UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SANDOZ INC.,
Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD,
Patent Owner.

Case IPR2017-02105
Patent No. 9,090,689

PATENT OWNER'S RESPONSE TO THE PETITION

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I. Introduction

AbbVie's U.S. Patent No. 9,090,689 ("the '689 patent") is directed to the treatment of moderate-to-severe chronic plaque psoriasis with the biologic anti-TNFα drug Humira® (adalimumab). The '689 patent claims require subcutaneously administering 40 mg of adalimumab every-other-week to a patient having moderate-to-severe chronic plaque psoriasis. Claims 16 and 19 further require that the treated patient has both moderate-to-severe chronic plaque psoriasis and psoriatic arthritis ("PsA") and achieves a significant treatment outcome: at least a 75% reduction in PASI score at week 12 of treatment (claim 16) or at least a PGA score of clear or almost clear at week 12 of treatment (claim 19).

The Board instituted two grounds under 35 U.S.C. § 103 for claims 1, 4, 7, 10, 13, 16, and 19: (1) over the combination of Keystone, Lorenz, and Chaudhari; and (2) over the combination of Keystone, Mease 2000, and Chaudhari.

The Board should enter a final written decision upholding the patentability of the challenged claims for several reasons. At the time of the claimed invention, adalimumab had only been approved to treat a materially different disease, rheumatoid arthritis ("RA"). Keystone, for example, only describes the use of adalimumab to treat RA. No cited prior-art reference describes treating moderate-to-severe chronic plaque psoriasis with adalimumab or any clinical testing of adalimumab in patients with this condition.

Indeed, it was unpredictable in 2003 whether the adalimumab dosing regimen for treating RA would be effective for treating moderate-to-severe chronic plaque psoriasis. No information was publicly available about: the rate or extent of adalimumab's distribution to affected psoriatic skin (as compared to affected RA joints); its metabolism in affected psoriatic skin (as compared to in affected RA joints); or its stability or disassociation with respect to TNFα complexes. Therefore, absent clinical trials in patients with moderate-to-severe chronic plaque psoriasis, there would have been no way to reasonably expect that the approved RA dosing regimen of adalimumab (40 mg every-other-week) would effectively treat such patients.

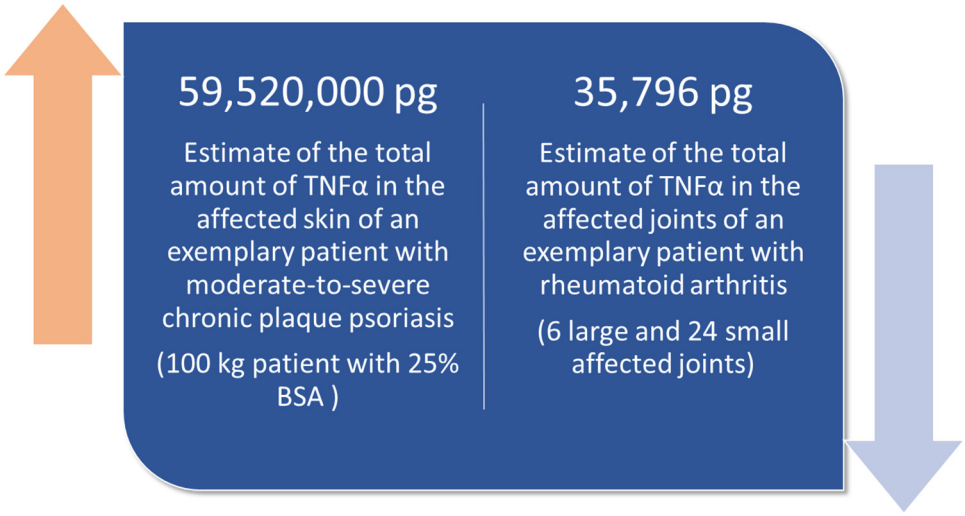
Moreover, even if one looked to results from different TNFα inhibitors, the great weight of prior-art information indicated that this dosing regimen would not be effective. A POSA would have viewed 40 mg of adalimumab every-other-week as *far too low* to effectively treat moderate-to-severe chronic plaque psoriasis for at least the following three reasons:

Higher TNFα Burden for Psoriasis vs. RA

In considering what dose of an anti-TNFα biologic drug such as adalimumab would be needed to potentially treat a TNFα-moderated disease such as moderate-to-severe chronic plaque psoriasis, a POSA in 2003 would have considered the total amount of TNFα in the typical patient's affected tissues that would have to be

neutralized by the anti-TNFα drug. A higher amount of TNFα suggests the need for a higher dose of anti-TNFα drug.

Moderate-to-severe chronic plaque psoriasis involves higher concentrations of TNFα in affected tissues compared to RA. In addition, moderate-to-severe chronic plaque psoriasis patients would be expected to have more affected tissue and thus, as illustrated below, significantly more total TNFα than RA patients:



The approved RA dose of adalimumab would have been considered too low in view of the significantly higher amount of TNFα involved in moderate-to-severe chronic plaque psoriasis. A POSA in 2003 thus would not have been motivated to use the same dose of adalimumab to treat moderate-to-severe chronic plaque psoriasis as used to treat RA. Rather, one would have been motivated to use a significantly *higher* dose of adalimumab to treat moderate-to-severe chronic plaque psoriasis.

Higher Doses of Infliximab for Psoriasis vs. RA

Petitioner fails to establish that any TNFα inhibitor would have been predictive of adalimumab's efficacy in treating moderate-to-severe chronic plaque psoriasis. Petitioner also fails to establish that infliximab's *intravenous, weight-based* dosing would be predictive of the efficacy of a *subcutaneous, fixed dose* of adalimumab. Infliximab's weight-based dosing accounted for, e.g., the increased weight of patients with moderate-to-severe chronic plaque psoriasis compared to RA, while adalimumab's fixed dose would not. Infliximab was also 100% bioavailable, while only 64% of adalimumab was bioavailable.

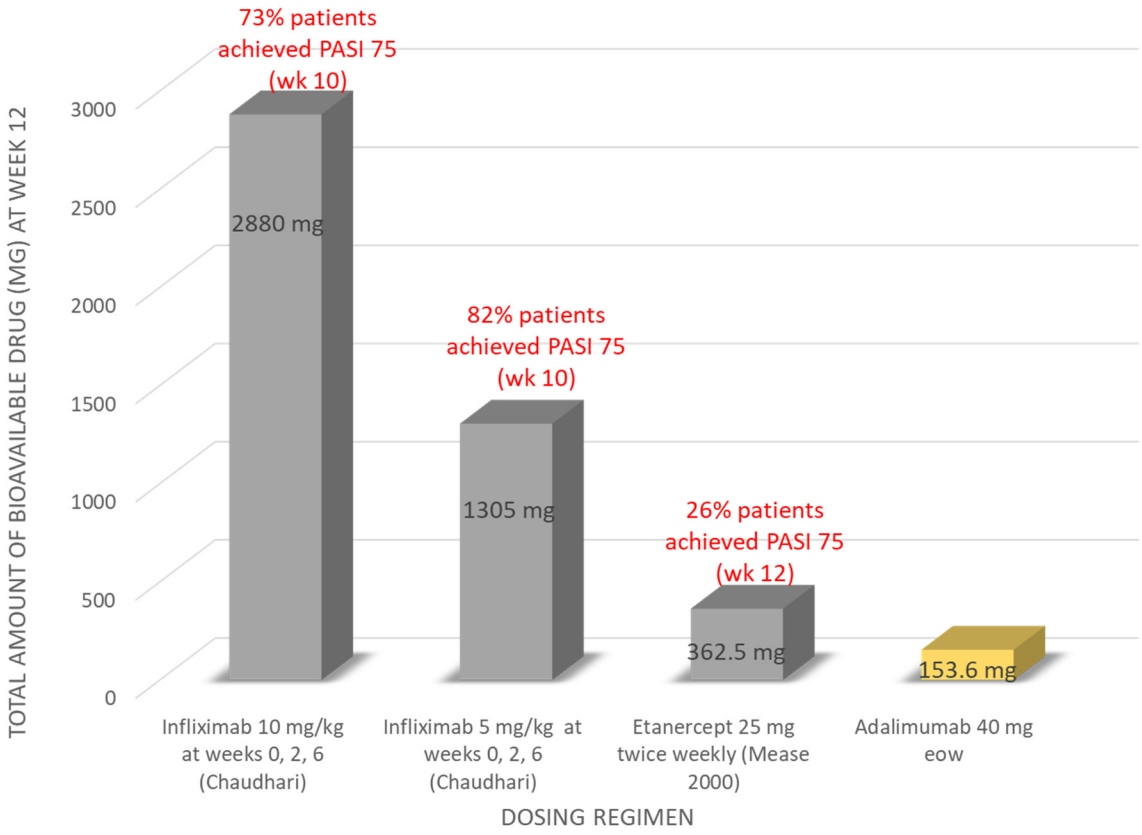
But even if one had looked to infliximab, the only TNFα inhibitor shown to treat moderate-to-severe chronic plaque psoriasis, it would *not* have suggested subcutaneously administering 40 mg of adalimumab every-other-week. Infliximab was approved to treat RA at a weight-based dose of 3 mg/kg (with methotrexate). But for patients with moderate-to-severe chronic plaque psoriasis, infliximab had *only* been tested using *higher* doses of 5 or 10 mg/kg.

The infliximab study therefore would have indicated, consistent with the higher TNFα burden associated with moderate-to-severe chronic plaque psoriasis, that one should use a higher weight-based dose of an anti-TNFα drug such as adalimumab to treat this disease compared to its RA dose.

Higher Doses of Anti-TNFα Drugs for Psoriasis vs. Adalimumab's RA Dose

Further, if one had looked to other anti-TNFα biologic drugs, one would have considered the amounts of those drugs administered to treat moderate-to-severe chronic plaque psoriasis. Patients administered 3, 5, or 10 mg/kg of infliximab by intravenous infusion were receiving significantly more drug per administration (300, 500, or 1,000 mg of drug for a 100 kg patient) than patients subcutaneously administered 40 mg of adalimumab as a fixed dose (25.6 mg of bioavailable drug per administration).

As shown below, patients also received vastly more total amount of bioavailable drug by week 12 under the prior art anti-TNFα biologic dosing regimens for infliximab and etanercept than they would receive under the claimed 40 mg every-other-week dose of adalimumab:



While etanercept was another TNFα inhibitor approved to treat RA, Mease 2000 reveals it was poorly effective in psoriasis when administered at its approved RA fixed dose (25 mg twice weekly), with no evidence of it working for patients with moderate-to-severe psoriasis. This additional information would have confirmed the lack of any expectation that 40 mg of adalimumab administered subcutaneously every-other-week would effectively treat moderate-to-severe chronic plaque psoriasis.

Petitioner has not shown that any challenged claim is unpatentable for obviousness. One of ordinary skill in 2003 would have had no motivation or reasonable expectation of successfully treating moderate-to-severe chronic plaque

psoriasis with the RA dose of adalimumab (40 mg every-other-week). This is particularly true for claims 16 and 19, which require that the patient achieve a significant clinical outcome at week 12 of treatment, especially when Petitioner failed to establish any correlation in clinical response between TNFα inhibitors. The Board should therefore enter a final written decision confirming the patentability of the challenged claims.

II. Background

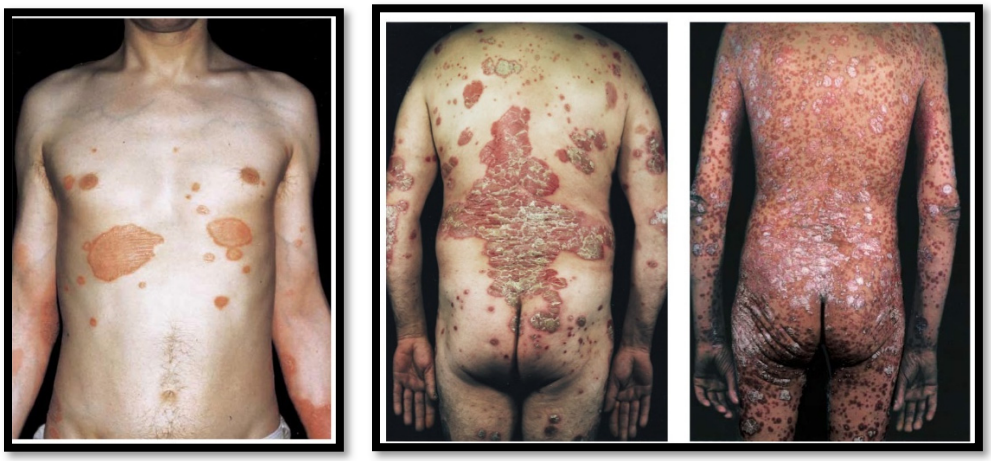
A. Chronic Plaque Psoriasis Is a Skin Disease with Varying Degrees of Severity and Distinct Patient Characteristics

Chronic plaque psoriasis is an inflammatory skin disorder affecting approximately 2% of the U.S. population. (Ex. 2035, ¶ 40; Ex. 2041, 4, 8; Ex. 2042, 6; Ex. 2084, 23:18-21.)[1] It is the most common form of psoriasis, occurring in more than 90% of the psoriatic population. (Ex. 1008, 11; Ex. 2042, 19.) Clinically, it is characterized by thick circular red patches covered with silvery scales, also known as plaques. (Ex. 2035, ¶ 40; Ex. 2041, 7; Ex. 2042, 18-19, 26.) The extent of disease can be quantified by percentage of body surface area ("BSA") affected, which can range from 0-100% of the skin surface. (Ex. 2035, ¶ 41; Ex. 2042, 19.)

[1] Citations refer to the original page numbering of each exhibit except for references that have been stamped with page numbers. Citations to such references refer to the stamped-on page numbers.

Patients with chronic plaque psoriasis are traditionally classified as having either mild disease or moderate-to-severe disease. (Ex. 2035, ¶ 41; Ex. 2041, 15-16.) Mild patients typically have a low percentage of BSA psoriasis coverage, such that it is practical to treat them using topical therapy. (Ex. 2035, ¶¶ 42-43; Ex. 2041, 15-16.) Most chronic plaque psoriasis patients have mild psoriasis (approximately 75-77%). (Ex. 2041, 16; Ex. 2043, 307; *see* Ex. 1036, 4; Ex. 2035, ¶¶ 42-43.)

In contrast, moderate-to-severe chronic plaque psoriasis patients make up about 23-25% of the psoriasis population. (Ex. 1036, 4; Ex. 2041, 16-17; Ex. 2035, ¶ 43; Ex. 2043, 307.) This population tends to include psoriasis patients with a higher percentage of BSA involved, where application of topical agents is cumbersome and inconvenient. (Ex. 2041, 16; Ex. 2035, ¶¶ 42-43.) The differences in severity between mild and moderate-to-severe psoriasis are illustrated below:



Mild **Moderate-to-Severe**

(Ex. 2044, 582.)

The Psoriasis Area and Severity Index ("PASI") is a widely used method to assess psoriasis severity. (Ex. 2005, ii65-66; Ex. 2084, 27:1-4; Ex. 2035, ¶¶ 44-48.) The score is a multi-factorial calculation generated by examining the intensity (redness, thickness, and scaling) and extent (BSA) of psoriatic plaques found in four body regions (head, trunk, arms, and legs). (Ex. 1036, 5; Ex. 1001, 27:64-28:3; Ex. 2045, 6; Ex. 2046, 195; Ex. 2005, ii66.) The intensity of the plaque's erythema (also known as redness), infiltration, and scaling are graded on a five-point scale and multiplied by the intensity score for that region and by the proportion of that region with respect to the overall body. (Ex. 2045, 6; Ex. 2005, ii66.)

PASI scores range from 0 to 72. (Ex. 2035, ¶¶ 44-48; Ex. 2045, 6; Ex. 2005, ii66; Ex. 2046, 195.) Patients with moderate-to-severe chronic plaque psoriasis typically have a PASI score above 7. (Ex. 2035, ¶¶ 44-48; Ex. 2046, 198; Ex. 2045, 6; Ex. 2083, 39:23-40:5.) Patients with mild chronic plaque psoriasis typically have a PASI score of 7 or less. (Ex. 2035, ¶¶ 44-48; Ex. 2046, 198.) "PASI 75," which is shorthand for a 75% reduction of the PASI score from the start of treatment, has been used as the treatment goal for many clinical trials. (Ex. 1001, 41:7-10.)

The Physician's Global Assessment ("PGA") is another tool for assessing psoriasis improvement. (*Id*., 41:11-23.) It is a seven-point scale for assessing the severity of either individual plaques or the entire extent of disease. (Ex. 2005, ii65; Ex. 2035, ¶ 49.) PGA categorizes mild psoriasis as only "slight plaque elevation,

scaling, and/or erythema," and moderate-to-severe psoriasis as "marked plaque elevation, scaling, and/or erythema." (Ex. 1001, 41:11-23.)

Chronic plaque psoriasis is associated with several comorbidities, including obesity. (Ex. 2035, ¶¶ 50-53.) On average, psoriasis patients are overweight compared to the average adult. (*Id*.; Ex. 2049, 102, 104 (documenting an increased body mass index for psoriasis patients compared to control); Ex. 2050, 982-983, 985; *see* Ex. 1050, 7 (patients weighed 100 kg); Pet., 34 n.31 (asserting an average adult weighed 70 kg); *see also* Ex. 1036, 6 (mean patient weights for the three psoriasis treatment groups were 85, 87, and 96 kg).) Psoriasis patients are twice as likely to be obese than control patients without psoriasis. (Ex. 2050, 982-983, 985.)

In addition, psoriasis severity was known to correlate with patient weight, with heavier patients typically exhibiting more severe disease. (Ex. 2017, 350-351; Ex. 2035, ¶¶ 50-53.) This "relationship between body weight and severity of psoriasis observed . . . is *striking*," with the percentage of overweight patients increasing with increasing psoriasis severity (Ex. 2017, 350 (emphasis added); Figure 2.)

B. PsA Patients Who also Have Psoriasis Usually Have a Mild Form of the Disease

While sometimes associated, PsA and psoriasis are distinct conditions affecting different anatomy. (Ex. 2037, ¶¶ 1-15, 16-17; Ex. 2035, ¶¶ 54-58.) In

contrast to psoriasis, which is primarily a skin disorder, PsA affects the ligaments, tendons, fascia, and spinal or peripheral joints. (Ex. 2007, 42; Ex. 2037, ¶¶ 16-17.)

The relationship between the skin disease of psoriasis and the joint disease of PsA is unclear, and patients with psoriasis often do not have PsA. (Ex. 2037, ¶¶ 16-17; Ex. 2035, ¶¶ 54-58.) PsA can precede or follow psoriasis by years, and remissions and exacerbations of PsA do not correlate with similar changes in psoriasis. (Ex. 2007, 45; Ex. 1009, 4; Ex. 2037, ¶¶ 16-17; Ex. 2035, ¶¶ 54-58.) No connection exists between the location, distribution, or pattern of psoriatic skin and the joints affected by PsA. (Ex. 2009, 1513; Ex. 2037, ¶¶ 16-17; Ex. 2035, ¶¶ 54-58.)

Further, the severity of PsA does not correlate with the severity of psoriasis, and patients with PsA generally have *mild* psoriasis. (Ex. 2035, ¶¶ 54-58; Ex. 2008, 2448-50; Ex. 2009, 1515 (skin disease in PsA patients "can often be very mild"); Ex. 2008, 2455 ("some studies suggest skin disease is milder in patients with arthritis"); Ex. 2053, 4-5, Table 2 (average PASI score of 115 PsA patients was only 4.1).) One study of the extent of psoriasis in patients with active PsA reported that 77% of those patients had minimal or mild psoriasis. (Ex. 2048, 1753, 1755 ("patients generally had mild skin disease").) The low prevalence of moderate-to-severe chronic plaque psoriasis in PsA patients was reinforced in a 2016 article reporting that only approximately 11% of PsA patients in Norway had moderate-to-severe psoriasis. (Ex. 2035, ¶ 57; Ex. 2055, PSY23.)

C. The Clinical Efficacy of TNFα Inhibitors Was Unpredictable

In 2003, the TNFα inhibitors infliximab (Remicade®) and etanercept (Enbrel®) were approved to treat RA. (Ex. 1006; Ex. 1027.) Researchers understood, however, that although infliximab and etanercept were both TNFα inhibitors that were effective in RA, they showed *different* efficacies in other TNFα-implicated diseases. (Ex. 2065, 425; Ex. 2035, ¶¶ 81-86.)

Sandborn, for example, reported that the RA dose of etanercept (25 mg twice weekly) was *ineffective* in treating Crohn's disease. (Ex. 2013, 6.) It was unknown why etanercept failed. (*Id.*; Ex. 2110, 1092-93; Ex. 2111, S33; Ex. 2035, ¶ 82.) In psoriasis, researchers also observed a significant difference in efficacy between 5 mg/kg infliximab and 25 mg etanercept, with a greater proportion of psoriasis patients responding to infliximab than to etanercept, despite similar clinical benefit in the treatment of RA. (Ex. 2065, 425; Ex. 2035, ¶¶ 83; *see infra* X.B.)

The clinical efficacy of the RA dose of a different TNFα inhibitor, such as adalimumab (Humira®), in a new condition such as moderate-to-severe psoriasis was unpredictable. (Ex. 2035, ¶¶ 81-86.) This unpredictability was due to various complex factors, many of which were unknown, including: (1) differences in the inhibitors themselves (e.g., differences in molecular structure, TNFα binding, stability of TNFα complexes, and antigen specificity); (2) differences in the diseases being treated (e.g., accessibility of involved tissues to the inhibitors at the doses

administered, the potential role of LTα, the amount of TNFα in the affected tissues, and the sensitivity of diseased tissues to TNFα); (3) differences in the dosing regimens (e.g., weight-based versus fixed dose) and routes of administration; and (4) differences in drug distribution to and drug metabolism in the affected tissues (e.g., psoriatic skin). (*See* Ex. 2065, 425; Ex. 2035, ¶¶ 81-86.)

In 2003, most of this information was not publicly known, including:

- the stability of TNFα complexes with adalimumab;
- the rate at which adalimumab disassociated from TNFα; and
- whether there were differences in the rate of distribution of TNFα inhibitors to affected psoriatic skin, the extent of drug distributed to the skin, or their metabolism in affected skin (as compared to the affected joints in an RA patient).

(Ex. 2035, ¶¶ 85-86.)

No test data were available to establish the efficacy of any dose of adalimumab in patients with moderate-to-severe chronic plaque psoriasis. (*Id*.)

D. Psoriasis Is Manifestly Different from RA

1. RA Affects Different Tissues and Has Distinct Patient Characteristics

Psoriasis is a chronic autoimmune disease primarily affecting the skin, the body's largest organ. (Ex. 2035, ¶¶ 53, 59-65; Ex. 2051, 5; Ex. 2052, 5; Ex. 2083, 47:15-24; Ex. 2084, 23:18-21.) RA, in contrast, is a chronic autoimmune disease that

primarily affects the joints. (*E.g.*, Ex. 2066, 4; Ex. 2037, ¶¶ 18-24; Ex. 2035, ¶¶ 87-88.)[2]

RA symptoms include tender, swollen joints and joint stiffness that usually begins in the hands and feet and can progress to larger joints. (Ex. 2037, ¶¶ 18-20.) RA patients with moderate-to-severe disease tend to have 20 to 30 involved joints. (Ex. 2066, 11; Ex. 2037, ¶¶ 18-20.) The volume of synovial fluid varies based on the size of the joint and level of inflammation. (Ex. 2085, 91; Ex. 2037, ¶¶ 18-20.) Patients with RA can have about 22 ml of synovial fluid in their knee joints. (Ex. 2085, 91; Ex. 2037, ¶¶ 22-24.)

In contrast to psoriasis patients, who are on average overweight, RA often results in weight *loss* such that RA patients are typically average or below weight compared to healthy adults. (Ex. 2037, ¶¶ 25-26; Ex. 2066, 11; Ex. 2077, 57; Ex. 2015, 1 (finding reduced body mass for RA patients compared to controls); Ex. 2019, 326.)

[2] Many drugs that were effective for treating RA were *ineffective* or *contraindicated* for treating moderate-to-severe chronic plaque psoriasis, including those cited by Petitioner. (Ex. 2035, ¶¶ 90-93.) As the Institution Decision also recognized, the small molecule drugs are less relevant as they are not biologic TNFα inhibitors. (Paper 14, 27 n.10; Ex. 2083, 68:2-24.)

2. Patients with RA Were Understood to Have a Lower Amount of TNFα in Their Affected Tissues than Patients with Moderate-to-Severe Chronic Plaque Psoriasis

While the etiology and pathogenesis for RA was not completely understood in 2003, RA was known to be associated with the creation and proliferation of cytokines, including TNFα, in the inflamed joints. (Ex. 2037, ¶¶ 27-28; Ex. 2066, 5; Ex. 2074, 282.) TNFα levels in RA patients were elevated in the synovial fluid and synovium. (Ex. 2037, ¶¶ 21, 27-28, 30-36; Ex. 2066, 4-5.) It was understood that the treatment of RA with TNFα inhibitors worked by neutralizing TNFα in the synovium. (Ex. 2037, ¶¶ 27-28; Ex. 2097, 2395-96.)

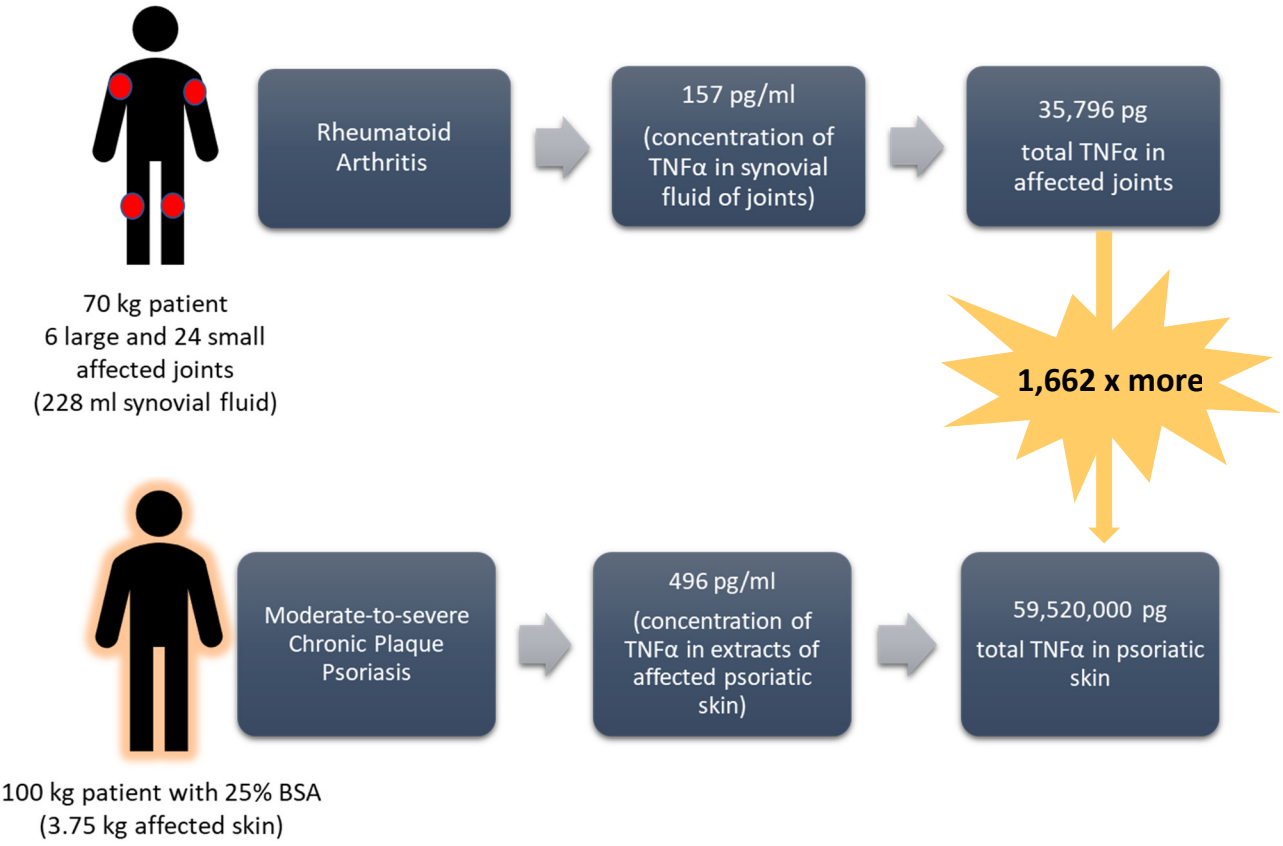
Moderate-to-severe chronic plaque psoriasis patients, however, were known to have higher levels of TNFα in their affected tissue than RA patients. (Ex. 2035, ¶¶ 66-80, 94-99.) Partsch (in 1996), Steiner (in 1999), and Ribbens (in 2000) all measured the concentration of TNFα in the synovial fluid of RA patients using Medgenix/Biosource ELISA, and reported consistent median concentrations of 114.2 pg/ml, 157 pg/ml, and 101 pg/ml, respectively. (Ex. 2037, ¶¶ 30-31; Ex. 2035, ¶¶ 97-98; Ex. 2070, 519; Ex. 2020, 202; Ex. 2071, 670.) In contrast, psoriatic lesions were reported to contain approximately 496 pg/ml, more than *three times higher* than the concentration of TNFα reported in the synovial fluid of patients with RA. (Ex. 1013, 3; Ex. 2035, ¶¶ 66-71, 98-99 (up to 100-times higher on a gram per gram

basis).) TNFα levels were also understood to increase with the severity of a patient's psoriasis. (Ex. 2035, ¶ 66.)

The high TNFα burden in patients with moderate-to-severe chronic plaque psoriasis is exacerbated because the disease affects the skin, the body's largest organ, accounting for about 15% of a patient's body weight. (Ex. 2051, 5; Ex. 2101, 5; Ex. 2035, ¶ 53.) In contrast, RA was understood to affect discrete and relatively small amounts of joint tissue. (Ex. 2037, ¶¶ 18-20; Ex. 2035, ¶ 88.) As a result of the higher concentration of TNFα and the greater amount of affected tissue in patients with moderate-to-severe chronic plaque psoriasis, it was understood that they had higher overall levels of TNFα in affected tissues than RA patients. (Ex. 2035, ¶¶ 100-104.)

For example, Dr. Krueger estimates that an exemplary 100 kg patient with moderate-to-severe chronic plaque psoriasis involving 25% BSA has about 59,520,000 pg of TNFα in their affected psoriatic skin. (Ex. 2035, ¶¶ 1-26, 72-80, 101-102.) A 25% BSA is typical for patients with moderate-to-severe chronic plaque psoriasis being treated by systemic therapies. (Ex. 2035, ¶ 75; *see* Ex. 2100, 1244 (median body surface area involvement was 25%); Ex. 2081, 449; Ex. 2023, 5; Ex. 2107, 668.) In contrast, an exemplary RA patient with 6 large and 24 small affected joints has only about 35,796 pg of TNFα in affected joints. (Ex. 2037, ¶¶ 32-36; Ex. 2035, ¶¶ 100-102.) In other words, a typical patient with moderate-to-severe chronic

plaque psoriasis would be expected to have over *1,662-times* more TNFα in affected tissues than a typical patient with severe RA, as illustrated below:



(Ex. 2035, ¶¶ 101-104.) An exemplary patient with moderate-to-severe chronic plaque psoriasis with only 5% BSA involved would still have 332 times the amount of TNFα in their affected tissues compared to an exemplary RA patient. (Ex. 2035, ¶¶ 72-80; 101-104.)

III. The Patented Invention

The '689 patent discloses and claims novel methods for preparing adalimumab for treating moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 27-31, 130-132.) It explains that psoriasis is a form of skin inflammation

characterized by frequent episodes of redness, itching, and silvery scales on the skin. (Ex. 1001, 25:64-67.) The patent describes the use of PASI and PGA to measure improvements in psoriasis. (*Id*., 27:58-28:3, 41:4-23.) The specification details the use of D2E7 (adalimumab) in treating human patients with moderate-to-severe chronic plaque psoriasis by filling adalimumab into vessels and subcutaneously administering to those patients 40 mg of adalimumab every-other-week with a primary endpoint of achieving at least a 75% reduction in PASI score at week 12. (*Id*., 40:1-16.)

Independent claims 1 and 7 of the '689 patent recite:

> 1. A method of administering adalimumab for treatment of moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week.
>
> 7. A method of preparing adalimumab for treating moderate to severe chronic plaque psoriasis, comprising filling adalimumab into vessels and providing said adalimumab for treatment, wherein said treatment comprises subcutaneously administering 40 mg of said adalimumab to a patient having moderate to severe chronic plaque psoriasis every other week.

(*Id*., 57:15-35.)

Claims 16 and 19, which depend from claim 7, recite:

> 16. The method of claim 7, wherein said patient has both psoriasis and psoriatic arthritis and achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment.
>
> 19. The method of claim 7, wherein said patient has both psoriasis and psoriatic arthritis and achieves at least a Physician Global Assessment (PGA) score of clear or almost clear at week 12 of the treatment.

(*Id*., 58:24-36.)

IV. The Asserted References

Petitioner's asserted references concern the use of adalimumab to treat RA or the use of different drugs to treat different diseases—not the use of adalimumab to treat moderate-to-severe chronic plaque psoriasis as claimed. (Ex. 2035, ¶¶ 4, 133-146.)

A. Keystone

The Keystone abstract discusses the use of 20, 40, or 80 mg of adalimumab every-other-week to treat RA. (*See* Ex. 1003.) Keystone does not discuss psoriasis or moderate-to-severe chronic plaque psoriasis, much less a dosing regimen for treating patients with those conditions. (*Id*.) Nor does it discuss adalimumab's

distribution to or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (*Id*.; Ex. 2083, 69:10-25; Ex. 2035, ¶ 133.)

B. Chaudhari

Chaudhari discusses the use of 5 or 10 mg/kg of infliximab administered intravenously as a monotherapy at 0, 2, and 6 weeks to treat patients with moderate-to-severe chronic plaque psoriasis. (Ex. 1036, 4.) Chaudhari states that the patients in the 5 mg/kg treatment group had a mean weight of 87 kg and mean baseline PASI score of 22.1; and in the 10 mg/kg treatment group, the mean weight was 96 kg with a mean baseline PASI score of 26.6. (*Id*., 6.) Nine of eleven patients (82%) in the 5 mg/kg group and eight of eleven patients (73%) in the 10 mg/kg group showed a PASI 75 response at week 10. (*Id*.)

Notably, Chaudhari used a *higher* dose of infliximab for moderate-to-severe chronic plaque psoriasis than the 3 mg/kg dose approved for RA. (*Id.*, 4; Ex. 1027, 4; *see infra* X.B.2; Ex. 2035, ¶¶ 111-117, 134-135.) Chaudhari does not disclose any clinical trials or results using adalimumab, any dosing regimen for adalimumab, any connection between adalimumab and moderate-to-severe chronic plaque psoriasis, or adalimumab's distribution or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (Ex. 1036; Ex. 2035, ¶¶ 134-135.)

C. Lorenz

Lorenz was asserted in Ground 1 only. It provides an overview of clinical trials using infliximab or etanercept to treat a variety of TNFα-mediated conditions. (Ex. 1028.) Lorenz discusses clinical trials using 5 or 10 mg/kg of infliximab or 25 mg twice a week of etanercept to treat PsA patients, a subset of whom had psoriasis of unspecified severity. (*Id.*, S18-19.) Lorenz does not disclose or suggest using the approved RA dose for infliximab or etanercept to treat moderate-to-severe chronic plaque psoriasis. (*Id.*; Ex. 2035, ¶¶ 119, 136-138.)

Lorenz discusses adalimumab (also referred to as D2E7) but *never* in connection with moderate-to-severe chronic plaque psoriasis. (Ex. 1028, S17-18.) It also does not disclose any clinical trials, dosage, or results for adalimumab in the treatment of moderate-to-severe chronic plaque psoriasis or discuss adalimumab's distribution to or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (Ex. 1028; Ex. 2035, ¶¶ 136-138.)

D. Mease 2000

Mease 2000 was asserted in Ground 2 only. It discusses twice-weekly administration of 25 mg of etanercept to treat patients with active PsA. (Ex. 1017A, 1.) Some patients also exhibited "evaluable psoriasis," with baseline PASI scores ranging from 2.3 to 30 (i.e., some patients had moderate-to-severe chronic plaque psoriasis while others had mild disease). (*Id*., 2-3.) Patients were

allowed to continue taking methotrexate and corticosteroids, although it is unclear how many patients were on both or either. (*Id*., 2-3; Ex. 2083, 63:6-16.; Ex. 2035, ¶¶ 118-119, 139-140.) Notwithstanding generally milder disease and the presence of these background therapies, Mease reports that only 5 of 19 (26%) of patients with evaluable skin disease achieved PASI 75 at week 12. (Ex. 1017A, 3.) Mease 2000 does not indicate that *any* of the 5 treated patients had moderate-to-severe skin disease. (*Id*., 3; Ex. 2035, ¶¶ 118-119, 139-140; *see* Ex. 2084, 48:9-16.) Further, the treatment did not achieve statistical significance for PASI 25 or PASI 50 versus placebo at week 12. (Ex. 1017A, 3; Ex. 2035, ¶¶ 119, 139.)

Mease 2000 does not disclose any clinical trials or results using adalimumab, any dosing regimen for adalimumab, any connection between adalimumab and moderate-to-severe chronic plaque psoriasis, or adalimumab's distribution or activity in skin affected by moderate-to-severe chronic plaque psoriasis. (Ex. 1017A; Ex. 2035, ¶¶ 139-140.)

V. Other Cited References[3]

A. Marzo-Ortega

The Marzo-Ortega abstract summarizes preliminary results from a study administering 3 mg/kg infliximab with concomitant methotrexate (the infliximab RA dose) to treat PsA and skin psoriasis. (Ex. 1004, 6.) It provides results from only five patients. (*Id*.) Marzo-Ortega provides no information, however, as to whether *any* of the patients studied had moderate-to-severe chronic plaque psoriasis. (*Id*.; Ex. 2083, 52:10-21; Ex. 2035, ¶¶ 113, 141-142.) A skilled person would have expected that, as with PsA patients generally, the skin psoriasis of most of the studied patients was mild. (*See supra* II.B; Ex. 2035, ¶¶ 54-58, 113, 141.) Indeed, a subsequent publication by Marzo-Ortega reporting results from the same study states that the median PASI score at baseline was 1.8, confirming that, in general, the tested patients did *not* have moderate-to-severe chronic plaque psoriasis. (Ex. 2033, 779; Ex. 2035, ¶¶ 113, 141; *see* Ex. 2083, 39:23-40:5, 57:8-12.)

[3] For purposes of this IPR only, Patent Owner does not challenge the printed publication status of the Humira label or Press Release. As these are background references cited only in passing in the petition, their printed publication status is irrelevant to resolving the patentability of the challenged claims.

B. Wollina

Wollina discusses results from the administration of infliximab to two 100 kg patients with "widespread plaque-type psoriasis" and baseline PASI scores of 35 and 21. (Ex. 1050, 7; Pet., 31; Ex. 2083, 60:12-17; Ex. 2035, ¶¶ 114, 143-144.) Wollina administered the RA dose of infliximab (3 mg/kg) *more frequently* (weeks 0, 2, 4, and 8, with weekly methotrexate) than the infliximab RA dosing regimen. (Ex. 1050, 7; Ex. 2035, ¶¶ 114, 116, 143-144.) Wollina also did not report that the patients achieved PASI 75. (Ex. 1050, 7; Ex. 2035, ¶¶ 114, 143.)

C. The Enbrel Label

The Enbrel Package Insert discusses treatment of patients with PsA and plaque psoriasis with the RA dose of 25 mg twice per week of etanercept. (Ex. 1006, 10-12.) Patients qualified as having plaque psoriasis if they had a target lesion of only $\geq$ 2 cm in diameter, which would include patients with mild psoriasis. (*Id*., 10; Ex. 2035, ¶¶ 120, 145-146.) Patients could continue methotrexate therapy. (Ex. 1006, 10.) In this study, *only 23%* of PsA patients with skin lesions achieved a PASI 75 score after *six months of treatment* with the RA dose of etanercept (25 mg twice weekly), notwithstanding the inclusion of patients with mild skin psoriasis. (*Id*., 11-12; Ex. 2035, ¶¶ 120, 145-146.) The Enbrel Label fails to disclose whether etanercept was effective for *any* patients with moderate-to-severe chronic plaque psoriasis using the RA dosing regimen. (Ex. 1006; Ex. 2035, ¶¶ 120, 145-146.)

VI. The Person of Ordinary Skill in the Art

Petitioner defines a POSA as an individual having "an M.D. and at least 3 years' post-residency experience treating patients for psoriasis, PsA and RA, including with TNFα inhibitors," who "would be familiar with dosing regimens for TNFα inhibitors that had been reported in the literature." (Pet., 14.) This definition, however, requires the POSA to have three years of experience treating RA patients, even though RA is not the patent's focus. The requirement would exclude Petitioner's dermatology expert, Dr. Plott. (*See* Ex. 2083, 26:20-27:14, 28:11-14, 35:25-36:5, 38:9-14.)

Further, Petitioner's definition does not require a POSA to have any experience with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 147-150.) As detailed above, moderate-to-severe chronic plaque psoriasis is a distinct form of psoriasis affecting only 23-25% of the psoriasis population, involving increased TNFα burden, and requiring different types of treatment. (Ex. 2041, 16-17; Ex. 1036, 4; Ex. 2035, ¶¶ 42-43, 66; *see supra* II.A, II.D.2.) Petitioner's POSA, however, incorrectly includes doctors lacking knowledge or experience with this patient population. (Ex. 2035, ¶¶ 147-150.) Such an individual would lack the requisite experience to investigate the dose of a new anti-TNFα therapy for the treatment of moderate-to-severe psoriasis. (*Id*.)

Patent Owner proposes that the POSA should be defined as an M.D. with at least 3 years' post-residency experience treating patients for moderate-to-severe chronic plaque psoriasis, and experience using TNFα inhibitors. (*Id*.; *see id*., ¶¶ 1, 5-26.) Patent Owner agrees that such a POSA would be familiar with dosing regimens for TNFα inhibitors that had been reported in the literature. (*Id*., ¶¶ 9-17; 147-150; Ex. 2083, 20:25-21:5.)

For the reasons set forth below, however, the Board should find that the challenged claims are not unpatentable regardless of the definition it applies for the POSA.

VII. Priority

Petitioner asserts alternative priority dates of July 18, 2003 (Ground 1) or July 19, 2002 (Ground 2). (Pet., 9.) Petitioner does not assert any reference post-dating July 18, 2003 or that the '689 patent is not entitled to the July 18, 2003 date. (*Id*., 6-9; Ex. 2035, ¶¶ 2-3.)

Accordingly, for purposes of this proceeding, Patent Owner does not dispute Petitioner's alternative effective filing dates for the challenged claims.[4] *In re*

[4] For purposes of this response, Patent Owner assumes, but does not concede, a priority date of July 2003 for both grounds.

Magnum Oil Tools Int'l, Ltd., 829 F.3d 1364, 1381 (Fed. Cir. 2016) ("[T]he Board must base its decision on arguments that were advanced by a party . . . .").

VIII. Claim Construction

A. Claims 16 and 19 Require That the Patient Has Both Moderate-to-Severe Chronic Plaque Psoriasis and PsA and Achieves the Specified Clinical Endpoints at Week 12 of Treatment

1. The Challenged Claims Are Directed to a Single Patient

The Institution Decision states that, "Patent Owner appears to argue that claims 16 and 19 require every patient receiving the claimed dosing regimen to achieve the recited clinical endpoints." (Paper 14, 34.) The Board is correct in the sense that, based on the claim language, specification, and use of the term "a patient" in the relevant art, claims 16 and 19 cover only those patients who achieve the specific clinical endpoints recited (PASI or PGA score) at week 12 of the treatment.

Independent claim 7 recites "subcutaneously administering 40 mg of said adalimumab to *a patient* having moderate to severe chronic plaque psoriasis every other week." (Ex. 1001, 57:30-37.) Claims 16 and 19 depend from claim 7 and additionally require "said patient" to have both psoriasis and PsA. (Paper 14, 31; Ex. 1001, 58:25-36.) And, claims 16 and 19 also recite clinical endpoints or efficacy requirements: namely, that "said patient" achieves at least a 75% reduction in PASI score at week 12 of treatment (claim 16) or achieves at least a PGA score of clear or almost clear at week 12 of treatment (claim 19). (*Id.*) The "said patient" claim

language is in the singular form and refers back to the term "a patient" recited in claim 7. (*Id*.) This makes sense, as PASI and PGA scores are patient-specific measurements. (Ex. 2035, ¶¶ 151-153.) Thus, the claim language is directed to a single patient. (*Id*.)

Petitioner's argument is consistent with this construction. Petitioner acknowledges that claims 16 and 19 "require *a patient* to achieve specific clinical outcomes." (Pet., 48.) Dr. Plott states that claim 16 indicates a "75% overall improvement in the extent and severity of *a patient's psoriasis plaques* at week 12." (Ex. 1012, ¶ 33 (emphasis added); *see also* Ex. 2083, 40:18-41:13, 42:24-43:8.) Dr. Helfogtt states that "the treated patient" achieves PASI 75 or a PGA score of clear or almost clear by week 12 of treatment. (Ex. 1002, ¶ 24.)

The specification is also consistent with this reading. (Ex. 2035, ¶ 152.) It uses the plural "patients" or the term "patient population" when referring to a group or collection of subjects. (*See, e.g.* Ex. 1001, 5:6-13, 40:13-15.) For example, the specification's examples use a primary endpoint of the "proportion of patients" achieving PASI 75. (*Id*., 40:13-15.) In contrast, the claims only use the term "a patient" or "the patient" when referring to an individual subject and do not refer to results on a proportion or population basis. (*See, e.g. id*., 58:25-36; Ex. 2035, ¶ 152.) The term "a patient" was also used in the relevant art to refer to a single patient. (*See* Ex. 2102, 430; Ex. 1050, 8.)

During prosecution of a parent application to the '689 patent, the same Examiner made clear that similar claim language directed to "a subject" was applicable to "treating a single patient." (Ex. 2086, 6; Ex. 2099, 40.)

Therefore, the Board should construe claims 16 and 19 consistent with their plain language to require that the patient has both moderate-to-severe chronic plaque psoriasis and PsA, and that the patient achieves the specified clinical outcomes at week 12 of treatment with the claimed regimen. *Harari v. Lee*, 656 F.3d 1331 at 1341-42 (Fed. Cir. 2011) (construing the term "a bit line" as a single bit line in view of the claims and the specification distinguishing between single and plural).

2. Claims 16 and 19 Require the Treated Patient to Achieve the Claimed PASI or PGA Score

The Petition did not expressly construe claims 16 or 19. The Institution Decision states, however, that "Petitioner appears to argue that the claims require nothing more than administering the claimed dosing regimen or, if the claims require more, they do not require every patient to achieve the recited clinical endpoints." (Paper 14, 34.) If this is indeed Petitioner's argument, it is incorrect for several reasons.

First, this construction would render the limitations of claims 16 and 19 meaningless, extending the claim to cover methods in which the recited patient does not achieve the clinical endpoints recited. Neither Petitioner nor its declarants argued that the PASI 75 or PGA score language was not limiting. (*See* Pet., 15-16.) On the

contrary, they acknowledge that these claims *require* achieving these endpoints. (*Id*., 48; Ex. 1012, ¶ 82; Ex. 1002, ¶ 112; Ex. 2083, 40:18-41:13, 42:24-43:8 (acknowledging that claims 16 and 19 "require" achieving the recited clinical endpoints).)

Second, claims should be interpreted "with an eye toward giving effect to all terms in the claim." *Bicon, Inc. v. Straumann Co.*, 441 F.3d 945, 950 (Fed. Cir. 2006). The PASI 75 and PGA score claim language substantively limits claims 16 and 19 in at least two ways. By referring to "week 12 of the treatment," the claim language requires at least a 12-week treatment duration. Otherwise, the reference to "week 12 of the treatment" would be superfluous. Additionally, requiring that the patient achieve at least a specific PASI or PGA score at week 12 introduces an efficacy requirement not otherwise found in the claim. These efficacy limitations of claims 16 and 19 should be given meaning.

Third, construing claims 16 and 19 to cover patients not achieving these endpoints would include all patients with moderate-to-severe chronic plaque psoriasis and PsA being administered adalimumab, regardless of clinical outcome.

This construction would be unreasonably broad. *See Microsoft Corp. v. Proxyconn, Inc.*, 789 F.3d 1292, 1298 (Fed. Cir. 2015) (claims must be construed reasonably).[5]

B. A Patient with Moderate-To-Severe Chronic Plaque Psoriasis Is One for Whom Topical Therapy Was Ineffective or Not Practical

The term "moderate-to-severe chronic plaque psoriasis" should be construed to have its ordinary and customary meaning in the art. Dermatologists understand this term to mean chronic plaque psoriasis that is different from mild psoriasis and of sufficient severity such that topical therapy was either ineffective or not practical due to the location or extent of body surface area covered. (Ex. 2035, ¶¶ 154-157; Ex. 2041, 16; *see* Ex. 2083, 21:14-22:5.) Chaudhari, for example, discloses that patients with moderate-to-severe psoriasis in that study had a "history of topical corticosteroid failure." (Ex. 1036, 5.)

Classification of moderate-to-severe psoriasis considers plaque severity, extent of disease, and quality of life factors. (Ex. 2035, ¶¶ 43, 154-157; Ex. 2041, 16.) In his deposition, Dr. Plott agreed with the understanding in the art that patients with PASI scores higher than 7 were considered moderate-to-severe. (Ex. 2083, 39:23-40:5; *see* Ex. 2035, ¶¶ 45, 155.) PASI reflects both the plaque severity *and*

[5] Patent Owner reserves the right to submit additional arguments and evidence in light of any change in the claim construction standard applied during *inter partes* review proceedings.

extent of disease. (Ex. 2035, ¶¶ 44-48, 155; *see* Ex. 2083, 52:10-21 (using PASI score as an indicator of moderate-to-severe chronic plaque psoriasis).)

Although Petitioner did not offer a construction for "moderate to severe chronic plaque psoriasis," its declarants applied an erroneous construction in evaluating the '689 patent. Specifically, both Drs. Plott and Helfgott ignored the extent of disease, instead asserting that the term means "marked plaque elevation, scaling, and/or erythema" of an *individual* plaque (Ex. 1002, ¶ 22; Ex. 1012, ¶¶ 29, 34; Ex. 2083, 42:12-23, 44:6-19.) This definition ignores both the extent of disease and its impact on quality of life. (Ex. 2035, ¶¶ 156-157.) By focusing only on individual plaques, Petitioner's experts bypass factors, such as increased patient weight and total amount of TNFα, that would have been highly relevant to a POSA choosing a dose of adalimumab to treat a *patient* with moderate-to-severe chronic plaque psoriasis. (*See supra* II.A, II.D; Ex. 2035, ¶¶ 49-53, 72-80, 156-157.) Petitioner's experts also ignored the use of PASI scores in the specification and claims, as the PASI expressly considers the extent of skin disease. (Ex. 2035, ¶¶ 44-48.)

Under Petitioner's incorrect definition, for example, a patient with plaques over 70% of his or her body would not be characterized as having moderate-to-severe psoriasis if those plaques had only slight plaque elevation, scaling, and erythema. (Ex. 2035, ¶¶ 157.) Similarly, under Petitioner's definition, a patient with

only one very severe plaque (e.g., a PASI of 4.8) would incorrectly be labeled as having moderate-to-severe psoriasis, despite the plaque being small and treatable with topical therapy and having a PASI score below 7. (*Id*.; Ex. 2083, 39:23-40:5.) Accordingly, Petitioner's definition does not reflect the ordinary and customary meaning of moderate-to-severe chronic plaque psoriasis. (*See* Ex. 2035, ¶¶ 154-157.) The Board should therefore discount Petitioner's expert testimony, which was based on their fundamentally flawed definition of this key claim term.

IX. Dosing Different TNFα Inhibitors Across Different TNFα-Implicated Conditions Was Unpredictable and Involved Many Unknowns

Petitioner asserts that the scientific basis for using TNFα inhibitors to treat psoriasis was their proven success in treating RA. (Pet., 31-35; Ex. 1002, ¶ 72; Ex. 1012, ¶ 72.) In 2003, however, treatments for chronic plaque psoriasis were "developed empirically . . . as with all other diseases of unknown cause." (Ex. 2007, 36.) In addition, researchers found that, although infliximab and etanercept were both TNFα inhibitors that were effective in RA, they showed *different* efficacies in other TNFα-implicated diseases. (Ex. 2065, 425; Ex. 2035, ¶¶ 32-34, 81-86, 160.)

Sandborn, for example, reported that the RA dose of etanercept (25 mg twice weekly) was *ineffective* in treating Crohn's disease. (Ex. 2013, 6.) A follow-up publication explained that the investigators had hoped to find an "anti-TNF-α class effect" for treating Crohn's disease with etanercept in view of its efficacy for RA and because infliximab had obtained FDA approval for both diseases. (Ex. 2110,

1092-93.) Etanercept's failure in Crohn's disease, however, contradicted any anti-TNFα class effect. (*Id*.; Ex. 2035, ¶¶ 32, 82, 160.)

In psoriasis, researchers also found a significant difference in efficacy between infliximab and etanercept, with a greater proportion of psoriasis patients responding to infliximab than to etanercept, despite similar clinical benefit in the treatment of RA. (Ex. 2065, 425; Ex. 2035, ¶¶ 32, 83, 118-122, 160; *see infra* X.B.)

This demonstrates that the clinical efficacy of the RA dose of a TNFα inhibitor in a new condition, such as moderate-to-severe psoriasis, was unpredictable. This unpredictability was attributed to: (1) differences in the inhibitors themselves (e.g., differences in molecular structure, TNFα binding, stability of TNFα complexes, and antigen specificity); (2) differences in the diseases being treated (e.g., accessibility of involved tissues to the inhibitors at the doses administered, the potential role of LTα, the amount of TNFα in the affected tissues, and the sensitivity of diseased tissues to TNFα); (3) differences in the dosing regimens (e.g., weight-based versus fixed dose) and routes of administration (e.g., intravenous versus subcutaneous); and (4) differences in drug distribution to and drug metabolism in the affected tissues (e.g., psoriatic skin). (*See* Ex. 2065, 425; Ex. 2035, ¶¶ 32, 81-86.) Petitioner fails to address any of these differences. Indeed, Dr. Plott admitted that he did not know if there were any molecular differences between infliximab, etanercept, and adalimumab; did not know of any differences in the distribution or metabolism of

these TNFα inhibitors; and that he did not investigate if there were any such differences. (Ex. 2083, 70:15-71:1, 72:15-73:9, 74:1-7.)

In 2003, little of this information was publicly known. (Ex. 2035, ¶¶ 33, 85, 160.) For example, the stability of TNFα complexes with adalimumab was unknown, as was the rate at which adalimumab disassociated from TNFα. (*Id*.) It was also unknown whether there were differences in the distribution of TNFα inhibitors to affected psoriatic skin and their metabolism in affected skin (as compared to the affected joints in an RA patient). (*Id*.) Without this information or any test data establishing the efficacy of any dose of adalimumab in moderate-to-severe chronic plaque psoriasis, one would not have been able to predict its efficacy at a dose of 40 mg every-other-week. (*Id*.); *In re Cyclobenzaprine*, 676 F.3d 1063 (Fed. Cir. 2012) (finding that, without knowing the PK/PD relationship for cyclobenzaprine, one could not predict whether any particular PK profile would produce a therapeutically effective formulation).

X. One of Ordinary Skill Would Have Had No Motivation or Reasonable Expectation of Success in Treating Moderate-to-Severe Chronic Plaque Psoriasis with a 40 mg Every-Other-Week Dose of Adalimumab

Challenged claims 1, 4, 7, 10, 13, 16, and 19 require subcutaneous administration of 40 mg of adalimumab every-other-week to patients having moderate-to-severe chronic plaque psoriasis. (Ex. 1001, 57:15-58:36.) The Institution Decision granted trial based on the combination of Keystone, Chaudhari,

and either Lorenz (Ground 1) or Mease 2000 (Ground 2). (Paper 14, 35.) Petitioner argues that it would have been obvious to administer adalimumab using this dosing regimen in patients with moderate-to-severe chronic plaque psoriasis because this regimen had been used for RA, but Petitioner fails to establish either motivation or reasonable expectation of success. (Ex. 2035, ¶¶ 158-159.)

Petitioner disregards several key factors: (1) the increased TNFα burden implicated in moderate-to-severe chronic plaque psoriasis compared to RA; (2) the consistent use in the art of significantly higher doses of infliximab to treat moderate-to-severe chronic plaque psoriasis; and (3) the difference in total drug administered between infliximab, etanercept, and adalimumab. (Ex. 2035, ¶¶ 34-39, 86-129, 161-167.) Each of these factors would have led a POSA to doubt the potential efficacy of the claimed 40 mg every-other-week dosing regimen in treating moderate-to-severe chronic plaque psoriasis. (*Id*.)

A. The Increased Amount of TNFα Involved in Moderate-to-Severe Chronic Plaque Psoriasis Would Have Dissuaded One from Using the Same Dose of Adalimumab Used to Treat RA to Treat Moderate-to-Severe Chronic Plaque Psoriasis

Keystone, the sole reference in the asserted grounds disclosing any dosing of adalimumab, describes subcutaneously administering 40 mg of adalimumab every-other-week to treat RA. (Ex. 1003.) This was the approved adalimumab dosing regimen for treating RA. (Ex. 2037, ¶ 29.)

Keystone does not describe the treatment of moderate-to-severe chronic plaque psoriasis or any dose of adalimumab to treat moderate-to-severe chronic plaque psoriasis. (Ex. 1003; Ex. 2035, ¶¶ 133, 159-160; Ex. 2083, 69:10-25.) Petitioner cites no other prior art, and Patent Owner is aware of none, describing the use of any adalimumab dosing regimen to treat moderate-to-severe chronic plaque psoriasis. Instead, Petitioner asserts that one would have expected 40 mg every-other-week of adalimumab to treat moderate-to-severe chronic plaque psoriasis because this regimen treated RA and both diseases are mediated by TNFα. (Pet., 1.) But Petitioner disregards known differences between RA and moderate-to-severe chronic plaque psoriasis that the Institution Decision noted "may have potential merit," including the higher TNFα concentration and greater amount of affected tissue in patients with moderate-to-severe chronic plaque psoriasis. (Paper 14, 30; Ex. 2035, ¶¶ 35, 66-80, 94-104, 162-163.)

1. Moderate-to-Severe Chronic Plaque Psoriasis Involves Higher Concentrations of TNFα Compared to RA

Petitioner asserts that RA and psoriasis "shared certain disease characteristics," such as being chronic inflammatory conditions and TNFα-related diseases. (Pet., 27-28.) But Petitioner disregards the many other fundamental differences between the diseases, including the involvement of different cytokines, cell types, risk factors, and co-morbidities. (Ex. 2035, ¶¶ 87-89.)

Petitioner also disregards the significantly higher concentrations of TNFα in psoriatic skin versus the synovial fluid in RA patients, and the increase in TNFα concentration with the severity of a patient's psoriasis. (Ex. 2035, ¶¶ 35, 66-80, 94-104, 162.) As Dr. Krueger explains, a POSA would have expected more anti-TNFα drug to be needed to neutralize the greater concentration of TNFα, and thus would have been motivated to use either higher doses or more frequent dosing in treating moderate-to-severe chronic plaque psoriasis with a TNFα inhibitor as compared to RA. (*Id*., ¶¶ 34-35, 75-80, 95-104.) Petitioner and its declarants ignore the higher TNFα concentration in patients with moderate-to-severe chronic plaque psoriasis.

The below table compares reported TNFα levels in the synovial fluid of RA patients to reported TNFα levels in the involved skin of psoriasis patients. (Ex. 2035, ¶¶ 67-71, 96-99; Ex. 2070, 519; Ex. 2020, 203; Ex. 2071, 670; Ex. 1013, 3; *see supra* II.D.) It shows that the median and mean values reported for TNFα concentration in synovial fluid of RA patients were 101 pg/ml (mean), 114.2 pg/ml (median), and 157 pg/ml (median). (Ex. 2070, 519; Ex. 2020, 203; Ex. 2071, 670; Ex. 2037, ¶¶ 30-31.) These values are far lower than those reported in psoriatic skin. (Ex. 2035, ¶¶ 97-99.) Ettehadi, for example, reports a mean value of 496 pg/ml of TNFα from extracts of psoriatic lesions. (Ex. 1013, 3; Ex. 2035, ¶¶ 67-71.)

Comparison of TNFα Concentrations in RA to Psoriatic Skin[6]

RA Synovial Fluid	**Psoriatic Skin**
Mean = 114.2 pg/ml, Range = 3.0 - 655.8 (Ex. 2070, 519.) Median = 157 pg/ml, Range = 39 - 382 (Ex. 2020, 206.) Median = 101 pg/ml, Range = 58-160 (Ex. 2071, 670.)	Mean = 496 pg/ml, Range = 125 - >1000 (*See* Ex. 1013, 3-4.)

As Dr. Krueger explains, the TNFα value reported in Ettehadi is a conservative estimate of the TNFα concentration in psoriatic skin. (Ex. 2035, ¶¶ 70-71, 78-80.) Because the TNFα in psoriatic lesions is most concentrated at the stratum basale (the inner most layer of the epidermis), skin taken from deeper layers (e.g., underrepresented in Ettehadi's scraping) would likely have even higher TNFα concentrations. (*Id*.) Thus, the TNFα levels present in the psoriatic skin of patients with moderate-to-severe chronic plaque psoriasis may be higher than Ettehadi reported. (*Id*.)

Regardless, Dr. Kreuger confirms the study is otherwise accurate. (*Id*., ¶¶ 70-71.) Petitioner itself relies on Ettehadi to establish the existence of TNFα in

[6] All TNFα measurements in the chart were conducted using commercial ELISA kits from the same company (Medgenix). (Ex. 2035, ¶¶ 67, 68, 97; Ex. 2070, 519; Ex. 2020, 203; Ex. 2071, 670; Ex. 1013, 2.)

psoriatic lesions, and Petitioner's references cite to Ettehadi for the TNFα concentration of psoriatic skin. (Pet., 28-29; Ex. 1002, ¶¶60, 66; Ex. 1012, ¶40; *see, e.g.,* Ex. 1036, 4, 9.)

Thus, based on the available data, a POSA would have understood that the concentration of TNFα in psoriatic skin was at least *three times higher* than in the synovial fluid of patients with RA (and over *100 times higher* on a gram-per-gram basis). (Ex. 2035, ¶¶ 67-69, 96-99; *see supra* II.D.2.) To be effective, additional TNFα inhibitor would be needed to neutralize this increased amount of TNFα in moderate-to-severe psoriasis while also maintaining an excess of unbound drug to account for additionally secreted TNFα, which rate of production was unknown. (*See* Ex. 2061, 17; Ex. 2035, ¶¶ 65, 76, 104, 162-163.)

2. Moderate-to-Severe Chronic Plaque Psoriasis Patients Have More Affected Tissue and Thus More Total TNFα Than RA Patients

In addition to having an increased *concentration* of TNFα in affected tissues, patients with moderate-to-severe chronic plaque psoriasis were understood to have a larger total *amount* of TNFα than RA patients because they have substantially more affected tissue. (Ex. 2035, ¶¶ 35, 72-75, 100-104, 162-163.) This would have further motivated a POSA to use higher doses or more frequent dosing in treating moderate-to-severe chronic plaque psoriasis with a TNFα inhibitor as compared to RA. (Ex. 2035, ¶¶ 35, 162-163); *see Pfizer, Inc. v. Biogen, Inc.* IPR2017-02127, Paper

10 (PTAB Apr. 19, 2018) (finding no reasonable expectation of success in using the NHL dose of rituximab for treatment of CLL when patients with CLL had a 100-fold increase in tumor burden relative to patients with NHL).

Psoriasis is a disorder of the skin, the largest organ of the body, accounting for about 15% of the total body weight of a patient. (Ex. 2035, ¶¶ 53; Ex. 2051, 5.) In RA, by contrast, the inflammatory sites containing TNFα are significantly smaller. (Ex. 2037, ¶¶ 18-24; Ex. 2035, ¶ 88; Ex. 1001, 27:53-57.)

Based on the respective concentrations of TNFα and the size of the affected tissues, Dr. Krueger calculates that an exemplary patient with moderate-to-severe chronic plaque psoriasis would be expected to have from 11,904,000 pg to 59,520,000 pg of TNFα just in affected psoriatic skin, depending on the BSA percentage involved. (Ex. 2035, ¶¶ 72-80, 100-104.) In contrast, an exemplary patient with severe RA would be expected to have only about 35,796 pg of TNFα in affected joints. (Ex. 2035, ¶¶ 100-104; Ex. 2037, ¶¶ 30-36.) In other words, a typical patient with moderate-to-severe chronic plaque psoriasis would be expected to have approximately 332-1,662 times the amount of TNFα in affected skin than in the affected joints of a typical patient with severe RA. (Ex. 2035, ¶¶ 100-104, 162.)

Petitioner's argument hinges on the theory that a POSA would have expected the RA dosing regimen for adalimumab to work for moderate-to-severe chronic plaque psoriasis because the diseases are similar. (Pet., 27.) Petitioner suggests that

a POSA could simply use the same dosing for both diseases because TNFα inhibitors would effectively block TNFα in both RA and psoriasis. (*Id*., 29-30.) But this argument ignores the significantly greater amount of TNFα associated with a typical patient with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 100-104, 162-163.)

In view of these fundamental differences, a POSA would not been motivated to subcutaneously administer, and would not have reasonably expected to succeed in subcutaneously administering, the adalimumab dosing regimen of 40 mg every-other-week to treat moderate-to-severe chronic plaque psoriasis. (*Id*.) As explained below, this would be particularly true for claims 16 and 19, as these claims require a robust clinical response. (*See infra* XI.B.)

B. Prior Art Infliximab and Etanercept Dosing Regimens Would Not Have Allowed One to Predict That the Claimed Adalimumab Dosing Regimen Would Successfully Treat Moderate-to-Severe Chronic Plaque Psoriasis

Petitioner and its experts argue that a POSA would have extrapolated from information about other anti-TNFα drugs, including infliximab and etanercept, to design a dosing regimen for adalimumab. (Pet., 29-39.) But Petitioner's reasoning ignores key differences among the various anti-TNFα drugs. (Ex. 2035, ¶¶ 36-37, 105-122, 164-165.)

1. Infliximab's Intravenous, Weight-Based Dosing Would Not Have Motivated One to Use the Claimed Subcutaneous Fixed Dose of Adalimumab

Infliximab is intravenously administered using weight-based dosing. (Ex. 1027; Ex. 2035, ¶¶ 105-107.) Weight-based dosing accounts for the increased patient weight associated with moderate-to-severe chronic plaque psoriasis compared to RA, ensuring drug doses commensurate with patient weight. (Ex. 2035, ¶ 108 (a 3 mg/kg dosing regimen would deliver over 40% more drug to a 100 kg patient than to a 70 kg patient).) In contrast, the claimed adalimumab dosing regimen involves a subcutaneous fixed dose of 40 mg every-other-week. (Ex. 2035, ¶¶ 107, 110.) This fixed dose remains the same regardless of patient weight, and thus does not account for the heavier patient population associated with psoriasis. (*Id*., ¶¶ 105-110.)

Like infliximab, other therapeutic antibodies under investigation for moderate-to-severe chronic plaque psoriasis in 2003 were dosed by patient weight. (Ex. 2035, ¶ 109.) Efalizumab, an anti-CD11a therapy, was administered based on patient weight. (Ex. 2080, 591.) Daclizumab, an anti-CD25 therapy, was administered based on patient weight. (Ex. 2081, 448.) ABX-IL-8, an anti-IL-8 therapy, was also administered based on patient weight. (Ex. 2082.) Thus, the art favored using weight-based dosing for treatment of moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶ 109.)

Additionally, under infliximab's intravenous route of administration, 100% of the drug would have been expected to be bioavailable. (Ex. 2035, ¶ 107.) In contrast, only 64% of adalimumab was bioavailable via subcutaneous administration. (*Id*.) As discussed below, this difference in bioavailability magnified the substantial discrepancy between the higher amounts of infliximab administered in the prior art versus the lower amounts of adalimumab recited in the challenged claims. (*See infra* X.C.)

Petitioner fails to address these differences between adalimumab and infliximab. But a POSA would have appreciated the differences in dosing and route of administration relevant to the clinical efficacy of a TNFα inhibitor. (Ex. 2065, 425; Ex. 2035, ¶ 110.) Indeed, Chaudhari noted that infliximab's superior efficacy in psoriasis may have been due to differences in route of administration (intravenous versus subcutaneous). (Ex. 1036, 8.)

Infliximab's intravenous weight-based dosing thus would not have motivated use of a subcutaneous fixed dosing regimen to treat moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 84, 110.)

2. The Cited Infliximab Studies Would Not Have Led to the Claimed Adalimumab Dosing Regimen

Petitioner alleges that infliximab studies reported in Chaudhari, Marzo-Ortega, and Lorenz would have provided a reasonable expectation of success in using the RA dosing regimen of adalimumab (40 mg every-other-week) to treat

moderate-to-severe chronic plaque psoriasis. (Pet., 17, 42.) Even if one would have considered prior art infliximab studies in designing an adalimumab dosing regimen for moderate-to-severe chronic plaque psoriasis, however, those studies would not have motivated one to use 40 mg of adalimumab once every-other-week or provided any reasonable expectation of success. (Ex. 2035, ¶¶ 36-37, 111-122, 158, 164-165.)

Chaudhari is the only asserted reference directed to the treatment of moderate-to-severe chronic plaque psoriasis and it discloses weight-based, intravenous infliximab dosing regimens using *higher* doses than the approved infliximab RA dose of 3 mg/kg. (*See, e.g.,* Pet., 40 (relying exclusively on Chaudhari for moderate-to-severe limitation); Ex. 1036, 4; Ex. 2035, ¶¶ 111-112, 116, 134-135, 164-165.) Indeed, Chaudhari acknowledges the prior approval of infliximab for RA at 3 mg/kg, but *still* used doses that were *66 to 233% higher* to treat moderate-to-severe psoriasis. (Ex. 1036, 4.)[7] Chaudhari's use of weight-based, intravenous, *higher* doses for moderate-to-severe chronic plaque psoriasis as compared to RA does not support any reasonable expectation of success in using a fixed, subcutaneous, adalimumab

[7] Petitioner attempts to avoid the higher dosing used for moderate-to-severe chronic plaque psoriasis by asserting that a POSA would have used the "same or similar" dose as used for RA. (Pet., 42, 44, 45.) But Petitioner cites no case law establishing obviousness based on doses purportedly "similar" to a claimed dosing regimen.

dose in moderate-to-severe chronic plaque psoriasis that is the *same* dose used to treat RA. (Ex. 2035, ¶¶ 36-37, 164-165.) Notably, infliximab was later approved for moderate-to-severe chronic plaque psoriasis at the *higher* 5 mg/kg dose. (Ex. 2012, 1.)

Other pre-2003 studies similarly reported using higher infliximab doses for psoriasis than for RA. (Ex. 2035, ¶¶ 113-117.) Ogilvie, for example, discusses the need for systemic treatments for "patients suffering from severe psoriasis with widespread skin lesions." (Ex. 1033, 6-8.) Ogilvie administered *higher* doses of 5 mg/kg of infliximab at weeks 0, 2, and 6, and reported that this regimen was effective in treating patients with moderate-to-severe chronic plaque psoriasis. (*Id*.) Similarly, Wollina also discloses using a more aggressive regimen for patients with "widespread plaque-type psoriasis," administering infliximab more frequently than the approved RA dosing regimen. (Ex. 1050, 7.)

Thus, Ogilvie and Wollina, like Chaudhari, used dosing regimens that provided *more* drug than the approved RA dosing regimen to help neutralize the increased levels of TNFα associated with moderate-to-severe psoriasis. (Ex. 2035, ¶¶ 114-117.)

Although not in either of Petitioner's grounds, the Institution Decision discusses an abstract by Marzo-Ortega providing preliminary results on just five patients administered the RA dose of infliximab (3 mg/kg) with concomitant

methotrexate. (Paper 14, 28-29.) But Marzo-Ortega reports results on patients with PsA and skin psoriasis of *unspecified severity*. (Ex. 1004; Ex. 2035, ¶¶ 113, 141-142.) Notably, Marzo-Ortega provides no information as to whether *any* of the patients studied had moderate-to-severe chronic plaque psoriasis. (Ex. 1004; Ex. 2035, ¶¶ 113, 141-142.) Dr. Plott agreed that it was unknown from Marzo-Ortega whether any of the five subjects had moderate-to-severe chronic plaque psoriasis at baseline. (Ex. 2083, 52:10-21.)

A POSA reading Marzo-Ortega would have expected that, as with PsA patients generally, most of the studied patients had mild skin psoriasis. (Ex. 2035, ¶¶ 54-58, 113, 141, 164; *see* Ex. 2083, 52:14-21.) Indeed, a subsequent non-prior-art publication of the same study by Marzo-Ortega and colleagues discloses that *the median PASI score at baseline was just 1.8*, confirming that, in general, the tested patients did *not* have moderate-to-severe chronic plaque psoriasis.[8] (Ex. 2033, 779; Ex. 2035, ¶¶ 46, 113, 141; Ex. 2083, 39:23-40:5, 57:8-12 (Dr. Plott agreed that the

[8] The Institution Decision quotes Dr. Plott's assertion that "when practitioners refer to 'psoriasis' in isolation, they generally mean plaque psoriasis." (Paper 14, 25.) But that does not refer to any common understanding in the prior art of the *severity* of psoriasis, only the *form* of psoriasis. (Ex. 1012, ¶ 31.)

median PASI score of 1.8 did not represent moderate-to-severe chronic plaque psoriasis).)

Marzo-Ortega's non-specific results on an unidentified PsA population, many with only mild psoriasis, would not have motivated use of, nor provided any reasonable expectation of success in administering, the RA dosing regimen of adalimumab to treat patients with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 36, 116-117, 164-165.) One also would not have reasonably expected to achieve the claimed clinical endpoints of claims 16 and 19 on a patient with PsA and moderate-to-severe chronic plaque psoriasis based on these preliminary results. (*See infra* XI.B.)

Petitioner also relies in Ground 1 on Lorenz's discussion of studies using infliximab for patients with PsA who also had "psoriasis." (Ex. 1028, S18-19.) Lorenz, however, consistently discusses the use of the higher 5 and 10 mg/kg doses of infliximab, and nowhere teaches or suggests use of a lower dose. (Ex. 1028; Ex. 2035, ¶¶ 136, 164-165.)

The Institution Decision states that the skilled artisan would have considered RA dosing regimens other than the approved regimen. (Paper 14, 28.) The critical point, however, is that only higher infliximab doses (5 and 10 mg/kg) and/or more frequent dosing (weeks 0, 2, 4, and 8) were ever shown in the prior art to work in patients with moderate-to-severe chronic plaque psoriasis. (Ex. 1036, Ex. 1028,

Ex. 1033; Ex. 1050; Ex. 2035, ¶¶ 36, 111-117, 164-165.) Based on this information, a POSA would have been motivated to use higher adalimumab doses or more frequent adalimumab doses to treat moderate-to-severe chronic plaque psoriasis than the 40 mg every-other-week regimen approved for RA. (Ex. 2035, ¶¶ 164-165.) Notably, both higher and more frequent adalimumab doses were disclosed in the prior art as successfully treating RA. (*See*, *e.g.*, Ex. 1003 (disclosing use of 80 mg every-other-week); Ex. 1021.)

Thus, Petitioner fails to prove that a POSA would have been motivated to administer the RA dosing regimen of adalimumab (40 mg every-other-week) to treat patients with moderate-to-severe chronic plaque psoriasis based on prior-art uses of infliximab to treat psoriasis, or that one would have reasonably expected that 40 mg of adalimumab every-other-week could successfully treat moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 36, 116-117, 164-165.) Instead, consistent with the higher TNFα amounts associated with moderate-to-severe chronic plaque psoriasis, a POSA would have been motivated to use higher adalimumab doses or more frequent adalimumab dosing. (*Id*.)

3. The Cited Etanercept Studies Would Not Have Led to the Claimed Adalimumab Dosing Regimen

In Grounds 1 and 2, Petitioner relies on a study administering 25 mg of etanercept subcutaneously twice per week for 12 weeks to PsA patients. (Pet., 9, 22,

24 (Ground 1 is based on Lorenz's summary of the study reported in Mease 2000; Ground 2 is based on Mease 2000 itself).)

By 2003, however, it was known that the approved RA dose of etanercept (25 mg twice a week) had failed to treat Crohn's disease, a TNFα-related disorder. (*E.g.*, Ex. 2013, 6; Ex. 2083, 68:11-13; Ex. 2035, ¶¶ 32, 82, 138.) In view of this failure, etanercept would not have provided any basis to predict the efficacy of the approved adalimumab RA dosing in a different disease (moderate-to-severe chronic plaque psoriasis). (Ex. 2035, ¶¶ 32, 82, 138; *see supra* II.C, IX.)

Even if a POSA would have considered prior-art etanercept dosing regimens in designing an adalimumab dosing regimen for moderate-to-severe chronic plaque psoriasis, those studies would not have motivated the use of 40 mg of adalimumab once every-other-week or provided any reasonable expectation of success. As discussed below, the etanercept studies revealed that the etanercept RA dosing regimen had poor efficacy in treating even mild psoriasis. (Ex. 2035, ¶¶ 118-122.)

Mease 2000 discusses administering 25 mg of etanercept subcutaneously twice weekly to patients with PsA. (Ex. 1017A, 1.) Patients receiving etanercept (as opposed to placebo) had baseline PASI scores as low as 2.3. (*Id*., 2; Ex. 2035, ¶¶ 118, 139.) A PASI score of 2.3 indicates mild chronic plaque psoriasis. (Ex. 2035, ¶¶ 45-48, 118-119, 139; Ex. 2083, 39:23-40:5.) Mease 2000 also discloses that some

unspecified percentage of patients could continue taking methotrexate as well as corticosteroids. (Ex. 1017A; Ex. 2083, 60:12-17.)

Despite the low starting PASI scores and use of other medications, Mease 2000 nonetheless reports that just 5 of the 19 patients tested (26%) reached a PASI 75 response at 12 weeks. (Ex. 1017A, 4.) Further, neither Lorenz nor Mease 2000 discloses whether any of the 5 patients achieving PASI 75 had moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 37, 118-119, 139, 165; Ex. 2084, 48:9-16.) Indeed, Lorenz and Mease 2000 fail to disclose whether etanercept was effective for *any* patient with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 37, 118-119, 139, 165.) Mease 2000 also does not disclose whether the 5 patients achieving PASI 75 were on methotrexate and/or corticosteroids. (Ex. 2035, ¶¶ 118-119; Ex. 2083, 60:12-17.) Even the less rigorous PASI 25 and 50 scores did not reach statistical significance at week 12 versus placebo, notwithstanding generally milder skin disease. (Ex. 1017A, 5; Ex. 2035, ¶¶ 118-119, 139.) Notably, etanercept was later approved for moderate-to-severe chronic plaque psoriasis at a higher 50-mg-twice-weekly dose. (Ex. 1048; Ex. 2083, 66:9-19.)

The results obtained with the subcutaneous, fixed RA dose of etanercept in psoriasis patients were significantly inferior to those achieved with the higher, intravenous, weight-based dosing of infliximab, and were recognized as such

contemporaneously. (Ex. 2035, ¶¶ 37, 122, 165; Ex. 2065, 425 (characterizing etanercept as worse than infliximab in treating psoriasis); Ex. 1036, 8 (noting the "lesser response" of etanercept compared to infliximab).) For example, Chaudhari reported that 82% of patients with moderate-to-severe chronic plaque psoriasis achieved PASI 75 using an infliximab dose of 5 mg/kg (higher than the infliximab RA dose of 3 mg/kg). (Ex. 1036, 6.) This is far better than the 26% of patients in Mease 2000 who achieved a PASI 75 response using the RA dose of etanercept, notwithstanding their generally mild psoriasis and background treatment with methotrexate and corticosteroids. (Ex. 2035, ¶¶ 122, 165.) Similarly, the Enbrel Package Insert states that only 23% of PsA patients with skin lesions achieved a PASI 75 score after *six months of treatment* with the RA dose of etanercept (25 mg twice weekly). (Ex. 1006, 11-12.) Like Mease 2000, the Enbrel Label fails to disclose whether etanercept was effective for *any* patients with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶ 120.)

The generally poor efficacy of the subcutaneous, fixed RA dose of etanercept in treating patients with mild skin psoriasis would not have motivated one to use a subcutaneous fixed RA dose of adalimumab to treat patients with moderate-to-severe chronic plaque psoriasis, particularly in view of the increased amount of TNFα required to be neutralized. (Ex. 2035, ¶¶ 37, 122, 165; *see* Ex. 2083, 32:9-23 (the goal in treating patients with moderate-to-severe chronic plaque psoriasis was

to treat the patient to "the fullest extent possible"); Ex. 2084, 90:9-15 (same).) Indeed, the prior art attributed infliximab's increased efficacy in psoriasis to the larger infliximab doses compared to etanercept's smaller doses. (Ex. 2065, 425.) A POSA therefore would not have reasonably expected that the RA dosing regimen of adalimumab could be successfully used to treat patients with moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 37, 122, 165) As discussed in Section XI.B below, these deficiencies with Petitioner's case apply in particular to claims 16 and 19, both of which recite specific efficacy parameters. (*See infra* IX.B.)

C. The Prior Art Disclosed the Need to Use Higher Doses of Anti-TNFα Drugs to Treat Moderate-to-Severe Chronic Plaque Psoriasis Than for RA

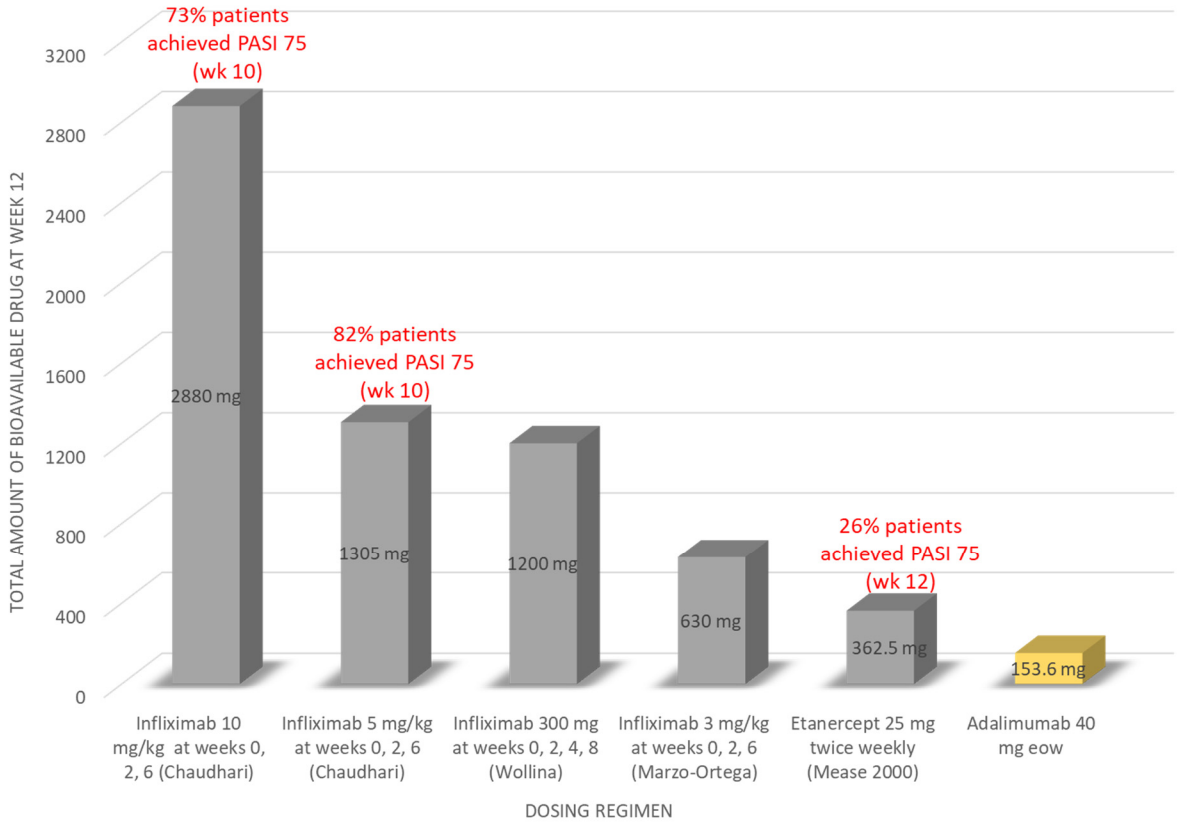
Even if one accepts Petitioner's unsupported assumption that infliximab and etanercept dosing regimens would have been predictive of adalimumab dosing regimens, a POSA nonetheless would have been motivated to use a higher dose for moderate-to-severe chronic plaque psoriasis than for RA because patients received vastly more total drug by week 12 under the prior art infliximab and etanercept dosing regimens than they would under the claimed adalimumab dosing regimen. (Ex. 2035, ¶¶ 38, 123-129, 166-167.)

Under the claimed adalimumab dosing regimen, a patient would have been administered just *240 mg* of adalimumab by week 12, regardless of patient weight. (Ex. 2035, ¶ 128.) This is *5-12 times lower* than the amount of infliximab

administered in Chaudhari that was effective in moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 123-124, 128-129; Ex. 1036, 6.) As shown below, this difference is magnified when accounting for the difference in bioavailability between adalimumab's subcutaneous administration and infliximab's intravenous administration. (Ex. 2035, ¶¶ 123-124, 128-129.)

The claimed adalimumab regimen also delivers less drug at week 12 than the infliximab regimens reported in Wollina and Marzo-Ortega. (Ex. 2035, ¶ 125; Ex. 1004; Ex. 1050.) Additionally, the amount of bioavailable drug under adalimumab's RA dosing regimen is *less than half* of the amount of bioavailable drug under the inadequate etanercept dosing regimen reported in Mease 2000, which was not specific to moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 126-129; Ex. 1017A; Ex. 2112, 6.)

Comparison of Total Bioavailable Drug Administered in Prior Art for Psoriasis as Compared to Claimed Adalimumab Dose



As discussed in Section IX above, there are many complexities in dosing TNFα inhibitors, none of which are meaningfully addressed by Petitioner. (Ex. 2035, ¶¶ 81-86, 160; Ex. 2083, 70:15-71:1, 72:15-73:9, 74:1-7.) But based on the respective dosing regimens, a POSA would have had no motivation to use, and would not have reasonably expected to successfully use, significantly *less* adalimumab for the treatment of moderate-to-severe chronic plaque psoriasis, as that disease was understood to involve approximately *332-1,662 times higher* amounts

of TNFα in affected tissues of a typical patient compared to a typical patient with RA. (Ex. 2035, ¶¶ 38, 123-129, 158, 166-167.)

The prior art infliximab regimens (*e.g.* 3, 5, or 10 mg/kg) deliver larger doses of drug compared to the approved RA dose of adalimumab (40 mg every-other-week). (Ex. 2035, ¶¶ 38, 123, 128-129, 166-167.) Infliximab's ability to adequately neutralize TNFα in patients with moderate-to-severe chronic plaque psoriasis, and thus treat the disease, therefore provides no expectation that a lower dose of adalimumab would also be sufficient. (*Id*.) To the contrary, one would have been motivated to use, and would have expected to need, higher adalimumab doses consistent with the infliximab doses used in the prior art. (*Id*.)

XI. Claims 16 and 19 Are Separately Patentable

Claims 16 and 19 require treating a patient with moderate-to-severe chronic plaque psoriasis and PsA with 40 mg adalimumab every-other-week *and* achieving specific clinical endpoints at week 12. (Ex. 1001, 58:25-35.) Specifically, claim 16 recites that the patient "achieves at least a 75% reduction in Psoriasis Area and Severity Index (PASI) score at week 12 of the treatment," and claim 19 recites that the patient "achieves at least a Physician Global Assessment (PGA) score of clear or at most clear at week 12 of the treatment." (*Id*.)

Petitioner fails to establish (1) that these clinical endpoints were inherent from the teachings of the prior art or (2) that a POSA would have had any reasonable expectation in achieving them. Claims 16 and 19 are therefore separately patentable.

A. The Efficacy Requirements Are Not Inherent Results of Practicing the Claimed Methods

Petitioner argues that the efficacy requirements of claims 16 and 19 are the inherent results of practicing the claimed method. (Pet., 48-49.) According to Petitioner, these recited endpoints would be inherently achieved by subcutaneously administering 40 mg of adalimumab every-other-week to psoriasis patients. (*Id*.)

Petitioner, however, must "meet a high standard in order to rely on inherency to establish the existence of a claim limitation in the prior art in an obviousness analysis—the limitation at issue necessarily must be present, or the natural result of the combination of elements explicitly disclosed by the prior art." *Par Pharm., Inc. v. TWi Pharm., Inc.*, 773 F.3d 1186, 1195-96 (Fed. Cir. 2014). Petitioner fails to meet this stringent legal standard.

In particular, Petitioner has not shown that the efficacy limitations of claims 16 and 19 would be *necessarily present* at week 12 of treatment with the claimed adalimumab dosing regimen. The claims cover only those patients who achieve the recited PASI or PGA scores. (*See supra* VIII.A.) Thus, to prove inherency, a patient must *necessarily* achieve the recited PASI or PGA score. Petitioner acknowledges that the claims *require* a patient to achieve the recited clinical endpoints yet asserts

that only "*some portion* of treated patients" would achieve them when treated with the claimed dosing regimen. (Pet., 48; Ex. 1002, ¶¶ 112-113; Ex. 1012, ¶¶ 85-86; Ex. 2035, ¶¶ 39, 168-169.)

Further, both Drs. Plott and Helfgott admit that not every patient with moderate-to-severe chronic plaque psoriasis and PsA administered subcutaneous adalimumab at 40 mg every-other-week will achieve the recited PASI 75 and PGA endpoints. (Ex. 2083, 41:3-20, 42:24-43:15; Ex. 2084, 89:23-90:8.) Dr. Plott conceded, for example, that "[i]t's correct that not every patient will achieve a 75 percent improvement in their PASI score" under the claimed dosing regimen. (Ex. 2083, 41:11-13.)

Petitioner's argument that *some* patients achieve the recited endpoints cannot prove inherency. "The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient" to establish inherency. *Par Pharm., Inc.*, 773 F.3d at 1195 (quoting *In re Rijckaert*, 9 F.3d 1531, 1533-34 (Fed. Cir. 1993)). Inherency "may not be established by probabilities or possibilities." *Id.* (quoting *In re Oelrich*, 666 F.2d 578, 581 (C.C.P.A. 1981)).

Therefore, because Petitioner fails to prove that the efficacy requirements of claims 16 and 19 would be necessarily present, as required under the strict legal test for inherency (especially in the context of obviousness), the Board should reject Petitioner's unsupported inherency argument.

B. One Would Have Had No Reasonable Expectation of Success in Achieving PASI 75 or a PGA Score of "Clear" or "Almost Clear" at Week 12 in a Patient with Moderate-to-Severe Chronic Plaque Psoriasis and PsA

Petitioner further asserts that the efficacy requirements of claims 16 and 19 "are the obvious result of anti-TNFα therapy," relying *only* on Chaudhari's PASI and PGA results. (Pet., 48; Paper 14, 32-33.) As discussed below, however, Petitioner's analysis does not establish any reasonable expectation of success in achieving the claimed endpoints in a patient with moderate-to-severe chronic plaque psoriasis and PsA.

1. The Asserted Prior Art Fails to Disclose or Suggest Achieving the Claimed Endpoints in a Patient with Moderate-to-Severe Chronic Plaque Psoriasis and PsA

Chaudhari does not disclose achieving PASI 75 or a PGA of "clear" or "almost clear" at week 12 in any patients with moderate-to-severe chronic plaque psoriasis *and* PsA. (*See generally* Ex. 1036; Ex. 2035, ¶ 170.) Petitioner's expert testimony does not overcome this deficiency in the prior art. Both experts assert that achieving the claimed PASI and PGA results would have been obvious in a patient with moderate-to-severe chronic plaque psoriasis, but they ignore the claims' requirement that the patient must also have PsA. (*See* Ex. 1012, ¶ 86; Ex. 1002, ¶ 113.) Thus, no record evidence supports any expectation that a patient with moderate-to-severe chronic plaque psoriasis *and* PsA would achieve the claimed PASI and PGA endpoints. *See Institut Pasteur v. Focarino*, 738 F.3d 1337, 1344-46

(Fed. Cir. 2013). Petitioner's analysis is therefore legally flawed for failing to consider the claims as a whole. *Gillette Co. v. S.C. Johnson & Son, Inc*., 919 F.2d 720, 724 (Fed. Cir. 1990) ("Focusing on the obviousness of substitution and differences, instead of on the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness.").

2. Petitioner Does Not Establish Any Class Effect Among TNFα Inhibitors That Would Support 40 mg of Adalimumab Achieving the Same Clinical Response as Infliximab

No prior art discloses administering adalimumab to patients with moderate-to-severe chronic plaque psoriasis and PsA or achieving any PASI or PGA results in such patients. (Ex. 2035, ¶ 170.) Petitioner's argument therefore rests on clinical results achieved with a different antibody (infliximab) in a broader patient population (moderate-to-severe psoriasis). (*See* Pet., 48.) Petitioner's experts try to bridge this gap by asserting that Chaudhari's results with infliximab are the result of TNFα inhibition, and therefore that one would have expected these results with adalimumab because it also inhibits TNFα. (Ex. 1002, ¶ 113; Ex. 1012, ¶ 86.)

As an initial matter, neither expert cites any support for this conclusion. (*Id*.) Dr. Plott even admitted that he was not aware of how adalimumab affects TNFα levels as compared to infliximab. (Ex. 2083, 74:1-7.) These conclusory opinions should be disregarded as lacking any objective evidence supporting a correlation in clinical response between adalimumab and infliximab. *See Upjohn Co. v. MOVA*

Pharm. Corp., 225 F.3d 1306, 1311 (Fed. Cir. 2000) (requiring factual support for an expert's opinion).

Moreover, Petitioner's arguments ignore the unpredictability in clinical response between different anti-TNFα inhibitors. (Ex. 2035, ¶ 170-172.) Dr. Helfgott's own publication also highlights this difficultly. (*Id*.) Specifically, Dr. Helfgott reported no correlation between the clinical response to infliximab as compared to etanercept in patients with RA. (Ex. 2034, 2-3 ("[O]ur findings suggest a lack of correlation between the clinical responses . . . when etanercept and infliximab were used in the same patients.").) He explained that a patient's joint count and acute-phase reactant responses to etanercept did not correlate with similar responses to infliximab, even though both drugs inhibited TNFα. (*Id*.)

Petitioner fails to address this unpredictability and *known* lack of correlation in clinical response between TNFα inhibitors, undermining Petitioner's assertion that successful inhibition of TNFα is predictive of a specific clinical response. Notably, Petitioner also fails to identify any prior art disclosing or suggesting that a PASI or PGA score may be predicted for one TNFα inhibitor based on the results from another TNFα inhibitor. (Ex. 2035, ¶¶ 170-172.)

Petitioner also fails to address any differences between adalimumab and infliximab to arguably support a correlation between the clinical response in Chaudhari and what a POSA would expect with 40 mg of adalimumab. (Ex. 2083,

70:15-71:1, 72:15-73:9, 74:1-7; Ex. 2035, ¶¶ 85-86.) Without information on the differences between infliximab and adalimumab or the distribution and pharmacokinetics of the drugs in the skin, a POSA would have had no reasonable expectation that the two agents would achieve the same magnitude of clinical response. (Ex. 2034, 2; Ex. 2035, ¶¶ 85-86, 170-172.)

Because Petitioner relies only on Chaudhari for the efficacy limitations of claims 16 and 19 (Pet., 48), the Board should not consider results from any other references. *Sirona Dental Sys. GMBH v. Institut Strauman AG*, 2018 WL 3028693, at *5 (Fed. Cir. June 19, 2018) (stating it would "not be proper for the Board to deviate from the grounds in the petition and raise its own obviousness theory. . . ."); *In re Magnum Oil*, 829 F.3d at 1381.

3. If Anything, One Would Have Expected to Need Higher Doses of Adalimumab to Achieve the Claimed PASI or PGA Score in a Patient with Moderate-to-Severe Chronic Plaque Psoriasis and PsA

Compounding Petitioner's failure to consider claims 16 and 19 as a whole or establish any correlation in clinical response between TNFα inhibitors, a POSA would have expected to need *higher* doses of adalimumab to treat moderate-to-severe chronic plaque psoriasis. (Ex. 2035, ¶¶ 39, 170-172; *see supra* X.A-C.) This is particularly true for claims 16 and 19, which require treating patients who also have PsA and reaching the difficult-to-achieve PASI or PGA scores recited in the claims. (Ex. 2035, ¶¶ 39, 170-172.)

Petitioner's reasonable expectation of success argument is based on the PASI and PGA results reported in Chaudhari. (Pet., 48.) But Chaudhari only achieved those results in patients with moderate-to-severe chronic plaque psoriasis by using 5 and 10 mg/kg of infliximab, which are 67% to 233% higher than the approved RA infliximab dose of 3 mg/kg. (Ex. 1036, 6; Ex. 2035, ¶ 112.) A POSA thus would not have expected to achieve the claimed clinical endpoints with the *lower* RA dose of adalimumab of 40 mg every-other-week. (Ex. 2035, ¶¶ 39, 170-172.)

Moreover, even if one were to draw comparisons between the prior art infliximab dosing regimen and the claimed adalimumab dosing regimen, the Chaudhari dosing regimen delivered approximately 5-12 times more total drug by week 12 than the adalimumab dosing regimen of 40 mg every-other-week, magnified further when accounting for differences in bioavailability. (Ex. 2035, ¶¶ 128-129.) Therefore, even if a POSA would have expected some correlation in clinical response between infliximab and adalimumab, they would have expected to need higher amounts of adalimumab (on the order of the infliximab dosing) for a patient to achieve the claimed endpoints. (Ex. 2035, ¶¶ 128-129, 170-172.)

For these reasons, the prior art does not support any motivation or reasonable expectation of success in achieving PASI 75 or a PGA score of clear or almost clear at week 12 by subcutaneously administering 40 mg of adalimumab every-other-

week to a patient with moderate-to-severe chronic plaque psoriasis and PsA. (Ex. 2035, ¶¶ 39, 170-172.)

XII. Conclusion

For these reasons, Petitioner has not met its burden of showing, by a preponderance of the evidence, that claims 1, 4, 7, 10, 13, 16, and 19 of the '689 patent would have been obvious. The Board should therefore enter a final written decision that the challenged claims have not been shown to be unpatentable.

Respectfully submitted,

Date: July 6, 2018 By: / *William B. Raich* /

William B. Raich, Reg. No. 54,386

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CERTIFICATE OF COMPLIANCE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response to the Petition** contains 13,761 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper and by including the words in the graphics.

Dated: July 6, 2018

By: */ William B. Raich /*

William B. Raich, Reg. No. 54,386

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response to the Petition** and Exhibits 2030-2053, 2055-2071, 2073-2074, 2076-2086, 2089-2097, 2099-2113 were served electronically via email on July 6, 2018, in their entirety on the following:

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Dated: July 6, 2018

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