*. EX1005 ¶¶397-400. As explained, this clinical trial employed the claimed dosing regimen. Thus, the claimed efficacy is merely the result of administering the claimed dosing regimen. It does not further limit that regimen in any way. Nor does it "result in a manipulative difference in the steps of the claim." *Bristol-Myers*, 246 F.3d at 1376.

Moreover, as discussed in Section V.A., although the claims cover administering the anti-TNFα antibody to a single patient, the results recited in the claims refer to the aggregate clinical trial results in the specification. That trial included 239 subjects receiving placebo, and 241 receiving 2mg/kg golimumab. EX1001, 116:28, :Table 8; EX1005 ¶¶401-2. A POSA reading claim 5 cannot glean from these aggregate results whether a particular patient will be among the 65% of patients who achieve ACR20 at week 14 or the 35% of patients who do not. EX1005 ¶¶401-03. When read in light of the clinical data in the specification, it is clear that the claims require only that a patient be administered the claimed dosing regimen—which has been shown to have the claimed clinical efficacy—not that the particular patient being treated experience the claimed clinical efficacy.

Regardless, as discussed in Section VI.A-C below, to the extent the results of administering golimumab at a dose of 2 mg/kg, over 30±10 minutes, at weeks 0 and 4, and then every 8 weeks thereafter are determined to be limiting, those results would have been anticipated or obvious to a POSA. EX1005, Sections VIII.B-D.

D. The Term "at least one isolated mammalian anti-TNF-α antibody comprising [the Claimed CDR Sequences]" Encompasses Golimumab and Other Antibodies

US824 defines SEQ ID NOs 36 and 37 as the "Golimumab Heavy Chain (HC)" and "Golimumab Light Chain (LC)", respectively. EX1003, 135-139. SEQ

ID NO 36 has the claimed heavy chain CDR sequences and SEQ ID NO 37 has the claimed light chain CDR sequences. *Id.* Accordingly, the term "at least one isolated mammalian anti-TNF-α antibody comprising [the Claimed CDR Sequences]" encompasses golimumab, but does not exclude other antibodies. EX1005 ¶405.

E. Administering "with or without methotrexate (MTX)" Is Not Limiting

Dependent claims 2, 4, and 7 each further recite administering the composition or antibody "with or without methotrexate (MTX)." This fails to limit independent claims 1, 3, and 5, as the word "or" causes the MTX to be optional. EX1005 ¶406.

VI. GROUNDS FOR UNPATENTABILITY

Independent claims 1, 3, and 5, and dependent claim 6, are drawn to a method for treating active PsA involving "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 CDR sequences. Each of those claims requires "a dose of 2 mg/kg, over 30±10 minutes, at Weeks 0 and 4, then every 8 weeks (q8w) thereafter." Dependent claims 2, 4, and 7 specify that the antibody be administered "with or without methotrexate."

As explained below, *NCT673-V23* anticipates and renders obvious the specific dosing regimen required by claims 1, 3, 5, and 6. It also anticipates dependent claims 2, 4, and 7, because it teaches use "without" MTX.

A. Ground 1: Claims 1-7 are Anticipated by *NCT673-V23*

NCT673-V23 anticipates claims 1-7 because it taught all of the steps required by the recited method, arranged as in the claim. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); EX1005 ¶407.

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, 5) "*A method for treating a TNF-α related condition, wherein the TNF-α related condition is active psoriatic arthritis, the method comprising:*"

NCT673-V23 disclosed a clinical study to evaluate the IV administration of golimumab for the treatment of PsA. As discussed above (Section V.D), a POSA would have understood that golimumab is an anti-TNFα antibody having a heavy chain (HC) comprising SEQ ID NO:36 and a light chain (LC) SEQ ID NO:37. EX1005 ¶405. Thus, NCT673-*V23* meets all of the limitations of the preamble. EX1005 ¶¶408-11.

(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]*"

As noted above, *NCT673-V23* studied the efficacy of 2 mg/kg of golimumab administered by IV infusion to patients with active PsA. EX1011, 1-2. Thus, *NCT673-V23* meets the limitation of a safe and effective amount as set forth in claims 1, 3, and 5. EX1005 ¶¶412-13.

Independent claims 1 and 3 further require "at least one pharmaceutically acceptable carrier or diluent." The claims limit the safe and effective amount to IV golimumab, 2 mg/kg, at weeks 0 and 4, and then every 8 weeks thereafter. Section V.B.; EX1005 ¶414. Thus, *NCT673-V23* meets the limitation of a safe and effective amount as set forth in claims 1, 3, and 5. EX1005 ¶¶413-15.

NCT673-V23 does not expressly state that the golimumab was dispersed in a pharmaceutically acceptable carrier or diluent as required by independent claims 1 and 4. But its disclosure must be viewed from the perspective of a POSA. *See Scripps Clinic & Res. Found. v. Genentech, Inc.*, 927 F.2d 1565, 1576 (Fed. Cir. 1991) (to anticipate, "[t]here must be no difference between the claimed invention and the reference disclosure, as viewed by a person of ordinary skill in the field of

the invention"). *NCT673-V23* disclosed that IV administration is the administration of a fluid to a vein. EX1011, 3. A POSA would understand that a fluid containing golimumab, a protein that when isolated is a solid, necessarily contains a liquid carrier or diluent. EX1005 ¶¶414-15. Because this was a double-blind study, a POSA would also know that the drug and placebo both have to be diluted to the same amount and infused at the same rate. *Id.* A POSA also would have been aware of *PI2013-Aria*, drawn to Janssen's IV golimumab product for treating RA, in which the golimumab is diluted with 0.9% w/v sodium chloride prior to infusion, which is a pharmaceutically acceptable carrier or diluent. EX1032, 1. A POSA 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. Accordingly, *NCT673-V23* disclosed this limitation. EX1005 ¶¶412-16.

(c) **(Claim 1) "*wherein said composition is administered via intravenous (IV) infusion"***

(Claim 3) "*wherein said composition is administered via IV infusion*"

(Claim 5) "*wherein said anti-TNF-α antibody is administered via intravenous (IV) infusion*"

As discussed above, *NCT673-V23* evaluated the efficacy of 2 mg/kg of golimumab administered intravenously to patients with active psoriatic arthritis.

Section I.C.2.a. Thus, *NCT673-V23* discloses the limitations of the independent claims. EX1005 ¶¶417-18.

(d) (Claims 1, 3) "*wherein said anti-TNF-α 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, and*"

(Claim 5) "*wherein said 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*"

NCT673-V23 discloses the recited dosing regimen for IV administration of golimumab to treat active PsA: IV infusion of 2 mg/kg at weeks 0, 4, and every 8 weeks thereafter. EX1011, 3-4. Although *NCT673-V23* does not expressly state that the golimumab was infused over a period of 30±10 minutes, its disclosure must be viewed through the eyes of a POSA. *See Scripps Clinic & Res. Found.,* 927 F.2d at 1576. A POSA would have recognized that in *NCT673-V23* Janssen was administering IV golimumab to PsA patients. The POSA would have been aware of *PI2013-Aria*, Janssen's FDA-approved label for IV golimumab, known as SIMPONI ARIA, which 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. Thus, *NCT673-V23* discloses this limitation. EX1005 ¶¶417-18.

(e) **(Claim 1)** ***"wherein at week 14 of treatment patients treated with the anti-TNF-αantibody 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 ≥65% of patients receiving the treatment achieve ACR20 at week 14 of treatment"***

As discussed in Section V.C., the clinical results recited in claims 1, 3, and 5 do not separately limit the claimed method, but merely describe the result of administering the claimed dosing regimen: 2 mg/kg of golimumab at weeks 0 and 4, and then every 8 weeks thereafter. EX1005 ¶¶397-404. This dosing regimen is expressly taught in *NCT673-V23*. Nothing more is required for anticipation.

Even if the efficacy further limited the claims, to the extent the dosing regimen of claims 1, 3, and 5 produces the claimed efficacy, so must the same regimen reported in *NCT673-V23*. The methods are the same, and in fact, are drawn to the same clinical trial performed on the same subjects. EX1005 ¶¶419-20. To the extent one produces the recited outcomes, so must the other. *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("It is a general rule that merely

discovering and claiming a new benefit of an *old* process cannot render the process again patentable."); *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("a compound and all its properties are inseparable; they are one and the same thing"); *King Pharms., Inc. v. Eon Labs., Inc.*, 616 F.3d 1267, 1275-76 (Fed. Cir. 2010) (to anticipate, the prior art need only meet the claimed limitation to the extent the patented method does); *Catalina Mktg. Int'l, Inc. v. Coolsavings.com, Inc.*, 289 F.3d 801, 809–10 (Fed. Cir. 2002) (an inventor may not obtain a patent on a process having the same steps as a prior art process, in which the new process merely identifies a new, advantageous property of the prior art process); *Celltrion,* IPR2022-00578, Paper 78 at 28-31.[2]

[2] *But see Allergan Sales, LLC. v. Sandoz, Inc.*, 935 F. 3d 1370, 1378-79 (Fed. Cir. 2019) (Chief Judge Prost, concurring) (adding the "narrow but crucial point" that because of the term "comprising…" there is "no basis for us to conclude with any certainty that the safety and efficacy requirements of the 'wherein' clauses would always result from two doses of (1) any formulation of the combination at (2) any interval in a 24-hour period."). *Allergan* is inapposite because, as noted by Chief Judge Prost, other components of the formulation could affect the safety of the composition. In contrast, *US824* discloses that a wide variety of compositions and excipients may be used (EX1003, 32:32-35:48), it does not identify any specific

For this reason, *NCT673-V23* anticipates the clinical results described in claims 1, 3, and 5.

2. Claim 6

Claim 6 is dependent on claim 5 and further recites "wherein said ≥65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%."

NCT673-V23 anticipates this claim for the same reasons as claim 5, as discussed above in Section VI.A.1.d. EX1005 ¶¶421-22.

3. Claims 2, 4, and 7

Claims 2, 4, and 7 further recite administering the composition "with or without methotrexate (MTX)." These claims are anticipated for the same reasons as claims 1, 3, and 6, as the golimumab must necessarily be administered "with or without methotrexate (MTX)." Section VI.A.1. *NCT673-V23* does not require MTX and thus teaches administration "without" it. EX1005 ¶¶423-24.

formulations (*id.*, Example 9), and a POSA would have understood that the safety and efficacy depend on the dose and dosing schedule of the golimumab, not the excipients. EX1005 ¶129.

B. Ground 2: Claims 1-7 are Obvious in View of *NCT673-V23* and *PI2013-Aria*

Ground 1 explains how *NCT673-V23* anticipates claims 1-7 and is incorporated by reference. Section VI.A. To the extent that a POSA would not have understood when reading *NCT673-V23* that the golimumab is in a pharmaceutically acceptable carrier or diluent as required by claims 1 and 3, that would have been obvious. EX1005 ¶¶423-27. A POSA would have understood that solid golimumab could not be infused intravenously without first being dissolved within a liquid carrier or diluent. Further, *PI2013-Aria*, which is drawn to treating patients with the same IV dose of golimumab, taught 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; EX1005 ¶¶429-37.

A POSA would have been motivated to use the diluent of *PI2013-Aria* when administering the IV golimumab in *NCT673-V23*, and would reasonably have 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. EX1005 ¶436. "Obviousness does not require absolute predictability of success.... *all that is required is a reasonable expectation of success.*" *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988) (emphasis added). Claims 5 and 6 do not recite this limitation and are obvious based on *NCT673-V23* alone or in combination with *PI2013-Aria.* EX1005 ¶¶435-39.

Independent claims 1, 3, and 5 also recite that the antibody (claim 1) or composition (claims 3 and 5) is administered such that said anti-TNFα antibody or composition "is administered at a dose of 2 mg/kg, over 30±10 minutes, at weeks 0 and 4, then every 8 weeks (q8w) thereafter." To the extent that a POSA would not have gleaned from *NCT673-V23* that the golimumab is to be infused over 30±10 minutes, that infusion time would have been obvious. As explained, *PI2013-Aria* expressly teaches this infusion time for the same golimumab dose and schedule. Section I.C.2.b.. A POSA would have been motivated to use the infusion time of *PI2013-Aria* with the dosing regimen of *NCT673*-V23 for the same reasons explained above with respect to the diluent, and would have reasonably expected success with it, since FDA had approved this infusion time for the dosing schedule common to both references. EX1005 ¶¶428-48.

Claims 2, 4, and 7 add the limitation that the anti-TNF-α antibody is "administered with or without methotrexate." Because, as explained in Section

V.E., the optional choice of administering MTX does not limit the claims, and *NCT673-V23* discloses administration without MTX, these claims are also obvious. EX1005 ¶¶449-52.

As explained in Section V.C., the clinical results recited in 1, 3, 5, and 6 do not comprise additional limitations of the claimed method, but merely describe the results produced by the claimed method. Although neither *NCT673-V23* nor *PI2013-Aria* disclose the claimed clinical outcomes, a POSA following the teachings of *NCT673-V23* would have observed precisely the claimed results because the trial cited in Example 9 of *US824* is the same clinical trial of *NCT673-V23*. EX1005 ¶¶397-404. Janssen cannot render the otherwise-obvious method of claims 1-7 non-obvious by merely reciting the results of that method, even if it produces somewhat better results than expected. *In re Kubin*, 561 F.3d 1351, 1357 (Fed. Cir. 2009) (as the prior art rendered the protein obvious, it also rendered obvious its binding properties, as it would remove from the public "that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art." (citing *In re Wiseman*, 596 F.2d 1019, 1023 (CCPA 1979)); *id.* at 1357 (citing *Gen. Elec. Co. v. Jewel Incandescent Lamp Co.,* 326 U.S. 242, 249 (1945) ("It is not invention to perceive that the product which others had discovered had qualities they failed to detect.")); *Woodruff*, 919 F.2d at 1578; *Papesch*, 315 F.2d at 391; *Catalina Mktg.*, 289 F.3d at 809–10.

For the above reasons, *NCT673-V23* and *PI2013-Aria* would have rendered claims 1-7 obvious to a POSA. EX1005 ¶¶428-452.

C. Ground 3: Claims 1-7 are Obvious in View of *NCT673-V23, PI2013-Aria, PI2015-Simponi*, *GO-REVEAL,* and *WO2013*

Grounds 1 and 2 are hereby incorporated by reference. EX1005 ¶¶408-452. As discussed above, *NCT673-V23* taught the only active step required by the claims—administering 2 mg/kg of golimumab intravenously to a patient with active PsA at weeks 0 and 4, and then every 8 weeks thereafter. *PI2013-Aria* taught the use of a carrier or diluent, as well as the 30-minute infusion time. Section I.C.2.b. This is where the obviousness analysis should end. But to the extent that the clinical results recited in claims 1-7 are deemed to be material additional limitations, *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi, GO-*REVEAL, and *WO213* would have rendered those results obvious. EX1005 ¶453. The efficacy parameters set forth in the claims recite nothing more than the standard clinical endpoints that had been assessed in connection with golimumab and other TNF-α therapies. Further, the claimed values of those endpoints are not clinically distinguishable from the efficacy reported in the prior art for golimumab and other TNF-α therapies.

1. Claims 1-2

Claim 1 recites the clinical results of "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, 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." EX1003; EX1005 ¶¶454-58.

NCT673-V23 would have taught a POSA to measure one or more of these efficacy parameters. *NCT673-V23* taught that the primary outcome measure of the study is the percentage of patients who achieve an ACR20 response at week 14. EX1011, 4. Secondary outcomes include determining the change from baseline in the HAQ-DI score at week 14, the change from baseline in dactylitis scores at week 14; the change from baseline in the SF-36 PCS at week 14, the change from baseline in the SF-36 PCS at week 14, and the change from baseline in the vdH-S score at week 24. *Id.*, 4. *NCT673-V23* would have motivated a POSA to assess the efficacy of the claimed method in exactly the same way as described in the claims. EX1005 ¶¶458-60. This is not surprising since the claimed parameters are nothing more than standard clinical endpoints that are routinely assessed in connection with golimumab and other TNFα therapies. EX1025, 23:24–27:21; EX1005 ¶460. *WO213* also provides a description of how to determine the

efficacy of a TNFα inhibitor, which includes these same parameters. EX1025, 80:14-20, 90:10, Table 10; EX1005 ¶461.

A POSA would have expected the method described in *NCT673-V23* to achieve similar efficacy to the claimed outcomes based on the efficacy of SC and IV golimumab reported in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*. EX1005 ¶462. *GO-REVEAL,* which reported the results of treating patients with active PsA with monthly 50 mg or 100 mg injections of SC golimumab, concluded that the 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. Patients received benefit from both the 50 mg and 100 mg doses at week 14. *Id.*, 979-80. Further, "subcutaneous golimumab (at doses of 50 mg and 100 mg) administered every 4 weeks significantly improved active PsA and associated skin disease." *Id.*, 984. In pertinent part, the GO-REVEAL study demonstrated the following improvements in two of the claimed clinical criteria:

> 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. These results have no clinically meaningful difference from the claimed results for the same criteria. EX1005, ¶¶462-65.

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; EX1005 ¶186.

The prior art also reported that SIMPONI ARIA, which employs the same IV golimumab dose and schedule as the claims, had efficacy similar to SIMPONI for the treatment of RA. EX1032, 1; EX1050, 6; EX1005 ¶466. This is unsurprising 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. EX1005 ¶466. Given that the same dose of SIMPONI was known to be equally effective to treat RA and PsA, and that SIMPONI ARIA was known to be effective to treat RA, a POSA would have expected that SIMPONI ARIA would also be effective at treating PsA. *E.g.*, EX1014, 5 (Janssen tested the exact same IV dose and dosing schedule in a clinical trial to treat AS).

Other similar TNFα therapies for the treatment of PsA also achieved similar clinical results. For example, *WO213*, which describes methods for treating PsA using TNF-α inhibitors such as golimumab and other anti-TNF-α antibodies, taught that anti-TNF-α antibody therapies generally met or exceeded the claimed efficacy parameters. EX1025, 1:24-25, 30-31; 32:34-35; Section I.C.2.e; EX1005 ¶467. Table 42 of Example 11 disclosed that when dosed subcutaneously, adalimumab, an anti-TNF-α antibody therapy approved for the treatment of RA, PsA, and AS, produced a HAQ-D1 clinical score of -0.3±0.5 SD, which overlaps with the claimed efficacy of -0.6±0.53 SD. EX1025, 117-118. *WO213* also taught that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents, including adalimumab. EX1025, 44:37-45:10; EX1005 ¶¶468-71.

To the extent that there are some small differences between the claimed parameters and the clinical data reported for prior art golimumab treatments, a POSA would not have regarded those differences as being clinically significant. EX1005 ¶472. 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. EX1005 ¶¶245-48, 473. *See* 21 C.F.R. §21.202.1(d)(2)(e)(6)(ii); EX1051, 3; EX1034, 134 ("In general, two adequate and well-controlled

superiority trials are needed to support a comparative efficacy claim."). 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 at 114; *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.")

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; EX1005 ¶¶249-60. That meta-analysis confirmed that these therapies had equivalent efficacy, concluding 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; EX1005 ¶474. Further, 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. *Id.* ¶475.

Further, as Dr. Fleishmann explains, the standard deviations of the claimed efficacy parameters are quite large, which a POSA would regard as further evidence there are no clinically meaningful differences between the efficacy data

in GO-REVEAL for SIMPONI and the claimed regimen. EX1005 ¶¶117-20, 454-58.

In summary, *NCT673-V23* would have motivated a POSA to apply the claimed dosing regimen to patients with active PsA, and to measure the resulting efficacy using the claimed parameters. The results of this obvious method cannot confer patentability. *Kubin*, 561 F.3d at 1357*; Woodruff*, 919 F.2d at 1578; *Papesch*, 315 F.2d at 391; *Catalina Mktg.*, 289 F.3d at 809–10. Even if they did, a POSA would have been motivated to consider the results in *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*, because they all concern the efficacy of golimumab and equivalent anti-TNFα antibody treatments. The data in those references would have caused the POSA to expect the regimen in *NCT673-V23* to be very efficacious, and similar to the claimed parameters. The claims therefore would have been obvious. EX1005 ¶476.

Indeed, a POSA would not have been surprised if the claimed IV dosing regimen produced a somewhat "better" clinical outcome in some individual patients, since the POSA would have appreciated 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. EX1005 ¶475. While there is no clinical proof of such a benefit here, as a matter of general clinical science it would be unsurprising if administering more drug led to more efficacy for at least some

individual patients. Further, any small differences between the prior art and the claimed parameters are at best a difference in degree and not a difference in kind. *See In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). In any event, there is no evidence that the IV dosing regimen is superior to the closest prior art.

Claim 2, which depends from claim 1, does not recite any additional clinical results, and would have been obvious for the same reasons as claim 1. Accordingly, *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213*, and render claims 1-2 obvious. EX1005 ¶476.

2. Claims 3-4

Claim 3 recites the clinical result "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." *NCT673-V23* expressly contemplates determining the change from baseline in vdH-S at Week 24 as a secondary outcome. EX1001, 4. *GO-REVEAL* reported modified Sharp/Van der Heijde score ["SHS"] radiographic progression results, at week 24, for patients administered 50 mg and 100 mg of SC golimumab. EX1042, 2504-05. These SHS scores were comparable to the claimed vdH-S score for the 50mg, 100mg, and placebo groups receiving methotrexate at baseline, at week 24, -0.34±1.10, -0.16±1.36, and 0.22±1.25, respectively. *Id.*, 2509. *GO-REVEAL* concluded that "patients in the golimumab 50 mg and 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. In addition, *WO2013* disclosed that by week 24, adalimumab, another TNFα inhibitor, "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; EX1042, 2516 (noting that the efficacy of golimumab was comparable to that observed with other commercially available anti-TNF agents.).

Given this reported efficacy, 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 "a mean change from baseline in van der Hejde-Sharp score (vdH-S)= -0.36±0.144 SE." EX1005 ¶¶477-79. As explained above (Section VI.C.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, since the claimed score is not the product of a head-to-head study of SIMPONI versus SIMPONI ARIA for PsA. EX1005 ¶¶480-484. Further, as explained, given the higher drug exposure of the IV versus SC formulation, a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy

from the IV formulation than the SC. *Id.* Janssen also did a meta-analysis which confirmed that SC and IV therapies had equivalent efficacies. *Id.* ¶483.

As explained, *NCT673-V23* would have motivated a POSA to apply the claimed dosing regimen to patients with active PsA, and to measure the resulting Van der Hejde-Sharp score in accord with the claims. The results of this obvious method cannot confer patentability. *Kubin*, 561 F.3d at 1357*; Woodruff*, 919 F.2d at 1578; *Papesch*, 315 F.2d at 391; *Catalina Mktg.*, 289 F.3d at 809–10. Even if they did, a POSA would have been motivated to consider the results in *PI2015-Simponi*, *PI2013-Aria*, *GO-REVEAL*, and *WO213*, since 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. Claim 3 would have been obvious. EX1005, ¶484.

Claim 4 depends from claim 3 and does not recite any additional clinical results, and would have been obvious for the same reasons as claim 3. *Id*.

3. Claims 5-7

Claim 5 recites the clinical result "wherein ≥65% of patients receiving the treatment achieve ACR20 at week 14 of treatment." Claim 6 adds the additional clinical result "wherein said ≥65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) of about 50%."

NCT673-V23 expressly contemplates determining the percentage of patients who achieve ACR20 at week 14 as the primary outcome, and also assesses ACR20 at week 14 for patients receiving the placebo treatment. EX1011, 4; EX1005, ¶485. The prior art was also replete with data showing that SC and IV golimumab were effective at achieving ACR20 at 14 weeks of treatment for a significant fraction of PsA patients. *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; EX1005, ¶¶486-87. Example 13 of *WO213* taught that anti-TNFα-antibody therapy achieved an ACR20 of 72% by week 12, from which a POSA would have expected a treatment difference (improvement compared to placebo) exceeding 50%. EX1025, 133:7-12, Table 48; EX1005 ¶¶488-93. *PI2015-Simponi* disclosed that TNFα has the same mechanism of action and SC dose for RA, AS, and PsA. EX1005 ¶491.

Given this reported efficacy, a POSA would reasonably have expected the claimed dosing regimen would be effective and would achieve ACR20 scores at week 14 similar to the claimed "≥65% of patients that achieve ACR20 at week 14 of treatment with a treatment difference (improvement compared to placebo) at about 50%." EX1005 ¶¶486, 494. As explained above, 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, a POSA would not have been surprised if some individual patients experienced somewhat higher efficacy from the IV formulation than the SC. *Id.*, ¶494. Jansssen also did a meta-analysis which confirmed that SC and IV therapies had equivalent efficacies. *Id.* ¶495.

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. The results of this obvious method cannot confer patentability. *Kubin*, 561 F.3d 1351, 1357*; Woodruff*, 919 F.2d at 1578; *Papesch*, 315 F.2d at 391; *Catalina Mktg.*, 289 F.3d at 809–10. Even if they did, 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. Claims 5-6 therefore would have been obvious. EX1005 ¶496.

Claim 7 depends from claim 5 and does not recite any additional clinical results, and would have been obvious to a POSA for the same reasons as claims 5

and 6. EX1005 ¶497. Accordingly, *NCT673-V23*, *PI2013-Aria*, *PI2015-Simponi*, *GO-REVEAL*, and *WO213* render obvious claims 5-7. *Id*., 485-97.

D. Objective Indicia of Non-Obviousness

During prosecution, Janssen argued that the claimed invention yielded surprising and unexpected results. EX1009, 41-42. According to Janssen, "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. To support this allegation, Janssen relied upon data in Table 8 of *US824*, corresponding to the clinical trial of Example 9, which assessed the effect of IV administration of golimumab 2 mg/kg in subjects with active PsA. EX1003, 76:45-77:13. Citing Table 8 and paragraph [324] (which corresponds to 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. *Id*., Table 8, 84:1-22. Janssen represented that these results achieved by the claimed method could not have been expected based on the references cited by the examiner. EX1009, 80-88; EX1005 ¶¶498-509.

The unexpected results presented by Janssen during prosecution do not support the patentability of the *US824* claims for at least four reasons. First, purported unexpected results must be presented relative to the closest prior art. *In*

re Baxter Travenol Labs., 952 F.2d 388, 392 (Fed. Cir. 1991) ("when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art"). Here, *Hoffman* and *Doyle* were not the closest prior art. The closest prior art is the clinical protocol *NCT673-V23*. *NCT673-V23* used the same 2 mg/kg IV golimumab as claimed in *US824* and indicated that the clinical outcomes claimed in *US824* would be measured during the clinical trial. Janssen, however, did not present *NCT673-V23* to the examiner. *NCT673-V23* provided the limitation that Janssen argued distinguished the claims over *Inman*—that is—it taught "'administration via intravenous.'" EX1009, 80-88; EX1005 ¶¶505-09.

Second, Janssen argued as to unexpected results 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, 90-91; EX1003, Table 8, 84:1-27. But as demonstrated by statements by the FDA in the *CDER Review*, it appears as if Janssen never directly compared SC administration to IV administration. EX1034, 114; *see also* EX1032, 15 ("Data directly comparing 2mg/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:Table 11 (reporting that 46% of subjects with PsA for

less than 2 years achieved ACR20, while 66% of subjects with PsA from 2-5 years achieved ACR20). Janssen's arguments as to unexpected results are not supported because Janssen never directly compared IV administration of golimumab to SC administration. *In re De Blauwe,* 736 F.2d 699, 705 (Fed. Cir. 1984) ("It is well settled that unexpected results must be established by factual evidence…."); EX1005 ¶¶505-507.

Third, Janssen presented statements to the FDA that contradict what it told the USPTO. As explained above in Section VI.C.1., Janssen never did any comparative, head-to-head studies of IV and SC golimumab. Thus, under Federal Regulations or FDA Guidance, it could not truthfully say that one is superior to the other. Indeed, during FDA review of SIMPONI ARIA for RA, FDA did not allow Janssen to simply rely on a pharmacokinetic comparison of SIMPONI ARIA with SIMPONI to establish efficacy, and complained that Janssen's failure to conduct a head-to-head comparison between SIMPONI and SIMPONI ARIA made its approval determination "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.* EX1034, 114; EX1005 ¶508. In the wake of FDA's complaint, Janssen cannot argue to the USPTO that IV golimumab is unexpectedly superior to SC golimumab to obtain allowance of the claims. *See Duties of Disclosure and Reasonable Inquiry During Examination, Reexamination, and Reissue, and for Proceedings*

Before the Patent Trial and Appeal Board, USPTO (July 29, 2022) ("[I]n PTAB proceedings, parties should not take a position about the patentability of challenged claims that is inconsistent with positions taken in submissions to other Government agencies regarding the same subject matter.").

Lastly, purported unexpected results must be commensurate in scope with the claims. *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). As explained above in Section V.D., claims 1-7 encompass, but are not limited to, golimumab. Janssen's alleged evidence of unexpected results is limited to golimumab. Such evidence is not commensurate with the scope of the claims, particularly in view of Janssen's arguments, during prosecution, that results with TNF inhibitors other than golimumab are not applicable/translatable to golimumab. EX1009, 87-90.

Petitioner reserves the right to respond to any allegations that objective indicia support the validity of the challenged claims.

E. Discretion Under §325(d) and §314

Consistent with the guidance provided by "FAQs for Interim Processes for PTAB Workload Management," Petitioner does not present affirmative arguments as to discretionary denial. Should Patent Owner elect to file a Discretionary Denial Brief, Petitioner will present arguments in its Opposition to that brief.

VII. CONCLUSION

For the reasons set forth above, claims 1-7 of *US824* are unpatentable. Petitioner requests that an *inter partes* review of these claims be instituted and that the claims be cancelled.

Respectfully submitted,

Dated: March 20, 2026

/ Lora M. Green /
Lora M. Green, Lead Counsel
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VIII. APPENDIX – LIST OF EXHIBITS CITED

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 *curriculum vitae*
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, "*A Study of Golimumab in Participants with Active Psoriatic Arthritis*" (Version 23, January 8, 2016), available at https://clinicaltrials.gov/study/NCT02181673? ("*NCT673-V23*")
1012	M. E. Weinblatt, et al., *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*, 72 ANN RHEUM DIS 381-389 (2013) ("*Weinblatt*")
1013	M. Rossini, et al., *Why golimumab in the treatment of psoriatic arthritis, ankylosing spondylitis and rheumatoid arthritis*?, 66 REUMATISMO 4:285-303 (Apr. 2014) ("*Rossini*")

Exhibit No.	Description
1014	U.S. National Library of Medicine, ClinicalTrials.gov, NCT02186873, "*A Study of Golimumab in Participants with Active Ankylosing Spondylitis*" (Version 24, October 27, 2015), available at https://clinicaltrials.gov/study/NCT02186873? ("*NCT873-V24*")
1015	*SIMPONI (golimumab) injection, for subcutaneous use*, FOOD AND DRUG ADMINISTRATION (June 2015), https://www.accessdata.fda.gov/drugsatfda_docs/label/2015/125289s024lbl.pdf ("*PI2015-Simponi*")
1016	R. D. Inman, et al., *Efficacy and Safety of Golimumab in Patients With Ankylosing Spondylitis,* 58 ARTHRITIS & RHEUMATISM 11:3402-3412 (Nov. 2008) ("*Inman*")
1017	*Understanding the Difference: Standard Error vs. Standard Deviations*, SIXSIGMA (September 25, 2024), *available at* https://www.6sigma.us/six-sigma-in-focus/standard-error-vs-standard-deviation/ ("*SixSigma*")
1018	*BLA Approved re BLA 125289*, FOOD AND DRUG ADMINISTRATION (Apr. 24, 2009) ("*2009 Approval*")
1019	*BLA Approved re BLA 125433*, FOOD AND DRUG ADMINISTRATION (July 18, 2013) ("*2013 Approval*")
1020	-- Intentionally Left Blank --
1021	-- Intentionally Left Blank --
1022	S. D'Angelo, *Psoriatic arthritis: treatment strategies using biologic agents*, 64 REUMATISMO (2):113-121 (Feb. 2012) ("*D'Angelo*")
1023	-- Intentionally Left Blank --
1024	U.S. Patent Publication 2009/0123378 to Wong et al. (May 14, 2009) ("*Wong*")
1025	International Publication WO 2008/063213 A2 to Medich et al. (May 29, 2008) ("*WO213*")
1026	J. Kay & M. U. Rahman, *Golimumab: A novel human anti-TNF-α monoclonal antibody for the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis*, Core Evidence 4:159-170 (2009) ("*Kay*")

Exhibit No.	Description
1027	E. C. Keystone & C. F. Ware, *Tumor Necrosis Factor and Anti-Tumor Necrosis Factor Therapies*, J RHEUMATOL SUPPL. 85:27-39 (May 2010) ("*Keystone*")
1028	H. Shim, *One target, different effects: a comparison of distinct therapeutic antibodies against the same targets*, 43 EXP MOL MED. 10:539-549 (Oct. 2011) ("*Shim*")
1029	J. Kalden, *Anti-TNF therapy: what have we learned in 12 years?*, ARTHRITIS RES THER. 13(Suppl 1):S1 (May 25, 2011) ("*Kalden*")
1030	L. C. Coates, et al., *Anti-TNF therapy in ankylosing spondylitis: insights for the clinician*, 2 THER ADV MUSCULOSKELET DIS. 1:37-43 (2010) ("*Coates*")
1031	-- Intentionally Left Blank --
1032	*SIMPONI ARIA (golimumab) injection, for intravenous use*, FOOD AND DRUG ADMINISTRATION (July 2013), https://www.accessdata.fda.gov/drugsatfda_docs/label/2013/125433s000lbledt.pdf ("*PI2013-Aria*")
1033	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"*)
1034	*Administrative and Correspondence Documents, Application Number: 125433Orig1s000,* CENTER FOR DRUG EVALUATION AND RESEARCH, (September 30, 2013) https://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/125433review.pdf ("*CDER Review*")
1035	M. K. Doyle et al., *Effects of subcutaneous and intravenous golimumab on inflammatory biomarkers in patients with rheumatoid arthritis: results of a phase 1, randomized, open-label trial*, 52 RHEUMATOLOGY 7:1214-9 (2013) ("*Doyle*")
1036	U.S. Publication No. 2008/0311043 to Hoffman et al. ("*Hoffman*")
1037	U.S. Patent No. 5,656,272 to Le et al. ("*Le*")
1038	Y. Zhuang, et al., *Golimumab Pharmacokinetics After Repeated Subcutaneous and Intravenous Administrations in Patients with Rheumatoid Arthritis and the Effect of Concomitant Methotrexate: An Open-Label, Randomized Study*, 34 CLINICAL THERAPEUTICS 1:77-90 (Jan. 2012) ("*Zhuang*")

Exhibit No.	Description
1039	*New Phase 3 Data Show Simponi Aria® (Golimumab) Significantly Improved Signs and Symptoms in Patients with Active Ankylosing Spondylitis*, JOHNSON & JOHNSON (Nov. 14, 2016) ("*J&J 2016"*)
1040	*New Phase 3 Data Show SIMPONI ARIA ® (golimumab) Significantly Improved Signs and Symptoms in Patients with Active Ankylosing Spondylitis*, JANSSEN RESEARCH & DEVELOPMENT, LLC (Nov. 14, 2016) ("*Janssen 2016"*)
1041	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*")
1042	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*")
1043	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*")
1044	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*")
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Exhibit No.	Description
1050	*Appendix 6 Summary of Comparators* in *Golimumab (Simponi) IV: In Combination with Methotrexate (MTX) for the Treatment of Adult Patients with Moderately to Severely Active Rheumatoid Arthritis*, CANADIAN AGENCY FOR DRUGS AND TECHNOLOGIES IN HEALTH (Jul. 2015) ("*CADTH*")
1051	*Guidance for Industry – Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES, FOOD AND DRUG ADMINISTRATION, CENTER FOR DRUG EVALUATION AND RESEARCH & CENTER FOR BIOLOGICS EVALUATION AND RESEARCH (May 1998) ("*Industry Guidance"*)
1052	*National Institutes of Health, Press Release: National Institutes of Health Launches "ClinicalTrials.gov",* U.S. NATIONAL LIBRARY OF MEDICINE (February 29, 2000), https://www.nlm.nih.gov/ archive/20040831/news/ press_releases/clntrlpr00.html ("*NLM Press Release*")

IX. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 13,996 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: March 20, 2026

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§42.6(e) and 42.105(a), this is to certify that I caused to be served a true and correct copy of the foregoing Petition for Inter Partes Review (and accompanying Exhibits 1001-1019, 1022, 1024-1030, 1032-1044, 1050-1052) by overnight courier (Federal Express Priority Overnight Delivery), on this 20th day of March, 2026, on the Patent Owner at the correspondence address of the Patent Owner Counsel as follows:

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Respectfully submitted,

Dated: March 20, 2026

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