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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

Petitioner,

v.

ABBVIE BIOTECHNOLOGY LTD.,

Patent Owner.

Case No. IPR2016-00409
U.S. Patent No. 8,889,135

PETITIONER'S REPLY TO PATENT OWNER'S RESPONSE

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I. Introduction

It is undisputed that the prior art references forming the basis of the two grounds adopted by the Board, all of which include as an author one of the inventors of the U.S. Patent No. 8,889,135 ("the '135 patent"), disclose or suggest each element of the claims at issue. For instance, with respect to the first ground, van de Putte 1999 discloses or suggests every claim element except every-other-week (*i.e.,* biweekly) administration, and Kempeni 1999, reviewing the prior art, expressly teaches just that. The cross-examination testimony of Patent Owner AbbVie's five experts only further confirms that, at the time of the alleged invention, a person of skill in the art ("POSA") would have been motivated to combine the teachings of van de Putte 1999 and Kempeni 1999 to arrive at the claimed dosing regimen with a reasonable expectation of success. Similarly, a POSA would have been motivated to combine the teachings of Rau 1998, Schattenkirchner 1998, and van de Putte 1999, which form the basis of the second ground, with a reasonable expectation of success. At a minimum, the claimed dosing regimen was one of a discrete number of promising approaches that would have been obvious to try.

In response, AbbVie largely does not dispute van de Putte 1999's efficacy-related teachings, and only half-heartedly contests Kempeni 1999's teaching to pursue biweekly dosing. Shifting from its prior public touting of 20mg weekly

and 0.5mg/kg biweekly doses, AbbVie now attempts to misdirect the Board from the instituted grounds through speculative, *post hoc* teaching away arguments. But these arguments fall well short of the mark. *First*, AbbVie's "up-dosing" argument (1) is rebutted by numerous prior art disclosures, including the state-of-the-art disclosures set forth in Petitioner's obviousness grounds, and (2) overlooks that neither obviousness nor the claims require the single most effective dose. *Second*, AbbVie's newly created, hypothetical pharmacokinetic ("PK") modeling does not support efficacy- or anti-drug antibody ("ADA")-related concerns pointing away from what the art actually taught. Because none of AbbVie's arguments shows that the prior art criticizes, discredits, or otherwise discourages investigation of the claimed dosing regimen, it cannot prove teaching away.[1] AbbVie's arguments addressing the second ground are essentially the same and should be rejected for similar reasons.

[1] Petitioner raised in IPR2016-00408, also involving the '135 patent, another invalidity ground. Although that ground presents an independent basis for invalidity, AbbVie's responses are nearly identical to those it provides here. Accordingly, Petitioner's reply arguments are similar to those it presents in IPR2016-00408. Further, while AbbVie asserts that Petitioner's arguments "should be rejected for the same reasons" outlined in its response to Coherus

Nor can AbbVie's three alleged secondary considerations — none of which are applicable to or commensurate with the scope of the claims — rebut Petitioner's strong obviousness showing. Accordingly, Petitioner respectfully submits that the Board should find the '135 patent claims obvious.

II. AbbVie Failed to Rebut the Petition's Key Arguments and Evidence

The starting point of Petitioner's first obviousness ground is van de Putte 1999's disclosure of the results of a large-scale Phase II efficacy and safety trial that built on earlier Phase I safety studies. (Ex. 1008, 7; Ex. 1037, 152:19-153:7.) AbbVie does not dispute that van de Putte 1999 discloses or suggests each limitation of claims 1-5 (long-term subcutaneous administration of fixed doses of D2E7) except for biweekly administration. (Response, 19-52.) AbbVie also admits that van de Putte 1999 discloses that each dose — including 20mg weekly — was statistically superior to placebo and "was not powered to provide

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(Response, 2), the record of this Petition includes additional prior art, expert testimony, and arguments, and thus should be considered independently, as the Board has recognized. (Decision, 8.)

statistically meaningful comparisons between doses." (Response, 11; Ex. 1037, 155:11-159:8.)[2]

Kempeni 1999 summarizes numerous Phase I and II studies concerning D2E7 and expressly teaches biweekly dosing, concluding 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." (Ex. 1011 at 4; Ex. 1038, 84:19-85:4.) Indeed, AbbVie's PK expert admitted that D2E7's then-developer[3] noted in June 2000 that it was "able to show

[2] At the same time, AbbVie ignores that, after these 20/40/80mg doses were continued through 6 and then 12 months, the prior art still reported that "all doses of D2E7 were statistically significantly superior to placebo." (Ex. 2086, 2; Ex. 2090, 5; Ex. 1037, 155:11-160:11.) Moreover, although AbbVie seeks to minimize van de Putte 1999 as an abstract (Response, 6), its rheumatoid arthritis ("RA") expert confirmed that it would have been peer-reviewed by four to twelve reviewers (Ex. 1037, 112:9-13).

[3] Various entities, including Knoll/BASF Pharma and Cambridge Antibody Technology plc ("CAT"), worked on the development of D2E7 before AbbVie purchased it.

efficacy through clinical trials with both a once weekly and an ***every other week*** dosing regimen" with "intravenous and ***subcutaneous*** dosing." (Ex. 1038, 112:18-113:8, 115:12-116:1 (emphasis added); Ex. 1052.)[4]

Given the advantages of less frequent subcutaneous dosing, which AbbVie's experts conceded were known in the prior art, a POSA would have been motivated to modify van de Putte 1999's safe and effective 20mg weekly dose to biweekly, as expressly taught by Kempeni 1999, with a reasonable expectation of success. (Ex. 1037, 67:1-68:8; Decision, 16 n.8.)

III. The Prior Art Does Not Teach Away

A. The Clinical Data Do Not Teach Away

1. Kempeni 1999's Clinical Data Do Not Teach Away

To argue that the clinical data in Kempeni 1999 teach away, AbbVie speculates that the 0.5mg/kg biweekly dose from the early DE001/003 Phase I study discussed in Kempeni 1999 "did not work" because of the option for up-dosing and because no data for 0.5mg/kg is reported after week 12 (at which time the dose, as explained below, ***was in fact effective***). (Response, 10-11, 25-28.) That argument does not withstand scrutiny, and AbbVie's experts were unwilling to take that position on cross-examination. (Ex. 1037, 197:21-198:6; Ex. 1038, 171:9-174:17.)

[4] Unless otherwise noted, all internal citations and modifications are omitted.

Kempeni 1999 does not show that 0.5mg/kg biweekly doses were ineffective. As a preliminary matter, Kempeni 1999 does not criticize or disparage the effectiveness of 0.5mg/kg biweekly doses. (Ex. 1011; *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013).) Rather, it concludes that the biweekly treatment of D2E7 "in the dose range from 0.5 to 10 mg/kg was well tolerated," without disclosing a minimum effective dose. (Ex. 1011, 4; Ex. 1037, 170:8-19.)[5] This is consistent with the data in Rau 2000, which characterizes the DE001/003 trial (and other D2E7 studies) and is cited in AbbVie's Response (Response, 24-31, Ex. 2158). Rau 2000 shows that 0.5mg/kg was effective at treating RA through 12 weeks, with substantial reductions in both DAS and ESR values. (Ex. 2040, 6-7, Figs. 4-5; Ex. 2070, 61:20-64:17; Ex. 1037, 61:9-15; 122:18-125:7; Ex. 1032; Response, 25.) Moreover, these conclusions are supported by the prior art as a whole, which likewise do not state that 0.5mg/kg biweekly was ineffective. (Ex. 1006, 5; Ex.

[5] AbbVie relies on Rau 2000's statement that doses greater than 1mg/kg provided long-term efficacy (Response, 26), but ignores that this refers to 1½-year data (Ex. 2040, 4.) The statement is therefore a positive report of efficacy at that time point, but is not expressly or impliedly reporting inefficacy for 0.5mg/kg, whose efficacy data was reported through 12 weeks.

1029, 3; Ex. 1056.) In fact, a D2E7 co-developer identified this dose in the prior art as the minimum "***effective dose***" after "***six months*** chronic administration." (Ex. 1054; Ex. 1038, 179:3-180:21.) And a later prior art study expressly confirmed that 0.5mg/kg biweekly — and, indeed, ***even half that dose*** — was effective. (Ex. 1014, 5.)[6]

In the face of the clear data from DE001/003, AbbVie speculates that the 0.5mg/kg arm included up-dosed patients. (Response, 26.) Yet AbbVie does not cite any evidence to support this conclusion, and unsupported speculation cannot constitute teaching away. *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1364 (Fed. Cir. 2006) ("We will not read into a reference a teaching away . . . where no such language exists."). Such a conclusion is in any event contradicted by the teachings of Kempeni 1999 (and Rau 2000), which are confirmed by the prior art disclosures summarized above.

Nor would up-dosing, even assuming it occurred, support the conclusion that 0.5mg/kg was ineffective. *First*, the prior art showed that even the FDA-approved dosing regimen for the then-most successful RA biologic, Remicade,

[6] AbbVie discussed this study in its Preliminary Response (at 13), yet its Response — accompanied by a new round of expert declarations — conspicuously ignored it.

was up-dosed for certain patients. (Ex. 1055, 29; Ex. 1038, 197:1-204:14.) Thus, a POSA would have been aware that more than one dosing regimen may be used to treat RA, and that the option of up-dosing does not itself imply that the original dose has no efficacy. (Ex. 1037, 94:19-95:5; Ex. 1038, 203:18-204:9.) *Second*, the reference does not state that all patients were up-dosed. (Exs.1011-12; Ex. 2070, 84:17-21, 86:10-18.) *Third*, AbbVie contends that 1.0mg/kg was also up-dosed (Preliminary Response at 11), yet that dose was reported to be effective after 1½ years of administration. (Ex. 2040, 4, 6-7 & Figs. 4-5.) *Fourth*, such a conclusion is also contradicted by the DE001/003 protocol, which indicates that up-dosing occurred only if a patient failed to exhibit a "good" response, although such patients may have exhibited a "moderate" response demonstrating efficacy. (Ex. 1011, 4; Ex. 2040, 4; Ex. 1002, 813; Ex. 1003, ¶¶20, 24, 26; Ex. 1056.) Moreover, as discussed above (*supra*, 7) and below (*infra*, n.12), 0.5 mg/kg and even lower doses continued to be used, and were shown to have efficacy, after this early study. Thus, at a minimum, a POSA would not have concluded, as AbbVie asserts (at 26-27), that up-dosing or any termination of the 0.5mg/kg dose means ***lack of efficacy*** such that the prior art teaches away.

AbbVie's entire teaching away argument with respect to Kempeni 1999 is based on an incorrect understanding of the Petition as well as the Board's

Institution Decision. The Petition relied on Kempeni 1999's teaching of ***biweekly dosing***, not its disclosure of a particular intravenous, weight-based dose (0.5mg/kg biweekly)[7] from early, smaller Phase I safety studies (Ex. 1038, 132:13-133:13), in asserting that a POSA would have been motivated to modify the van de Putte 20mg weekly subcutaneous dose (Petition, 19-40).

2. Van de Putte 1999's Clinical Data Do Not Teach Away

In arguing that van de Putte 1999 discloses that a 20mg weekly dose was "sub-optimal," AbbVie merely rehashes erroneous arguments that have already been considered and rejected. (Response, 32-33; Preliminary Response, 22-25, Decision, 16 n.8.) As noted in Section II above, van de Putte 1999 expressly teaches that "all doses of D2E7 [20, 40, and 80mg] were statistically significantly superior to placebo . . . [and] were nearly equally efficacious," and

[7] AbbVie's teaching away assertion is not credible considering that, in obtaining the '135 patent, it argued to the Patent Office that a skilled artisan would have "***gleaned nothing*** about the efficacy of a flat" dose from a "weight-based dosing schedule." (Ex. 1002, 1702 (emphasis in original).) In other words, AbbVie told the Patent Office one thing to obtain its patent, and now states the opposite in attempting to defend its grant.

AbbVie's RA expert conceded this, as he had to. (Ex. 2089, 2; Ex. 1037, 157:4-158:18; Petition, 22-25.)[8]

And even if 20mg/weekly had marginally lower efficacy data, that still does not meet the legal standard for "teaching away." *See Galderma*, 737 F.3d at 739 ("A teaching that a composition may be optimal or standard does not criticize, discredit, or otherwise discourage investigation into other compositions."). This is particularly true given that the claims do not require the single most effective dose, and that there would be therapeutically desirable reasons to treat RA patients with lower effective doses. (Decision, 6-7; Ex. 1037, 44:16-45:4, 93:20-94:17, 95:11-96:7.) Indeed, it was known that even efficacious FDA-approved dosage regimens for RA may involve up-dosing. (*Supra*, 8.) And finally, obviousness does not require the single most desirable combination, especially where, as here, there is a motivation toward the ***lower*** effective dose. *See In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) ("Our case law does not require that a particular combination must be the preferred, or

[8] Indeed, even AbbVie's cited non-prior art publication stated that study DE007 "was neither designed nor powered to show statistical differences between the adalimumab groups" and that "all adalimumab groups had consistently better ACR responses and improvements in ACR core criteria from baseline." (Ex. 2041, 9.)

the most desirable, combination described in the prior art in order to provide motivation for the current invention.").

B. The Pharmacokinetic Data Do Not Teach Away

1. AbbVie's PK Modeling of Hypothetical C_{min} Values and "Fluctuations" with Biweekly Dosing Is Irrelevant

Contrary to AbbVie's assertions (which are not even supported by the declaration paragraphs it cites, Ex. 1038, 117:6- 119:21), the PK data do not suggest "that a 40 mg every-other-week dose would have delivered too low a dose of D2E7 to be safe and effective." (Response, 34-41.) AbbVie's argument is based on the unremarkable assertion that biweekly 40mg doses may have somewhat lower steady-state C_{min} values than its corresponding 20mg weekly dose.[9] (*Id*.) As its PK expert admitted, however, he never "identif[ied] a specific threshold C_{min} for which efficacy in treating RA is necessary." (Ex. 1038, 127:11-16; *see also* Ex. 1002, 1220 n.2 (AbbVie prosecution declarant

[9] AbbVie's PK modeling is 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. (Ex. 1038, 155:10-16.) Moreover, Dr. Jusko's testimony that the magnitude of C_{min} differences focused on by AbbVie would be considered "inconsequential" stands unrebutted. (Ex. 1004, ¶23.)

explaining that the minimum effective dose for assessing potential overdosing and underdosing "was undefined in June 2001").) This is consistent with AbbVie's Response. (Response, 40 ("This ***could be*** the difference between a drug working and a drug not working").) Thus, AbbVie's PK modeling exercise can be dismissed as lacking context.

AbbVie also focuses on alleged "greater fluctuations" in concentration levels. (Response, 39.) But the literature relied upon for this argument makes clear that this concern applies to "drug[s] that ha[ve] a narrow therapeutic range." (Ex. 2075, ¶148.) AbbVie's PK expert admitted he never suggests that D2E7 has such a narrow range. (Ex. 1038, 128:22-129:7.) Nor could he based on the efficacy shown for various doses in the prior art. (Exs.1006-1007, 1011-1014, 2039-40.) Accordingly, a POSA would not have concluded that AbbVie's PK modeling taught away.[10]

[10] AbbVie asserts that the Petition and accompanying declarations "fail[] to address steady-state concentrations." (Response, 36.) But even a cursory review of these papers reveals that this argument lacks merit. (Ex. 1004, 10, 14-15 (referring to "steady state" data); Ex 1003, 30 (referring to steady state D2E7 concentrations "*over time*").) AbbVie later acknowledges this when referring to Dr. Jusko's "steady-state C_{min}" analysis. (Response, 37.)

2. Hypothetical Concerns about Potential ADAs Do Not Teach Away

Equally unavailing is AbbVie's assertion that the C_{min} values associated with biweekly dosing ***could*** lead to ADAs, which would in turn allegedly dissuade a POSA from pursuing the claimed dosing regimen. (Response, 41-45.) As an initial matter, AbbVie's discussion of ADAs is not directed to D2E7, but instead relies on equivocal reports of ADAs associated with ***other*** proteins that are ***not*** fully human. (*See* Response, 41-45; Ex. 1037, 48:16-52:7; Ex. 1036, 18:6-20:6, 59:11-61:6; Ex. 2024 (discussing, *e.g.*, Remicade, Enbrel, and lenercept).) Because D2E7, unlike these other treatments, is a "fully human antibody against TNFα" with "no non-human or artificial sequences," a POSA would have expected it to be "less immunogenic" and less likely to cause ADAs. (Ex. 2040, 5; Ex. 1029, 3; Ex. 1011, 3 & Tbl.1; Ex. 1036, 33:7-22; Ex. 1037, 166:20-167:7; Ex. 1002, 1309.)

Indeed, AbbVie's ADA expert[11] admitted that ***no*** prior art reported the development of D2E7 ADAs or any lack of efficacy or side effects resulting

[11] AbbVie's PK expert, Dr. Vinks, spent much of his 99-page declaration discussing ADAs, but acknowledged that he has never participated in an ADA study, has no publications focused on ADAs, has never consulted regarding ADAs, and is not an ADA expert. (Ex. 1038, 24:13-25:15.) Similarly, Dr. Vinks opines

therefrom, irrespective of dosing regimen. (Response, 44; Ex. 1036, 36:14-37:9, 43:16-44:7, 53:9-14, 86:8-87:20, 115:14-116:2; Ex. 1037, 114:18-115:1.) Rather, the prior art positively reported the safety and efficacy of D2E7. (Ex. 2040, 8; Ex. 2089, 2.[12]) In any event, AbbVie's ADA expert explained that the possibility of ADAs developing at the "low" C_{min} values discussed by AbbVie refers to situations where the plasma concentration drops to "unmeasurable or

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on RA clinical data, yet conceded that he is not an expert in treating RA and never interpreted ACR_{20} data or RA-related up-dosing data before these proceedings. (*Id.* at 14:6-9, 126:10-14, 160:17-20; *see also id.*, 29:5-8.)

[12] AbbVie asserts that ADA risk increases "as serum concentrations of the biologic decrease" and that drugs "administered subcutaneously often display greater immunogenicity" (Response, 42), yet AbbVie's ADA expert confirmed that no prior art publications applied these points to D2E7 (Ex. 1036, 72:9-13, 76:10-14). In fact, 0.25 mg/kg IV biweekly D2E7 (*i.e.*, roughly ***half*** the claimed dosing regimen) was known to be "well tolerated, safe and efficacious." (Ex. 1014 at 5.) That C_{min} values would have been generally expected to be comparatively higher, and "concentration fluctuations" lower, for subcutaneous versus intravenous dosing only further undermines AbbVie's argument. (Ex. 1038, 71:3-73:20; Ex. 1051, 69; Ex. 2069, 120:24-122:11; Ex. 1033.)

close to measurable" levels between doses (Ex. 1036, 53:15-54:17, 61:7-11), which its PK expert confirmed does ***not*** occur even in AbbVie's PK model (Ex. 1038, 141:22-142:15; Ex. 2075, ¶140, Fig.7a).

Finally and most importantly, even if ADAs were a theoretical possibility, that would not have dissuaded a POSA from biweekly versions of the van de Putte 1999 dosing regimens. (Ex. 1036, 40:9-14, 41:17-42:9, 43:11-15.) As AbbVie's experts acknowledged, no drug is completely safe in every patient, and clinicians focused on the safety and efficacy of treatment regardless of the development of ADAs (particularly given that they do not necessarily abolish efficacy or cause adverse events). (Ex. 1036, 37:15-38:4, 80:14-17; 85:18-86:7; Ex. 1037, 100:16-102:6.) Indeed, ADAs were associated with Remicade and Enbrel, yet both drugs were approved and went onto great success, as AbbVie acknowledges. (Response, 41-45; Ex. 1002, 1284; Ex. 2071, ¶¶ 32-33; Ex. 1036, 46:8-20, 49:5-51:14; Ex. 1037, 97:2-13.)[13] Accordingly, the asserted theoretical potential for ADAs is not a teaching away. *Galderma*, 737 F.3d at 738-39 (no

[13] Given the reported concerns about infections associated with higher doses of anti-TNFα treatments and patient compliance associated with IV administration, this further supports a motivation toward a lower effective subcutaneous dose. (*See* Ex. 1037, 88:6-13; Ex. 1002, 805.)

teaching away even where prior art reported "increased side effects" with higher dose, yet "failed to discourage" its use).

3. D2E7's Half-Life and Linear Pharmacokinetics Further Support Biweekly Dosing

AbbVie makes the straw-man argument that "[h]alf-life does not provide sufficient information to design a dosing regimen." (Response, 45-48.) As an initial matter, even AbbVie and its experts have acknowledged that half-life is a "meaningful parameter" in developing a dosing regimen. (Ex. 1002, 1324; Ex. 1038, 88:6-90:17.) More importantly, the prior art did not simply disclose D2E7's half-life divorced from all other information, but correlated that PK parameter with ***clinical data*** supporting the safety and efficacy of biweekly dosing. (Ex. 1011, 4; Ex. 2040, 8.) For example, Kempeni 1999 reports D2E7's half-life as 11.6 to 13.7 days, and explains that patients began to lose response after 2.5 weeks.[14] (Ex. 1011, 4; Ex. 1052, 1-2 (explaining that "the half-life [of D2E7] could be extended, which may mean it is possible to administer the drug

[14] AbbVie's reliance (at 49-50) on an April 9, 2010 study report involving 80mg administered every four weeks — which discusses a "noncomplian[t]" investigator whose data was excluded (Ex. 2015, 4) — is misplaced given the prior art teachings regarding this mean dosing interval.

on a less frequent basis," and that this hypothesis was confirmed through clinical studies).)

That other PK parameters can also be considered (Response, 45-48) is therefore irrelevant to whether a POSA would have pursued the claimed dosing regimen based on prior art expressing a clear relationship between D2E7's half-life and dosing frequency. Likewise, irrespective of whether ***other, different*** "antibodies were dosed both more and less frequently than their half-lives" (Response, 48), or certain drugs were assertedly ineffective when dose and interval are doubled (Response, 49-50), a POSA would not be taught away from the D2E7-specific teachings supporting a reasonable expectation of success with regard to the claimed D2E7 dosing regimen (Ex. 1038, 144:15-146:9; Ex. 1011, 4; Ex. 2040, 8).[15]

IV. AbbVie Admitted That 40mg Biweekly Is Equivalent to 20mg Weekly

AbbVie's *post hoc* explanations of its prior statements confirming the equivalence of 20mg weekly and 40mg biweekly doses are unpersuasive. In

[15] None of the cases AbbVie cites (at 46-47) supports a general rule requiring "complete PK/PD data," especially where, as here, the prior art disclosed multiple, clinically effective doses and associated that efficacy with pertinent PK parameters.

addressing its concession that, "[o]ver time, patients treated . . . with [a] 40 mg flat dose, subcutaneously biweekly, receive the same amount of D2E7 as those treated . . . with [a] 20 mg flat dose weekly" (Ex. 1023, 45), AbbVie cites its own statements that the PK profiles of these dosing schedules would have been different. (Response, 51-52.) As explained above, a POSA would not have found such differences meaningful for safety and efficacy.

Likewise, while AbbVie tries to limit its statement to the FDA that every-other-week doses are assumed to be similar to one-half the same dose given weekly to a "post-hoc" comparison of "infection rates," no such qualification is found in the cited documents. (Ex. 1016, 2; Ex. 1017, 109; Response, 52.) This is not surprising, for AbbVie cannot credibly contend that the stated equivalence is relevant for certain clinical considerations, but not others. Tellingly, AbbVie's Response does not even address the statement of the European Medicines Agency, the FDA's European counterpart, in the context of dose-response studies that "40 mg every other week" is "equivalent to 20 mg weekly." (Ex. 1018, 14; Petition, 28-29.) Accordingly, consistent with the teachings of the prior art, these statements and admissions confirm the therapeutic equivalence of 20mg weekly and 40mg biweekly.

V. AbbVie Fails to Overcome Arguments That the Claims Would Have Been Obvious to Try and the Result of Routine Optimization

In addition to repeating its teaching away arguments that are flawed for the reasons discussed above, AbbVie asserts that a POSA would have faced "a large range of different dosing regimens." (Response, 54.) The Board, however, has already considered and rejected that argument. (Decision, 15 n.7.) Moreover, in seeking to inflate the number of dosing options, AbbVie disregards the prior art's (1) progression from Phase I, weight-based-dosing safety studies to a large-scale, efficacy-based Phase II dose-finding study demonstrating a preference for a finite number of subcutaneous fixed doses and (2) disclosure that the early clinical trials supported one of two dosing intervals (Ex. 1052). Thus, AbbVie's assertions that drug development generally may involve many choices, if anything, only emphasize that in this case a POSA would have been motivated by the prior art's specific teachings.

Further, even if more than one dosing regimen is theoretically available, that does not mean that a dosing regimen suggested by the prior art is nonobvious. *See Hoffmann-La Roche v. Apotex*, 748 F.3d 1326, 1329-34 (Fed. Cir. 2014) (affirming invalidity of a claimed dosing regimen of 150mg monthly

over a prior art dose of 5mg daily).[16] This is particularly true given that the '135 patent is not purporting to claim the single most effective dosing regimen. (Decision, 6-7.)

Finally, the fact that drugs under development may not gain FDA approval under strict regulatory standards does not mean that the claimed dosing regimen is not the result of routine optimization. (Response, 7, 56.) In the same way that regulatory approval is not a requirement of patentability, an obvious combination need not carry absolute certainty of regulatory approval. *Compare 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."), *with* Ex. 1035, 35:2-16, 38:15-40:11 (applying wrong standard). Moreover, while AbbVie asserts that "[p]oor dose selection was ***the leading reason*** for delay and denial of FDA approval for new drug products" (Response, 56 (citing Ex. 2080)), only 4.9% of NDAs (15 of 302) were rejected for that reason, and by "the time drugs enter the

[16] *See also Warner Chilcott Co. v. Teva Pharms. USA*, 594 F. App'x 630 (Fed. Cir. 2014); *In re Copaxone*, Civ. No. 14-1171-GMS, Dkt. No. 294 (D. Del. Jan. 30, 2017); *Mylan Pharms. Inc. v. Yeda Research & Dev. Co.*, IPR2015-00643, Paper 85 (Aug. 24, 2016).

later stages of development extensive clinical and nonclinical information is already available and sponsors are often confident about the safety and potential efficacy of investigational drugs." (Ex. 2080, 4, 6; Ex. 1035, 44:9-18, 49:1-52:20.) That is the case here. The claimed subject matter would have at a minimum been obvious to try and resulted from routine optimization.

VI. Alleged Secondary Considerations Do Not Overcome Petitioner's Showing of Obviousness

Evidence of secondary considerations cannot overcome a strong *prima facie* showing of obviousness, like that made here. (Petition, 44; *Agrizap, Inc. v. Woodstream Corp.*, 520 F.3d 1337, 1344 (Fed. Cir. 2008).) Moreover, none of the purported secondary considerations identified by AbbVie supports nonobviousness.

A. There Was No Long-Felt, But Unmet Need for "New RA Therapies"

By AbbVie's own admission, as of 2001, there were already multiple "breakthrough" anti-TNFα agents for treating RA, along with other more-established methods. (Response, 57.) Moreover, while AbbVie asserts that there was a need "for additional biologics with more advantageous dosing regimens," the prior art already had also disclosed biweekly and subcutaneous D2E7 regimens satisfying any purported need. (Response, 58 (criticizing

intravenous and twice weekly dosing regimens)[17]; Ex. 2089, 2.) Not surprisingly, then, neither AbbVie nor its declarants attempted to connect the alleged unmet need to the allegedly inventive aspects of the claims. (*See* Response, 57-58; Ex. 2071, ¶¶96-97.) And, at his deposition, Dr. Gibofsky conceded that his discussion of "failure of others and long-felt need" referred to "***other antibodies*** than . . . D2E7" and that D2E7's beneficial properties were disclosed in the prior art, including U.S. Patent No. 6,090,382 ("the '382 patent"). (Ex. 1037, 63:11-64:16; Ex. 1048.[18])

AbbVie's evidence fails to show a long-felt, unmet need over the prior art. *Merck v. Gnosis, S.P.A.*, 808 F.3d 829, 838 (Fed Cir. 2015) (long-felt need "not sufficiently connected with the novel elements of the asserted claims").

[17] The putative disadvantages of Enbrel and Remicade identified by AbbVie (multiple doses per week; intravenous administration at a doctor's office) provide additional evidence that a POSA would have been motivated to pursue subcutaneous, fixed-dose administration of D2E7 on a less frequent basis.

[18] Dr. Gibofsky did not even review the '382 patent before his declaration and AbbVie did not supply it to him. (Ex. 1037, 54:8-55:21.)

B. The Claimed Dosing Regimen Was Not "Unexpectedly Effective"

AbbVie's "unexpectedly effective" argument should be rejected as a mere repackaging of its alleged teaching away. *Hoffmann-La Roche,* 748 F.3d at 1330-1334.

Contrary to its current position, AbbVie consistently touted the safety and efficacy of each element of the claimed invention in prior art publications. (Ex. 1008, 7; E. 1011, 5; Ex. 2040, 8.) Moreover, "unexpected results . . . must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U.S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006). AbbVie does not show that the claimed dosing regimen has unexpectedly better properties than the 20 or 40mg weekly doses disclosed in van de Putte 1999, and indeed the Humira label itself allows for 40 mg weekly dosing if the claimed biweekly dosing regimen does not provide sufficient efficacy. (Ex. 1024, 1; Response, 58-60; Ex.1037, 65:4-9.) Finally, AbbVie does not and cannot demonstrate any unexpected difference "in kind" against the closest prior art. *Galderma*, 737 F.3d at 740.

C. Commercial Success Is Within the Exclusivity of AbbVie's Blocking Patent and Not Due to the Claimed Subject Matter

In arguing that the sales of Humira support a finding of nonobviousness, AbbVie largely rehashes arguments that the Board has already considered and rejected. (Preliminary Response, 48-50; Decision, 19-20; Response, 60-61.) AbbVie again fails to show that Humira's sales are due to the claimed 40mg

biweekly dose, as opposed to prior art features (including the attributes of the fully humanized D2E7 antibody itself). *Galderma*, 737 F.3d at 740 ("[I]f the feature that creates the commercial success was known in the prior art, the success is not pertinent."). Indeed, AbbVie expressly relies on a number of features — including active ingredient (D2E7), method of administration (subcutaneous), and dosing interval (biweekly) — that were disclosed in the prior art. (Response, 60-61.) And AbbVie's commercial success expert conceded that he did not consider the properties of the active ingredient itself or other uses of Humira in his analysis. (Response, 60-61; Decision, 19-20; Ex. 1034, 14:3-6, 16:24-18:2, 49:23-50:10.)

The probative value of Humira's sales is especially minimal here. AbbVie and its expert do not dispute that the prior art '382 patent covering D2E7 itself (issued July 18, 2000) blocked competitors from commercializing any D2E7 product for years (expiring in 2016). (Ex. 1034, 21:9-22:4, 23:5-26:14; Ex. 2188, 7.) "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." *Galderma*, 737 F.3d at 740; *Merck & Co. v. Teva*

Pharm. USA, Inc., 395 F.3d 1364, 1376-77 (Fed. Cir. 2005) (same);[19] *In re Copaxone*, Dkt. No. 294, at 45. That is the case here, and the alleged commercial success of Humira does not support a finding of nonobviousness.

VII. Ground 2 Presents an Independent Basis for Obviousness

AbbVie's assertion that Ground 2 "[adds] no additional information material to the issue of patentability" is contradicted by the Board's institution of review based on both grounds. (Response, 62; Decision at 22). As discussed above, one of AbbVie's primary arguments is that a POSA would not have modified van de Putte 1999's doses from weekly to biweekly. (Response, 30-32.) Ground 2, however, ***starts*** with the prior art teaching of biweekly dosing and modifies that dosing regimen in accordance with state-of-the-art Phase II clinical data. As AbbVie's expert admitted, DE003 (described by Kempeni 1999) discloses biweekly IV dosing. (Ex. 1038, 84:19-85:4.) Schattenkirchner 1998 teaches the well-known advantages of subcutaneous dosing (Ex. 1037, 67:19-68:8), and van de Putte 1999 identifies the doses to employ. Accordingly,

[19] Contrary to AbbVie's assertions (Response, 61), *Merck* is not limited to situations where "the claimed invention was a modification of an already-marketed dosage," but was expressly based on the existence of blocking patents (and regulatory exclusivity). 395 F.3d at 1377.

given the known efficacy of biweekly and fixed, subcutaneous dosing, a POSA would combine the teachings of these references and reasonably expect success in doing so. This ground therefore provides an independent basis for obviousness. AbbVie's failure to rebut this ground in the manner it was presented and adopted by the Board is fatal to patentability.

VIII. Claim Construction

AbbVie concedes that "the proper interpretation of the claims and the level of efficacy they require is irrelevant to resolving the IPR," and does not cite any new intrinsic evidence supporting its proposed construction. (Response, 55.) There is thus no need or basis for the Board to reconsider its claim construction. And because the prior art asserted here discloses meaningful therapeutic efficacy, AbbVie's argument is largely academic, as the prior art would have rendered the claims obvious even under AbbVie's construction (Ex. 1037, 109:18-110:17 (ACR_{20} used to assess efficacy)).[20]

[20] In fact, the '135 patent cites efficacy data from van de Putte 1999 as putative support for the claimed subject matter. (Ex. 1037, 74:1-75:9; *see also id.*, 69:15-71:7 (disclosing efficacy over a broad dosage range).)

IX. Conclusion

For at least the reasons set forth in the Petition and above, the Board should enter judgment against AbbVie and find claims 1-5 of the '135 patent unpatentable as obvious.

Dated: February 16, 2017

Respectfully Submitted,

By: /Naveen Modi/
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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), the undersigned certifies that the foregoing Petitioner's Reply to Patent Owner's Response contains, as measured by the word-processing system used to prepare this paper, 5,430 words. This word count does not include the items excluded by 37 C.F.R. § 42.24.

Respectfully submitted,

Dated: February 16, 2017

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served on the counsel for Patent Owner a true and correct copy of the foregoing Petitioner's Reply to Patent Owner's Response by electronic means on February 16, 2017 at the following addresses of record:

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