**Nos. 2017-2304, -2305, -2306, -2362, -2363**

# United States Court of Appeals for the Federal Circuit

**ABBVIE BIOTECHNOLOGY, LTD.,**

***Appellant,***

*v.*

**COHERUS BIOSCIENCES, INC.,**

***Appellee.***

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**ABBVIE BIOTECHNOLOGY, LTD.,**

***Appellant,***

**v.**

**BOEHRINGER INGELHEIM INTERNATIONAL GMBH, BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.,**

***Appellees.***

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APPEALS FROM THE UNITED STATES PATENT AND TRADEMARK OFFICE, PATENT TRIAL AND APPEAL BOARD, *INTER PARTES* REVIEW NOS. IPR2016-00172, IPR2016-00188, IPR2016-00189, IPR2016-00408, AND IPR2016-00409

## RESPONSE BRIEF OF COHERUS BIOSCIENCES, INC.

Jonathan E. Singer
W. Chad Shear
Craig E. Countryman
Oliver J. Richards
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070

Michael J. Kane
John C. Adkisson
Elizabeth M. Flanagan
Fish & Richardson P.C.
3200 RBC Plaza
60 South Sixth Street
Minneapolis, MN 55402
(612) 335-5070

March 23, 2018

## CERTIFICATE OF INTEREST

Counsel for Coherus BioSciences, Inc. certifies the following.

1. The full name of every party represented by me: Coherus BioSciences, Inc.

2. The name of the real party in interest represented by me: Coherus BioSciences, Inc.

3. Parent corporations and publicly held companies that own 10% or more of stock in the party: Wellington Management Company, LLP; Fidelity Management & Research Company (FMC LLC); Temasek Holdings Pte. Ltd.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this Court (and who have not or will not enter an appearance in this case): Fish & Richardson P.C.: Dorothy Whelan; Jenner & Block LLP: Louis E. Fogel and Steven R. Trybus.

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this court's decision in the pending appeal: There are no other related cases known to counsel other than the consolidated cases in the caption above.

Dated: March 23, 2018

*/s/Craig E. Countryman*
Craig E. Countryman

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## STATEMENT OF RELATED CASES

There have been no prior appeals in this case, nor are there any related cases in this Court other than those consolidated in this appeal. Counsel are aware of no other cases that will directly affect or be directly affected by the outcome in this case.

## STATEMENT OF THE ISSUE

Whether the Board correctly found that all claims of U.S. Patent Nos. 8,889,135; 9,017,680; and 9,073,987 were unpatentable as obvious where:

(a) the claims cover biweekly administration of a 40 mg subcutaneous dose of the antibody D2E7 to treat rheumatoid arthritis, with some claims requiring treatment for at least 24 weeks;

(b) the Board found the van de Putte prior art reference taught that administration of a range of subcutaneous doses of D2E7 was safe and effective;

(c) the Board found that the Kempeni prior art taught that biweekly administration of a dose equivalent to a 40 mg subcutaneous dose of D2E7 was safe and effective;

(d) the Board found that a skilled artisan would select the claimed 40 mg biweekly, subcutaneous dose to increase patient compliance, to successfully balance efficacy and safety, and to lower costs; and

(e) the Board carefully considered and rejected AbbVie's contrary interpretation of the prior art and its alleged secondary considerations.

## INTRODUCTION

These appeals begin and end with the Board's well-supported factual findings. The patents cover a method for treating rheumatoid arthritis by administering 40 mg, biweekly, subcutaneous injections of the D2E7 antibody, the active ingredient in AbbVie's HUMIRA® product. AbbVie's own prior art clinical trial results led directly to the claimed invention. One reference, van de Putte, disclosed that weekly D2E7 subcutaneous injections of 20, 40, and 80 mg produced positive responses that were "nearly equally efficacious" to one another. Another reference, Kempeni, disclosed that biweekly administration of a range of D2E7 doses—including a dose equivalent to a 40 mg subcutaneous injection—demonstrated "sustained therapeutic effects," were "well-tolerated," and were "safe and effective." The Board held that a skilled artisan would have modified van de Putte to incorporate biweekly dosing because it would result in less frequent injections that were easier to administer, while balancing efficacy and safety. The Board also found the prior art taught that the claimed dosing regimen would succeed in treating rheumatoid arthritis.

AbbVie tries to escape the Board's fact-finding by manufacturing alleged legal errors. The Board made no such errors. The Board carefully addressed all of AbbVie's arguments and evidence in the manner presented by AbbVie and found the explicit disclosures in AbbVie's own prior art refuted each of AbbVie's arguments. The only question now is whether the Board's factual findings were supported by substantial evidence. Because they were, its decision must be affirmed

## STATEMENT OF THE CASE

### I. Technology Background: Methods of Treating of Rheumatoid Arthritis with anti-TNFα Proteins, including D2E7.

These appeals arise from proceedings in which the Board found unpatentable claims directed to methods of treating rheumatoid arthritis using the antibody D2E7 (also called adalimumab), the active ingredient in HUMIRA®. The challenged patents do not cover D2E7 itself—that patent expired in 2016. *See* Appx2780–Appx2820. Nor do they cover HUMIRA®'s formulation. Instead, these are line-extension patents that cover a specific dosing regimen to treat rheumatoid arthritis with biweekly 40 mg subcutaneous injections of D2E7.

Rheumatoid arthritis is a chronic, inflammatory auto-immune disease that has been linked to Tumor Necrosis Factor α (TNFα), which activates tissue inflammation and causes joint destruction. Appx244 at 1:12–35; Appx256 at 25:33–39; Appx2720–2720 at ¶¶ 18–20. In rheumatoid arthritis patients, this can cause painful joint swelling, joint tenderness, bone erosion, and deformity. Appx2720 at ¶¶ 18–19. Treatments had been developed to inhibit or counteract TNFα, and consequently reduce the signs, symptoms, and progression of rheumatoid arthritis. *See* Appx2721 at ¶ 20; *see also* Appx2721–2723 at ¶¶ 23–25; Appx2763–2765 at ¶¶ 18–22; Appx2792, at 1:23–48. These treatments involve administering antibodies or other proteins that bind to and neutralize TNFα. *See id.*

Physicians measure the efficacy of rheumatoid arthritis treatments in the clinic using the American College of Rheumatology (ACR) improvement criteria and the Disease Activity Score (DAS). Appx2725–2726, at ¶¶ 31–33; Appx2703–2704. The ACR criteria include (1) a count of the improved swollen joints, (2) a count of the improved tender joints; and (3) a combination of five other criteria, including patient and physician assessment of disease activity, patient assessment of pain, a phase reactant (such as erythrocyte sedimentation rate or C reactive protein), and a measure of disability (according to, for example, a standardized health assessment questionnaire). Appx2725, at ¶ 32; Appx2704. An "ACR 20" response is a 20% improvement in both the count of swollen and tender joints, and a 20% improvement in three of the other criteria. *Id.* It is considered the "gold standard for efficacy for FDA approval of new rheumatoid arthritis medications." Appx 2767, at ¶ 28. The DAS "is a composite score of tender joints, swollen joints, ESR [erythrocyte sedimentation rate], and patients' assessment of disease activity as measured on a visual analogue scale." Appx2726 at ¶ 33; Appx2704.

Other TNFα blockers had been used to treat rheumatoid arthritis before D2E7, including the FDA-approved treatments ENBREL® and REMICADE®. App2721–2722, at ¶¶ 23–24; Appx2763, at ¶¶ 18–19. D2E7 was seen as an improvement, however, because it is a "fully human-recombinant" antibody that is less likely to induce an unintended immune response in the patient. *See* Appx2722–2724, at ¶¶ 25, 27; Appx2792, at 1:23–2:47.

## II. The Prior Art: Treatment of Rheumatoid Arthritis Using Biweekly 40 mg Subcutaneous Injections of D2E7 Had Well-Known Advantages.

The Board's decision in the Coherus IPRs relied principally on two prior art publications by AbbVie's predecessor that reported clinical trials of D2E7 for treating rheumatoid arthritis patients. The first publication—Kempeni—summarized several Phase I studies administering D2E7. *See* Appx2703–2705. Kempeni reported that biweekly intravenous dosing was effective and that intravenous dosing was equivalent to subcutaneous dosing. Appx2704–2705; Appx2728–2731, at ¶¶ 38–44; Appx2744–2745, at ¶ 72; Appx2765, at ¶ 24. The second publication—van de Putte 1999—reported a Phase II dose-finding clinical study that administered 20, 40, and 80 mg doses of D2E7 subcutaneously on a weekly basis and concluded they were all safe and effective. Appx2706; Appx2731, at ¶ 45; Appx2737, at ¶ 58; Appx2740, at ¶ 63; Appx2766, at ¶ 26. Both prior art publications included a co-inventor of the challenged patents (Kempeni) as an author.

### A. Kempeni Teaches Treating Rheumatoid Arthritis Patients with Biweekly Intravenous Doses of D2E7 and that Intravenous and Subcutaneous Delivery of D2E7 Are Equally Effective.

Kempeni describes the results from several early clinical trials investigating the use of D2E7 to treat rheumatoid arthritis, and concludes each dosing regimen tested D2E7 was safe and effective. *See* Appx2703–2705; Appx2728–2731, at ¶¶ 38–44; Appx2744–2745, at ¶ 72; Appx2765, at ¶ 24.

Kempeni begins by discussing a van de Putte 1998 (DE001) study where patients were given a single dose of D2E7 to investigate its safety and pharmacokinetic profile. *See* Appx2704; Appx2728–2729, at ¶ 39; *see also* Appx2969. The van de Putte 1998 study involved giving patients a single intravenous dose of 0.5, 1, 3, 5, or 10 mg/kg body weight of D2E7. *Id.* AbbVie has admitted that a 0.5 mg/kg dose is equivalent to a 40 mg fixed dose for an 80 kg (*i.e.*, average) patient. Appx3846–3847. Patients responded positively at each dosing level, and the results were "very encouraging." Appx2704; Appx2969; *see also* Appx2728–2729, at ¶ 39. The drug "reached maximum effect after 1–2 weeks, with dose response reaching a plateau at 1 mg/kg," and "[t]he estimated mean terminal half -life was 11.6 to 13.7 days." *Id.*

Kempeni next describes an "open label extension study" involving patients from the original van de Putte 1998 study that was intended to "last[] several years." *See* Appx2704; Appx2729, at ¶ 40; *see also* Appx2970. This study is sometimes called the "DE003" study. As Kempeni explains, "[p]atients who participated in the open label extension study received a second blinded dose identical to their first dose" and then, "[f]rom the third dose onwards, all patients were given active drug (that is, the placebo patients received D2E7 doses according to their dose group)." Appx2704. The dose groups were the same as in the prior study (intravenous administration of 0.5 mg/kg–10 mg/kg). *Id.* The study used the DAS criteria to score patient response, where a "[p]ositive response was defined as a decrease of at least 1.2 (compared with

baseline) in the DAS," *id.*, which would include both a "good" and a "moderate" response on the DAS scale. Appx3529–3530. "D2E7 was administered ***every two weeks*** until responses could be rated as 'good'" as defined by a particular DAS. Appx2704. After achieving a "good" response, patients were treated only upon disease flare up to measure the duration of the "good response." *Id.*

Based on the results after a year of study the authors concluded that "the response in the DAS over time demonstrated sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7," Appx2704, and that "D2E7 has been shown to be safe and efficacious in patients with active RA over 12 months," Appx2970; Appx2727, at ¶ 36. "Response rates of more than 80% have been achieved ***with a mean dosing interval of 2.5 weeks***." Appx2704 (emphasis added). Kempeni concluded from these results that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id.*

Another prior art reference, Rau 2000, provided further detail on the DE001 and DE003 studies that was consistent with Kempeni's disclosures. *See* Appx7314–7319. For example, Rau 2000 disclosed that the number of swollen joints decreased in the two weeks after patients received a 0.5 mg/kg intravenous dose of D2E7, and that about 42% of patients on that dose achieved an ACR20 response "at any point in time." Appx7316. Rau 2000 also included graphs showing that the 0.5 mg/kg dose performed similarly to the other intravenous doses, and that it reduced the initial median DAS score (which was 5.3) by about 30%, *see* Appx7316–7317, a response

that AbbVie's expert admitted would have reduced the signs and symptoms of rheumatoid arthritis. *See* Appx4369–4370. Such a response also counted as a "positive" response using the criteria reported in Kempeni, because it reduced the DAS by more than 1.2 from baseline. *See* Appx2704.

Kempeni also described a third trial where patients were given weekly subcutaneous doses of 0.5 mg/kg of D2E7, which, as noted above, the Board found was equivalent to a 40 mg subcutaneous dose. *See* Appx2704–2705; Appx2729–2730, at ¶ 41; *see also* Appx25. In this study, known as the "DE004" study, "patients were treated with subcutaneous D2E7 or placebo for three months." Appx2705. After this initial period, "[a]ll responding patients continued in an open label extension of this study." Appx2705. The results showed that "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration," that "[u]p to 78% of patients achieved a DAS/ACR20 response after three months of treatment with subcutaneous D2E7," and that only "mild and transient injection site reactions" presented as compared to the placebo. *Id.* The investigators concluded that "D2E7 given subcutaneously was safe and as effective as when administered intravenously[,] demonstrating that subcutaneous self-administration is a promising approach for D2E7 delivery." Appx2705.

Kempeni concluded by summarizing the results of all the studies as follows: "[c]ollectively, these early data suggest that the fully human anti-TNFα antibody [D2E7] is safe and effective as monotherapy or in combination with methotrexate

when administered by single and multiple intravenous injections and subcutaneous injections." Appx2705. Kempeni noted that additional studies were underway to "further define the optimal use of this novel treatment." *Id.*

### B. Van de Putte 1999 Teaches Treating Rheumatoid Arthritis with a Range of Weekly, Subcutaneous, Fixed Doses of D2E7.

Van de Putte 1999 (reporting the "DE007" study) describes a Phase II dose finding study that treated rheumatoid arthritis by administering weekly subcutaneous injections of D2E7 at 20, 40, and 80 mg doses over 3 months. *See* Appx2706; Appx2731, at ¶ 45; Appx2737, at ¶ 58; Appx2766, at ¶¶ 26–27. Based on the encouraging results the study authors noted that "[f]or all efficacy parameters studied," each of 20, 40, and 80 mg/week doses "were statistically significantly superior to placebo" and were "nearly equally efficacious when given s.c. in patients with active RA." Appx2706; Appx2737, at ¶ 58; Appx2766, at ¶ 26.

The authors summarized the study data in the table below. The first row shows the percentage of patients achieving an ACR 20 response, with a much higher percentage in all the treatment groups (49–57%) achieving it as compared with placebo (10%). Appx2706; Appx2737, at ¶¶ 58–59; Appx 2766, at ¶¶ 26–27.

| | Placebo (n=70) | D2E7 20 mg (n=71) | D2E7 40 mg (n=70) | D2E7 80 mg (n=72) |
|---|---|---|---|---|
| % of pts achieving ACR 20 response | 10 | 49 | 57 | 56 |
| Median % improvement in TJC | 5 | 57 | 61 | 55 |
| Median % improvement in SWJC | 16 | 42 | 59 | 61 |
| Median % improvement in CRP | 1 | 55 | 67 | 65 |

The other data shows impressive percentage improvements in tender joint count (TJC), swollen joint count (SWJC), and C-reactive protein (CRP). *See Id.*

The improvements reported in van de Putte 1999 were notable when compared with then-existing FDA-approved treatments. For example, REMICADE®'s clinical trials reported that 50–58% of patients achieved an ACR20 response compared to 20.5% of patients who received a placebo. Appx3039; Appx2738, at ¶ 60; Appx2767–2768, at ¶ 32. Based on those results, the FDA approved REMICADE® in 1999 and concluded that "all of the dosing regimens evaluated" would be beneficial "as adjunctive therapy . . . in the treatment of patients with rheumatoid arthritis." Appx3045; Appx2738, at ¶ 60; Appx2768, at ¶ 32. Skilled artisans would have understood that each dosing regimen in van de Putte 1999 effectively treated rheumatoid arthritis. Appx2738–2739, at ¶ 61; *see also* Appx2766–2768, at ¶¶ 26–32.

### C. The Prior Art Showed that Long-Term, Fixed Dose, Subcutaneous Administration with Longer Intervals Between Doses Were Preferred.

Not only did van de Putte and Kempeni collectively disclose all the limitations of the challenged claims, but the prior art and prevailing wisdom taught that there were many reasons to use a dosing protocol for D2E7 that involved (1) subcutaneous injection, (2) "fixed" doses (*i.e.,* a constant dose for all patients, rather than a variable dose based on the patient's weight), and (3) longer intervals between doses. In each case, this type of dosing regimen increased patient compliance and lowered the cost of treatment. The evidence included both contemporaneous publications and

declarations from two experts—Dr. James O'Dell and Dr. Sharon Baughman. *See*, *e.g.*, Appx3122–3130; Appx2710–2756; Appx2757–2779. Dr. O'Dell is a practitioner who treated rheumatoid arthritis patients, is an editor of one of a leading treatises in the field, and is the former president of the American College of Rheumatology. *See* Appx2757–2760, at ¶¶ 2–9; *see also* Appx2776–2779. Dr. Baughman is a pharmacokinetics expert who has conducted extensive studies on several antibody treatments. *See* Appx2710–2713, at ¶¶ 2–8; *see also* Appx2748–2756.

With respect to subcutaneous injections, skilled artisans recognized that "subcutaneous administration is more desirable for doctors and patients than intravenous administration" when treating chronic diseases like rheumatoid arthritis. *See* Appx3130. The reason is simple—intravenous injections are complicated and usually must be given by a doctor in a hospital-type setting. *See* Appx3124 ("iv administration requires catheterization for administration in a home setting, medical attention when administered in a clinic or physician's office, or hospitalization in more extreme circumstances"); *see also* Appx3130 (explaining that "iv infusion is either administered: (i) in hospitals; (ii) or physician's offices; (iii) or in a patient's home, with catheter"). By contrast, subcutaneous injections can be performed anywhere and are easy for patients to self-administer. *See* Appx3130. Subcutaneous injections also take less time than intravenous injections, and they can even "result in a longer circulating half-life for therapeutic proteins" such as D2E7 "when compared to iv administration." Appx3130; Appx3124. These benefits lead to increased patient

compliance with the treatment regimen. *See* Appx3124; Appx3130; Appx2734, at ¶ 51.

With respect to fixed doses, skilled artisans recognized that it was easier for all patients to use a "fixed" dose (say, 40 mg), rather than calculating and measuring a dose based on the patient's body weight. To use a "weight-based" dose, patients would need to draw the correct volume of the drug formulation into a syringe based on their weight, whereas with fixed doses, "each unit contain[s] a predetermined quantity of active compound calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier." Appx2803. A fixed dose is much easier to administer "since it requires no patient interaction beyond injection." Appx2734–2735, at ¶ 56. Fixed dosing is also less prone to error (*e.g.*, the patient calculates or measures the wrong amount), less costly (no active compound is wasted), and increases patient compliance (it is easier and faster). *See* Appx2734–2735, at ¶ 56. Indeed, during prosecution of the challenged patents, the Examiner found that a skilled artisan would prefer fixed dosing for these very reasons. Appx2546 ("A weight based dosing would require a means for administration more complicated and difficult to use than a pre-filled, single use disposable syringe which was an advantageous means of delivery at the time of applicant's invention.").

Skilled artisans sought to lengthen dosing intervals for multiple reasons. For example, Dr. O'Dell explained that doctors reduced the dosing frequency of prior art anti-TNFα inhibitors such as ENBREL® and REMICADE®. *See* Appx2763–2764,

at ¶¶ 20–21. Doctors did this to "minimiz[e] side effects" and "drug related toxicities" associated with dosing. *Id.* They also reduced dosing frequency to lower the cost of treatment and decrease the number of doctor visits required for treatment, while maintaining efficacy. Apps2763–2764, at ¶¶ 20–21. Dr. O'Dell's experience comports with the testimony of Dr. Baughman, who explained that "reduc[ing] the frequency of injection" increases patient compliance because, among other reasons, "injections hurt" and patients prefer to be stuck with needles as infrequently as possible. Appx2740, at ¶ 64.

Further, the prior art patent originally disclosing D2E7 also suggested that it was straightforward to adjust the dosing frequency, explaining that "[d]osing regimens may be adjusted to provide the optimum desired response" and that the dose "may be proportionally reduced or increased as indicated by the exigencies of the therapeutic situation." *See* Appx2802, at 22:60–65; *see also* Appx2764–2765, at ¶ 22.

## III. The Challenged Patents: AbbVie's Patents Claim Obvious Dosing Regimens.

AbbVie's U.S. Patent Nos. 8,889,135; 9,017,680; and 9,073,987 all claim obvious modifications of the dosing regimens that had been reported in the prior art. *See* Appx231–266; Appx267–305; Appx306–348. AbbVie filed the provisional application that led to the patents in June 2001, after acquiring the rights to D2E7. By filings patent applications to the dosing regimen after the Phase 1 and Phase 2 clinical

trial data had already been made public, AbbVie tried to claim from the public domain what had been rendered obvious by its predecessor's detailed publications.

The patents' common specification touts the already well-known benefits of subcutaneous administration and longer dosing intervals. For example, the specification acknowledges that "[s]ubcutaneous dosing is advantageous because the patient may self-administer a therapeutic substance . . . which is convenient for both the patient and the health care provider." *E.g.* App244–245, at 2:66–3:2. The specification also explains that "[b]iweekly dosing has many advantages over weekly dosing including, but not limited to, a lower number of total injections, decreased number of injection site reactions (e.g., local pain and swelling), increased patient compliance." Appx244, at 2:58–66. The inventors make no claim to have discovered these advantages. Nor could they have, given the prior art discussed above.

After describing the prior art details of the D2E7 antibody and compositions including D2E7, the specification discusses three examples of clinical testing of D2E7 to treat rheumatoid arthritis. *See* Appx257–Appx258, at 28:1–30:37. The first two examples are very similar to what the prior art already disclosed—the first is a study of intravenous dosages (including 0.5 mg/kg) that largely tracks what is disclosed in Kempeni, *see* Appx257 at 28:5–17, while the second describes the same Phase 2 study reported in van de Putte 1999. *See* Appx257–258 at 28:62–29:11; Appx238. The third example provides the only "new" data but simply followed what the prior art already taught skilled artisans to do. It involved administering fixed 20, 40, or 80 mg

subcutaneous doses of D2E7 biweekly, for up to 24 weeks. Appx258, at 29:12–30:37. As with the prior-art studies described above, this study, too, concluded that "[a]ll three doses of D2E7 were statistically significantly more effective than placebo." Appx258, at 30:28–30. The specification remarks that "D2E7 at 40 mg and 80 mg had better efficacy than the 20 mg dose," *id.* at 30:30–31, but it does not further differentiate between 40 mg and 80 mg. It also does not address any of the issues regarding updosing or pharmacokinetics that AbbVie now portrays as difficult hurdles to surmount.

Claim 1 of the '135 patent is representative of all claims at issue on appeal. It covers treating rheumatoid arthritis by subcutaneous administration of D2E7 (the "anti-TNFα antibody" with the listed amino acid sequence) in biweekly (every 13–15 days), fixed doses of 40 mg:

> 1. A method for treating rheumatoid arthritis in a human subject, comprising
>
> administering subcutaneously to a human subject having rheumatoid arthritis a total body dose of 40 mg of a human anti-TNFα antibody once every 13 -15 days for a time period sufficient to treat the rheumatoid arthritis,
>
> wherein the anti-TNFα antibody comprises an IgG1 heavy chain constant region; a variable light ("VL") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:7, a CDR2 having the amino acid sequence of SEQ ID NO:5, and a CDR3 having the amino acid sequence of SEQ ID NO:3; and a variable heavy ("VH") chain region comprising a CDR1 having the amino acid sequence of SEQ ID NO:8, a CDR2 having the amino acid sequence of SEQ ID NO:6 and a CDR3 having the amino acid sequence of SEQ ID NO:4.

Appx266, at 45:12–25. Claim 5 of the '135 patent is identical to claim 1, except that it is a "consisting" claim that requires "the human anti-TNFα antibody is administered in the form of a pharmaceutically acceptable composition." Appx266, at 46:12–30.

The other independent claims are materially the same for purposes of this appeal. Claim 1 of the '987 patent mirrors claim 1 of the '135 patent with a few immaterial wording changes. *See* Appx348, at 59:37–60:42. Claim 1 of the '680 patent is again nearly identical, except that the claim requires D2E7 to be administered "in combination with methotrexate," Appx305, at 51:23–52:25, another well-known prior art treatment for rheumatoid arthritis. *See* Appx61, *citing* Appx2704–2705. None of these differences are relevant on appeal since AbbVie does not rely on them.

The only dependent claims that are addressed separately on appeal by AbbVie are claims 3 and 4 of the '135 patent, requiring treatment "for a period of at least 24 weeks." *See* Appx266, at 45:30–46:12. But AbbVie did not argue the patentability of those claims separately below. *See* Appx43206–43275 (Patent Owner response).

## IV. The Proceedings Below: The Board Correctly Finds that a Skilled Artisan Would Choose a Subcutaneous Administration of a Fixed Dose of D2E7, Given Biweekly.

Coherus filed three IPR petitions against all claims of the challenged patents, based on the combination of van de Putte 1999 and Kempeni. Appx43001–43053; Appx43544–46605; Appx44089–44138. In each IPR, the Board agreed the claims would have been obvious based on van de Putte 1999's teaching that 20, 40, and 80 mg weekly, fixed doses of D2E7 administered subcutaneously are safe and effective,

and Kempeni's teaching of biweekly administration of doses equivalent to 40 mg subcutaneous injections. The Board's decision on the '135 patent is representative, especially because AbbVie does not argue the '680 or '987 patents separately.

The Board first addressed the parties' claim construction dispute regarding the claim requirement of administering D2E7 "for a time period sufficient to treat rheumatoid arthritis." *See* Appx7–9. AbbVie had argued that the claim term required the treatment regimen "reduce ***significantly*** the signs and symptoms of rheumatoid arthritis." Appx43082–43084; Appx43272–43274. AbbVie did not define the word "significantly," but implied that it meant some threshold that was not in the prior art. The Board rejected AbbVie's arguments, construing the claim to have its plain meaning—"for a time period sufficient to reduce the signs, symptoms, and/or progression of RA"—and to "not require any particular level of efficacy." Appx7–9. The Board also noted the prior art disclosed that patients achieved an ACR20 response, rendering any claim construction dispute immaterial. *See* Appx8 n.4.

Turning to the obviousness analysis, the Board first noted that AbbVie "does not challenge Petitioner's showing that the prior art discloses each element of claims 1–5" of the '135 patent. Appx15. That of course includes the requirement of dependent claims 3 and 4 for treatment of "at least 24 weeks." Appx266. In particular, the Board found that van de Putte "discloses all of the elements" except for biweekly dosing and 6 months of treatment, while Kempeni "accounts for the differences between van de Putte and the recited biweekly dosing frequency required

by all of the challenged claims, as well as the dosing period of at least 24 weeks that is recited in claims 3 and 4." Appx15.

The Board then turned to whether a skilled artisan would have been motivated to administer a 40 mg dose subcutaneously on a biweekly basis with a reasonable expectation of success. Appx16–38. The Board began by noting that AbbVie did not challenge Coherus's showing that subcutaneous administration of fixed doses was far easier, faster, and cheaper than other methods of administration, leading to better to better patient outcomes because of better patient compliance. *See* Appx17–18; Appx43039–43041. The Board also noted that Kempeni described this treatment as a "promising approach for D2E7" delivery. *See* Appx18, *citing* Appx2705; Appx2735–2736, at ¶¶ 54–55. Therefore, the Board found a skilled artisan would prefer to treat rheumatoid arthritis patients with subcutaneous injections of a fixed dose of D2E7.

The Board then addressed whether a skilled artisan would have used 40 mg biweekly subcutaneous doses. The Board found that the skilled artisan would have done so because Kempeni disclosed that a dosing protocol equivalent to a 40 mg biweekly subcutaneous dose was a "viable treatment protocol." Appx24, *citing* Appx43043 and Appx2744, at ¶ 72. Both AbbVie's expert (Dr. Vinks) and its lawyer at oral argument admitted the 0.5 mg/kg biweekly intravenous dosing in Kempeni was equivalent to a 40 mg subcutaneous biweekly dose. Appx25, *citing* Appx3846–3847; Appx43456. Moreover, the benefits of biweekly (as opposed to weekly) injections were well-known. *See* Appx2740, at ¶ 64; Appx2773, at ¶ 43. The Board

correctly found that Kempeni explicitly provided a motivation to select a 40 mg biweekly subcutaneous dose, because it "expressly discloses a dose that is equivalent to the recited 40 mg subcutaneous dose" and "teaches biweekly administration." Appx25. The Board also found that the skilled artisan "would have balanced efficacy with other factors including safety and patient preference," and would not have necessarily sought to reduce activity "to the fullest extent possible." Appx37, *citing* Appx2743 at ¶ 69; Appx4597 at ¶ 23; Appx5385; Appx6299–6301; Appx7521.

The Board also concluded that a skilled artisan would reasonably expect such a treatment to succeed, because Kempeni explicitly disclosed that the treatment protocols reported were successful. Appx25, *citing* Appx2704 (explaining that "treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated"); Appx2706 (concluding that "all doses of D2E7 were statistically significantly superior to placebo"); *see also* Appx2727, at ¶ 36; Appx2731, at ¶ 45; Appx2737–2739, at ¶¶ 58–61; Appx2740, at ¶ 63; Appx2766–2768, at ¶¶ 26–32. The Board also cited other evidence (*e.g.*, Rau 2000) that a biweekly intravenous 0.5 mg/kg dose was effective. Appx7318 (explaining that D2E7 "can be administered every two weeks as an intravenous injection over 3–5 minutes or subcutaneously" and is "well tolerated and must be called a therapeutic step forward"); Appx7316 (reporting an ACR20 response in 42% of patients "at any point in time" receiving the 0.5 mg/kg dose).

The Board then turned to AbbVie's arguments, addressing each carefully, considering all of the evidence. First, the Board rejected AbbVie's argument that

Kempeni teaches away from the claimed dosing regimen because treatment was discontinued in some patients once a response was rated "good" and only restarted upon disease flare up. *See* App26; *see also* Appx43260-43261. The Board found that this was, "at most, an alternative dosing schedule to the biweekly dosing Kempeni discloses." Appx 27. Notably, Kempeni explains that retreating patients achieving a "good" response only upon flare up was done for the purpose of studying the length of the "good" response, not as part of the treatment protocol. Appx2704. Kempeni and other references repeatedly taught using fixed and biweekly doses. Appx27.

The Board next rejected AbbVie's arguments that a skilled artisan would have thought that the 0.5 mg/kg intravenous dose disclosed in Kempeni delivers substantially more drug than the equivalent 40 mg subcutaneous dose. Appx27; *see also* Appx43261. As the Board explained, AbbVie's arguments were directly contrary to Kempeni itself, which explicitly discloses that plasma concentrations of D2E7 after multiple subcutaneous doses are "comparable to those achieved with intravenous administration," and that D2E7 administered subcutaneously is "as effective as when administered intravenously." Appx28, *quoting* Appx2704.

The Board also rejected AbbVie's related argument that a skilled artisan would not have chosen the 40 mg biweekly dose because Kempeni and Rau 2000 reported that patients receiving the 0.5 mg/kg intravenous dose were "updosed" to higher dose levels. Appx29 ("[T]he updosing reported in Kempeni and Rau 2000 would not have dissuaded a person of ordinary skill from pursuing 40 mg biweekly dosing."). The

Board again noted Kempeni's endorsement of "long term" treatment with a dose range that included 0.5 mg/kg and its statement that the entire dose range "was well tolerated." Appx31, *citing* Appx2705. The Board also found that Rau 2000 taught "the 0.5 mg/kg dose was effective in treating patients (*i.e.*, reducing the signs, symptoms, and/or progression of RA")." Appx31. For example, Rau 2000 reported that 42% of the patients receiving the 0.5 mg/kg dose achieved an ACR20 response. Appx30–31, *citing* Appx7316. The relative efficacy of the 0.5 mg/kg dose was irrelevant, because "the claims do not require superior efficacy or treatment with the most effective dose." *Id.*

AbbVie's last argument on this front was that a skilled artisan would not have modified the van de Putte's dosing schedule based on the then-available pharmacokinetic data regarding D2E7. The Board concluded that as of the critical date, the record evidence (including a declaration submitted by AbbVie in prosecution) showed there were two approaches to designing a dosing regimen, (1) a clinical approach testing different methods and dosing intervals, as AbbVie itself used; and (2) a theoretical model approach. Appx33. Because AbbVie's modeling expert admitted the publicly available pharmacokinetic information available at the critical date would not have permitted a PK/PD correlation for modeling purposes, the Board found AbbVie's modeling evidence unpersuasive. Appx33–35.

Finally, the Board addressed secondary considerations before reaching its conclusion on obviousness. *See* Appx38–44. With respect to commercial success, the

Board acknowledged HUMIRA® is successful but found that this success had not been adequately tied to the claimed dosing regimen, as opposed to the antibody (D2E7) or formulation. Appx39–40. Indeed, AbbVie had argued in other *inter partes* review proceedings of different patents that it was the stability of the formulation that drove the product's success. Appx40, *citing* Appx3507. The Board also cited other evidence that it was the D2E7 antibody—which was fully human and thereby avoided triggering undesired immune response side effects—that drove the product's success. Appx40, *citing* Appx5031. The Board further noted that AbbVie had blocking patents covering both D2E7 and the commercial formulation, weakening the inference that the claimed dosing regimen was tied to HUMIRA®'s success. Appx40.

Turning to the other indicia, the Board again found a lack of nexus between the claimed dosing regimen and any alleged long-felt need. The Board noted that the prior art already disclosed biweekly dosing of D2E7 and subcutaneous dosing of other anti-TNFα agents, including D2E7. Appx42. Nothing suggested that the 40 mg biweekly subcutaneous dose distinguished HUMIRA® from other treatments. Moreover, other evidence again suggested that HUMIRA®'s improvement over prior techniques was due to the D2E7 antibody, not any particular dosing regimen. Appx42–43, *citing* Appx2703, Appx5534 at ¶ 88. The Board also found no unexpected results, as AbbVie did not point to any evidence that the efficacy of a 40 mg biweekly subcutaneous dose was unexpected, nor did AbbVie attempt to compare the claimed dosing regimen to the closest prior art. Appx43.

## SUMMARY OF THE ARGUMENT

The Board's obviousness determination should be affirmed, as it was dictated by the Board's well-supported factual findings. The Board found that van de Putte disclosed all but one claim limitation in its description of using fixed, subcutaneous doses of 20, 40, and 80 mg D2E7 as "nearly equally efficacious" to treat rheumatoid arthritis. The only element missing from van de Putte was biweekly, rather than weekly, dosing. The Board found that Kempeni disclosed that biweekly treatment with a dose equivalent to a 40 mg subcutaneous dose achieved "sustained therapeutic effects," was "well-tolerated," and "safe and effective," and that "subcutaneous self administration is a promising approach." The Board explained the strong motivation for selecting the claimed dosing regimen, including increased patient compliance and balancing safety and efficacy. It also found a reasonable expectation of success given the prior art teachings that such a dose is effective. Those findings were supported by substantial evidence, and the conclusion of obviousness necessarily followed.

AbbVie tries to manufacture a cadre of legal errors, but its real dispute is with the Board's factual findings. A fair reading of the Board's opinion shows it did not use hindsight, shift any burden, or fail to consider the claims as a whole. Rather, it carefully considered the parties' competing interpretations of the prior art and competing theories about what drove HUMIRA®'s success. Those are quintessential questions of fact, and the substantial evidence standard precludes second-guessing the Board's well-supported findings. The Board's decisions should be affirmed.

## STANDARD OF REVIEW

"Whether an invention would have been obvious to one of ordinary skill in the art is a legal determination based on underlying findings of fact." *In re Mouttet*, 686 F.3d 1322, 1330 (Fed. Cir. 2012). "What the prior art teaches, whether a person of ordinary skill in the art would have been motivated to combine references, and whether a reference teaches away from the claimed invention are questions of fact." *Meriresonne v. Google, Inc.*, 849 F.3d 1379, 1382 (Fed. Cir. 2017).

"While this court reviews the Board's legal conclusion of obviousness without deference, it upholds the Board's factual findings if supported by substantial evidence." *Mouttet*, 686 F.3d at 1330-31. Substantial evidence is "such relevant evidence as a reasonable mind might accept as adequate to support a conclusion." *Consol. Edison Co. v. NLRB*, 305 U.S. 197, 229 (1938). Under substantial evidence review, the Court must examine "the record as a whole [and] draw all reasonable inferences in favor of the prevailing party, and not make credibility determinations or substitute [its own] view of the conflicting evidence." *SIBIA Neurosciences, Inc. v. Cadus Pharm. Corp.*, 225 F.3d 1349, 1354 (Fed. Cir. 2000). Where "two different, inconsistent conclusions may reasonably be drawn from the evidence in record, an agency's decision to favor one conclusion over the other is the epitome of a decision that must be sustained upon review for substantial evidence." *In re Jolley*, 308 F.3d 1317, 1329 (Fed. Cir. 2002).

## ARGUMENT

### I. The Board's Determination that the '135, '680, and '987 Patents Were Obvious Should Be Affirmed.

The Board's legal conclusion of obviousness inexorably flows from its factual findings on motivation to combine, reasonable expectation of success, the lack of teaching away, and the lack of nexus between the claimed invention and alleged secondary indicia. The Board's task was relatively simple, because AbbVie's predecessor had already published detailed clinical trial results that provided a prior art path leading skilled artisans directly to the claimed dosing regimen.

It was undisputed that the prior art disclosed all the claim elements. The question was whether a skilled artisan would have selected a 40 mg biweekly, subcutaneous dose for treating rheumatoid arthritis and reasonably expected it to succeed. The Board found that van de Putte disclosed that weekly subcutaneous doses of 20, 40, and 80 mg were effective, and that Kempeni (and Rau 2000) taught that an intravenous dose equivalent to a 40 mg biweekly subcutaneous dose was effective. The Board also noted the typical benefits of fixed, subcutaneous dosing over longer intervals, many of which were undisputed. Moreover, the objective indicia did not help AbbVie, because HUMIRA®'s success was not tied to the claimed dosing regimen. Although AbbVie has a different perspective on the facts, the Board's findings were supported by substantial evidence, and it did not make any of the legal errors that AbbVie asserts. The Board's decision should be affirmed.

### A. The Board Properly Found Obviousness Given its Well-Supported Underlying Factual Findings.

#### 1. The Board's Finding of Motivation to Select a 40 mg Biweekly Subcutaneous Dose Is Supported by Substantial Evidence.

The Board correctly determined that a skilled artisan would select a 40 mg biweekly subcutaneous dose to treat rheumatoid arthritis. Most of that determination was easy. Skilled artisans knew that subcutaneous injections were preferable to intravenous administration, that fixed doses were easier than weight-based doses, and that longer dosing intervals were preferable to shorter ones. *See* pp. 9–12. Kempeni showed that biweekly dosing worked. The only real question was the amount of the fixed, biweekly, subcutaneous dose. But even this was straightforward, because the record evidence showed that doctors strive to give the lowest effective dose to balance efficacy with safety. The prior art disclosed that a dose equivalent to a 40 mg biweekly subcutaneous dose was effective and was the lowest biweekly dose that had been tried in Kempeni.

Skilled artisans were strongly motivated to select a subcutaneous dose (as disclosed in van de Putte), because, as the Board found, "subcutaneous dosing would have been more convenient and less expensive for patients." *See* Appx17–18. Prior art explained that "subcutaneous administration is more desirable for doctors and patients than intravenous administration." *See* Appx3130; Appx3124. Subcutaneous injections are more convenient, because patients can administer the drug without the

need of a doctor. *Id.* Dr. Baughman explained that "[e]liminating the requirement to go into a doctor's office for chronic treatment—which would have been required with an i.v. injection—would have been desirable to increase patient compliance and reduce costs associated with treatment by eliminating doctor's office visits and associated travel costs among other costs (e.g., loss of time from work)." Appx2734, at ¶ 51. The inventors ultimately selected subcutaneous dosing for precisely these known reasons. *See e.g.* App244–245, at 2:66–3:2.

Next, skilled artisans were strongly motivated to select fixed doing (as in van de Putte), because, as the Board found, "fixed dosing would have been easier and less costly for patients." *See* Appx17. The prior art patent initially disclosing D2E7 explained that "it is especially advantageous to formulate parenteral compositions in dose unit form [i.e. fixed dose form] for ease of administration and uniformity of dose." Appx2802–2803, at 22:65–23:1. Moreover, Dr. Baughman explained that fixed doses are preferable "since it requires no patient interaction beyond injection"—leading to increased patient compliance and better patient outcomes. Appx2734–2735, at ¶ 52. Dr. Baughman also explained that fixed dosing had the added benefit of being more cost efficient because, unlike weight-based dosing where unused medicine may remain, nothing in a fixed dose goes to waste. *Id.* Dr. Baughman's statements mirrored the findings of the examiner during prosecution, who found that "[a] weight based dosing would require a means for administration more complicated and difficult to use than a pre-filled, single use disposable syringe which was an

advantageous means of delivery at the time of applicant's invention." Appx2546. By contrast, weight-based doses force the patient to calculate and measure the appropriate amount of drug to inject—a laborious and error-prone process. *See* Appx2803; Appx2734–2735 at ¶ 52.

The Board also correctly found that skilled artisans would prefer biweekly dosing (as in Kempeni) to increase patient compliance and comfort while still maintaining efficacy. *See* Appx37. Dr. O'Dell credibly explained that doctors preferred to reduce dosing frequency to minimize side effects and drug related toxicities, to lower cost and reduce the number of treatments. Appx2763–2764, at ¶¶ 20–21. He added that "[t]here can be no real dispute that decreasing the number of injections equates to a real benefit for patients" including reducing the potential for injection site reactions and that he had "never met a patient that has asked to have more injections." Appx2773, at ¶ 44. Dr. Baughman similarly testified that longer intervals between treatments were preferable because less frequent treatment is more convenient and less painful for the patient. Appx2740, at ¶ 64. The challenged patents provide the same rationale for selecting biweekly dosing, again showing that this was not inventive. *See* Appx244, at 2:60–66.

In addition, the prior art taught that biweekly dosing would achieve these goals while still maintaining efficacy. Kempeni reported that "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks" and concluded that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10

mg/kg was well tolerated." Appx2704. Moreover, Rau 2000 showed that biweekly treatment with the equivalent to a 40 mg subcutaneous dose was effective in reducing the signs and symptoms of rheumatoid arthritis. *See* Appx7316–7318; Appx4369–4370. The Board's finding of motivation to select biweekly dosing was well-supported. *See Warner Chilcott Co. v. Teva Pharms. USA, Inc.*, 594 F. App'x 630, 635-36 (Fed. Cir. 2014) ("As longer dosing intervals suit patient convenience and compliance, the prior art therefore provided express motivation to pursue a monthly dosing regimen.").

Finally, the Board correctly found that a skilled artisan would be motivated to select 40 mg as the biweekly subcutaneous dose. As the Board found, skilled artisans prefer using the lowest effective dose to balance efficacy with safety. *See* Appx37 ("[We agree with Petitioner that the skilled artisan designing a dosing regimen through clinical trials would have balanced efficacy with other factors including safety and patient preference."). As Dr. Baughman testified, "the desirability of administering the lowest effective drug dose" is "the central principle of drug development." Appx2743, at ¶ 69. She added that a clinician's goal "is to treat the patient with as little drug as possible so as to reduce potential side effects, yet attain a therapeutic response." *Id.* Here, the lowest biweekly dose shown to be efficacious in Kempeni was 0.5 mg/kg, which even AbbVie's expert admitted was equivalent to a 40 mg subcutaneous dose. *See* Appx2743, at ¶ 69; Appx3846–3847.

The prior art also taught that the 0.5 mg/kg intravenous dose was effective. After describing a study in which the 0.5 mg/kg dose was administered, Kempeni reported that "[t]he response in the DAS over time demonstrated sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7," and added that "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks." Appx2704. Kempeni did not qualify these statements or limit them to doses higher than 0.5 mg/kg. Moreover, Kempeni added that "long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated," that "D2E7 given subcutaneously was safe and as effective as when administered intravenously[,] demonstrating that subcutaneous self-administration is a promising approach for D2E7 delivery," and that D2E7 "is safe and effective." Appx2705. Again, Kempeni specifically included the 0.5 mg/kg dose in the range to be considered for "long term treatment" and did not qualify any of its positive statements about safety or efficacy to exclude the 0.5 mg/kg dose.

In addition, Rau 2000 corroborated Kempeni's disclosure that the 0.5 mg/kg intravenous dose was effective. Rau 2000 reported that 42% of patients obtained an ACR20 response from the 0.5 mg/kg dose, showed that it performed similarly to higher doses when administered biweekly, and demonstrated that the 0.5 mg/kg dose achieved a "positive response" as defined by the study criteria. *See* Appx7316–7317; Appx2704. Even AbbVie's expert admitted that Rau 2000's data showed the 0.5 mg/kg dose achieved a response that "treated" patients as that term was construed by

the Board—*i.e.*, it reduced the signs and symptoms of rheumatoid arthritis. *See* Appx4369–4370; *see also* Appx9.

Given all the evidence above, the Board correctly found that it was obvious to select the 40 mg biweekly subcutaneous dose. *See, e.g., Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1371, 1376 (Fed. Cir. 2011) (affirming obviousness and noting evidence that "physicians always seek to prescribe the lowest effective dose of any medication").

### 2. The Board's Finding that a Skilled Artisan Would Reasonably Expect a 40 mg Biweekly Subcutaneous Dose to Succeed Is Supported by Substantial Evidence.

The Board correctly determined that a skilled artisan would have reasonably expected a 40 mg biweekly subcutaneous dose to succeed—*i.e.,* to treat the signs, symptoms, and/or progression of rheumatoid arthritis. The Board found that the prior art expressly teaches that administering doses equivalent to a 40 mg biweekly dose were effective. *See, e.g.,* Appx25 (concluding that "Kempeni also suggests that the person of ordinary skill would have expected success in treating RA with such a dosing regimen"); Appx31 ("Rau 2000 indicates that the 0.5 mg/kg dose was effective in treating patients (i.e., reducing the signs, symptoms, and/or progression of RA)."). Those findings were supported by substantial evidence.

For example, Kempeni disclosed biweekly treatment with a 0.5 mg/kg intravenous dose was effective, a dose that both AbbVie's expert and lawyer at the oral hearing admitted is equivalent to a 40 mg biweekly subcutaneous dose. *See*

Appx25; Appx3846–3847; Appx43456. Kempeni explains that overall response rates (including the 0.5 mg/kg dose level) "demonstrated sustained therapeutic effects and some continuing improvement after multiple infusions of D2E7" with "[r]esponse rates of more than 80%." Appx2704. "After six months, 86% of patients continued to receive treatment with D2E7 indicating that long term intravenous treatment with D2E7 in the dose range from 0.5 to 10 mg/kg was well tolerated." *Id.* Kempeni concluded by explaining that the studies it reported suggest that D2E7 "is safe and effective," without ever limiting that statement to a subset of the doses reported. Appx2705. Moreover, Kempeni teaches that intravenous administration would be equivalent to subcutaneous administration, explaining that "D2E7 given subcutaneously was safe and as effective as when administered intravenously demonstrating that subcutaneous self-administration is a promising approach for D2E7 delivery." Appx2705; *see also* Appx2730, at ¶ 43; Appx7318. As a result, Kempeni disclosed that a 40 mg subcutaneous dose would be effective to treat rheumatoid arthritis. *See* Appx25.

In addition, Rau 2000, which describes the DE001/DE003 studies and which AbbVie entered into the proceeding, underscores that the 0.5 mg/kg biweekly intravenous dose was effective. *See* Appx25, Appx31, *citing* Appx7311–7321. As reflected in the annotated figures below from AbbVie's brief (at 39), Rau 2000 shows that the 0.5 mg/kg biweekly, intravenous dose significantly outperformed the placebo and performed similarly to the other doses used in the study. *See* Appx7316–7317,

Figs. 4, 5. Rau 2000's Figure 4 also shows that patients receiving the 0.5 mg/kg dose had their DAS (disease activity score) drop over 30% from the starting baseline, which Rau reports had an initial median of 5.3. *See* Appx7316 at Fig. 4.

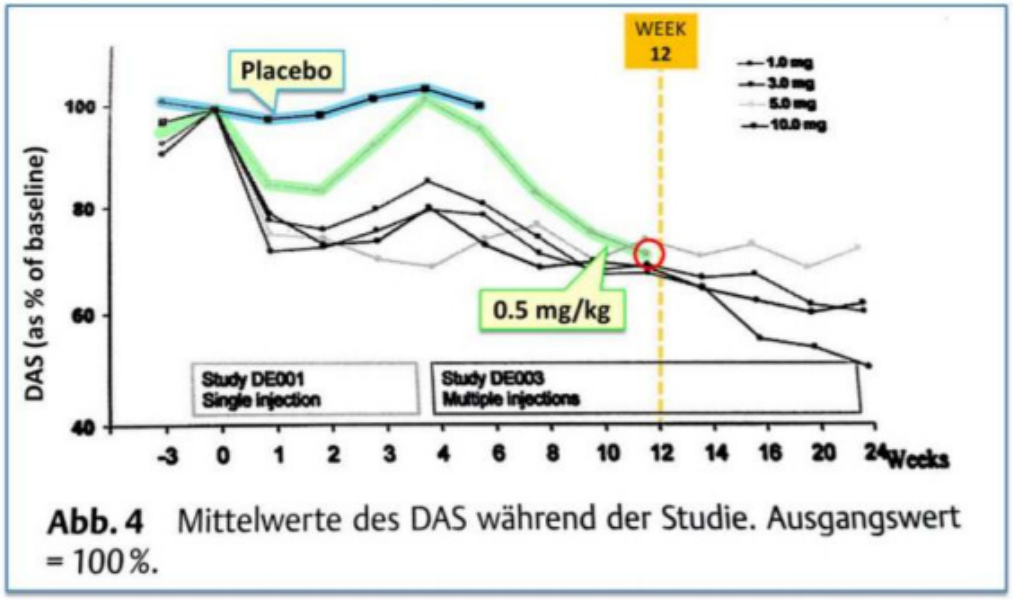


**Abb. 4** Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

**Fig. 4** (Rau 2000)

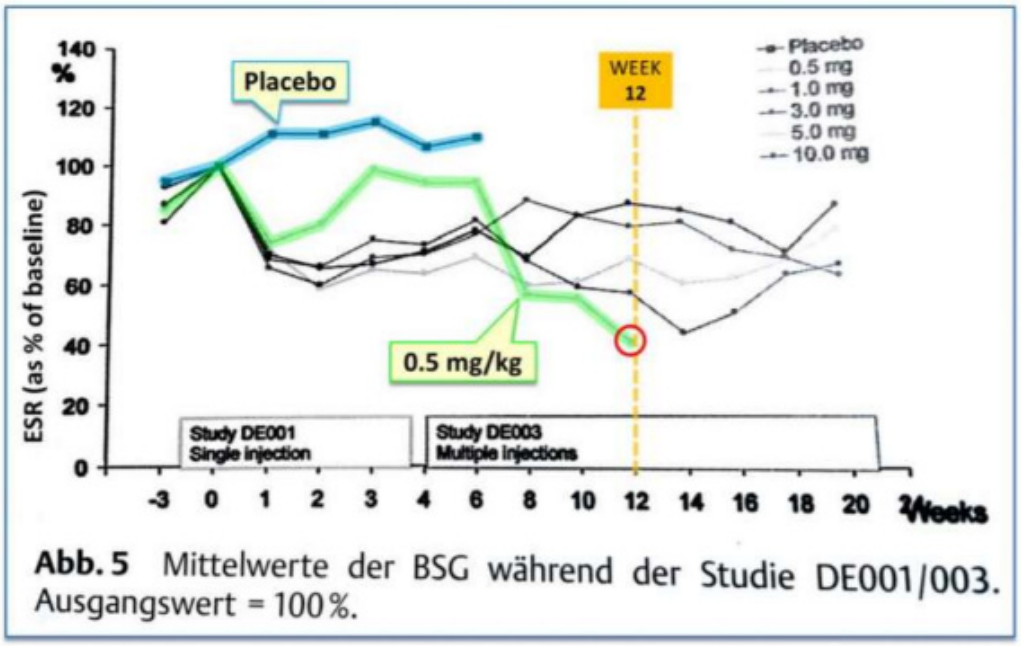


**Abb. 5** Mittelwerte der BSG während der Studie DE001/003. Ausgangswert = 100 %.

**Fig. 5** (Rau 2000)

AbbVie's expert admitted that this improvement in DAS score reduces the signs and symptoms of rheumatoid arthritis:

> Q. If a patient started at 5.2 and then the next measurement was 3.6, would that be a meaningful therapeutic response in 2001?
>
> ***
>
> A. It would be a moderate response, according to this chart in 2001.
>
> Q. Would that patient have seen a reduction in his or her signs and symptoms of RA?
>
> ***
>
> A. For some of them, yes, but I couldn't tell you which ones. It's a composite measure.
>
> Q. Overall, the patient's signs and symptoms would have been reduced since you first saw the patient; correct?
>
> A. That's correct.

Appx4369–4370. That satisfies the Board's now-unchallenged construction for the efficacy limitation in all claims of the challenged patents. *See* Appx9 (construing claims to require treatment "for a time period sufficient to reduce the signs, symptoms, and/or progression of RA"). It also satisfies Kempeni's definition of a "positive" efficacy response from the study. *See* Appx2704. Rau 2000 further explains that, at any given time during the study, roughly 42% of patients receiving the 0.5 mg/kg biweekly, intravenous dose achieved an ACR20 response. Appx7316. Rau 2000 ultimately concluded from this data that D2E7 "can be administered every two weeks as an intravenous injection over 3–5 minutes or subcutaneously. D2E7 is well tolerated and must be called a therapeutic step forward." Appx7318. Rau 2000 did not qualify those statements in any way or suggest that they did not apply to the 0.5

mg/kg intravenous dose, which, as noted above, is equivalent to a 40 mg subcutaneous dose. *See* Appx25; Appx3846–3847; Appx43456.

Given the substantial record evidence, the Board's finding that both Kempeni and Rau 2000 showed that a 40 mg biweekly subcutaneous dose had a reasonable expectation of success was well-supported.

### 3. The Board's Finding that the Secondary Indicia Were Not Tied to the Claimed Dosing Was Well-Supported.

The Board's factual finding that there was no nexus between the alleged secondary indicia and the claimed dosing regimen was also supported by substantial evidence. *See* Appx38–43. The Board correctly found that HUMIRA®'s commercial success and satisfaction of any alleged long-felt need were not due to the claimed dosing regimen. Indeed, the evidence showed that it was the D2E7 antibody, being the first fully-human antibody, that improved upon prior treatments. *See* Appx2703; Appx5534 at ¶ 88; Apx5031–5033; *see also* Appx42–43. Moreover, AbbVie itself had argued in other IPRs related to its formulation patents that the formulation was critical to HUMIRA®'s success. *See* Appx3507; *see also* Appx40. These other possible factors for HUMIRA®'s success were sufficient for Coherus to rebut any presumption of nexus, especially where there was no evidence that the claimed dosing regimen drove HUMIRA®'s success. The fact that both the D2E7 antibody and the formulation were covered by other blocking patents was further reason for the Board to find that any objective indicia were not attributable to the challenged patents. *See,*

*e.g., Galderma Labs., LP v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013) ("Where market entry by others was precluded due to blocking patents, the inference of non-obviousness of the asserted claims, from evidence of commercial success, is weak.") (internal quotation marks and alterations omitted).

### B. The Board Did Not Make Any of the Legal Errors AbbVie Alleges, and It Properly Rejected AbbVie's View of the Facts.

Perhaps recognizing the robustness of the Board's factual findings, and this Court's required deference to those well-supported findings, AbbVie characterizes the Board's decision as a series of legal errors. The Court should reject those arguments. AbbVie's main points—about "updosing" and pharmacokinetic parameters ($C_{min}$)—are factual disputes that the Board properly resolved against AbbVie. AbbVie's other complaints, in which it accuses the Board of using "hindsight," of improper burden-shifting, and of failing to consider the claims as a whole, do not withstand scrutiny upon reading the Board's opinion.

#### 1. The Board's Opinion Is Free of Hindsight and Properly Rejected AbbVie's Factual Arguments.

Contrary to AbbVie's characterization (at 30–35), the Board did not use impermissible hindsight to reach its conclusions regarding a skilled artisan's motivation. AbbVie never identifies any specific statement by the Board that would suggest it used hindsight. AbbVie is even forced to acknowledge (at 35) that "the Board did not come out and say that it was relying on hindsight." AbbVie's hindsight

allegation reflects its disagreement with the Board's factual findings and weighing of the various prior art disclosures.

Nothing in the Board's analysis constitutes impermissible hindsight. For example, the Board did not look to the challenged patents to determine the problems that needed to be solved by a skilled artisan in developing a treatment method. *Compare Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998) (a pre-*KSR* case finding impermissible hindsight based on the district court's explicit statement defining the problem in terms of the claimed solution), *with Sci. Plastic Products, Inc. v. Biotage AB*, 766 F.3d 1355, 1361 (Fed. Cir. 2014) (finding the Board did not use impermissible hindsight because the problem facing the skilled artisan was known). Instead, the Board defined the problem as one skilled artisans faced long before the patents-in-suit, namely, how to develop a "practically achievable" treatment method that balanced drug efficacy with other important factors, such as safety and patient compliance. *See*, *e.g.*, Appx37; *see also* Appx2768–2769, at ¶ 33 (explaining that consideration of practical realities, like cost, factor into treatment plans); Appx2734–2736, at ¶¶ 51–52 (same). Moreover, the Board relied on substantial evidence that skilled artisans had long preferred fixed dose, subcutaneous injections given over longer intervals, using the minimum effective dose. *See* pp. 9–12, 25–30. None of that was hindsight: it reflected what skilled artisans thought at the time.

Nor did the Board's decision lack for any explanation—the primary hallmark of hindsight bias. *See, e.g.*, *Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1068–69 (Fed. Cir. 2018) (finding the use of impermissible hindsight when the analysis was based solely on conclusory statements); *Trivascular, Inc. v. Samuels*, 812 F.3d 1056, 1066 (Fed. Cir. 2016) (cautioning the Board to be "careful not to allow hindsight reconstruction of references without any explanation as to *how* or *why* the references would be combined to produce the claimed invention" (internal quotation marks omitted)). Rather, the Board extensively analyzed the prior art and expert declarations explaining a skilled artisan's knowledge, and articulated specific reasons why a skilled artisan would have chosen the claimed dosing regimen. As this Court has found, "the best defense against hindsight-based obviousness analysis is the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." *Ecolochem, Inc. v. S. California Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000). The Board's decision here met that standard.

The Board also carefully considered AbbVie's evidence of secondary considerations, itself a check against hindsight bias, and correctly concluded that the lack of nexus undermined any inference of non-obviousness. *See*, *e.g.*, *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 36 (1966) (explaining that proper consideration of secondary considerations "guard[s] against slipping into use of hindsight"); *Apple Inc. v. Samsung Elecs. Co., Ltd.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (explaining same).

AbbVie's real complaint is with the Board's factual findings, but these were supported by substantial evidence. For example, AbbVie complains (at 31–32) about the Board focusing on the lowest end of the disclosed range of effective doses. But the Board gave a good reason for doing so that was supported by expert testimony: picking the lowest effective dose would minimize side effects. *See* Appx37; Appx2743 at ¶ 69. AbbVie's reliance on *Merck Sharp & Dohme B.V. v. Warner Chilcott Co., LLC*, 711 F. App'x 633 (Fed. Cir. 2017) (non-precedential), is misplaced, because the fact-finder there made a mistake about what the prior art disclosed and the claimed values involved were "outside the usual ranges." Neither is true here. The Board's findings about the prior art disclosures are all well-supported, and the Board did not go beyond the lowest dose in the prior art—it picked a dose that was equivalent to one the prior art repeatedly reported to be effective.

AbbVie's other arguments are similarly factual and were properly rejected by the Board. AbbVie complains (at 32) that a biweekly dosing interval "would have been expected to result in a lower average $C_{min}$ than the weekly dosing" in van de Putte. But AbbVie's own expert admitted that a skilled artisan could not have calculated $C_{min}$ at the time, *see* Appx33; Appx5674, at ¶ 131, and the skilled artisan would have had no reason to think that biweekly dosing would result in an unacceptably low $C_{min}$. The clinical studies of D2E7 administered biweekly showed that it ***was*** effective for a 0.5 mg/kg intravenous dose (equivalent to a 40 mg subcutaneous dose). *See* pp. 4–9, 30–34.

AbbVie likewise argues (at 32) that subcutaneous dosing can lower bioavailability. But the Board found that the clinical studies of D2E7 showed that subcutaneous dosing was as effective as intravenous dosing. *See* Appx28; Appx 2705; Appx2727-2728, at ¶ 37. AbbVie's points on fixed dosing are similarly unpersuasive, given the Board's finding that it increases patient compliance and lowers cost, and the fact that multiple other prior art treatments used fixed dosing. *See, e.g.,* Appx16–18; pp. 10-11, 25-26. Indeed, AbbVie's prior art patent on D2E7 teaches that fixed dosing is a "preferred" method. *See* Appx2802–2803 at 22:65–23:1.

AbbVie's argument (at 32–33) regarding the requirement of 24 weeks of treatment in some of the dependent claims is also wrong. As an initial matter, AbbVie did not separately argue this requirement below, and it has waived any ability to dispute it here. *See, e.g., In re NuVasive, Inc.*, 842 F.3d 1376, 1380 (Fed. Cir. 2016) ("[A] party waives an argument that it failed to present to the [PTAB] because it deprives the court of the benefit of the [PTAB]'s informed judgment.") Nevertheless, the Board properly found this limitation was in the prior art. *See* Appx15. Kempeni described a study in which patients received D2E7 biweekly for at least 6 months, noted that "[t]reatment lasting several years is intended," and repeatedly referenced "long term" treatment. *See* Appx2704–2705; Appx2970 ("D2E7 has been shown to be safe and effective in patients with active RA over 12 months"); *see also* Appx2727 at ¶ 36. AbbVie also ignores that another prior art clinical trial (Weisman) that disclosed treating rheumatoid arthritis with a biweekly 0.5 mg/kg intravenous dose for 6

months and resulted in 67% of patients on that dose achieving an ACR20 response. *See* Appx3168. Weisman confirms that skilled artisans would use the claimed dosing regimen for at least 6 months.

The Board's factual findings refute AbbVie's characterization that there were many possible options or that the Board opted for "mediocrity" with a high risk of failure. There were few real options given the overwhelming and well-known benefits of fixed doses over weight-based doses, subcutaneous doses over intravenous doses, and biweekly doses over weekly doses. It was clear from AbbVie's prior art publications that a fixed, subcutaneous, biweekly dose would be effective (*i.e.*, reduce the signs and symptoms of rheumatoid arthritis), and there were a finite number of dose options. The 40 mg dose was the straightforward choice because it was both effective and minimized side effects. And the 40 mg biweekly dose was not mediocre—it was effective in a significant percentage of patients, especially when compared with other existing prior art products like ENBREL® and REMICADE®. *See* Appx3039, Appx2738–39 at ¶¶ 60–61; Appx2766–2768 at ¶¶ 26–32. AbbVie's citations to *Rembrant Wireless Techs. LP v. Samsung Elecs. Co.*, 853 F.3d 1370 (Fed. Cir. 2017) and *Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc.*, 231 F.3d 1339 (Fed. Cir. 2000), are inapposite, because neither included prior art teaching the benefits of the claimed method, while in both cases the fact-finder had found there were drawbacks to the claimed method. Neither is true here.

### 2. The Board Applied the Correct Burdens of Proof.

AbbVie alleges (at 35) that the Board applied incorrect burdens of proof when evaluating (1) whether a skilled artisan would have combined the teachings of the prior art and (2) secondary considerations. AbbVie's argument has no support in the Board's opinion. The Board correctly stated and applied the law on the parties' relative burdens. *See, e.g.,* Appx5 ("Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner."); Appx21 ("Petitioner bears the burden of proving that the skilled artisan would have been motivated to make such a modification."); Appx38-39 (correctly stating the law regarding presumption of nexus for commercial success). The Court should reject AbbVie's arguments that the Board did not correctly apply the burdens of proof.

#### a. The Structure of the Board's Decision Reflects AbbVie's Arguments Below, Not Improper Burden Shifting.

AbbVie alleges (at 36-37) that the "structure" of the Board's opinion suggests improper burden shifting because it supposedly examines AbbVie's evidence based on whether it would have "discouraged" a skilled artisan. That misreads the Board's opinion. The Board properly framed its analysis in terms of whether a skilled artisan would have selected a 40 mg biweekly, subcutaneous dose and expected it to succeed. *See, e.g.,* Appx16. The Board considered the affirmative evidence of motivation and reasonable expectation of success, and then turned to AbbVie's arguments before

reaching the conclusion that Coherus had met its burden on those issues. *See* Appx24–38. The Board correctly found that the prior art expressly taught the claimed dosing regimen would be effective, *see* Appx25, Appx31, which means that there was no "uncertainty" or "unpredictability" about whether it would work. The Board committed no legal error in its analysis.

The Board addressed many of AbbVie's arguments in the context of teaching away, and whether a skilled artisan would have been "discouraged," because that is how AbbVie framed the arguments below. *See, e.g.,* Appx43233 (arguing its evidence "discouraged a POSA from the claimed dosing regimen"); Appx43232 (arguing the prior art "taught away from the claimed dosing regimen"); Appx43238 ("This would have discouraged a POSA from pursuing the claimed dosing regimen"); Appx43248 ("a POSA would have been unlikely to pursue the 20 mg weekly dose of van de Putte and would have been discouraged from making changes to that dosing regimen that would be expected to decrease its efficacy"); Appx43249 ("Collectively, the available PK and clinical information thus taught away from the claimed invention"); Appx43260 ("Indeed, in its focus on personalized doses and schedules, Kempeni teaches away from the fixed dosing regimen of the claims."); Appx43261 ("The prior art as a whole therefore taught away from using a 0.5mg/kg dose (or even a 1 mg/kg dose) across all patients, and instead favored higher doses."); Appx43263 ("the available D2E7 PK/PD information taught away from the claimed invention.").

Having used that framework, AbbVie cannot now complain to this Court about the Board's treatment of its arguments. The Board simply responded to the arguments presented. Regardless, the structure of the Board's decision ultimately does not matter, because it considered all the evidence together and properly found a reasonable expectation of success.

**b. The Board Did Not Shift the Burden When Rejecting AbbVie's Factual Arguments about Updosing.**

AbbVie complains (at 38–42) about the Board's treatment of the "updosing" evidence. But, in doing so, it makes an incorrect legal argument and tries to reargue the Board's well-supported factual findings.

The claimed dosing method is obvious so long as a skilled artisan had a reason to select it and a reasonable expectation that it would succeed. *See, e.g.*, *In re Kubin*, 561 F.3d 1351, 1360 (Fed. Cir. 2009) ("Obviousness does not require absolute predictability of success . . . all that is required is a reasonable expectation of success."); *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1198 (Fed. Cir. 2014) ("The reasonable expectation of success requirement for obviousness does not necessitate an absolute certainty for success."); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) ("[O]nly a reasonable expectation of success, not a guarantee, is needed."). AbbVie is wrong to suggest that any level of uncertainty would somehow undermine the Board's opinion, and the Board certainly did not err in rejecting AbbVie's argument that the prior art contained an "actual report[] of

failure." *Boehringer Ingelheim Vetmedica, Inc. v. Schering-Plough Corp.,* 320 F.3d 1339, 1354 (Fed. Cir. 2003).

The Board properly found that AbbVie's "updosing" evidence did not outweigh the fact that both Kempeni and Rau 2000 showed that the 0.5 mg/kg dose was effective for a significant number of patients, as discussed above at pp. 30–34. AbbVie nevertheless tries to reargue the facts and notes (at 40) that patients on the 0.5 mg/kg dose had been moved to a higher dose after 12 weeks. But, as discussed above, the figures in Rau 2000 show that the 0.5 mg/kg dose performed similarly to the others, and AbbVie's expert admitted that the response from the 0.5 mg/kg dose resulted in reducing the signs and symptoms of rheumatoid arthritis. *See* Appx4369–4370. That meets the Board's claim construction of the efficacy limitations, *see* Appx7–9, making the 0.5 mg/kg dose an obvious choice. *See, e.g., Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1328 (Fed. Cir. 2017) ("[O]bviousness does not require that the motivation be the best option, only that it be a suitable option from which the prior art did not teach away." (internal quotation marks omitted)). Moreover, AbbVie's clinical study director confirmed what Rau 2000 already showed: patients were updosed not because they achieved no response, but to test whether patients who had achieved a "moderate" response could obtain an even better ("good") response. *See* Appx4593–4594 at ¶ 13 ("During the first treatment year in DE003, if no ***good*** EULAR response could be achieved with 0.5 or 1.0 mg/kg D2E7, the dose could be increased stepwise up to a maximum of 3.0 mg/kg.").

AbbVie protests (at 47–48) that Rau 2000's statement that D2E7 can be administered biweekly cannot apply to the 0.5 mg/kg dose and that the Board somehow shifted the burden in finding otherwise. That is incorrect. The Board read Rau 2000's statement "in context," as AbbVie's cited cases require. That relevant context indicated that the 0.5 mg/kg intravenous dose performed similarly to all the other doses, that it reduced the signs and symptoms of the disease (by AbbVie's own expert's admission), that it achieved an ACR20 response in a significant number of patients, and that intravenous and subcutaneous dosing are equivalent. *See* pp. 4–7, 30–34. AbbVie has a different interpretation, but what a prior art reference teaches is the quintessential question of fact, and substantial evidence supports the Board's interpretation.

Finally, AbbVie repeats (at 44) its argument that a reference can create doubt even if it does not affirmatively teach away. But, as noted above, AbbVie made all its arguments to the Board in the guise of the references either teaching away or discouraging a skilled artisan from pursuing the claimed dose method. *See* pp. 42. The Board properly addressed (and rejected) the arguments AbbVie made. And, ultimately, AbbVie's attempt to respin the argument on appeal relies on a distinction without a difference. The Board rejected the argument that Rau 2000 created any "doubt," finding instead that "Rau indicates that the 0.5 mg/kg dose was effective in treating patients (*i.e.*, reducing the signs, symptoms, and/or progression of RA)." *See* Appx31. That finding was well-supported for all the reasons discussed above.

### c. The Board Correctly Rejected AbbVie's Pharmacokinetic Arguments.

The Board correctly found that the prior art clinical studies suggesting that a 40 mg biweekly subcutaneous dose would be effective outweighed the theoretical concerns that AbbVie attempted to raise based on the $C_{min}$ value for that dosing regimen. AbbVie is wrong to suggest (at 45) that the Board somehow shifted the burden by noting that D2E7's $C_{min}$ was unknown in the relevant timeframe. The Board recognized (and AbbVie's expert acknowledged) that there were two approaches to selecting the dosing regimen—(1) using clinical results for a range of doses to select the dose with the desired balance of efficacy and safety, or (2) attempting to model the pharmacokinetic behavior of the drug and selecting a dose with the desired parameters. *See* Appx33; Appx4559–4560 at ¶¶ 62–63.

Here, there was a multitude of prior art reporting clinical trial results, such as van de Putte, Kempeni, and Rau 2000, yet a key parameter for the second, a theoretical approach ($C_{min}$), was unknown. The skilled artisan would have followed the first approach, and, guided by the benefits of selecting a fixed, subcutaneous dose with the longest interval in the lowest effective amount, would have arrived at the claimed dose regimen. *See* pp. 25–30. After all, pharmacokinetic models are simply attempts to predict how patients will react to a dosing regimen, and a dosing regimen must be judged based on how it actually performs in the real-world. *See* Appx7479 ("Ultimately, however, the value of a dosing regimen must be assessed by the

therapeutic and toxic responses produced."). AbbVie's expert admitted that patient responses are typically validated through clinical trials. *See* Appx3771–3772. Here, the skilled artisan ***had*** the Phase 1 and Phase 2 clinical trial data in hand because AbbVie's predecessor had published it already. There was no need to try theoretical modeling.

Selecting the 40 mg biweekly, subcutaneous dose did not, as AbbVie alleges at (45–46), "push beyond the lower boundary of what had been tried." It was equivalent to the 0.5 mg/kg biweekly intravenous dose that Kempeni and Rau 2000 showed was effective. The Board did not err in finding the clinical results outweighed AbbVie's theoretical speculation.

The Board was also correct to reject AbbVie's arguments about $C_{min}$, because AbbVie's own expert admissions undermined it. AbbVie's pharmacologist, Dr. Vinks, refused to say that the parameter $C_{min}$ was the best parameter for assessing efficacy. *See* Appx3872; *see also* Appx4563 at ¶ 73 (listing multiple parameters that might be important). AbbVie's experts also admitted that patient-specific data was necessary to do such modeling yet no such data was available at the relevant time period. *See* Appx4559–4561 at ¶¶ 62, 64, 68; Appx5674 at ¶¶ 130–131. Moreover, AbbVie's experts refused to say that the 20 mg dose on which AbbVie based its pharmacokinetic modeling was the least effective—only that they had been instructed to make that assumption. *See* Appx3887–3892; *see also* Appx4557 at ¶ 53 n.2 (opining the least effective dose was unknown at the filing date). Without any evidence on

these points, the Board correctly found that AbbVie's modeling of the $C_{min}$ for a 20 mg dose was irrelevant. *See* Appx33.

AbbVie misreads (at 46) the holding in *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063 (Fed. Cir. 2012), which did not establish the rule that AbbVie suggests. In *Cyclobenzaprine*, the claims recited particular pharmacokinetic parameters. *See id.* at 1067 (noting that "[t]he pharmacokinetic ("PK") values recited in claim 3 measure various characteristics about the drug's behavior in a patient's blood plasma"). The Court applied a traditional obviousness analysis and found that the lack of prior art disclosure of those limitations supported non-obviousness. The Court also tied its ruling to "the facts of this case," rather than announcing a general rule about PK parameters. *Id.* at 1083. Here, by contrast, the claims do not recite pharmacokinetic parameters ($C_{min}$ or otherwise) but merely recite a dosing regimen. The Board found the skilled artisan would arrive at that dosing regimen by another path—using the actual clinical data showing it would be effective—so AbbVie's modeling evidence was ultimately unavailing.

#### d. The Board Properly Found that Any Presumption of Nexus Between the Claimed Methods and HUMIRA®'s Commercial Success Was Rebutted.

AbbVie is also incorrect (at 48–50) to attack the Board's treatment of the secondary considerations. "[T]he patentee bears the burden of showing that a nexus exists between the claimed features of the invention and the objective evidence offered to show non-obviousness." *See WMS Gaming, Inc. v. Int'l Game Tech.*, 184 F.3d

1339, 1359 (Fed. Cir. 1999); *see also Polaris Industries, Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1072 (Fed. Cir. 2018) ("We have held that a patentee cannot demonstrate commercial success, for purposes of countering the challenge of obviousness, unless it can show that the commercial success of the product results from the claimed invention." (internal quotation marks omitted)). The patentee is entitled to a "presumption" of nexus if it shows "that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them." *Polaris*, 882 F.3d at 1072. But a presumption is not proof, and the "patent challenger may rebut the presumption of nexus by presenting evidence to show that the commercial success was due to extraneous factors other than the patented invention, additional unclaimed features and external factors, such as improvements in marketing." *Id.* The patent challenger need not "disprove" nexus, as AbbVie contends, but simply must meet a "burden of production" to come forward with evidence to the contrary. *See WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1330 n.4 (Fed. Cir. 2016).

The Board correctly summarized this law and found that Coherus had "present[ed] sufficient evidence to rebut the presumption of nexus between the commercial success of HUMIRA." *See* Appx38–40. That finding was supported by substantial evidence. AbbVie had argued in other IPR proceedings that HUMIRA®'s formulation was responsible for the drug's success, which strongly undercut its position here that the claimed dosing regimen was responsible. *See* Appx3507.

Moreover, other evidence suggested that the D2E7 antibody, and the advantages associated with using a fully human antibody, were what propelled HUMIRA® over its competitors. By contrast, there was no actual evidence that the claimed dosing regimen had any impact on HUMIRA®'s success. And the key elements of the dosing regimen—fixed dose, subcutaneous administration, biweekly dosing, and the equivalent of a 40 mg dose—were already known in the prior art. *See* pp. 4–12. The Board correctly found that any presumption of nexus was rebutted by the record evidence. *See Ethicon Endo-Surgery, Inc. v. Covidien LP*, 812 F.3d 1023, 1034 (Fed. Cir. 2016).

The Board also did not err in its reference to the blocking patents on HUMIRA®. As an initial matter, the Board had already found that AbbVie's position on nexus here conflicted with its position in other proceedings, so its additional observation on blocking patents was not even necessary to its decision. *See* Appx39–40. Regardless, the Board correctly applied this Court's precedent that the existence of other blocking patents undermine the inference that secondary considerations are due to the challenged follow-on patent, rather than the earlier blocking patents. *See, e.g., Galderma*, 737 F.3d at 740. That is especially true here when those prior patents covered an essential part of HUMIRA®—*i.e.*, the D2E7 antibody—that the Board had previously found may have been responsible for the drug's success. Nothing in *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724 (Fed. Cir. 2017), is to the contrary. The Court there simply observed that blocking patents "do not necessarily

detract" from nexus, but noted that the inquiry was "fact-specific." *Id.* at 731. Here, the Board analyzed all the facts and concluded that the secondary considerations were not tied to the claimed dosing regimen. That finding was supported by substantial evidence.

### 3. The Board Properly Analyzed the Claims as a Whole.

AbbVie's final allegation of legal error (at 50–54) is that the Board failed to consider the claims as a whole when assessing obviousness. That is incorrect. The Board carefully evaluated each part of the claims, moving first through the parts (*e.g.,* fixed dosing, subcutaneous injections) that were largely undisputed below, and then focusing on the key dispute (*i.e.*, whether a skilled artisan would select the 40 mg biweekly, subcutaneous dose). *See* Appx16–18, Appx24–38. The Board then considered all the elements together: in deciding whether a skilled artisan would select a 40 mg biweekly, subcutaneous dose, it addressed all the variables that AbbVie lists. AbbVie's contrary arguments again devolve into a series of factual disputes with the Board's interpretation of the prior art.

AbbVie first states (at 51) that the Board should have considered the fact that "some patients" on the claimed dosing regimen may have received an insufficient amount of D2E7. This is irrelevant, because both Kempeni and Rau 2000 showed that a dose equivalent to the claimed dose was effective in other patients. *See* pp. 4–7, 30–34. Again, the claims simply require that D2E7 "reduce the signs, symptoms, and/or progression of RA," which is exactly what Kempeni and Rau showed that the

0.5 mg/kg dose did. *See* Appx7–9. And, as noted above, the Board found that there was a strong reason to pick a dose that balanced both efficacy and safety, rather than a dose that simply maximized efficacy. *See* Appx37.

AbbVie repeats its argument (at 51) that subcutaneous doses can be less bioavailable than intravenous doses. But the Board properly found that is not true for D2E7, given Kempeni's teaching that "plasma concentrations of D2E7 after multiple subcutaneous doses were comparable to those achieved with intravenous administration," and that "D2E7 given subcutaneously was safe and as effective as when intravenously demonstrating that subcutaneous self-administration is a promising approach for D2E7 delivery." Appx2705. AbbVie complains that these statements were made in the context of a study on a higher intravenous dose than 0.5 mg/kg, but Kempeni did not qualify the statements or limit them to a particular dose. So the Board was correct in finding that they applied equally to the 0.5 mg/kg dose.

Finally, AbbVie complains (at 52–53) about the Board's treatment of dependent claims 3 and 4 of the '135 patent, which require administration for 24 weeks. AbbVie did not argue these claims separately below, *see* Appx43206–43275, so it has waived any ability to do so here. *See In re NuVasive*, 842 F.3d at 1380. That waiver is particularly important, given that AbbVie is now criticizing the Board for its supposed lack of analysis on an issue that AbbVie did not raise below. Regardless, the Board did properly analyze these claims. It observed that the prior art disclosed biweekly dosing for at least 24 weeks. *See* Appx15, *citing* Appx2704; *see also* Appx2727

at ¶ 36. That is no surprise: rheumatoid arthritis is a chronic disease, and D2E7 does not "cure" the disease but merely relieves symptoms on an ongoing basis. It was straightforward to take prior art that reported that the equivalent of a 40 mg biweekly subcutaneous dose was effective and extend the treatment regimen on that dose to 24 weeks, and the prior art Weisman study did just that. *See* Appx3168.

AbbVie alleges (at 52) that there was "a complete absence of information regarding the performance of the relevant dose beyond 12 weeks." That is false. Both Kempeni and Rau 2000 demonstrated that a biweekly dose equivalent to a 40 mg subcutaneous dose was effective through 12 weeks. *See* pp. 4–7, 30–34. There is no reason to think that the dose would have somehow become ineffective if continued longer, and, in fact, Kempeni repeatedly stresses that D2E7 is safe and effective when administered over the long term. *See* Appx2704–2705. Moreover, the prior art Weisman article reported that an equivalent to a 40 mg biweekly subcutaneous dose was effective for 24 weeks, achieving an ACR20 in 67% of patients. *See* Appx3168. Had AbbVie actually raised the argument it is making now below, the Board would have no doubt pointed this out, and, in fact, it did rely on it in the Boehringer IPRs. *See* Appx166; Appx214.

### C. The Court Should Reject AbbVie's Constitutionality Argument.

As AbbVie acknowledges, existing precedent forecloses any challenge to the constitutionality of IPR. *See MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284

(Fed. Cir. 2015). If the Supreme Court's impending decision in *Oil States* has an effect on this case, Coherus will address it in a supplemental letter, as appropriate.

## CONCLUSION

For the reasons above, this Court should affirm the Board's determination that all of the claims of the '135, '680, and '987 patents are unpatentable as obvious.

Dated: March 23, 2018

Respectfully submitted,

*/s/ Craig E. Countryman*

Craig E. Countryman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070

*Attorneys for Appellee Coherus BioSciences, Inc.*

**CERTIFICATE OF SERVICE AND FILING**

I certify that I electronically filed the foregoing document using the Court's CM/ECF filing system on March 23, 2018. Counsel was served via CM/ECF on March 23, 2018.

*/s/ Craig E. Countryman*
Craig E. Countryman

## CERTIFICATE OF COMPLIANCE

The undersigned attorney certifies that the Response Brief for Coherus BioSciences, Inc. complies with the type-volume limitation set forth in the Federal Circuit Rule 32(a). The relevant portions of the brief, including all footnotes, contain 13,370 words, as determined by Microsoft Word.

Dated: March 23, 2018

*/s/ Craig E. Countryman*

Craig E. Countryman
Fish & Richardson P.C.
12390 El Camino Real
San Diego, CA 92130
(858) 678-5070

*Attorneys for Appellee Coherus BioSciences, Inc.*