United States Court of Appeals for the Federal Circuit

2017-2304, -2305, -2306

ABBVIE BIOTECHNOLOGY, LTD.,

Appellant,

v.

COHERUS BIOSCIENCES INC.,

Appellee.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00172, IPR2016-00188, and IPR2016-00189

2017-2362, -2363

ABBVIE BIOTECHNOLOGY, LTD.,

Appellant,

v.

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

Appellees.

Appeals from the United States Patent and Trademark Office, Patent Trial and Appeal Board in Nos. IPR2016-00408 and IPR2016-00409

BRIEF FOR APPELLEES BOEHRINGER INGELHEIM INTERNATIONAL GMBH AND BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.

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March 23, 2018

EXEMPLARY CLAIMS

U.S. Patent No. 8,889,135:

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 [D2E7].

4. The method of claim 1, wherein the anti-TNFα antibody is administered for a period of at least 24 weeks.

CERTIFICATE OF INTEREST

Counsel for the:

☐ (petitioner) ☐ (appellant) ☐ (respondent) ☑ (appellee) ☐ (amicus) ☐ (name of party)

Boehringer Ingelheim International GmbH and
Boehringer Ingelheim Pharmaceuticals, Inc.

certifies the following (use "None" if applicable; use extra sheets if necessary):

1. Full Name of Party Represented by me	2. Name of Real Party in interest (Please only include any real party in interest NOT identified in Question 3) represented by me is:	3. Parent corporations and publicly held companies that own 10 % or more of stock in the party
Boehringer Ingelheim International GmbH	Boehringer Ingelheim GmbH; Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim USA Corporation	C. H. Boehringer Sohn AG & Co. KG
Boehringer Ingelheim Pharmaceuticals, Inc.	Boehringer Ingelheim GmbH; Boehringer Ingelheim Pharma GmbH & Co. KG; Boehringer Ingelheim USA Corporation	C. H. Boehringer Sohn AG & Co. KG

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**) are:

James T. Evans, formerly of Paul Hastings LLP
Siegmund Y. Gutman, Proskauer Rose LLP
Colin G. Cabral, Proskauer Rose LLP

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. *See* Fed. Cir. R. 47. 4(a)(5) and 47.5(b). (The parties should attach continuation pages as necessary).

AbbVie Inc., et al. v. Boehringer Ingelheim International GmbH., et al., DED-1-17-cv-01065-MSG-RL

Dated: March 23, 2018

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TABLE OF ABBREVIATIONS

Abbreviation	Description
"the '135 patent"	U.S. Patent No. 8,889,135
van de Putte 1999	L. B.A. van de Putte et al., *Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 42(Supp.) Arthritis & Rheum. S400 (1999) (Appx28063)
van de Putte 2000	L. B.A. van de Putte et al., *Six Month Efficacy of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 59 (Supp.) Ann. of the Rheum. Dis. OP.056 (2000) (Appx28070)
van de Putte 2000 (II)	L. B.A. van de Putte et al., *One Year Efficacy Results of the Fully Human Anti-TNF Antibody D2E7 in Rheumatoid Arthritis*, 43 (Supp.) Arthritis & Rheum. S269 (2000) (Appx28072)
Rau 1998	R. Rau et al., Long-term Efficacy and Tolerability of Multiple I.V. Doses of the Fully Human Anti-TNF- Antibody D2E7 in Patients with Rheumatoid Arthritis, 41(Supp.) Arthritis & Rheum. S55 (1998) (Appx28053)
Rau 2000	R. Rau et al., Experience with D2E7, 25 Akt. Rheumatol. 83 (2000) (English Translation) (Appx28082)
Kempeni	J. Kempeni, Preliminary Results of Early Clinical Trials with the Fully Human Anti-TNFα Monoclonal Antibody D2E7, 58 (Supp. I) Ann. Rheum. Dis. I70 (1999) (Appx28077)
Schattenkirchner	M. Schattenkirchner et al., Efficacy and Tolerability of Weekly Subcutaneous Injections of the Fully Human Anti-TNF-Antibody D2E7 in Patien[t]s with Rheumatoid Arthritis - Results of a Phase I Study, 41 (Supp.) Arthritis & Rheum. S57 (1998) (Appx28058)

TABLE OF ABBREVIATIONS
(continued)

Abbreviation	Description
Weisman 2000	M. Weisman et al., A Dose Escalation Study Designed to Demonstrate the Safety, Tolerability and Efficacy of the Fully Human Anti-TNF Antibody, D2E7, Given in Combination with Methotrexate (MTX) in Patients with Active RA, 43 (Supp.) Arthritis & Rheum. S391 (2000) (Appx28103)

STATEMENT OF RELATED CASES

Appellant AbbVie Biotechnology, Ltd. and its parent AbbVie Inc. have asserted a patent related to those at issue against Appellees Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc. (collectively, "Boehringer") in Civil Action No. 17-1065-MSG-RL (D. Del.), which may be affected by this Court's decision on appeal.

INTRODUCTION

The patents at issue in these consolidated appeals recite dosing regimens for treating rheumatoid arthritis ("RA") with the anti-TNFα antibody "D2E7." These patents are part of a more-than-100-patent thicket AbbVie has amassed in seeking to extend the monopoly on its drug product Humira® now that the patent claiming the discovery of D2E7 and its use to treat RA—after providing more than 15 years of exclusivity—has expired. (*See* Appx33923 (AbbVie proclaiming that "[t]hese other patents . . . may allow Abbott to continue to maintain exclusivity . . . after the expiration of the original compound patent"); Appx33706; Appx33708-33710.)

In thorough, carefully reasoned decisions, the Board found the claims at issue obvious because all but one claim limitation was expressly disclosed in the largest, state-of-the-art "[d]ose finding" clinical study, while the remaining limitation was taught in two contemporaneous review articles discussing that and other clinical studies establishing D2E7's efficacy. Contrary to AbbVie's

suggestion, the challenged patents do not represent a "plunge into the unknown," but are instead a predictable combination of known elements that AbbVie's own prior art consistently touted as effective.

AbbVie's appeal is based on failed attempts to couch limited factual challenges to the Board's findings as "legal errors." (*E.g.*, Br. 27.) Those arguments are meritless, as shown by even a cursory review of the Board's comprehensive analysis based on many thousands of pages of exhibits and expert testimony. Moreover, each of the Board's findings—regarding the prior art disclosures, motivation to combine, reasonable expectation of success, and secondary considerations—are amply supported by record evidence, much of which AbbVie ignores on appeal.

AbbVie alleges three errors residing in the following factual issues: (i) the significance of up-dosing in an early Phase I clinical trial; (ii) the potential implications of a hypothetical C_{min} associated with subcutaneous biweekly dosing; and (iii) whether Humira®'s sales derive from the patent claims. But in each case, the Board specifically considered AbbVie's arguments and made detailed factual findings in rejecting them. *First*, substantial record evidence overwhelmingly contradicts AbbVie's speculative up-dosing arguments. And AbbVie's own Humira® product contemplates up-dosing as part of the treatment regimen; its efforts to create prior art "uncertainty" based on up-dosing, besides being incorrect,

logically cannot support patentability where they apply equally to the claimed subject matter itself. *Second*, AbbVie's hypothetical pharmacokinetic arguments are likewise contradicted by record evidence, as well as the testimony of its own experts. *Third,* the Board properly found that Humira®'s sales are attributable to factors other than the patents at issue, including the properties of the active ingredient itself.

Accordingly, Boehringer respectfully submits that the Board's obviousness determinations should be affirmed.

STATEMENT OF THE ISSUES

1. Whether the Board applied the correct legal analysis in holding that the claims at issue are unpatentable as obvious.

2. Whether substantial evidence supports the Board's determinations that the claims at issue are unpatentable as obvious.

3. Whether the Board's decisions are constitutional under Article III and the Seventh Amendment.

STATEMENT OF THE CASE

These appeals concern three AbbVie's patents[1] claiming methods of subcutaneously administering 40 mg of D2E7 every 13-15 days for a period of time sufficient to treat RA. Other claims recite, *inter alia*, administering D2E7 for a period of at least 24 weeks. For the convenience of the Court, exemplary claims are included in the inside front cover of this brief.

In the proceedings below, the Board applied the correct legal standard and found that the prior art disclosed each limitation of the challenged claims (*see, e.g.*, Appx149), and that a person of ordinary skill in the art would have combined the prior art with a reasonable expectation of success (*see, e.g.*, Appx157-159). These factual findings are supported by substantial—and often uncontested—evidence.

I. THE DISCLOSURE AND PATENTING OF D2E7 AND ITS USES

AbbVie owns U.S. Patent No. 6,090,382 ("the '382 patent"), granted on July 18, 2000, which disclosed D2E7, its properties as a fully human antibody, and its ability to treat RA by inhibiting TNFα activity. (Appx28675, Appx28687-28688.) The '382 patent and its progeny claimed the antibody, compositions thereof, and methods of treatment, including treating RA.

[1] As explained below, Boehringer filed two IPR petitions challenging AbbVie's '135 patent. In separate IPRs proceedings, Appellee Coherus BioSciences Inc. challenged that patent as well as two other nearly identical patents, U.S. Patent Nos. 9,017,680 and 9,073,987, for which AbbVie has not raised any unique issues. (*See* Br. 50-52.) Boehringer's brief focuses on the '135 patent claims.

The '382 patent expired in December 2016, but provided AbbVie more than 15 years of Humira® exclusivity from its issuance. (*Id.*) In addition, the protection afforded Humira® under that patent was extended 326 days through a patent term extension premised substantially on the clinical studies forming the extensive prior art to the challenged patents, discussed below. (Appx29847-29848.) Yet, having benefited from those prior art clinical studies via additional patent protection, AbbVie now seeks to discount their relevance—and, indeed, rely upon them in an attempt to create alleged "uncertainty" despite their uniform, positive reports of D2E7's efficacy—to further extend its D2E7 RA treatment monopoly.

By June 8, 2001, the challenged patents' earliest possible priority date, it was well-established that D2E7, the active ingredient in Humira®, could be used to successfully treat RA. (*See, e.g.*, Appx28089.) It was also known that D2E7, as a fully human anti-TNFα antibody, intrinsically possessed distinct advantages over other known antibodies used to treat RA, including greater therapeutic benefit through less negative interactions with a patient's immune system. (Appx30246; Appx28079; Appx28086; Appx28820.)

Further, the mechanism of action of anti-TNFα agents was understood to modulate the immune system in such a way that they can otherwise increase the risk of infections. (Appx30246.) As a result, a low effective maintenance dose

was generally favored (Appx28026; Appx29340 (88:3-13)), and individual patients could be up-dosed, if desired (Appx30268).

II. ADDITIONAL PRIOR ART DISCLOSING REGIMENS FOR TREATING RHEUMATOID ARTHRITIS WITH D2E7

Boehringer advanced three obviousness grounds in two IPR proceedings below. First, Boehringer contended that the '135 patent claims would have been obvious over the combination of van de Putte 2000 and Rau 2000. Second, Boehringer contended that those claims would have been obvious over the combination of van de Putte 1999 and Kempeni.[2] Third, Boehringer contended that the combination of Rau 1998, Schattenkirchner, and van de Putte 1999 rendered the '135 patent claims obvious.

These publications[3] fit within a larger context of prior art D2E7 clinical trials, progressing from initial Phase I studies focused on safety and efficacy to a large-scale, Phase II dose-finding study. At each step of the way, the prior art

[2] Coherus's IPRs focused on this obviousness ground, and proceeded on a slightly earlier track than the Boehringer IPRs. Boehringer's IPRs thus included record evidence from the Coherus IPRs as well as additional prior art and expert testimony. The record in either set of IPRs is sufficient to affirm the Board's decisions. As those decisions confirm, however—and contrary to AbbVie's allegation that Boehringer's IPRs "largely mirrored" Coherus's (Br. at 24-25)—the Boehringer IPRs contained, *inter alia*, further evidence rebutting AbbVie's up-dosing and C_{min} arguments (*see infra* at Argument Sections II.C.1-2).

[3] AbbVie seeks to minimize certain of these prior art documents by casting them as mere abstracts. (*See, e.g.*, Br. 8, 14.) In doing so, AbbVie ignores that its own expert admitted they would have been peer-reviewed by four to twelve reviewers. (Appx29364 (112:9-13).)

publications reporting the results of these studies confirmed that D2E7 was safe and effective for administration (i) intravenously and subcutaneously, (ii) on a weekly and biweekly basis, and (iii) in weight-based Phase I doses ranging from 0.25 mg/kg to 10.0 mg/kg (*i.e.*, roughly 20-800 mg) as well as a narrower range of 20, 40, and 80 mg flat doses studied in Phase II. Indeed, AbbVie's pharmacokinetics ("PK") expert, Dr. Alexander Vinks, agreed that AbbVie's predecessor publicly reported in 2000 (*i.e.*, before the priority date of the challenged patents) that it "had been able to show efficacy through clinical trials with both a once-weekly and an every-other-week dosing regimen," and that this "had been done with intravenous and subcutaneous dosing." (Appx29604-29605 (115:12-116:1); Appx30246-30247.)

Consistent with AbbVie's own prior art statements, as explained below, the prior art D2E7 clinical trials illustrate that the challenged patents are nothing more than an obvious combination of elements that a person of skill in the art would have been motivated to pursue—and, indeed, was expressly instructed to pursue—given the progression of that art and the known benefits of fixed, subcutaneous, low doses.

A. Early Published Phase I Clinical Trials Involving D2E7 RA Treatment

The prior art disclosed the results of four Phase I D2E7 clinical studies, which established that D2E7 (i) safely and effectively treated RA over a 0.25-

10.0 mg/kg (*i.e.*, roughly 20-800 mg) biweekly dosing range and (ii) could be effectively administered intravenously and subcutaneously on both a biweekly and weekly basis. Those studies also disclosed certain key PK parameters, including D2E7's half-life (approximately 12 days) and its mean dosing interval for maintaining efficacy (2.5 weeks).

DE001/003. The "first" human clinical trial for D2E7, the DE001 study, involved single doses of D2E7 administered intravenously at 0.5, 1.0, 3.0, 5.0, or 10.0 mg/kg body weight. (Appx28052; Appx28086; Appx28007-28008.) The results showed that these single D2E7 doses elicited a therapeutic response "within 24 hours to one week after D2E7 administration and reached the maximum effect after 1-2 weeks," and "[t]he estimated mean terminal half life was 11.6 to 13.7 days." (Appx28080; Appx28052.)

These same doses were continued in the DE003 study, with "[t]he possibility [of] dose escalation [for] patients treated with 0.5 and 1 mg D2E7/kg body weight." (Appx28057; Appx28008; Appx28086-28088; Appx28079-28080.) The DE003 results were reported in Rau 1998 (among other publications), which disclosed that patients received D2E7 ***biweekly*** until they achieved a "good" European League against Rheumatism ("EULAR") response, defined as a Disease Activity Score ("DAS") of less than 2.4. (Appx28057; Appx28005-28006; Appx28008-28009.) Thereafter, patients were "retreated only when the DAS value

increased to above 2.4 again." (Appx28057.) This treatment protocol resulted in an overall "mean dosing interval" of 2.5 weeks. (*Id.*) In other words, the study found that the effects of a single dose of D2E7 wore off, on average, shortly after two weeks. (Appx36277-36278; Appx28008-28009.)

DE004. The DE004 study involved subcutaneous 0.5 mg/kg D2E7[4] administration in RA patients, the results of which were published in, *inter alia*, Kempeni (Appx28077) and Schattenkirchner (Appx28058). Based upon data collected for "up to 6 months," Schattenkirchner concluded that "plasma concentrations of D2E7 after multiple s.c. [subcutaneous] injections" were "comparable" to "those after i.v. [intravenous] injections." (Appx28062.) Kempeni similarly reported that DE004 showed that "D2E7 given subcutaneously was safe and as effective as when administered intravenously." (Appx28081.)

DE005.[5] The Weisman 2000 publication (Appx28103) reported the results of DE005, a "later" Phase I study (Appx166) in which patients received biweekly intravenous D2E7 doses ranging from 0.25 mg/kg to 5.0 mg/kg—*i.e.*, half of the

[4] The possibility of up-dosing to 1 mg/kg for "[n]on-responders" was noted. (Appx28062; Appx28080-28081.)

[5] Before the Board, AbbVie discussed Weisman 2000 in its summary of the prior art clinical trials in its Preliminary Response (Appx44704), yet omitted this prior art from the corresponding summary in its appeal brief.

"first" DE001/003 dosage range—with methotrexate for 24 weeks.[6] (Appx28107; Appx28402.) One of the doses studied was 0.5 mg/kg, *i.e.*, ***the very dose that AbbVie incredibly alleges would not have been used because an earlier study had allowed for up-dosing*** (*see infra* at 45-52).

Patients in each study arm, including those receiving 0.25 mg/kg (*i.e.*, 20 mg) and 0.5 mg/kg (*i.e.*, 40 mg) biweekly doses, showed substantial improvements in ACR20 and ACR50 scores, among other criteria. (Appx28107.) Based on this data, Weisman 2000 concluded that "D2E7 is well tolerated, safe and efficacious," and reported that "[t]he response [wa]s sustained through at least 24 weeks." (*Id.*; Appx44704.)

DE010. In the DE010 study, patients first received 1 mg/kg D2E7 doses administered subcutaneously or intravenously, or placebo, and, after the second dose, received D2E7 biweekly subcutaneously. (Appx28089; Appx28081; Appx28824; Appx29568-29569 (79:20-80:2).) Reporting only the results from "the placebo controlled part of the study," the DE010 investigators concluded that

[6] Methotrexate was commonly administered in combination with anti-TNFα antibodies to treat RA. (*See, e.g.*, Appx28118; Appx29333-29334 (81:20-82:10); Appx43589-43590; Appx30261.)

both doses "were safe and efficacious when given with standard, stable doses of [methotrexate] in patients with active RA." (Appx28824.)[7]

B. The Large-Scale, Dose-Finding Phase II Clinical Trial

DE007. DE007 was a large-scale, Phase II "[d]ose-finding" study that compared the efficacy of weekly subcutaneous 20, 40, and 80 mg D2E7 doses. (Appx28071; Appx29406-29407 (154:3-155:16); Appx29404-29405 (152:19-153:7).) "A total of 283 patients" with "long standing active rheumatoid arthritis" were "included in this randomised double-blind, placebo-controlled study." (*Id.*) Clinical efficacy was determined through American College of Rheumatology ("ACR") criteria, which were reported as percent improvement. (*Id.*) For example, an "ACR20" response means that a patient achieved a 20% improvement in tender joint count, swollen joint count ("SJC"), and three of five other indicators, including the level of C-reactive protein ("CRP"). (Appx28005-28006.)[8]

The successful results of the DE007 study at various time periods were reported in multiple prior art publications, including van de Putte 1999 (three months), van de Putte 2000 (six months), and van de Putte 2000 (II) (one year).

[7] The prior art DE010 data, along with the DE004 study results, correspond to Example 1 of the '135 patent (Appx257 (28:1-54)), though the specification does not acknowledge those data as having existed in the prior art.

[8] "ACR50" and "ACR70" responses likewise correspond to 50% and 70% improvements, respectively. (*Id.*)

(Appx28063; Appx28070; Appx28072.) The 20, 40, and 80 mg D2E7 doses produced ACR20 improvements over placebo at three months of 39%, 47%, and 46%, respectively.[9] (Appx28069.) By way of comparison, the placebo-adjusted ACR20 responses for infliximab (Remicade®), the then-state-of-the-art anti-TNFα antibody RA treatment, ranged from roughly 30-38%. (Appx150-151; Appx28016-28017; Appx28127; Appx28133.) These significant ACR20 responses in treating severe RA were sustained for all doses after six and 12 months of treatment, and the 12-month data also showed substantial ACR50 responses. (Appx28071; Appx29408-29411 (156:11-159:8); Appx28076; Appx29411-29412 (159:10-160:11).)

Consistent with this robust efficacy showing for all doses, each van de Putte publication reported that "all doses of D2E7 were statistically significantly superior to placebo." (Appx28069; Appx28071; Appx28076.) These references also concluded that "20, 40 and 80 mg/week" doses were "nearly equally efficacious" after three months and "statistically equally efficacious" after six months and one year. (*Id.*; Appx150-151; Appx164-165.) van de Putte 2000 and

[9] The DE007 ACR20 data largely track the data set forth in Example 2 of the '135 patent (Appx257-258 (28:56-29:10); Appx29326 (74:1-8)), although the specification again does not describe those data as having existed in the prior art. Example 3—the only non-prior art study disclosed in the specification—describes the results of methotrexate in combination with 20, 40, and 80 mg of D2E7 dosed subcutaneously and biweekly. (Appx258 (29:12-30:37).)

2000 (II) further noted that "[t]he treatment benefit was stable for all parameters over time." (Appx28071; Appx28076.)[10]

C. Prior Art Commentary on the D2E7 Clinical Trials Confirming D2E7's Efficacy and Teaching Every-Other-Week Administration

Rau 2000. Rau 2000, which was co-authored by Dr. van de Putte, summarizes and analyzes many of the Phase I and II studies discussed above, including the van de Putte DE007 study. (Appx28085-28089.) After surveying this extensive prior art, Rau 2000 concluded:

> In summary, it can be established that the completely human TNFα antibody D2E7 is quickly (within the space of days) effective in the majority of patients, and has not lost its efficacy in the course of long-term treatment, up to now, two and one-half years. ***D2E7, with a half-life of 12 days, can be administered every two weeks*** as an intravenous injection over 3-5 minutes or ***subcutaneously.***

(Appx28089.)[11] This express teaching of biweekly subcutaneous dosing is made without limitation or caveat, including with respect to dose. (Appx165.)[12]

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[10] Given their similar disclosures, the three van de Putte publications are referred to collectively as "van de Putte."

[11] Unless otherwise noted, all internal citations and modifications are omitted and all emphases added.

[12] AbbVie contended before the Board that Rau 2000 somehow denigrated the weekly equivalent of the claimed biweekly dose (*i.e.*, 20 mg) by reporting SJC and CRP data for only the 40 mg and 80 mg doses. (Appx44812.) As explained below, AbbVie does not challenge the Board's finding that the 20 mg dose would have been understood to demonstrate robust RA efficacy. (*See infra* at 36-38.)

In discussing the DE003 study, although Rau 2000 reported biweekly 0.5 mg/kg data for only 12 weeks, that data showed it effectively treated RA during this time period. (Appx28087-28088 (Figs. 4-5); Appx31655; Appx167; Appx31347-31348 (91:21-92:6).)[13] This is confirmed by an earlier, prior art press release by a D2E7 co-developer[14]—conspicuously omitted from AbbVie's brief—proclaiming 0.5 mg/kg to be the "minimum effective dose" in this initial study. (*See, e.g.*, Appx29668 (179:3-12); Appx30249.)[15] The reported efficacy of the 0.5 mg/kg dose is also consistent with the "later" DE005 study (Appx166) continuing to administer that dose—and, indeed, even ***half*** that dose—on a biweekly interval (Appx28107).

Nor is AbbVie permitted to do so for the first time on reply. *See Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1385 (Fed. Cir. 2015).

[13] AbbVie does not dispute this 12-week efficacy in its brief.

[14] AbbVie acquired D2E7 after it was developed by Cambridge Antibody Technology plc and Knoll/BASF Pharma.

[15] At no point in Rau 2000 is it stated, or even implied, that any particular dose of D2E7, including 0.5 mg/kg, is ineffective or suboptimal. With no supporting expert testimony, AbbVie quotes isolated portions of Rau 2000 in suggesting that the 0.5 mg/kg dose was less effective than other doses. (Br. 10.) AbbVie's arguments concerning these statements, however, were considered and rejected by the Board. (Appx167-168.) In any event, these statements concerned *single* D2E7 doses, and do not support AbbVie's assertions concerning the steady-state efficacy (*i.e.*, the subject of the challenged claims) established in the prior art at issue. (Appx31317-31320 (61:20-64:17).)

Kempeni. Kempeni, which was authored by one of the named inventors on the challenged patents, similarly analyzed many of the prior art D2E7 clinical studies. (Appx28079-28081; Appx28010-28011.) Like Rau 2000, Kempeni expressly disclosed biweekly dosing, reporting that D2E7—consistent with its "11.6 to 13.7 day[]" half-life—"was administered every two weeks until [the] responses could be rated as 'good'" in the DE003 study. (Appx28080; Appx28010-28011; Appx29573-29574 (84:19-85:4).) In line with Rau 2000's disclosure of efficacy for every D2E7 dose, including 0.5 mg/kg, Kempeni noted that "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks." (Appx28080.) Moreover, as confirmed by expert testimony, because the DE003 patients were "retreated only upon flare-up," Kempeni's reported 2.5-week mean dosing interval would have been understood as the longest duration one could go between doses while maintaining efficacy. (Appx36277-36278; Appx36241-36242; Appx36251-36252; Appx36256.)

Kempeni further reported 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 administered intravenously***[,] demonstrating that subcutaneous self administration is a promising approach for D2E7 delivery." (Appx28081.) Kempeni also noted that the fully human D2E7 was expected to have greater

therapeutic potential than chimeric antibodies (*e.g.*, infliximab) by reducing adverse immune responses (Appx28079), and concluded by stating that "these early data suggest that the fully human anti-TNFα mAb D2E7 is safe and effective as [a] monotherapy or in combination with methotrexate when administered by single and multiple intravenous and subcutaneous injections" (Appx28081).

* * *

Based on the foregoing clinical studies, first-named inventor Dr. Steven Fischkoff, who was "responsible for the development of D2E7," reported in a June 2000 prior art publication that AbbVie's clinical studies established "efficacy with both a once-weekly and once-fortnightly [*i.e.*, biweekly] dosing regimen." (Appx30246-30247.) And as Dr. Vinks confirmed, a person of ordinary skill in the art would have understood Dr. Fischkoff—consistent with the prior art relied upon by the Board—to have represented that weekly and biweekly efficacy was achieved using both subcutaneous and intravenous routes of administration.[16] (Appx29598-29605 (109:20-116:1).)

III. THE PROCEEDINGS BELOW AND THE BOARD'S DECISIONS

Boehringer petitioned the Board to conduct *inter partes* reviews of the '135 patent, contending that its claims would have been obvious in view of the

[16] AbbVie dedicates pages of its Statement of the Case to "multi-dose pharmacokinetics." (Br. 16-18.) Many of these statements are incorrect and/or irrelevant, as explained in Argument Section II.B.3 below.

references discussed above describing the prior art use of D2E7: (i) van de Putte 2000 and Rau 2000 (the IPR2016-00408 Ground); (ii) van de Putte 1999 and Kempeni (IPR2016-00409 Ground 1); and (iii) Rau 1998, Schattenkirchner, and van de Putte 1999 (IPR2016-00409 Ground 2). Boehringer's petitions were supported by expert declarations from Dr. Michael Weisman, a highly respected rheumatologist who participated in various D2E7 clinical trials, and Dr. William Jusko, a leading PK expert.

With respect to the first two grounds—as Boehringer contended, the Board found, and AbbVie does not dispute—van de Putte disclosed every limitation of the '135 patent claims except biweekly administration. (Appx149-151; Appx197-199.) And Rau 2000 and Kempeni both taught this limitation, as the Board correctly found. (Appx151-152; Appx199.) On appeal, AbbVie does not dispute Rau 2000's and Kempeni's disclosure of biweekly dosing. (*E.g.*, Br. 22 (acknowledging "Kempeni's discussion of every-other-week 0.5 mg/kg intravenous dos[ing]").) And Dr. Vinks admitted during his deposition that a skilled artisan would have understood Rau 2000 to also disclose *subcutaneous* biweekly dosing. (Appx29568-29569 (79:20-80:2); Appx28089.)

With respect to Ground 2 of IPR2016-00409 ("the 409 proceedings"), Boehringer contended that the '135 patent claims would have been obvious based on Rau 1998's disclosure of every-other-week dosing, Schattenkirchner's

disclosure that D2E7 plasma concentrations were comparable for subcutaneous and intravenous administration, and van de Putte's efficacy-related disclosures, including the efficacy of the equivalent of a 40 mg biweekly dose (*i.e.*, 20 mg weekly). (Appx226-227.)

In both proceedings, after "reviewing . . . the complete record"—totaling more than 7,100 pages of exhibits and 1,400 pages of expert testimony, including deposition testimony from AbbVie's five experts—the Board concluded that Boehringer had "met its burden" of showing that the '135 patent claims would have been obvious. (Appx139; Appx149.) The Board began its detailed analysis by considering all of the claim limitations, including the 24-week limitation from claim 4 of the '135 patent. For example, the Board expressly found that van de Putte 2000 disclosed significant efficacy for "six months" (*i.e.*, 24 weeks), as required by that claim limitation. (Appx148; Appx150-151.)[17]

The Board also interpreted the only claim term proposed for construction, "for a time period sufficient to treat the rheumatoid arthritis," to mean "for a time period sufficient to reduce the signs, symptoms, and/or progression of RA."

[17] AbbVie therefore cannot credibly complain that the Board did not consider this limitation. (Br. 52-53.) While AbbVie contends that van de Putte "failed to fill the gap" because it disclosed results "for *weekly* subcutaneous injection" (Br. 53), that simply means that van de Putte 2000 does not anticipate the '135 patent. The issue here is obviousness. Regardless, Weisman 2000 reports biweekly efficacy data over 24 weeks. (*Supra* at 9-10; *infra* at 48-50.)

(Appx140-145.) In so doing, the Board further noted that this construction and "the claims encompass," for example, "treating patients to achieve an ACR20 or EULAR moderate response." (Appx8-9; Appx144.) AbbVie thus wrongly contends that the Board's construction focuses on mere *de minimis* efficacy or some therapeutic level only marginally better than "baseline." (Br. 33-34.)[18]

Having considered and construed the claims, the Board then turned to the cited prior art. The Board first found, "[b]ased on the full trial record," that "van de Putte 2000 and Rau 2000 collectively disclose each limitation of the challenged claims." (Appx149; Appx197-199 (reaching the same conclusion for van de Putte 1999 and Kempeni).)[19] Specifically, the Board found that "van de Putte discloses all of the elements of all challenged claims 1-5, except for biweekly dosing." (Appx149-151; Appx28071; Appx28013-28014.) The Board also found that van de Putte "demonstrated the clinical effectiveness of each dose," including 20 mg weekly, and "credit[ed]" Dr. Weisman's declaration testimony that this dose would have in fact been understood to have considerable efficacy given that it compared

[18] The Board made clear that these proceedings did not turn on issues of claim construction, and referred to its (unchallenged) construction as only one reason for rejecting AbbVie's since-abandoned argument "that the 20 mg[] dose was sub-optimal." (Appx162-164.) The Board also noted that it "d[id] not agree with [AbbVie's] assessment of what the art teaches one of skill in the art" (Appx163) and, as explained below (*see, e.g.*, *infra* at 36-38), found this dose to have robust efficacy based on the prior art.

[19] AbbVie does not challenge these findings of the Board on appeal.

favorably to the then-gold standard, infliximab. (Appx150-151 (citing Appx28071; Appx28013-28014; Appx28016-28017; Appx28133); Appx165 (finding 20 mg would not have been viewed as any "better or worse than another dose" from the van de Putte study).)

The Board further found that Boehringer met its burden of proving that Rau 2000 and Kempeni taught every-other-week dosing. (Appx151-152 (citing Appx28086-28089 (Figs. 4-5); Appx28021-28023); Appx165; Appx199; Appx212-213.) The Board relied on substantial evidence, including: (i) Rau 2000's discussion of "a study in which patients received D2E7 via intravenous injection ***every two weeks***"; (ii) Rau 2000's conclusion that D2E7 can be administered "***every two weeks***" intravenously or subcutaneously; (iii) prior art reports that subcutaneous and intravenous D2E7 administration were comparable; and (iv) evidence that, given its 12-day half-life, "D2E7 concentrations would have remained high enough to achieve clinical results ***over two weeks***." (Appx151-152 (citing Appx28086-28089 (Figs. 4-5); Appx28021-28023); Appx199; Appx206-207; Appx212-213 (making similar Kempeni-based findings).)

The Board then correctly asked whether a person of skill in the art would have been motivated to combine van de Putte's efficacy-related teachings with Rau 2000's and Kempeni's teaching of biweekly dosing with a reasonable expectation of success. (Appx152 (citing *Merck & Cie v. Gnosis S.p.A.*, 808 F.3d

829, 833 (Fed. Cir. 2015)); Appx199-200 (same).) After considering both parties' arguments and evidence (Appx152-155), the Board found that a person of ordinary skill in the art would have been so motivated in light of, *inter alia*, the known benefits of such features and Rau 2000's express teaching of biweekly subcutaneous administration (Appx155-158; Appx159 ("[O]ne of skill in the art would have been motivated to modify van de Putte 2000's 20 mg weekly dose to a 40 mg biweekly dose based on the express teaching of Rau 2000 of a two-week interval for dosing, in addition to Rau 2000's teaching of D2E7's 12-day half-life."); Appx207 (drawing the same conclusion based on Kempeni).) Indeed, Rau 2000 provides this teaching ***after*** discussing the van de Putte study. (Appx158-159; Appx28088-28089.)

In making these findings, the Board considered AbbVie's proffered evidence—including its "up-dosing"- and "C_{min}"-based contentions raised on appeal—and found them unpersuasive in light of "what the references as a whole teach one of skill in the art." (Appx164.)[20] The Board rejected AbbVie's then-

[20] AbbVie seeks to criticize the Board because it phrased its analysis at times in terms of whether the art taught away. (Br. 36-37.) In doing so, AbbVie fails to disclose that it had in fact argued to the Board that the prior art taught away from the claims as a basis for patentability. (Appx44799; Appx44802; Appx44809; Appx44815-44825; Appx44843-44844; Appx44846-44847.) The Board's decisions show that it assessed AbbVie's arguments and evidence in light of the prior art's teachings as a whole, and found that art to have rendered the claims obvious. (Appx163-164.)

argument that the 20 mg dose from van de Putte was "sub-optimal," finding each dose to be highly effective. (Appx162-164 (crediting evidence that "each dose was superior to placebo" and that no "dose was better or worse than another"); Appx150-151 (comparing van de Putte's 20 mg efficacy favorably with Remicade®).) The Board also found that record evidence established that the 0.5 mg/kg biweekly dose in DE001/003 was ***effective*** (*see, e.g.*, Appx167 (explaining that Rau 2000 "show[s the] 0.5mg/kg dose was effective at treating RA through 12 weeks")), and noted that AbbVie conceded that such a dose would have been viewed as equivalent to a 40 mg every-other-week dose (Appx160 n.7 (citing Appx30007-30008 (159:4-160:1)).

The Board further noted that Boehringer's rebuttal evidence, including Weisman 2000, further demonstrated the effectiveness of a 0.5 mg/kg (*i.e.*, 40 mg) biweekly dose to a person of skill in the art. (Appx151; Appx166-168 (explaining that the prior art as a whole showed 0.5 mg/kg efficacy).) This finding is supported by substantial evidence, including the Board's citation of the 2000 Remicade® label—a document ignored entirely in AbbVie's brief—which showed that prior art anti-TNFα dosing regimens were desirable and pursued by skilled artisans despite being up-dosed in certain patients. (Appx150-151; Appx167.) Finally, the Board rejected AbbVie's hypothetical C_{min}-related arguments, finding AbbVie's PK modeling was "not entitled to much weight" and

that the prior art's correlation of PK parameters with clinical data showing safety and efficacy was sufficient. (Appx169-172; *see also* Appx31409-31410 (153:8-154:15).)

Before reaching its conclusion on obviousness, the Board also considered AbbVie's arguments concerning objective indicia of nonobviousness, namely alleged long-felt need, unexpected results, and commercial success. (Appx172-177.) In rejecting AbbVie's long-felt need argument, the Board found that the prior art already disclosed subcutaneous, biweekly D2E7 dosing, concluding: "[I]t appears from the evidence that the driving force behind the satisfaction of a long-felt need and success where others had failed was ***the introduction of the first fully human anti-TNFα antibody, not the claimed dosing regimen***." (Appx176 (citing Appx28079; Appx31667).) The Board also rejected AbbVie's unexpected results argument because, *inter alia*, AbbVie did not "compare that dosing regimen to the closest prior art." (Appx177; Appx44934-44935.)[21] Nor could it, as the Humira® label states that the claimed dosing regimen is up-dosed to the prior art 40 mg weekly regimen for certain patients. (Appx44935; Appx28641.)

With respect to the commercial success issue, the Board found that Boehringer had presented "sufficient evidence to rebut the presumption of nexus"

[21] AbbVie does not challenge the Board's rejection of AbbVie's long-felt need or unexpected results arguments.

between Humira® sales and the claimed dosing regimen, citing record evidence concerning, *inter alia*, the substantial attributes of the fully human D2E7 antibody itself disclosed in the prior art. (Appx174-175.) The Board thus concluded that the '135 patent claims were unpatentable as obvious. (Appx177-178 (recognizing that "a fact finder must consider all evidence relating to obviousness before finding patent claims invalid").)

The Board also agreed that Ground 2 of the 409 proceedings independently justified finding the '135 patent claims obvious. (Appx226-228.) The Board explained how Rau 1998 included every limitation but a 40 mg subcutaneous dose, which was taught by Schattenkirchner and van de Putte 1999. (*Id*.) In doing so, the Board incorporated by reference its reasoning with respect to Ground 1, which cited and applied the correct legal standards throughout, as explained above. (Appx182; Appx191-192; Appx196-225.)

SUMMARY OF THE ARGUMENT

The Board properly found the challenged claimsobvious.

1. In finding those claims unpatentable, the Board applied the correct obviousness analysis as set forth in *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007), *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966), and this Court's precedent. Contrary to AbbVie's unsupported assertions, the Board's opinions are free from hindsight and burden-shifting, and properly take into

account the claims as a whole. The purported "legal" errors AbbVie alleges—the probative value of DE001/003 up-dosing, the hypothetical C_{min} values associated with every-other-week dosing, and the extent to which factors other than the claimed dosing regimen are responsible for Humira®'s sales—are nothing more than transparent attempts to challenge isolated portions of the Board's factual findings shorn of context. AbbVie itself acknowledges as much when it bases its ***entire*** substantial evidence challenge on its "legal" arguments. (Br. 53-54.) Regardless, viewed in context, the Board clearly considered Boehringer's evidence supporting their obviousness case, AbbVie's evidence, as well as Boehringer's responses and, based on the "complete record," found that Boehringer demonstrated obviousness by a preponderance of the evidence. (Appx149.)

2. The Board's decisions are supported by substantial evidence, and AbbVie's conclusory assertion to the contrary—made in less-than-half-a-page of its 55-page brief—tacitly acknowledges this truth. The Board found, and AbbVie does not dispute, the key facts of Boehringer's obviousness case. van de Putte expressly discloses every claim limitation of the challenged '135 patent but biweekly dosing, and Rau 2000 and Kempeni teach just that. Given these teachings, along with the known advantages of less-frequent, subcutaneous, fixed doses, a person of skill in the art would have been motivated to combine van de Putte's state-of-the-art, highly effective dosing regimens with the prior art's

teaching of biweekly dosing and had a reasonable expectation of success in doing so. AbbVie's only response to Boehringer's obviousness case is that the Board wrongly decided certain factual issues regarding potential up-dosing, C_{min} values, and commercial success. In each case, however, the Board considered and rejected AbbVie's arguments, making specific findings based on the considerable record evidence (including extensive expert testimony), much of which AbbVie ignores.

3. The only asserted error AbbVie identifies that is unique to Ground 2 of the 409 proceedings is a single typographical error appearing in the Board's discussion of the standard of proof. This Court reviews judgments, not single statements, and the Board's decision indeed applied the correct legal standard, as is clear from its opinion as a whole.

STANDARD OF REVIEW

AbbVie has the burden to show that the Board committed reversible error. *In re Watts*, 354 F.3d 1362, 1369 (Fed. Cir. 2004). Obviousness is a question of law based on underlying factual findings. *See, e.g.*, *KSR*, 550 U.S. at 427; *In re DBC*, 545 F.3d 1373, 1377 (Fed. Cir. 2008). Those factual findings include: (1) what the prior art teaches, *e.g.*, *Idemitsu Kosan Co. v. SFC Co.*, 870 F.3d 1376, 1379 (Fed. Cir. 2017); (2) whether there is "motivation to combine references" with "a reasonable expectation of success," *e.g.*, *Par Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1196 (Fed. Cir. 2014); and (3) whether objective indicia

support a finding of nonobviousness, including the existence of nexus, *e.g.*, *Merck & Cie*, 808 F.3d at 833.

This Court upholds the Board's factual findings if they are supported by substantial evidence, and reviews legal conclusions *de novo*. *In re Gartside*, 203 F.3d 1305, 1316 (Fed. Cir. 2000); 5 U.S.C. § 706(2)(E). 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, 1354-55 (Fed. Cir. 2000). Thus, "[i]f the evidence in [the] record will support several reasonable but contradictory conclusions," this Court "will not find the Board's decision unsupported by substantial evidence simply because the Board chose one conclusion over another plausible alternative." *In re Jolley*, 308 F.3d 1317, 1320 (Fed. Cir. 2002).

ARGUMENT

I. THE BOARD APPLIED THE CORRECT LEGAL ANALYSIS

AbbVie wrongly contends that the Board applied an incorrect legal analysis by allegedly (i) relying on hindsight, (ii) improperly shifting the burden of proof,

and (iii) failing to consider the claims as whole. In doing so, AbbVie asks the Court to set aside "the details of the references" and the Board's discussion of them (Br. 35), which only reveals the true nature of AbbVie's attacks on the Board's factual findings. As explained in more detail in Section II below, the Board's factual findings were correct and unquestionably supported by substantial evidence. AbbVie's legal challenges are equally unavailing.

A. The Board Was Careful to Avoid Hindsight

The Board conducted its careful analyses free from hindsight. As noted by the Board, obviousness requires a showing that "the differences between the claimed subject matter and the prior art are such that the subject matter, as a whole, would have been obvious at the time the invention was made." (Appx145 (citing *KSR*, 550 U.S. at 406).) In making this determination, the Board considered: "(1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness." (Appx145 (citing *Graham*, 383 U.S. at 17-18).) The Board also noted that the "'motivation to combine' and 'reasonable expectation of success' factors are subsidiary requirements for obviousness subsumed within the *Graham* factors." (Appx152.)

The Board correctly applied these standards to the record evidence in each of its decisions. The Board first determined the level of skill in the art, which

AbbVie does not challenge. (Appx140-141.) The Board then assessed the scope and content of the prior art, and whether any differences existed between that art and the claimed subject matter, finding that the combinations of (1) van de Putte and Rau 2000 or Kempeni and (2) van de Putte, Schattenkirchner, and Rau 1998 each "disclose[d] or suggest[d] each and every element of the challenged claims," which AbbVie does not dispute on appeal. (Appx149-152; Appx197-199; Appx227-228.) The Board further found that a person of skill in the art "would [have been] motivated to combine those references" with "a reasonable expectation of success." (Appx152; *see also* Appx152-172 (analyzing these requirements in more than 20 pages of analysis).) This analysis follows this Court's precedent. *See, e.g.*, *Merck & Co. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1375 (Fed. Cir. 2005).

The Board's detailed analysis of the motivation-to-combine and reasonable-expectation-of-success requirements—supported with record evidence showing why a skilled artisan *at the time* would have desired fixed, subcutaneous, biweekly dosing based on the prior art's teachings (Appx155-159)—undermines AbbVie's claim of hindsight bias. *See, e.g.*, *Ecolochem, Inc. v. S. Cal. Edison Co.*, 227 F.3d 1361, 1371 (Fed. Cir. 2000) ("Our case law makes clear that 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."); *Optivus Tech., Inc. v. Ion Beam Applications S.A.*, 469 F.3d 978, 991 (Fed. Cir. 2006) ("The court determined that a motivation to combine the prior art references existed, and that the references did not teach away from [that] combination or modification, thereby guarding against a hindsight reconstruction of the invention."). So too does the Board's careful consideration of the parties' expert testimony. *See, e.g.*, *Outside the Box Innovations, LLC v. Travel Caddy, Inc.*, 695 F.3d 1285, 1297 (Fed. Cir. 2012) ("The foil to judicial hindsight is the testimony of persons experienced in the field.").

Indeed, the Board expressly considered and rejected AbbVie's hindsight accusations in its Institution Decision. (Appx44762-44763 & n.5 (rejecting AbbVie's argument that the petition used "impermissible hindsight" to reduce the number of prior art options and noting that, in light of van de Putte's "disclosure of three doses as a starting point for a dose-finding phase II study[,] the argument that one of skill in the art faced a limitless number of dosing regimens appears not well-taken").) AbbVie's baseless contention should be similarly dismissed on appeal.

B. The Board Correctly Applied the Burden of Proof

The Board also recited and applied the correct burden of proof, reserving its decision on obviousness until it had considered all of the evidence, including that

presented by AbbVie.[22] (Appx139 ("Petitioner bears the burden of proving unpatentability of the challenged claims, and that burden never shifts to Patent Owner. . . . Petitioner must establish the facts supporting its challenge . . . . We find that Petitioner has met its burden . . . ."); Appx136; Appx149; Appx158; Appx172-178 (noting that secondary considerations evidence must be considered "***before*** reaching our conclusion on obviousness").) This Court has repeatedly rejected the type of bald assertions made by AbbVie that the Board did not do what it said it did in its decisions. *See, e.g.*, *In re Omeprazole Patent Litig.*, 281 F. App'x 974, 979 (Fed. Cir. 2008) (non-precedential) (rejecting patent owner's assertion that the court applied the wrong standard in light of the "court's clear understanding and repeated recitation of the applicable burden of proof"); *Novo Nordisk A/S v. Caraco Pharm. Labs., Ltd.*, 719 F.3d 1346, 1353-54 (Fed. Cir. 2013) (rejecting burden-shifting argument where, as here, the "court reserved its ultimate conclusion on validity until after it considered the evidence from both sides").

AbbVie wrongly claims that the Board shifted the burden of proof when it stated that AbbVie failed to show that the prior art taught away. (Br. 27, 36-48.) But, in so doing, the Board was simply rejecting AbbVie's own characterization of

[22] AbbVie's concedes that the Board "correctly recited [Boehringer's] burden of proof." (Br. 35-36.)

the art as teaching away (Appx44799; Appx44802; Appx44809; Appx44815-44825; Appx44843-44844; Appx44846-44847), not shifting the burden of proof of obviousness onto AbbVie, *Merck & Cie*, 808 F.3d at 836 (explaining that, "[b]y rejecting [the patent owner's] argument that the prior art taught away . . . the Board impliedly found a reasonable expectation of success"); *Optivus Tech.*, 469 F.3d at 991. In essence, AbbVie seeks reversal because the Board considered and responded to AbbVie's (since-abandoned) teaching away arguments, a paradigmatic case of chutzpah.[23] The Board was entitled to disagree "with Patent Owner's assessment of what the art teaches one of skill in the art" and instead credit Boehringer's responses. (*See, e.g.*, Appx163-164.) This is indisputably a factual issue reviewed for substantial evidence.[24]

[23] *See, e.g.*, *Checkpoint Sys., Inc. v. ITC*, 54 F.3d 756, 763 n.7 (Fed. Cir. 1995) ("Commonly used to describe the behavior of a person who kills his parents and pleads for the court's mercy on the ground of being an orphan.").

[24] Not only is AbbVie's claim of burden shifting unfounded, but it would not justify reversal even if true. In an *inter partes* review, the petitioner must prove "unpatentability by a preponderance of the evidence." 35 U.S.C. § 316(e). Thus, any alleged burden-shifting cannot be grounds for reversal absent a showing that the evidence was in equipoise and that the Board reached its conclusion by assigning the burden of persuasion to AbbVie. *See, e.g.*, *Gent v. CUNA Mut. Ins. Soc'y*, 611 F.3d 79, 83 (1st Cir. 2010) ("[W]here, as here, the burden of proof is the preponderance of the evidence standard, how the burden is allocated does not much matter unless one or both parties fail to produce evidence, or the evidence presented by the two sides is in 'perfect equipoise.'"). AbbVie has not even attempted to make this showing.

C. The Board's Analysis Accounted for the Claims as a Whole

The structure and substance of the Board's analysis further demonstrates that it considered the claims as a whole in finding them obvious. The Board began each opinion with a detailed discussion of the challenged claims, reproducing independent claim 1 in its entirety (Appx138-139), identifying various claim limitations from the dependent claims, including the 24-week limitation from claim 4 of the '135 patent (Appx139; *see also supra* at 18 & n.17), and addressing the parties' disputes regarding claim construction (Appx141-145). After expressly acknowledging that obviousness involves an analysis of the claims "***as a whole***" (Appx145), the Board made detailed findings that the prior art "discloses or suggests each and every element of the challenged claims," noting where AbbVie did not dispute these disclosures. (Appx149-152; Appx197-199; Appx227-228.) Specifically, the Board found, and AbbVie does not dispute, that "that van de Putte discloses all of the elements of all challenged claims 1–5, except for biweekly dosing," and that Kempeni and "Rau 2000 account[] for the differences between van de Putte 2000 and the recited biweekly dosing frequency required by all" of the '135 patent claims. (Appx149; Appx151; Appx197; Appx199.)

Because van de Putte disclosed all but a single limitation of the challenged claims, the Board's further finding that "a person of ordinary skill in the art would have been" motivated to modify van de Putte's "20 mg weekly dose to a 40 mg

biweekly dose based on the express teaching of Rau 2000" and Kempeni (Appx158; Appx205-206) necessarily considered the claims as a whole. *See, e.g.*, *Merck v. Teva*, 395 F.3d at 1375 (where, as here, a single prior art reference disclosed all but one claim limitation, obviousness requires only a "suggestion or motivation to modify the dosages from those in [that reference] to those in the claims"). The Board's analysis thus directly belies AbbVie's assertion that "the Board never put all the elements together." (Br. 4, 50.)

II. THE BOARD'S DECISIONS ARE SUPPORTED BY SUBSTANTIAL EVIDENCE

As explained below, "[b]ased on the full trial record" (Appx149), the Board found that van de Putte—the only Phase II D2E7 "[d]ose-finding" study in the prior art—disclosed all but one limitation of the '135 patent claims. (*See* Section II.B.1, *infra*.) The only limitation not expressly disclosed, biweekly dosing, was taught in another contemporaneous review article discussing the van de Putte study, among others. (*See* Section II.B.2, *infra*.) As the Board further found, a skilled artisan would have been motivated to modify the van de Putte weekly dosing regimen to a biweekly regimen based on the known benefits of less-frequent dosing and the express teachings of Rau 2000 and Kempeni. (*See* Section II.B.3, *infra*.) The Board then considered and rejected AbbVie's factual allegations that up-dosing (*see* Section II.C.1, *infra*) and a hypothetical C_{min} (*see* Section II.C.2, *infra*) would have dissuaded a skilled artisan from pursuing the

claimed dosing regimen, and that objective indicia supported a finding of nonobviousness (Section II.C.3, *infra*). Each of the Board's findings is, at a minimum, supported by substantial evidence.

A. AbbVie Has Waived Its Substantial Evidence Challenge by Failing to Present Argument under the Correct Legal Standard Applied to the Record as a Whole

By offering only a conclusory, single-paragraph argument (Br. 53-54) that the Board did not have substantial evidence to support its obviousness findings (set forth in roughly 30 pages in each of its decisions), AbbVie has waived that challenge. Federal Rule of Appellate Procedure 28(a)(8)(A) requires any such argument to contain "appellant's contentions and the reasons for them, with citations to the authorities and parts of the record on which the appellant relies." When, as here, a purported issue is not so briefed, it is waived. *See, e.g.*, *Cavallo v. Star Enter.*, 100 F.3d 1150, 1152 n.2 (4th Cir. 1996); *SmithKline Beecham Corp. v. Apotex Corp.*, 439 F.3d 1312, 1319-20 (Fed. Cir. 2006) (holding that an opening brief focused on legal arguments with "mere statements of disagreement with the district court as to the existence of factual disputes do not amount to a developed argument").

AbbVie merely argues again (incorrectly, relying on selective evidence) that the Board would have ruled in its favor had it not committed the alleged legal errors. That is a far cry from a substantial-evidence challenge, which demands

consideration of the entirety of the record evidence, acknowledges the Board's authority to disregard evidence it was not required to believe, and demonstrates that—with every inference drawn in favor of the Board's ruling—no reasonable mind could have reached the Board's conclusion based on the evidence ***adverse*** to AbbVie. (*Supra* at 26-27.) AbbVie does not even address the mountain of evidence that supports the Board's ruling, much less analyze that evidence under the proper legal standard. It is improper, and presumptuous, for AbbVie to ask this Court to wade through the roughly 9,500-page underlying record of the Boehringer IPR proceedings and apply the substantial-evidence standard without guidance because of AbbVie's incantation of the phrase "legal error."

Having failed to include ***any*** argument specific to its substantial-evidence challenge, AbbVie has waived that challenge, and cannot attempt to resurrect it on reply. In any event, AbbVie's challenge is meritless for the reasons explained below.

B. The Board's Obviousness Findings Are Supported by Substantial Evidence

1. Substantial Evidence Supports the Board's Finding That van de Putte Discloses Every Claim Limitation Except Biweekly Administration

The starting point of the Board's obviousness analysis—and a logical starting place for a skilled artisan treating RA in the 2000-2001 time period—is van de Putte's disclosure of the results of the then-state-of-the art, large-scale

D2E7 Phase II "[d]ose-finding" study, which built on earlier Phase I safety and efficacy studies. (Appx146-148; Appx28071; Appx29404-29406 (152:19-154:10); Appx192-196; Appx28069.) As explained above, AbbVie does not dispute, and the Board found, that van de Putte expressly teaches each limitation of claims 1-5 of the '135 patent except for biweekly administration. (Appx149-151; Appx197-199.) AbbVie also does not dispute, and the Board found, that van de Putte discloses that each dose—including 20 mg weekly—was "statistically significantly superior to placebo," "statistically equally efficacious," and, at a minimum, no "better or worse than" any other dose over a one-year treatment period. (Appx150; Appx164-165; Br. 9; Appx44810; Appx28069; Appx28071; Appx29407-29411 (155:11-159:8); Appx28018.)[25]

Moreover, as the Board found based on expert testimony, the clinical data reported in van de Putte, including a 39% ACR20 improvement at three months versus placebo in treating severe RA patients with a 20 mg weekly dose, demonstrate a high level of efficacy. (Appx150-151; Appx164-165; Appx28071; Appx28016-28017; Appx29408-29411 (156:14-159:8).) By way of comparison, the corresponding placebo-adjusted ACR20 improvements for Remicade®, the

[25] During prosecution, AbbVie sought patentability by arguing that "persons of ordinary skill would not have understood the 20 mg [subcutaneous] weekly dose of van de Putte to be sufficiently efficacious . . . ." (Appx27601; Appx27604.) AbbVie does not pursue that argument on appeal.

state-of-the-art anti-TNFα antibody for treating RA at the time, ranged from 30 to 38%, as found by the Board. (Appx150-151; Appx28016-28017; Appx28127; Appx28133.) In other words, the 20 mg weekly dose from van de Putte performed at least as well as, if not better than, the then-market-leading anti-TNFα product.[26]

On appeal, AbbVie has not disputed the Board's findings regarding the significant efficacy of each van de Putte dose, including 20 mg weekly, in treating severe forms of RA. Nor has AbbVie even addressed (and should therefore not be heard to address for the first time in reply) the numerous statements from third-party experts like the European Medicines Agency—as well as ***AbbVie itself***—that the claimed 40 mg biweekly dosing regimen would have been viewed as "equivalent" or "similar" to 20 mg weekly. (Appx28384; Appx28343; Appx28211; Appx28262; Appx28026-28027; Appx28581.)

2. Substantial Evidence Supports the Board's Finding That Rau 2000 and Kempeni Teach Biweekly Administration

The above facts are fatal to AbbVie's appeal in light of the express disclosure to pursue such biweekly dosing regimens in both Rau 2000 and

[26] The Board's recognition that 20 mg weekly D2E7 doses showed ACR responses that were at least comparable (and, indeed, numerically superior) to the then-recommended infliximab dosing regimen further refutes AbbVie's suggestion that the Board was focused on "achieving mediocrity." (Br. 34.) This is especially true because a skilled artisan would have known that Remicade® achieved not only ACR20 responses, but also ACR50 and ACR70 responses. (Appx150-151; Appx28016-28017; Appx28127; Appx28133; Appx30642.)

Kempeni, as the Board found. (Appx151-152; Appx165; Appx199; Appx206-207; Appx28089; Appx28080; Appx29573-29574 (84:19-85:4).) Indeed, Rau 2000 provides this teaching ***shortly after summarizing the van de Putte study***,[27] among others. Specifically, Rau 2000 concludes that "D2E7, with a half-life of 12 days, can be administered every two weeks as an intravenous injection over 3-5 minutes or subcutaneously" without limiting that conclusion to a particular minimum dose, as found by the Board and supported by expert testimony. (Appx151-152; Appx165; Appx28089; Appx29371 (119:7-13); Appx29422 (170:8-19).) Likewise, Kempeni concludes that D2E7—consistent with its "11.6 to 13.7[-]day[]" half-life—"was administered every two weeks until response could be rated as 'good,'" and that "[r]esponse rates of more than 80% have been achieved with a mean dosing interval of 2.5 weeks." (Appx28080; Appx29415-29418 (163:16-166:4); Appx29573-29574 (84:19-85:4); Appx199; Appx212-213.)

Persisting in a failed argument it made repeatedly before the Board (*see, e.g.*, Appx44727; Appx44809), AbbVie contends that Rau 2000 does not teach

[27] AbbVie notes that Rau 2000 does not expressly mention the 20 mg weekly dose (Br. 13), but a person of skill in the art would have known that the 20, 40, and 80 mg doses were continued through six and then 12 months, and the prior art still reported that "all doses of D2E7 were statistically significantly superior to placebo" and "statistically equally efficacious." (Appx28071; Appx28076; Appx29407-29412 (155:7-160:11).) In any event, again, AbbVie does not challenge on appeal the Board's findings regarding the significant efficacy shown by this dose in treating patients suffering from severe RA.

biweekly *subcutaneous* dosing (*e.g.*, Br. 15 (asserting that the subcutaneous dosing "[f]requency [is] not reported" in Rau 2000)). Not only is this argument contradicted by the above-quoted statement from Rau 2000, AbbVie's expert Dr. Vinks conceded at deposition that "a person of ordinary skill in the art[] would have known from the prior art that the [DE010] study discussed by Rau 2000 involved every other week subcutaneous dosing." (Appx29568-29569 (79:13-80:2); Appx28824 (cited in Appx28090).) The Board's findings that van de Putte and Rau 2000 or Kempeni disclose every claim limitation are thus supported by substantial evidence, and indeed cannot be legitimately disputed.

3. Substantial Evidence Supports the Board's Findings of Motivation to Combine and Reasonable Expectation of Success

Given the significant clinical efficacy shown in the state-of-the-art, Phase II van de Putte study, the Board had substantial evidence that a person of ordinary skill in the art would have been motivated to pursue fixed, subcutaneous dosing in view of its known advantages. Indeed, as AbbVie's experts admitted, such dosing was known to be "less expensive," "more convenient," and allows patients to "self-administer the dose in a short amount of time." (Appx156-157 (citing Appx44632-44633; Appx28020-28021; Appx31892); *see also* Appx28014-28015; Appx29319-29320 (67:19-68:8).) Subcutaneous dosing also "avoids complications that can occur with intravenous administration" and reduces "the potential for dosing

errors." (Appx28020-28021 (cited at App157); Appx244-245 (2:60-3:2).) AbbVie has not disputed on appeal that these benefits were known in the prior art. Nor can it in view of the admissions of its RA expert, Dr. Allan Gibofsky. (Appx29319-29321 (67:19-69:10).)

The evidence also demonstrated that a skilled artisan would have been further motivated to modify the van de Putte dosing regimens to every-other-week administration based upon both the known benefits of less-frequent dosing and the express teachings of Rau 2000 and Kempeni. Those benefits include increased "patient compliance" and preference, "a lower number of total injections" and "injection site reactions," as well as lower cost, as recognized by both parties' experts. (Appx28025-28026; Appx29318-29319 (66:18-67:18).)[28] AbbVie has not disputed any of these known benefits on appeal, which both sides' experts confirmed were known to a person of ordinary skill. (*Id.*) Moreover, as the Board found based on expert testimony, Rau 2000 and Kempeni provided express motivation to modify van de Putte 2000's safe and highly effective "20 mg weekly

[28] *See also Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance . . . ."); *Warner Chilcott Co., LLC v. Teva Pharm. USA, Inc.*, 594 F. App'x 630, 635 (Fed. Cir. 2014) (non-precedential) (explaining that, because "longer dosing intervals suit patient convenience and compliance, the prior art therefore provided express motivation to pursue a [longer] monthly dosing regimen").

dose to a 40 mg biweekly dose" by teaching the desirability of this very dosing interval. (Appx159; Appx207; Appx28089; Appx28080.)

Contrary to AbbVie's assertion that the Board lacked any basis to focus on the biweekly equivalent to van de Putte's 20 mg dose (Br. 26, 31), there was substantial evidence that this dose would have been desirable given the strong safety- and cost-related reasons for pursuing a ***low, effective dose***. (Appx28026.) The Board expressly noted this motivation in its opinion (Appx153 (agreeing that "'a person of ordinary skill would have been particularly attracted to'" converting "'the lowest weekly dose (*i.e.*, 20 mg) that had shown to be efficacious in the prior art'" to "'an every-other-week equivalent (*i.e.*, 40 mg)'"); *see also* Appx37 ("[W]e agree with Petitioner that the skilled artisan designing a dosing regimen through clinical trials would have balanced efficacy with other factors including safety . . . ."), which was confirmed by both sides' experts (Appx29340 (88:3-13); Appx28026).

This motivation is particularly strong here given the known risks of infection and weakened immune-system response associated with anti-TNFα agents generally, as well as the fact that higher doses inherently carry an additional risk of adverse events.[29] (Appx29340 (88:3-13); Appx29337-29340 (85:5-88:2);

[29] AbbVie noted this "[o]ver-dosing" safety concern below (Appx44698-44700), but not in its appeal brief.

Appx30246; Appx28079; Appx28086; Appx28820.) Tellingly, AbbVie's brief addresses neither the common-sense motivation to pursue a low effective dose, *see, e.g.*, *Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1371, 1376 (Fed. Cir. 2011) (affirming summary judgment of obviousness based on undisputed evidence that "physicians always seek to prescribe the lowest effective dose of any medication"), nor the added motivation to do so here in light of the known immunogenicity mechanism of this class of drugs.

Given the above prior art, substantial evidence also supports the Board's finding of a reasonable expectation of success in pursuing the claimed dosing regimen. As experts testified, Rau 2000's teaching of every-other-week subcutaneous administration and Kempeni's teaching of every-other-week administration, each well-correlated to D2E7's disclosed half-life and/or mean dosing interval, would have allowed a skilled artisan to reasonably conclude that van de Putte's 20 mg weekly subcutaneous dose could be administered efficaciously as 40 mg biweekly.[30] (Appx28089; Appx28080; Appx28021-28025 (cited at Appx159); Appx28039-28041 (cited at Appx159); Appx28024; Appx28028; Appx28041.) Indeed, as Dr. Vinks admitted, the developer of DE27 and named inventor Steven Fischkoff reported—in a prior art publication—"that

[30] This is further confirmed by statements from third-party experts and AbbVie itself that these dosing regimens would have been viewed as "equivalent." (*See supra* at 38.)

AbbVie had been able to show efficacy through clinical trials with both a once-weekly and an every-other-week dosing regimen," and that this "had been done with intravenous and subcutaneous dosing." (Appx29598-29605 (109:20-116:1); Appx30246-30247.)

In light of the substantial evidence that the prior art discloses every limitation of the challenged claims and a person of skill in the art would have been motivated to combine the prior art's teachings with a reasonable expectation of success, AbbVie cannot assail the Board's obviousness finding on appeal.

C. AbbVie's Substantive Challenges to the Board's Decisions Lack Merit

Because it cannot legitimately dispute the above facts, in the proceedings below, AbbVie asserted that certain prior art references supposedly "teach away" from the claims. (*See, e.g.*, Appx44799; Appx44802; Appx44809; Appx44814-44825; Appx44843-44844; Appx44846-44847.) Now that the Board has considered and rejected those arguments, AbbVie recasts its factual challenges on appeal as "legal error[]." (*E.g.*, Br. 27.) As explained above, there was no legal error, and this Court should reject AbbVie's request to reweigh the evidence and inferences drawn by the Board in reaching its conclusion. *Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1052 (Fed. Cir. 2016) (en banc) (explaining that the court's "job is ***not to review*** whether [a party]'s ***losing position*** was ***also supported***

by substantial evidence ***or to weigh the relative strength*** of [that party]'s evidence against [the prevailing party's] evidence").

AbbVie bears a "heavy burden" in showing that the Board lacked substantial evidence to find the disputed claims obvious. *T. Brown Constructors, Inc. v. Pena*, 132 F.3d 724, 727 (Fed. Cir. 1997). It must show that the evidence on which it relies—regarding alleged up-dosing efficacy concerns, minimum blood-serum levels, and Humira® sales—would compel any reasonable fact finder to reach a contrary finding after considering the record as a whole. *See SIBIA Neurosciences*, 225 F.3d at 1354. AbbVie cannot meet that standard.

1. AbbVie's "Up-Dosing" Argument Does Not Support a Finding of Nonobviousness

Contending that the Board incorrectly analyzed its "up-dosing" evidence, AbbVie asserts that a skilled artisan would have doubted whether "a 0.5 mg/kg every-other-week dose was a reliable guide to developing a new treatment regimen for RA." (Br. 40.) That argument misses the mark for numerous reasons, and the Board's findings concerning the teachings of Rau 2000 and Kempeni are supported by extensive record evidence, including expert testimony.

As an initial matter, the issue before the Board was not whether Rau 2000's and Kempeni's disclosure of a particular intravenous weight-based dose (*i.e.*, 0.5 mg/kg biweekly) from early, smaller Phase I safety studies (Appx29621-29622 (132:13-133:13)) alone taught the claimed dosing regimen. Rather, the Board

relied upon Rau 2000's and Kempeni's teaching of ***biweekly dosing*** in asserting that a person of skill in the art would have been motivated to modify van de Putte's lowest effective dose. (Appx151-159; Appx199-207.) Moreover, AbbVie's repeated assertions that weight-based, intravenous dosing is substantially different from fixed, subcutaneous dosing (Br. 26, 32) undermine its attempt to use earlier studies involving the former type of dosing regimen to attack the latter—which were already proven significantly effective in treating severe RA in the largest and most-state-of-the-art D2E7 clinical study, *i.e.*, van de Putte (Appx28071).

Again, AbbVie does not dispute that van de Putte showed robust efficacy for all doses, including the 20 mg weekly dose, and at most half-heartedly disputes that Rau 2000 (as well as Kempeni) teaches that biweekly equivalents of those doses should be pursued. Nor does it even address the numerous statements from third-party experts and AbbVie itself that the claimed 40 mg biweekly dosing regimen would have been viewed as "equivalent" to 20 mg weekly dosing. (*See supra* at 38.) These facts alone are sufficient to affirm the Board's decisions. Regardless, AbbVie's arguments are further contradicted by the undisputed record facts found by the Board, which established that: (i) the 0.5 mg/kg biweekly dose was reported as effective in numerous prior art references, including Rau 2000; and (ii) mere up-dosing alone does not evidence a lack of efficacy.

First, AbbVie's speculation that the 0.5 mg/kg dose was "either up-dosed or withdrawn" in the early DE001/003 study because it was (allegedly) an ineffective dose does not withstand scrutiny. (Br. 39-40.) Neither Rau 2000 nor Kempeni criticizes or disparages the effectiveness of 0.5 mg/kg biweekly dosing.[31] To the contrary, as Boehringer's RA expert, Dr. Weisman, testified, the Rau 2000 data demonstrate that 0.5 mg/kg was ***effective*** at treating RA through 12 weeks with substantial reductions in both DAS and erythrocyte sedimentation rate values. (Appx31347-31350 (91:5-94:18); Appx31319-31320 (63:13-64:17); Appx31386-90 (130:12-134:1); Appx28087-88 (Figs. 4-5); Appx29313 (61:7-15); Appx28825.)[32] The Board was entitled to credit Dr. Weisman's analysis (Appx167 (citing Appx31319-31320 (63:13-64:17)), which was consistent with Dr.

[31] AbbVie relies on Rau 2000's statement that doses greater than 1 mg/kg provided long-term efficacy (Br. 41), but ignores that this refers to "1½ year" data (Appx28085). The statement is therefore a positive report of efficacy at that time point, but is not expressly or impliedly reporting inefficacy for 0.5 mg/kg, whose efficacy data was reported through 12 weeks. *See, e.g.*, *Allergan, Inc. v. Apotex Inc.*, 754 F.3d 952, 963-64 (Fed. Cir. 2014) (explaining that "silence does not imply teaching away"). The Board considered and rejected AbbVie's reliance on this statement (Appx166-168), and AbbVie has not even attempted to explain on appeal why the Board's finding lacks substantial-evidence support.

[32] AbbVie quotes Dr. Weisman's testimony that the 0.5 mg/kg dose was discontinued after 12 weeks (Br. 33), but ignores his subsequent testimony relied upon by the Board that this dose was reported as effective in treating RA through 12 weeks (Appx167).

Gibofsky's deposition testimony, as the Board noted (*id.* (citing Appx29374-29377 (122:18-125:7))).

Indeed, as the Board found, "the prior art as a whole does not support a conclusion by one of skill in the art that the 0.5 mg/kg biweekly dose of D2E7 was ineffective." (Appx166 (citing Appx44917 (page 7 of Boehringer's Reply to AbbVie's Patent Owner Response)); Appx28057; Appx28080; Appx28820-28821; Appx30273.) This includes a 1998 press release issued by a D2E7 co-developer, which was summarized in the briefing page cited by the Board (Appx44917), identifying 0.5 mg/kg as the "minimum ***effective dose***" in "clinical trials with D2E7," including the DE001/003 study (Appx30248-30249). As Dr. Vinks conceded, "This news report says that dosing with .5 milligram[s] per kilogram [is] the minimum effective dose." (Appx29668-29669 (179:3-180:21).)

Putting this issue firmly to rest, the Board found (Appx166) that the Weisman 2000 publication expressly reported "sustained" efficacy for 0.5 mg/kg biweekly—and, indeed, ***even half that dose***—through 24 weeks (Appx28107) in connection with a "later" prior art D2E7 study. *See Warner Chilcott*, 594 F. App'x at 635 (non-precedential) (explaining that "any serious doubt about the efficacy of a monthly regimen . . . would have been put to rest" when the prior art showed efficacy over "a dose-free interval of up to 10 weeks").) This prior art efficacy showing, which even Dr. Gibofsky acknowledged (Appx29402-29404 (150:9-

152:7)), refutes AbbVie's misguided assertion that there was "a complete absence of information regarding the performance of [the 0.5 mg/kg] dose beyond 12 weeks" (Br. 28-29). At the very least, it provides further substantial evidence supporting the Board's reasonable expectation of success finding. *See, e.g.*, *Merck & Co. v. Biocraft Labs., Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) ("But, 'absolute predictability of success' is not the criterion; 'for obviousness under § 103, all that is required is a reasonable expectation of success.'").

Contrary to AbbVie's assertions (Br. 42), the Board appropriately relied on Weisman 2000, of which AbbVie had notice and an opportunity to respond,[33] as rebuttal evidence. *See, e.g.*, *Genzyme Therapeutic Prods. LP v. BioMarin Pharm. Inc.*, 825 F.3d 1360, 1366-67 (Fed. Cir. 2016) ("[T]he introduction of new evidence in the course of the trial is to be expected in *inter partes* review trial proceedings and, as long as the opposing party is given notice of the evidence and

[33] *EmeraChem Holdings, LLC v. Volkswagen Grp. of America, Inc.*, 859 F.3d 1341 (Fed. Cir. 2017), is inapposite. (Br. 42.) In that case, "neither the petition nor the Institution Decision put the patentee on notice that Stiles would be ***used to reject*** claims 3, 16, and 20." *Id.* at 1350. Here, by contrast, Weisman 2000 was not used to reject the claims, but rather to rebut AbbVie's teaching away arguments. In any event, AbbVie in fact ***discussed Weisman 2000 in its Preliminary Response below*** (Appx44704), yet its subsequent papers—including a new round of expert declarations—conspicuously ignored it, just like the D2E7 clinical trial summary in its appeal brief (Br. 8-15). Moreover, AbbVie questioned Boehringer's expert about this reference during his deposition (Appx31277-31278 (21:7-22:7)), never sought any additional briefing to address it, and discussed it during oral argument (*see, e.g.*, Appx45182-45183 (69:4-70:10)).

an opportunity to respond to it, the introduction of such evidence is perfectly permissible under the APA."); *Idemitsu*, 870 F.3d at 1381 (rejecting argument that Board could not consider evidence that "simply countered" patent owner's teaching away arguments). AbbVie raises a baseless procedural challenge to Weisman 2000 because it demonstrates the lack of credibility of AbbVie's "counterintuitive" (Appx166) argument that the 0.5 mg/kg dose would have somehow been viewed as not worth pursuing given that the ***prior art literature reported*** that AbbVie ***did just that***.[34]

[34] AbbVie refers to possible up-dosing in the Weisman 2000 study (Br. 43), but as explained below and the Board found (Appx167 (citing Appx30268)), any such up-dosing does not undermine the uncontested reported efficacy for the 0.5 mg/kg dose. In an argument raised for the first time on appeal, AbbVie criticizes the Board's "premise for relying on Weisman [2000]" (Br. 43 n.6), yet the prior art made clear that DE001/003 was the "first" study (Appx28086; Appx44806), the results of which were reported as early as Rau 1998 (Appx28057). Thus, Weisman 2000, by later testing the 0.5 mg/kg dose *and even half that dose*, would have dispelled any potential confusion as to whether 0.5 mg/kg was effective in the earliest D2E7 study. Finally, AbbVie does not cite any record evidence supporting its new contention (Br. 43) that the co-administration of methotrexate somehow makes Weisman 2000 irrelevant. In fact, the ***only*** non-prior art study cited in AbbVie's specification involves methotrexate co-administration. (*Supra* at 12 n.9; Appx258 (29:11-30:37); Appx29331 (79:4-10).) In any event, the claims at issue either do not preclude such co-administration (Appx29333-29334 (81:20-82:10)) or expressly require it (Appx305 (51:22-52:25)). AbbVie never contended otherwise below, despite raising other claim construction issues (*see, e.g.*, Appx43081-43085), and may not do so for the first time on appeal, *Kennametal*, 780 F.3d at 1385.

Second, even assuming any efficacy-related up-dosing occurred,[35] that still would not support nonobviousness. As the Board found (Appx167), supported by Dr. Vinks's testimony (Appx29692-29693 (203:18-204:14)), the prior art showed that even the FDA-recommended dosing regimen for the then-most successful RA biologic, Remicade® (infliximab), was up-dosed for certain patients (Appx30268). A skilled artisan would have therefore been well-aware that more than one dosing regimen may be used to treat RA and that, particularly in light of potential patient variability, up-dosing does not itself imply that the original dose is undesirable or even suboptimal. (Appx29346-29347 (94:19-95:5); Appx29686-29693 (197:13-204:9); Appx29336-29337 (84:21-85:4).) The Board's finding in this regard is consistent with this Court's case law. *E.g.*, *Par Pharm.*, 773 F.3d at 1197-98 (rejecting assertion "that there were better methods available to address the viscosity and interpatient variability concerns [because obviousness] 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") (emphasis in original).

AbbVie submitted below a version of the Remicade® label that lacked the reference to up-dosing (Apx44699; Appx30644), which Boehringer then pointed

[35] AbbVie complains about the Board's finding that up-dosing may have occurred even if patients exhibited a "moderate" response demonstrating efficacy (Br. 40), but does not explain why the Board's finding is not supported by substantial evidence. Ample record evidence supports this finding. (*See, e.g.*, Appx28080; Appx28085; Appx27107; Appx28006; Appx28008-28011; Appx30273; Appx167.)

out in its submissions (Appx44918) and the Board relied upon (Appx167). On appeal, AbbVie ***does not even address*** this prior art teaching, which makes short shrift of its "up-dosing" concerns. This is likely because, in addition to continuing to have no response (*see* Appx45193-45194),[36] this teaching only further exposes AbbVie's circular logic that the claimed dosing regimen is somehow inventive based on up-dosing in early prior art studies when that regimen ***is in fact up-dosed for certain patients*** (*supra* at 23).

2. The C_{min} Associated with Every-Other-Week Dosing Does Not Support a Finding of Nonobviousness

Equally unavailing is AbbVie's assertion that a hypothetical C_{min} for every-other-week dosing would have dissuaded a person of ordinary skill in the art from modifying the van de Putte 20 mg weekly regimen to 40 mg every other week. (Br. 44-46.) In rejecting this argument, the Board specifically credited Boehringer's evidence, including expert testimony, that "the 12-day half-life as described in Rau 2000 'would have suggested to a person or ordinary skill in the art that ***D2E7 concentrations would have remained high enough*** to achieve clinical results over two weeks.'" (App159 (citing Appx28089; Appx28021-28022); Appx151; Appx31407-11311 (151:20-155:2); *see also* Appx29607-29608 (118:7-119:1); Appx28040-28041; Appx28043-28046.) That conclusion is

[36] AbbVie may not address the Board's findings regarding this prior art document for the first time in reply. *Kennametal*, 780 F.3d at 1385.

bolstered by the Board's further finding that van de Putte's 20 mg dose demonstrated significant efficacy (Appx148; Appx150-151; Appx164-165)—*i.e.*, there would have been no basis to believe that this undisputed, high level of efficacy (*supra* at 36-38) would be lost when converted to its biweekly "equivalent" (*supra* at 38).[37] Both of these unchallenged findings amply support the Board's conclusion.[38]

The Board also weighed Dr. Vinks's testimony and PK modeling (*e.g.*, Br. 32), and Boehringer's criticisms thereof, and found that Dr. Vinks's conclusions "are not entitled to much weight" (Appx170). That finding is likewise supported by substantial record evidence considered by the Board. (Appx149.) For example, Dr. Jusko, Boehringer's PK expert, offered unrebutted testimony that the magnitude of hypothetical C_{min} differences focused on by AbbVie would have been considered "inconsequential." (Appx28043-28046; Appx29627 (138:5-17).) By contrast, Dr. Vinks admitted that, in his PK analysis, he was "not talking about effectiveness" and never "identif[ied] a specific threshold C_{min} for which efficacy in treating RA is necessary." (Appx29607-29608 (118:10-119:1); Appx29616

[37] AbbVie does not even attempt to demonstrate a lack of substantial evidence supporting the Board's finding that D2E7 had a "wide therapeutic window and a relatively long half-life." (Appx171.)

[38] Given these findings, AbbVie is wrong that the Board's analysis is predicated on following the path of the inventor. (Br. 46 n.8.) As is clear from the Board's decisions, its analysis was based upon the teachings of the prior art.

(127:11-16); Appx29619 (130:9-17).)[39] As the Board found, "the clinical data coupled with D2E7's half life is . . . enough of a predictor for a dosing interval." (Appx172; Appx28080; Appx28089.)

In any event, AbbVie's argument is premised on the assertion that the claimed dosing regimen would have been predicted to "yield a lower average C_{min} at steady state" than the prior art analyzed by the Board. (Br. 44.) In addition to being scientifically inaccurate,[40] AbbVie's assertion is decisively rebutted by Weisman 2000's conclusion that biweekly 0.25 mg/kg—*i.e.*, ***half the claimed dose***—was "safe and efficacious" for "24 weeks." (*See supra* at 48-50.)

Simply put, this is not a case where the Board required AbbVie to dispel all uncertainty; rather, the Board rejected AbbVie's hypothetical arguments based

[39] AbbVie's PK modeling is also suspect because the figures it chose to exemplify its analysis were based on parameters that correlate to a roughly 7.8-day half-life, which would have been known to be incorrect for D2E7 based on prior art PK data. (Appx29644 (155:10-16).)

[40] As Dr. Vinks testified when confronted with authoritative PK textbooks, subcutaneous dosing regimens were generally known to produce higher C_{min} values after multiple administrations as compared to intravenous regimens (*see* Appx29559-29564 (70:7-75:11); Appx30238; Appx31153-31155 (120:24-122:11); Appx44925-44926 n.11). And while making an oblique reference to "safety concerns" on appeal (Br. 44), AbbVie conspicuously failed to mention its previous "anti-drug antibodies" argument, which drove this issue below (*see, e.g.*, Appx44765-44766; Appx44832-44836). This is because AbbVie's own experts admitted such safety concerns could arise only when the C_{min} reaches baseline (Appx29159-29160 (53:15-54:10)), which would never occur even under AbbVie's own PK modeling (Appx29630-29631 (141:22-142:8); Appx45107).

upon errors in those arguments and record evidence (unaccounted for by AbbVie) of D2E7's clinical efficacy correlating with the available PK information. *See, e.g.*, *Hitachi Metals, Ltd. v. All. of Rare-Earth Permanent Magnet Indus.*, 699 F. App'x 929, 936 (Fed. Cir. 2017) (non-precedential), *reh'g denied* (Aug. 23, 2017) (finding no error where "[t]he Board reviewed the competing evidence and made a factual determination that a skilled artisan would not have been demotivated by the potential reduction in yield").

In light of these findings and record evidence, AbbVie's assertion that a complete PK/PD model was lacking (*compare* Br. 46 *with* Appx172; Appx28080; Appx28089) is irrelevant. *See, e.g.*, *Warner Chilcott,* 594 F. App'x at 636 (finding patent to monthly dosing obvious in the absence of a complete PK/PD model where prior art disclosed daily and weekly regimens and, separately, monthly dosing). AbbVie's position is particularly lacking in credibility given that neither the specification nor the challenged claims ***even mention any*** PK parameter, let alone purport to recite an invention based on a discovery of a PK-related correlation.[41] *See, e.g.*, *Merck v. Teva*, 395 F.3d at 1374 (rejecting an assertion of

[41] AbbVie's reliance on *In re Cyclobenzaprine Extended-Release Capsule Patent Litigation* is misplaced because the claims at issue there recited specific PK values and the Court noted that, because of "the lack of a known PK/PD relationship for ***any*** formulation of cyclobenzaprine," a person of skill in the art "could not predict whether ***any*** particular PK profile, including a bioequivalent one, would produce a therapeutically effective formulation." 676 F.3d 1063, 1070-71 (Fed. Cir. 2012).

nonobviousness where "the Lunar News articles may have invited skepticism based on concerns for dose-related GI problems," but "the claimed invention adds nothing beyond the teachings of those articles").

3. Humira®'s Sales Do Not Support a Finding of Nonobviousness

The Board correctly found that Boehringer "present[ed] sufficient evidence to rebut the presumption of nexus between the commercial success of HUMIRA® and the claimed dosing regimen." (Appx175.) In reaching this conclusion, the Board considered AbbVie's commercial success evidence (Appx173-174) and Boehringer's evidence showing that Humira®'s sales were "due to extraneous factors other than the patented invention" (Appx173-174; Appx44669-44670; Appx44935-44936). In doing so, the Board did not engage in burden-shifting, but instead made a factual determination based on the record as a whole.

Specifically, Boehringer presented substantial evidence, and the Board found, that Humira®'s sales lacked the required nexus because they were due to ***features in the prior art***—most prominently, properties of the D2E7 molecule itself—that AbbVie's experts failed to consider. (Appx28929 (14:3-6); Appx28931-28933 (16:24-18:2); Appx28964-65 (49:23-50:10); Appx28675; Appx174; Appx28985 (70:6-14).) But "if the feature that creates the commercial success was known in the prior art, the success is not pertinent." *Galderma Labs.,*

L.P. v. Tolmar, Inc., 737 F.3d 731, 740 (Fed. Cir. 2013). Tellingly, AbbVie does not address this evidence, or the Board's related findings, in its brief.

The Board also correctly found that "the D2E7 antibody was known and patented," and thus concluded that AbbVie's commercial success evidence was weak. (Appx174-175; Appx245 (3:28-38); Appx28675.) In this case, the record fully supported finding that the prior patent creating the exclusivity for Humira® itself, and the public disclosure thereof, further rebutted the assertion of nexus between the claimed success of Humira® and the '135 patent. (Appx28936-28937 (21:9-22:4); Appx28938-28941 (23:5-26:13); Appx33923; Appx33706; Appx33708-33709; *Galderma*, 737 F.3d at 740 ("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.'"); *Merck v. Teva*, 395 F.3d at 1376-77 (same).)[42]

AbbVie's reliance on *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724, 730-31 (Fed. Cir. 2017), and its assertion that the Board's "reliance on 'blocking patent' cases was misplaced" (Br. 49), does not alter the analysis. As an initial matter, *Merck* stands for the unremarkable proposition that commercial

[42] That the '382 patent did not issue until after certain of the prior art references at issue were published is a red herring, as the underlying disclosure was publicly available in 1997. (Appx30315 (citing Salfeld *et al.*, WO 97/29131).) Further, because AbbVie did not make this argument below, it is waived. *See, e.g.*, *Watts*, 354 F.3d at 1368.

success is a "fact-specific inquiry" in which "all the evidence" must be considered and weighed in an obviousness analysis, 874 F.3d at 731, as the Board did in these proceedings (Appx173-175). *Merck* does not purport to create the opposite rule, *i.e.*, that commercial success exists even if there is an earlier patent disclosing attributes relevant to the question of nexus to the patent-in-suit. *See, e.g.*, *Galderma*, 737 F.3d at 740; *Merck v. Teva*, 395 F.3d at 1376-77. And, in any event, the Court in *Merck* ultimately concluded that a finding of commercial success, and even a finding of nexus, did not justify finding the claims at issue nonobvious. 874 F.3d at 730-31. Here, no nexus was found.

III. THE BOARD CORRECTLY EVALUATED GROUND 2 IN THE 409 PROCEEDINGS

In IPR2016-00409, the Board also found the '135 patent claims obvious over the combination of Rau 1998, Schattenkirchner, and van de Putte 1999. AbbVie's only argument on appeal specific to this combination is that, at one place in its decision, the Board recited the standard for institution of an *inter partes* proceeding. (Br. 54; Appx228.) But this Court "review judgments . . . not statements in memoranda," and a single typographical error or misstatement does not warrant reversal. *Medtronic, Inc. v. Cardiac Pacemakers, Inc.*, 721 F.2d 1563, 1567 (Fed. Cir. 1983).

Here, the Board addressed the disclosures of these references and the parties' arguments, and concluded that this combination rendered the '135 patent

unpatentable as obvious, correctly applying the proper legal standards—which are recited throughout the Board's opinion—and incorporating its analysis of the van de Putte 1999 and Kempeni combination. (Appx226-228.) For example, the Board correctly stated that Boehringer "demonstrate[d]" or "establishe[d,] by a preponderance of evidence, that claims 1–5 [of the '135 patent] are unpatentable" in both its introduction and conclusion. (Appx182; Appx229; *see also* Appx186; Appx191-192.)

Rau 1998 disclosed administering 0.5 mg/kg intravenous biweekly D2E7 doses (Appx28057), which the Board found—and AbbVie concedes—is equivalent to 40 mg biweekly doses. (*See* Appx160 n.7; *see also* Appx14; Appx60.) The Board also found that subcutaneous administration was comparable to intravenous administration (*supra* at 9, 15), and AbbVie does not dispute that there would have been a motivation to pursue the latter route of administration (*supra* at 40-41). In light of the Board's uncontested finding that the weekly equivalent to the Rau 1998 dose (*i.e.*, 20 mg) had a high level of efficacy that compared favorably to the then-gold standard infliximab (*supra* at 37-38), one of ordinary skill would have also had a reasonable expectation of success in pursuing the claimed dosing regimen.

For the reasons set forth above, the Board's analysis is supported by substantial evidence, and its decision regarding this ground should be affirmed. *In re Depomed, Inc.*, 680 F. App'x 947, 953 (Fed. Cir. 2017) (non-precedential)

(affirming obviousness "despite the Board's misstatement of the law" because "substantial evidence support[ed] its" analysis).

IV. THIS COURT HAS ALREADY DETERMINED THAT *INTER PARTES* REVIEW PROCEEDINGS ARE CONSTITUTIONAL

AbbVie acknowledges that its constitutionality argument is foreclosed by this Court's decision in *MCM Portfolio LLC v. Hewlett-Packard Co.*, 812 F.3d 1284, 1291 (Fed. Cir. 2015), yet raises the issue (without accompanying argument) in an attempt to preserve the issue in light of *Oil States Energy Services LLC v. Greene's Energy Group, LLC*, No. 16-712 (U.S.) (pending). Unless reversed by the Supreme Court, *MCM Portfolio* controls.

CONCLUSION AND STATEMENT OF RELIEF SOUGHT

For the above reasons, this Court should affirm the Board's decisions.

Dated: March 23, 2018

Respectfully submitted,

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United States Court of Appeals for the Federal Circuit

AbbVie Biotechnology, Ltd. v. Coherus BioSciences Inc.,
Nos. 2017-2304, -2305, -2306 and 2017-2362, -2363

CERTIFICATE OF SERVICE

I, Eric W. Dittmann, being duly sworn according to law and being over the age of 18, upon my oath depose and say that:

On **March 23, 2018,** I caused the foregoing **Brief for Appellees Boehringer Ingelheim International GmbH and Boehringer Ingelheim Pharmaceuticals, Inc.** to be filed with the Clerk of Court using the CM/ECF System, which will serve via e-mail notice of such filing to all counsel registered as CM/ECF users, including the following principal counsel for the other parties:

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Upon acceptance by the Court of the e-filed document, six paper copies will be filed with the Court within the time provided in the Court's rules.

March 23, 2018

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CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS, AND TYPE STYLE REQUIREMENTS

1. This brief complies with the type-volume limitation of Federal Circuit Rule 32(a). The brief contains 13,660 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(f).

2. This brief complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6). The brief has been prepared in a proportionally spaced typeface using MS Word 2013 in a 14 point Times New Roman font.

Dated: March 23, 2018

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