Filed: October 28, 2016

Filed on behalf of: AbbVie Biotechnology Ltd.

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 IPR2016-00409
Patent No. 8,889,135 B2

PATENT OWNER'S RESPONSE

TABLE OF CONTENTS

Page(s)

TABLE OF AUTHORITIES

Page(s)

Federal Cases

Federal Statutes

I. INTRODUCTION

The Board instituted *inter partes* review of claims 1-5 of U.S. Patent No. 8,889,135 ("the '135 patent") to determine whether they would have been obvious based on (1) the combination of van de Putte 1999 (Ex. 1008) and Kempeni 1999 (Ex. 1011) and (2) the combination of van de Putte 1999 (Ex. 1008), Rau 1998 (Ex. 1006), and Schattenkirchner 1998 (Ex. 1007). In its decision, the Board indicated that, on the record before it, the selection of the claimed dosing regimen would "have been no more than a routine optimization" of the dosing regimens disclosed in the prior art. Paper 9, 19. The full record now before the Board proves otherwise.[1]

A person of ordinary skill in the art ("POSA") would not have been motivated to "optimize" the dosing regimens in the prior art to arrive at the claimed dosing regimen. Nor would a POSA have expected that the claimed

[1] With this response, Patent Owner submits the declarations of Allan Gibofsky, an expert rheumatologist, Alexander Vinks, an expert in pharmacokinetics, Jeffrey Sailstad, an expert in anti-drug antibodies, Bryan Harvey, a former FDA official who addresses the non-routine nature of biologic clinical trials, and Jerry Hausman, an economics expert who discusses the commercial success of the claimed invention. *See* Exs. 2071-2075.

dosing regimen would work. To the contrary, the clinical and pharmacokinetic ("PK") data in the prior art taught away from the claimed invention because a POSA would have believed that the claimed dosing regimen would result in drug concentration levels that were too low to treat rheumatoid arthritis ("RA").

Ground 1 of the Petition relies on the same prior art as the Petitions filed by Coherus Biosciences, Inc. ("Coherus"; *see* IPR2016-00172, IPR2016-00188, IPR2016-00199). The nominally different art of Ground 2 discusses the identical clinical trials as the art at issue in Ground 1. Petitioner relies on the same arguments as Coherus, at best repackaging them with different emphases. But Petitioner's repackaged arguments have no more merit than those made by Coherus and should be rejected for the same reasons.

First, like Coherus, Petitioner relies on weight-based dosing regimens in the prior art to supply both the motivation to modify the 20mg weekly dosing regimen of van de Putte 1999 and a reasonable expectation of success. The prior art, however, showed that the weight-based dose of 0.5mg/kg that Petitioner alleges is equivalent to the claimed 40mg dose (obtained by multiplying 0.5mg/kg by an average patient weight of 80kg) was ***insufficient*** to treat RA. In the primary study relied on by Petitioner, ***every single patient*** receiving the 0.5mg/kg dose was switched to a higher dose by 12 weeks after the trial began (or withdrew from the study altogether) because the 0.5mg/kg dose did not work. These clinical results

would have indicated to a POSA that the claimed methods of treatment would have been insufficient. Consequently, a POSA would not have been motivated to try the claimed dosing regimens and would not have expected them to succeed.

Second, also like Coherus, Petitioner bases its obviousness theory on a comparison between the drug concentrations resulting from the weekly doses disclosed in van de Putte 1999 and the claimed 40mg every-other-week dose. But Petitioner's oversimplification of the amount of D2E7 antibody in the body after two weeks is incorrect and ignores the multiple, complex PK parameters involved in predicting drug concentration at steady state. In particular, as Petitioner's PK expert conceded, a POSA would have expected the minimum drug concentration between each dose ("C_{min}") to be less in the claimed dosing regimen than the minimum drug concentration in the dosing regimens disclosed in van de Putte 1999. Ex. 2069, 126:1-10 (acknowledging that a lower C_{min} was a "logical expectation"). Lower troughs of drug concentration would have raised both efficacy and safety issues.

A POSA would have been particularly concerned about under-dosing patients with D2E7 because of the fear that too little drug in the blood would increase the risk of anti-drug antibodies ("ADAs"). In addition to presenting safety concerns, ADAs were known to decrease the efficacy of biologic drugs by increasing the speed at which they are removed from the body or by interfering

with the ability to bind to their targets. Once an immune response to an anti-TNFα biologic is generated, any loss of efficacy is typically permanent and the patient may no longer respond to the drug at all.

In short, because the prior art taught away, the claimed invention could not have resulted from "routine optimization." The clinical and PK evidence available to a POSA would have suggested that a fixed 40mg every-other-week dose would not be an effective dose across the patient population. A POSA seeking to develop a safe and effective dosing regimen for D2E7 from among the numerous dosing options that were possible would therefore not have been led to the claimed invention or found it "obvious to try." *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (2007). And a POSA who nonetheless tried the claimed invention would not reasonably have expected it to work. Petitioner has thus failed to carry its burden of proving that the challenged claims are unpatentable. *In re Magnum Oil Tools, Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) ("[T]he Board must base its decision on arguments that were advanced by a party, and to which the opposing party was given a chance to respond.").

Further, the objective evidence confirms the patentability of the claims. Although available clinical and PK data suggested the claimed dosing regimen would have been insufficient to treat RA, the claimed dosing regimen has unexpectedly been one of the most effective treatments for RA since its

introduction in 2003, achieving substantial commercial success and satisfying a long-felt need for new RA therapies. These achievements are directly attributable to the claimed invention.

II. FACTUAL STATEMENT

A. The Prior Art

In June 2001, biologic agents designed to block TNFα activity were a new class of drugs that had shown promise for treating RA. Ex. 1011, 3; Ex. 2071 ¶16; Ex. 2075 ¶52. At that time, there were two FDA-approved anti-TNFα biologics: ENBREL® (a TNFα receptor fusion protein) and REMICADE® (a chimeric monoclonal antibody containing both murine and human sequences). Ex. 2071 ¶¶31-33, 74; Ex. 2075 ¶53.

D2E7 (HUMIRA®) is also a monoclonal antibody but was developed solely from human genetic material. Ex. 2071 ¶40; Ex. 2075 ¶76. It was the first fully-human antibody to be approved by the FDA and the first antibody of any kind approved by FDA for subcutaneous administration. Ex. 2071 ¶40; Ex. 2072 ¶11; Ex. 2075 ¶58; Ex. 2027, 10-12. Notably, the use of monoclonal antibodies as therapeutic agents was in its infancy in 2001. Only 11 such antibodies had been approved, most for acute rather than chronic conditions. Ex. 2072 ¶11.

The prior art pertaining to D2E7 contained preliminary data from four Phase I clinical trials and one Phase II trial. *See* Ex. 2071 ¶¶43-51; Ex. 2075 ¶77, 91.

Limited information about these early trials was published in abbreviated form in review articles and conference abstracts, including van de Putte 1999 (Ex. 1008), Kempeni 1999 (Ex. 1011), Rau 1998 (Ex. 1006), and Schattenkirchner 1998 (Ex. 1007).[2] Collectively, the D2E7 prior art discussed a variety of dosing strategies involving different routes of administration, dosing schedules, dosing amounts, and response rates. Ex. 2071 ¶16; Ex. 2070, 50:7-52:6; 53:9-53:22; Ex. 2075 ¶78, 85, 88, 92.

The different trials were denominated by number, e.g., DE001, and individual trials are discussed in several references. A summary of the D2E7 trials relied on by Petitioner involving weight-based doses (every trial except the DE007 trial) is shown in the table below.

[2] As explained in a publication co-authored by Petitioner's declarant Dr. Weisman, abstracts are "Category D evidence" (the lowest form) because "they are not complete and may change by the time the data are published, or may not be published as full papers at all." Ex. 2038, 7; *see also* Ex. 2070, 284:12-285:1; 286:18-287:19.

Weight-based D2E7 Study (Reference)	Doses (mg/kg)	Route	Dose Frequency	Up-dosing
DE001 (Kempeni 1999, Rau 2000)	0.5, 1, 3, 5, and 10	IV	Single	N/A
DE003 (Kempeni 1999, Rau 1998, Rau 2000)	0.5, 1, 3, 5, and 10	IV	Based on efficacy; mean interval of 2.5 weeks	YES
DE004 (Kempeni 1999, Schattenkirchner 1998, Rau 2000)	0.5 and 1	SC	Weekly	YES
DE010 (Kempeni 1999, Rau 2000)	1 (with MTX)	IV, SC	Single*	N/A

* Open-label study continued but data not available in prior art

The clinical trials that led to the claimed invention did ***not*** constitute the exercise of "routine optimization" of a dosing regimen. Developing a clinical trial for an investigational new drug is a complex and unpredictable endeavor. Ex. 2072 ¶¶7-9, 13-18. Clinical trials of a biologic product—particularly an investigational new drug that has not yet been approved for human use—require an enormous investment of resources and face a high risk of failure. *Id*. ¶¶8, 15-20. Notably, biologics routinely fail to advance towards approval at even the later phases of clinical trials for any number of reasons, including the failure of a drug's dosing regimen. *Id*. ¶¶9, 18-20. Indeed, poor dose selection was ***the leading reason*** for delay and denial of FDA approval based on a review of NDAs submitted between 2000 and 2012. *Id*. ¶18; Ex. 2080, 4, 6.

1. Kempeni 1999

Kempeni discloses several early "weight-based" D2E7 prior art trials. Ex. 1011, 4-5; Ex. 2075 ¶77; Ex. 2071 ¶¶43-48. The first Phase I study (DE001) examined 120 total patients, divided into 5 groups, who received placebo or a single intravenous dose of D2E7 based on weight (0.5 to 10mg/kg). Ex. 1011, 4; Ex. 2075 ¶¶79, 83-84; Ex. 2070, 55:13-56:2.

The DE001 study was followed by an open-label extension (DE003) in which patients continued to receive intravenous injections based on their body-weight. Ex. 1011, 4; Ex. 2075 ¶85. Specifically, patients received a first dose identical to the dose received in the DE001 study (0.5, 1, 3, 5 or 10mg/kg) a minimum of four weeks after the DE001 dose, and only after losing response status. Ex. 1011, 4; Ex. 1006, 5. Thereafter, patients received D2E7 every 2 weeks "until responses could be rated as 'good', defined as an absolute DAS [Disease Activity Score] of < 2.4." Ex. 1011, 4. They were then re-treated on a schedule having a minimum of two week intervals, but only upon disease flare-up. Ex. 2040, 5; Ex. 1011, 4; Ex. 1006, 5; Ex. 2070, 58:20-59:21; 117:24-118:10. The mean dosing interval across all doses was 2.5 weeks. Ex. 1011, 4; Ex. 1006, 5; Ex. 2070, 128:17-20; Ex. 2075 ¶87. Kempeni 1999 does not disclose the mean dosing interval for the 0.5 mg/kg dose or any other specific dose. Ex. 2070, 129:12-130:25.

In the second Phase I study (DE004), just 24 patients received weekly subcutaneous weight-based doses of either placebo or 0.5mg/kg D2E7 for three months. Ex. 1011, 4-5; Ex. 2075 ¶¶88-89. The third Phase I study reported in Kempeni (DE010) involved a head-to-head comparison of a single, 1mg/kg weight-based dose of D2E7 administered either subcutaneously or intravenously in combination with methotrexate (MTX). Ex. 1011, 5; Ex. 2075 ¶90.

Kempeni reports substantial variability in the effects of D2E7 on patients (called pharmacodynamic ("PD") responses) following single administration. Ex. 2075 ¶83. Specifically, in the three highest dose groups of the DE001 trial (the 3, 5, and 10mg/kg groups), "40-70% of patients achieved DAS and ACR20 response status at 24 hours to 29 days" post-treatment, indicating significant patient-to-patient variability both with respect to whether the drug would work and how long it would take.[3] Ex. 1011, 4.

[3] DAS (Disease Activity Score) and ACR20 (American College of Rheumatology) are composite criteria used to measure the effectiveness of RA treatments. Ex. 1011, 3-4; Ex. 2071 ¶42; Ex. 2092, 1; Ex. 2075 ¶¶80-82. ACR20 requires a 20% or greater improvement in certain outcomes, while another more robust measure called ACR50 requires a 50% or greater improvement. Ex. 2071 ¶41.

In both of the multi-dose trials reported in Kempeni (DE003 and DE004), patients who received a weight-based dose of 0.5mg/kg had to be "up-dosed" to maintain their responder status. Ex. 1011, 4-5; Ex. 2070, 77:16-82:7; Ex. 2075 ¶¶86, 88. In the DE003 trial, ***all*** of the patients receiving the 0.5mg/kg dose were up-dosed to higher doses (or withdrew from the study altogether) by week 12. Ex. 2158, Figs. 4 and 5. This need to up-dose indicated that a 0.5mg/kg dose is ***insufficient*** for treating RA across the patient population. *See* Ex. 2071 ¶¶17, 45-46, 61, 63-65, 94; Ex. 2075 ¶¶155-156. Petitioner equates this dose with the claimed 40mg dose (by assuming an average patient weight of 80kg). Pet. 44; Ex. 2069, 129:16-23; Ex. 2070, 61:16-19. Applying Petitioner's premise, the claimed 40mg dosing regimen also would have been understood to be insufficient.

Moreover, the 0.5mg/kg dose in the DE003 trial was administered ***intravenously***. Ex. 1011, 4; Ex. 2071 ¶45; Ex. 2070, 55:20-56:8. Compared to intravenous dosing, subcutaneous administration (administration under the skin) decreases the bioavailability of the administered drug, because less drug reaches the bloodstream. Accordingly, subcutaneous dosing of 40mg would have been understood to result in lower concentrations of drug than those resulting from intravenous administration of a 0.5mg/kg dose to an 80kg patient. Ex. 2075 ¶¶32-35, 71, 126-127; *see also* Ex. 2017, 29; Ex. 2091, 19-20.

The 0.5mg/kg dosing regimen of DE004 would also have delivered more drug than the claimed 40mg every-other-week regimen. The dosing interval for DE004 was weekly (Ex. 1011, 4); thus, twice as much drug would have been delivered to an 80kg patient. The evidence of the need to up-dose patients receiving either a 0.5mg/kg dose ***weekly*** (DE004) or 0.5mg/kg ***intravenously*** (DE003) indicates that a subcutaneously administered every-other-week 40mg dose would be insufficient.

2. van de Putte 1999

van de Putte 1999 is a conference abstract that reports preliminary data from the first D2E7 Phase II trial. Ex. 1008, 7; Ex. 2071 ¶49; Ex. 2075 ¶91. This trial, called DE007, featured a three-month placebo-controlled study in which patients received a fixed dose of 20, 40, or 80mg D2E7 administered subcutaneously on a weekly schedule. Ex. 1008, 7; Ex. 2075 ¶92; Ex. 2069, 83:20-22. DE007 was the first fixed dose trial; all of the previous trials used weight-based dosing. Ex. 2071 ¶43.

The DE007 study was not powered to provide statistically meaningful comparisons between doses, but only to determine the statistical significance of each of the doses compared to placebo. Ex. 2071 ¶79; Ex. 2069, 84:5-12. While the authors concluded that "20, 40 and 80 mg/week were nearly equally efficacious," this statement was based on a comparison of each group to placebo,

not to each other. Ex. 1008, 7. As discussed in §IV.A.1 *infra*, the data showed that while each dose was statistically superior to placebo, the 40 and 80mg doses were numerically superior to the 20mg dose. Ex. 2071 ¶¶18, 50-51; Ex. 2075 ¶93.

After 3 months, patients receiving placebo were switched to a 40mg weekly dose. Ex. 2086, 2; Ex. 2075 ¶94. Those patients showed greater improvement in ACR20, SJC, and CRP after just 3 months of 40mg weekly dosing compared to patients who received 20mg weekly for 6 months.[4] Ex. 2086, 2; Ex. 2071 ¶81.

The difference between 20mg and the higher weekly doses becomes even more evident at 12 months. For example, the ACR50 for the 20mg weekly group remains essentially the same between 3 and 12 months (24% vs. 25%), whereas the 40mg weekly dose experiences a 59% improvement (27% vs. 43%). Ex. 2090, 5; Ex. 2071 ¶82. Further, the percent response for patients receiving 40 and 80mg weekly doses was numerically superior for every clinical measure compared to 20mg weekly. Ex. 2090, 5; Ex. 2071 ¶82.

[4] SJC refers to Swollen Joint Count. CRP refers to C reactive protein, a biomarker of inflammation. Ex. 2071 ¶¶41, 49.

	Percent Response or Improvement		
	20mg 3 mos./12 mos.	40mg 3 mos./12 mos.	80mg 3 mos./12 mos.
ACR20	49/**46**	59/**60**	56/56
ACR50	24/**25**	27/**43**	19/31
TJC (median)	52/**51**	57/**60**	53/60
SJC (median)	39/**52**	56/**65**	54/59
CRP (median)	53/**55**	61/**64**	64/60

Other contemporaneous reports of the DE007 study do not even mention the efficacy of 20mg weekly dosing, indicating that the 40mg weekly regimen was preferred among the three regimens. Ex. 2020, 4; Ex. 2071 ¶83. Moreover, in the full-length, peer-reviewed article reporting the data, the authors state that "***40 mg was associated with better results than the other doses***." Ex. 2041, 9 (emphasis added); Ex. 2071 ¶84; Ex. 2075 ¶95.

3. Rau 1998

Rau 1998 is an abstract that reports data from the DE003 study also discussed in Kempeni. Rau 1998 does not add any material information to the prior art not also available from Kempeni. Ex. 2071 ¶73; Ex. 2075 ¶85.

As indicated above, DE003 was an open-label continuation of the DE001 study involving intravenously dosed amounts based on body weight. Ex. 1006, 5. Patients who did not respond well after 0.5 or 1mg/kg received higher doses. Ex. 1011, 4; Ex. 2070, 78:10-80:1. Six patients dropped out of the DE003 study due to lack of efficacy. Ex. 1006, 5; Ex. 2070, 124:12-25.

Based on Petitioner's conversion of a 0.5mg/kg weight-based dose to a 40mg fixed dose, the logical conclusion a POSA would have drawn from the DE003 study, and in particular the up-dosing in that study, is that 40mg of D2E7 administered subcutaneously every-other-week would have been insufficient across the patient population for reasons noted in §II.A.1, above. *See also* §IV.A.1, *infra*.

4. Schattenkirchner 1998

Like Rau 1998, Schattenkirchner 1998 is also an abstract that reports on data from a study (DE004) discussed in Kempeni. Schattenkirchner 1998 does not add any material information to the prior art not also available from Kempeni. Ex. 2071 ¶73; Ex. 2075 ¶¶88-89.

The DE004 trial included weekly, subcutaneous administration of a weight-based dose of 0.5mg/kg. Ex. 1011, 4-5; *see also* Ex. 1007, 5. "[N]on-responders or those losing their responder status" were up-dosed to 1mg/kg weekly. Ex. 1011, 5; Ex. 1007, 5; *see* Ex. 2070, 75:6-77:10; 80:2-82:7. Thus, as with the DE003 study (in which up-dosing was also reported), the logical conclusion a POSA would have drawn from the DE004 study is that the claimed every-other-week dosing regimen would have been insufficient across the patient population.

B. The PK Data in Kempeni

Kempeni reports three PK parameters: (1) mean total serum clearance, (2) steady-state volume of distribution, and (3) an "estimated mean terminal half life" of 11.6 to 13.7 days. Ex. 1011, 4; Ex. 2075 ¶79. These three metrics are reported as ranges in Kempeni, which does not report any patient-specific PK information.

Clearance refers to the rate at which a drug is eliminated from the body and is typically expressed as mL/min. Ex. 2075 ¶31. Volume of distribution refers to the theoretical volume over which the drug is distributed. It is typically expressed as L/kg, where kg is the weight of the patient. *Id.*

Terminal half-life, a calculated value, refers to the time taken for the concentration of the drug in the blood to fall by 50% during the elimination phase of a PK profile (the period when the rate of drug elimination due to excretion and/or metabolism predominates). *Id*. ¶30. Terminal half-life provides no information about the "absorption" phase (the period when the drug moves from the site of administration to the blood) or "distribution" phase (the period in which the drug is distributed to other areas in the body). *Id.* ¶¶26-27, 33, 37; *see also* Ex. 2017, 14-20. Thus, in the case of a subcutaneously administered drug, the terminal half-life does not reflect how long the drug is in the body, nor does it provide any information about how long the drug is at the site of action. Ex. 2075 ¶111. Importantly, half-life also does not itself reveal any information about the

concentration of drug in the blood, the PK parameter of primary importance for designing a dosing regimen. *Id.* ¶¶37, 110, 112; Ex. 2091, 41.

Neither Kempeni nor any other prior art reference reports key exposure metrics, such as C_{min}, C_{max}, or AUC, for D2E7. Ex. 2075 ¶132; Ex. 2069, 92:18-93:20. C_{max} and C_{min} respectively refer to the peaks and troughs of a curve that graphs exposure to a drug over time. Ex. 2075 ¶¶36, 40. AUC is the total area under a PK curve and reflects overall exposure to a drug. *Id.* ¶36.

C. The '135 Patent

The '135 patent claims priority to an application filed June 8, 2001. Ex. 1001, (60). It contains five claims directed to methods of treating RA in a human involving administering an anti-TNFα antibody having the six CDRs and heavy chain constant region of D2E7. *Id.*, 45:11-46:30. The claims cover the first-approved dosing regimen for HUMIRA®. Each of the claims requires administering a total body dose of 40mg subcutaneously once every 13-15 days for a period of time sufficient to treat RA. *Id.*

D. HUMIRA®

HUMIRA® was first approved for the treatment of RA at the end of December 2002. Ex. 2071 ¶40; Ex. 2134, 1; Ex. 2135, 14. As the Panel recognized, it is uncontroverted that HUMIRA® has been a commercial success in the treatment of RA. *See* Paper 9, 19-20.

The success of HUMIRA® is largely attributable to its safety and efficacy, which is inextricably bound up with the invention of a safe and efficacious dosing regimen. Ex. 2073 ¶14-15. HUMIRA® also satisfied the need for an anti-TNFα therapy that could be safely self-administered at home, that did not require weight-based calculations of dose amount, and that maximized patient comfort and convenience by limiting the number of injections. Ex. 2071 ¶¶102-103. Each of these features results from the claimed invention as a whole.

III. INSTITUTION DECISION

The Board instituted *inter partes* review of claims 1-5 of the '135 patent based on the combination of Kempeni 1999 and van de Putte 1999 (Ground 1) and the combination of Rau 1998, Schattenkirchner 1998, and van de Putte 1999 (Ground 2) under 35 U.S.C. §103. Paper 9, 22-23.

The Board did not expressly define the level of skill of a POSA. *See* Paper 9, 9 n.5. In IPR2016-00172, however, the Board defined a POSA for the '135 patent as a person possessing the skill sets of both a physician treating RA patients and a pharmacokineticist with experience in monoclonal antibodies. *Coherus*

Biosciences Inc. v. AbbVie Biotechnology Ltd., IPR2016-00172, Paper 9, 5-6 n.3 (May 17, 2016). The Board should adopt the same definition here.[5]

The Board declined to construe the phrase "for a time period sufficient to treat the rheumatoid arthritis" but noted that the claim term "does not require a particular level of efficacy." Paper 9, 7. The Petition should be denied regardless of the construction of this phrase, at least because (1) the prior art teaches away and (2) a POSA would have been motivated to pursue an effective treatment regimen, not one that merely provided baseline functionality. *See Yamanouchi Pharm. Co. v. Danbury Pharmacal, Inc*., 231 F.3d 1339, 1345 (Fed. Cir. 2000) (expectation that modification of compound would have achieved "baseline level" of functionality insufficient to show motivation). Nevertheless, Patent Owner addresses the question of the degree to which efficacy is required by the claims in §VI *infra*.

[5] Petitioner excludes a pharmacokineticist from its definition of a POSA, but asserts that a POSA would have basic familiarity with, among other PK concepts, half-life, drug exposure over time, the interpretation of plasma concentration measurements, and general PK properties that are determined in clinical trials (such as C_{min}, C_{max}, and AUC). Ex. 2069, 28:5-29:6.

IV. GROUND 1: THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS FROM VAN DE PUTTE AND KEMPENI

In attempting to meet its burden of proving obviousness, Petitioner makes three arguments: (1) Kempeni 1999 would have motivated a POSA to modify the van de Putte 1999 dosing regimens; (2) the claimed invention is merely the result of routine optimization of the dosing regimens disclosed in van de Putte 1999; and (3) the claimed dosing regimen "at a minimum" would have been "obvious to try." Pet. 21-31. All three theories are contrary to the evidence, which demonstrates that the clinical and PK information in the prior art as a whole taught away from the claimed dosing regimen. *Syntex (U.S.A.) LLC v. Apotex, Inc*., 407 F.3d 1371, 1380 (Fed. Cir. 2005) ("Under the proper legal standard, a reference will teach away when it suggests that the developments flowing from its disclosures are unlikely to produce the objective of the applicant's invention.").

Both the clinical and the PK data disclosed in the art cited by Petitioner teach away from the claimed invention. A POSA would have understood that the weight-based dose Petitioner relies upon as analogous to the claimed dose failed to treat RA, as every patient receiving that dose on an every-other-week schedule was up-dosed to higher doses (or withdrawn from the study). A POSA would have further understood that the C_{min} associated with the claimed dosing regimen would be substantially lower than those produced by the 20mg weekly van de Putte regimen. Based on this data, a POSA would have been dissuaded from trying the

claimed invention and would not reasonably have expected it to treat RA, particularly in light of well-founded concerns about ADAs when the amount of drug in the body falls to too low a level.

Because the prior art taught away from the claimed invention, it also would not have been "obvious to try." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1359 (Fed. Cir. 2007) (invention not obvious to try because the prior art "would have directed one of ordinary skill in the art away" from the claimed invention); *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357-58 (Fed. Cir. 2013) (combination of drugs not obvious to try where the prior art taught away from the claimed combination). Moreover, a subcutaneous, fixed dose of 40mg every-other-week was not one of a finite number of ***predictable*** solutions. The claimed dosing regimen was a single option among myriad possibilities that a POSA would have rejected in light of the prior art.

Petitioner's attempt to invoke "routine optimization" as grounds for the Petition is likewise mistaken. Routine optimization is not a legal test, and in in any event there is nothing in the record suggesting that there was anything routine about development of the claimed invention. What the record actually reflects is a group of skilled scientists struggling to understand how to treat a difficult disease with a new type of drug. They experimented with weight-based versus fixed-dose regimens, intravenous versus subcutaneous dosing, weekly versus every-other-

week versus symptom-driven intervals, and numerous different possible doses. This struggle led to the claimed invention, an invention that was unexpectedly efficacious in treating RA and a tremendous commercial success. Petitioner's obviousness argument is hindsight advocated by a party that now wishes to appropriate for its own use the fruit of the years of trial and error research underlying the claimed invention.

A. The Clinical And PK Data in Kempeni 1999 Would Not Have Motivated A POSA To Practice The Claimed Invention

1. The available clinical data taught away from the claimed invention

Petitioner's motivation argument relies on a combination of the clinical and PK information in Kempeni 1999. With respect to the clinical data, Petitioner makes three points. First, Petitioner asserts that the data from the DE001 study shows that intravenous doses of D2E7 were effective for a period of at least two weeks. Pet. 26. Second, Petitioner contends that the DE003 study showed efficacious "biweekly" dosing of weight-based intravenous doses. *Id*., 26-27. Third, Petitioner relies on the weekly subcutaneous dosing of DE004 to argue that a POSA would have expected that subcutaneous dosing would have produced results similar to those observed with intravenous dosing. *Id*., 27-28. Each of these contentions is belied by the data itself, which shows that every-other-week administration of 0.5mg/kg dose (the weight-based dose Petitioner contends is

equivalent to a fixed 40mg dose) was insufficient to treat RA across a patient population.

a. The 0.5mg/kg doses in the prior art taught away

Petitioner observes that the 0.5mg/kg weight-based dose disclosed in Kempeni 1999 (and Rau 1998) "would have been understood to correspond roughly to a 40 mg fixed dose" based on "the reasonable assumption of an average RA patient weight of 80 kg (about 176 lbs.)." Pet. 44; Ex. 1003 ¶49; Ex. 1004 ¶26; Ex. 2069, 129:16-23. As an initial matter, a POSA would have understood that subcutaneous administration of the claimed 40mg fixed dose would have been expected to produce lower drug levels in an 80kg patient than the intravenous administration of a 0.5mg/kg dose because of the loss of drug through absorption. *See supra* §IIA.1.

More importantly, a POSA would have also understood from the prior art that the 0.5mg/kg dose was insufficient to treat RA even when administered

intravenously.[6] In the DE003 trial, "patients who did not respond well after 0.5 or 1 mg/kg received higher doses of up to a maximum of 3 mg/kg." Ex. 1011, 4. Likewise, in the DE004 trial, "[t]he dose of D2E7 [of 0.5mg/kg] was increased to 1 mg/kg subcutaneously weekly for non-responders or those losing their responder status." *Id.*, 5.

At their depositions, Drs. Jusko and Weisman attempted to dismiss this evidence of up-dosing by suggesting that the number of patients who were up-dosed is unknown, that it may have involved only a small number of patients, and that up-dosing may have been for reasons other than the inadequacy of the dose. Ex. 2069, 131:22-132:4, 132:21-133:4; Ex. 2070, 85:16-86:18, 89:21-90:7. But this speculation is contradicted by the prior art, which shows that ***all*** of the patients receiving 0.5mg/kg in the DE003 study were up-dosed from 0.5mg/kg to higher doses (or withdrew from the study altogether).

[6] The prior art showed the superiority of intravenous dosing in a trial comparing subcutaneous and intravenous administration of equivalent doses of D2E7. Ex. 2071, ¶72; Ex. 2082, 3; Ex. 2040, 8 (stating that intravenous injection gives advantages for TJC, ESR, and CRP and produces better DAS and ACR20 responses).

In particular, Rau 2000 includes two graphs reporting on two outcome measures for all of the dosing amounts of the DE003 study, Figures 4 (DAS) and 5 (ESR).[7] As noted above in §II.A.1 and as shown below, under the DE003 protocol, patients in the placebo arm moved into one of the D2E7 dose groups at week 6, and patients in the 0.5mg/kg and 1mg/kg dosing groups received higher doses if they did not respond well (defined as an improvement in DAS). Ex. 1011, 4; Ex. 2040, 5-6. Annotated versions of these figures are shown below.

[7] Rau 2000 is relied on by Petitioner in IPR2016-00408 as Ex. 1013. Patent Owner submitted a copy of that paper in this proceeding as Ex. 2039 and an English translation as Ex. 2040. Patent Owner submits a higher-resolution copy of Rau 2000 herewith as Ex. 2158.

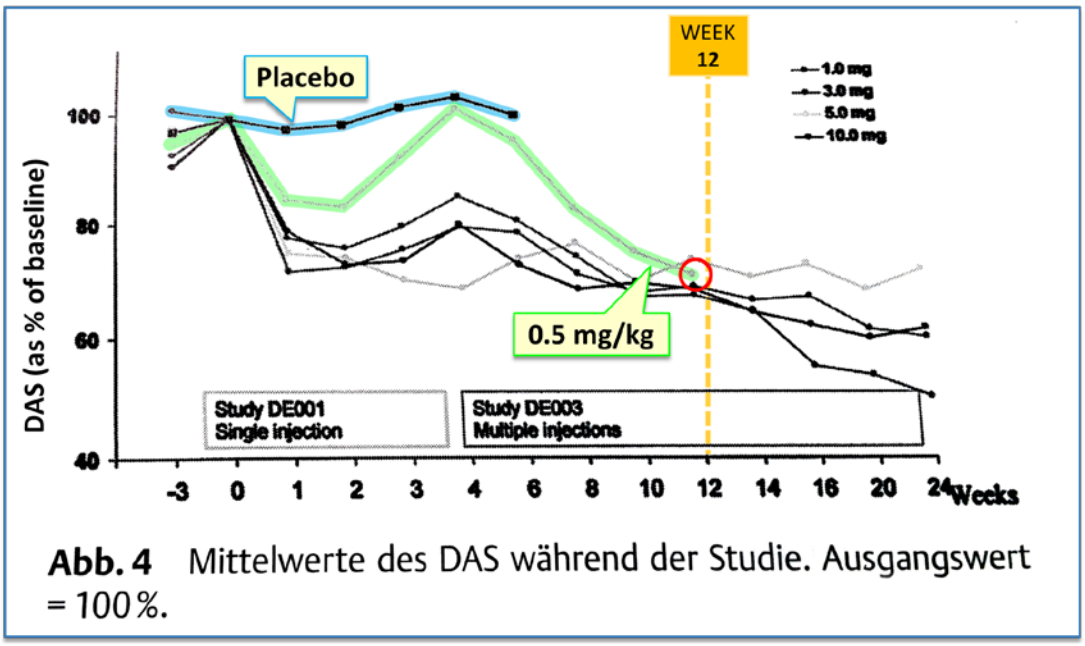


Abb. 4 Mittelwerte des DAS während der Studie. Ausgangswert = 100 %.

Fig. 4 (Rau 2000)

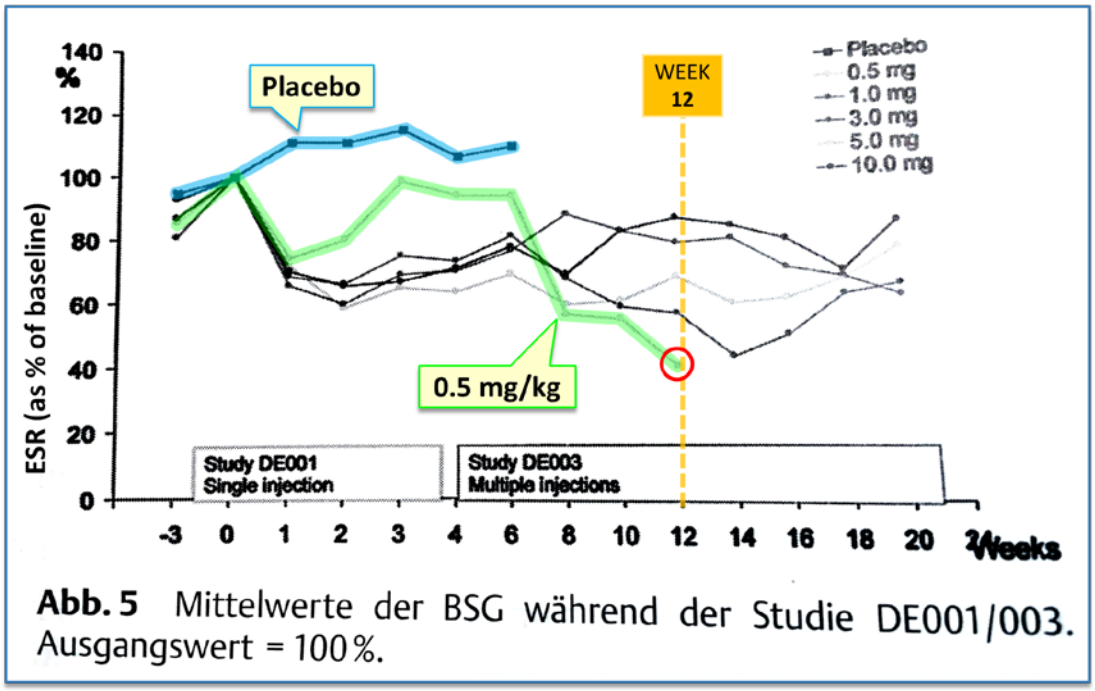


Abb. 5 Mittelwerte der BSG während der Studie DE001/003. Ausgangswert = 100 %.

Fig. 5 (Rau 2000)

Although the graphs extend beyond 12 weeks, in both Figures 4 and 5, the data for the 0.5mg/kg line ***ends at 12 weeks*** (unlike all of the other administered doses).

Ex. 2158, 6-7, Figs. 4-5; Ex. 2071 ¶64; *see* Ex. 2070, 65:17-67:21, 69:11-17, 70:1-17 (acknowledging that termination of the 0.5mg/kg line in Figures 4 and 5 "indicates that ***nobody*** received the .5mg/kg dose after week 12") (emphasis added). A POSA reviewing the prior art would have understood that ***all*** of the patients in the DE003 study were up-dosed after 12 weeks (or withdrew from the study altogether) because the 0.5mg/kg dose was insufficient. Ex. 2071 ¶64; Ex. 2075 ¶86. Consistent with this data, Rau 2000 unambiguously states that only doses greater than 1mg/kg (i.e., greater than an 80mg fixed dose) provided long-term efficacy. Ex. 2040, 4.

In their depositions, Petitioner's experts sought to ignore the design of the DE003 protocol and the clear implications of the data by suggesting that it was unknown why the 0.5mg/kg arm may have been discontinued. *E.g*., Ex. 2070, 67:22-68:2. But this purported gap in the art ignores both the express conclusion of the study highlighting the efficacy of only those doses greater than 1mg/kg (Ex. 2040, 4) and Petitioner's burden before this tribunal. Petitioner's obviousness theory depends on the claim that the 0.5mg/kg dose was effective; this is the basis relied on by Dr. Jusko for dismissing as immaterial the undisputed fact, discussed in §IV.A.2 *infra*, that a 40mg every-other-week dose would produce lower C_{min} levels than the 20mg weekly dose of van de Putte. Ex. 1004 ¶26; Ex. 2069, 129:4-

15. Given its burden of proof, Petitioner's case fails because the prior art shows that the 0.5mg/kg dose is ineffective.

Nor can Petitioner take refuge in the suggestion that the 0.5mg/kg dose may have been efficacious for some patients for some period of time. First, the Board should not be misled by the downward slope of the 0.5mg/kg line between weeks 6 and 12 in Figures 4 and 5. Consistent with the DE003 protocol, a POSA would have understood that non-responding patients were being ***up-dosed*** from 0.5mg/kg to higher doses between weeks 6 and 12—such that the plot would not indicate efficacy of the 0.5mg/kg dose even for that limited period of time.[8] Ex. 2071 ¶65.

Further, the claims require administration of the dose for "a time period sufficient to treat" RA, and claims 3 and 4 expressly require a period of 24 weeks. Ex. 1001, 45:16-17, 45:30-46:12. A POSA would have understood from the DE003 trial that an every-other-week dose of 0.5mg/kg was not even effective in treating RA for a period of twelve weeks—an explicit teaching away from the

[8] Given the absence of statistical information, it would be inappropriate for Petitioner to argue about the relative efficacy of the various doses. According to Petitioner, in "any parallel study . . . statistical information regarding clinical responses would have been essential in attempting to ascertain whether any meaningful difference existed between each dose." Pet. 24; Ex. 2070, 95:4-13.

"sufficient to treat" limitations of both the dependent and independent claims. Ex. 2071 ¶65.

"When a piece of prior art 'suggests that the line of development flowing from the reference's disclosure is unlikely to be productive of the result sought by the applicant' the piece of prior art is said to 'teach away' from the claimed invention." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)). Here, the prior art indicates that the 0.5mg/kg every-other-week dose, which indisputably was abandoned as of week 12 of the DE003 study, would have been "unlikely to be productive." This constitutes a teaching away from the development of an allegedly comparable fixed-dose amount. *See, e.g., Endo Pharms, Inc. v. Depomed, Inc.*, IPR2014-00652, Paper 68, 31-32 (Sept. 16, 2015) (concluding Petitioner failed to establish motivation or expectation of success where prior art taught away from the claimed combination).

Petitioner's reliance on the DE001 trial is also misplaced. Petitioner argues that the duration of the response in this single-dose trial supports every-other-week administration of 40mg, because therapeutic effects "reached the maximum effect after 1-2 weeks, with dose response reaching a plateau at 1 mg/kg D2E7." Pet. 26. However, the purportedly equivalent dose of 0.5mg/kg worked less well than higher doses, including by showing earlier symptom relapse. Indeed, Rau 2000

reports that "[i]n the 0.5 mg group there was a worsening again already after one week." Ex. 2040, 6; Ex. 2071 ¶62; Ex. 2070, 61:5-62:21. Thus, as with the DE003 trial, the DE001 trial would have suggested that the 0.5mg/kg dose, and any equivalent fixed dose, would be inadequate.

Finally, Petitioner's argument is not helped by Kempeni's statement that "preliminary data" from the DE004 study showed that D2E7 blood levels after multiple subcutaneous doses were "comparable" to those obtained following intravenous administration. Ex. 1011, 5. No information was provided regarding the IV doses to which the comparison was made, the PK parameters being considered, the concentration levels of D2E7, and the number of subcutaneous administrations of D2E7 needed to achieve "comparable" concentration levels. Ex. 2075 ¶89; Ex. 2070, 170:20-172:19, 176:18-177:4, 179:4-180:13. More importantly, if a POSA had concluded anything from this statement, it would have been that a subcutaneous dosing regimen equivalent to the intravenous 0.5mg/kg dosing regimen of the DE003 study would have similarly proved inadequate. Ex. 2071 ¶¶70-71; Ex. 2075 ¶175-177. And, indeed, that is exactly what Kempeni taught in reporting that the DE004 patient population was also up-dosed from a 0.5mg/kg weekly regimen—even though the DE004 study featured ***weekly*** dosing. Ex. 1011, 5.

In short, the weight-based studies on which Petitioner relies taught away from every-other-week administration of a 0.5mg/kg dose across all patients, and instead favored higher doses. Based on these results, a POSA would have considered a 40mg every-other-week, subcutaneous dose too low to serve as a "one-size-fits-all" dose.

b. The "biweekly" dose described in Kempeni taught away

The DE003 study's "biweekly" phase included the following protocol. As with DE001, patients received doses of 0.5, 1, 3, 5, or 10mg/kg. Ex. 1011, 4-5; Ex. 2040, 5. In DE003, an injection was given a minimum of four weeks after the injection administered in the DE001 study. Ex. 2040, 5. Thereafter, additional injections were given on a "biweekly" schedule until a "good" response was observed. *Id.* Treatment was then discontinued and resumed "only upon disease flare up" but no earlier than two weeks after the last injection. *Id.*; Ex. 2070, 116:21-118:10. After 12 months of dosing in the open-label study, a ***mean*** dosing interval of 2.5 weeks was reported. Ex. 1006, 5.

Petitioner points to the mean dosing interval of 2.5 weeks not only as proof of motivation, but as suggesting that every-other-week dosing was "preferred" because it "would have suggested not only that every-other-week dosing is effective to treat RA at the disclosed doses, but that slightly longer dosing intervals (*i.e.*, 2.5 weeks) may result in loss of efficacy." Pet. 27. But the "biweekly"

dosing purportedly disclosed in Kempeni actually teaches away from the invention because a POSA would have understood it did not apply to the 0.5mg/kg dose. Ex. 2071 ¶¶66-68; Ex. 2075 ¶¶15, 85-87.

First, the 2.5 week figure was calculated after 12 months of dosing D2E7 in the open-label portion of the DE003 study. Ex. 2071 ¶67; Ex. 1006, 5. As discussed above, a POSA would have understood from the data in Rau 2000 that the 0.5mg/kg dose had been discontinued after only 12 weeks due to up-dosing and patient withdrawal (*see* Ex. 2070, 70:10-17), while the 1, 3, 5, and 10mg/kg doses were all continued. Ex. 2158, 7, Fig. 5; Ex. 2071 ¶64. Given that all patients receiving the 0.5mg/kg dose were up-dosed or discontinued by 12 weeks, a POSA would have understood that the mean dosing interval of 2.5 weeks is inapplicable to the 0.5mg/kg dose because ***no patients*** received that dose for 40 weeks out of 52. Ex. 2071 ¶67.

Second, the 2.5 week figure is the average dosing time across ***all*** of the tested doses, which ranged from the purportedly equivalent dose of 0.5mg/kg up to 10mg/kg. Ex. 2070, 118:11-119:7, 128:17-20. A POSA would have expected that patients administered the 0.5mg/kg dose would flare up earlier than patients receiving higher doses, particularly in view of the data from the DE001 study and its failure in the DE003 study. Ex. 2071 ¶67. Consequently, a POSA would have

expected that the dosing interval for the 0.5mg/kg dose would have been less than the reported 2.5 week average for all doses. *Id*.

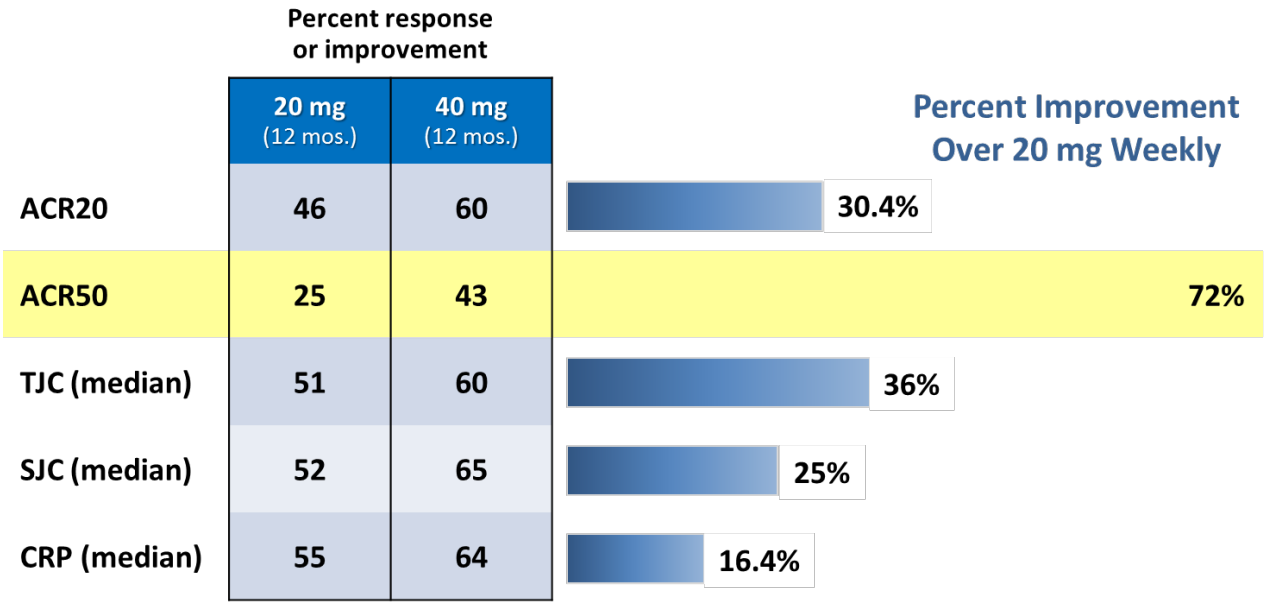
Third, under the DE003 protocol, if a patient relapsed before two weeks, the injection still would not be made until two weeks after the prior injection. Ex. 2040, 5. The mean dosing interval would thus skew towards a number higher than the average period during which a relapse would occur because it excluded patients that relapsed prior to two weeks. In other words, the reported mean dosing interval in the DE003 study would have been understood to be ***longer*** than the mean relapse time. Ex. 2071 ¶67.

Given these considerations, the "biweekly" dosing study of DE003 would not have directed a POSA towards every-other-week subcutaneous administration of 40mg, nor would it have resulted in a reasonable expectation that such a regimen would effectively treat RA.

c. The data in van de Putte taught away

The van de Putte abstracts demonstrate a trend of better efficacy with higher doses. Ex. 2071 ¶¶49-51, 80-82; Ex. 2075 ¶93. As explained in §II.A.2 above, weekly administration of 20mg of drug produced numerically inferior clinical results to the 40mg and 80mg weekly doses. Ex. 1008, 7. The van de Putte abstracts reporting 6- and 12-month data similarly showed that the 20mg weekly

dose was numerically inferior to the 40mg weekly dose.[9] Ex. 2086, 2; Ex. 2090, 5; Ex. 2075 ¶94; Ex. 2071 ¶¶81-82. This is illustrated graphically in the following demonstrative for the 12-month data.



These data indicate that the 20mg weekly van de Putte regimen was a sub-optimal dose. Ex. 2071 ¶¶79-82. Although not prior art, the full-length, peer-reviewed article reporting on the DE007 study, published long before this proceeding, reinforces this conclusion. It states that "[i]n most measures of efficacy at week 12, adalimumab [D2E7] 40 mg was associated with better results than the other doses." Ex. 2041, 9; Ex. 2075 ¶95.

[9] Rheumatologists routinely rely on numerical trends, even if not statistically validated. Ex. 2071 ¶85; Ex. 2057, 6; Ex. 2026, 4-6; Ex. 2142, 18.

2. The available PK data taught away from the claimed invention

Based on the half-life of D2E7 (which Petitioner's PK expert now characterizes as merely "supportive"), Petitioner argues that a POSA would have considered an every-other-week dose of 40mg to be "equivalent" to the 20mg weekly dose reported in van de Putte. Pet. 28; Ex. 2069, 119:22-120:2. Specifically, Petitioner argues that "the approximate amount of D2E7 circulating in the body two weeks after administering a 40 mg dose would have been roughly one half that dose (*i.e.*, approximately 20 mg)," an amount that "would have been considered clinically effective in light of van de Putte 1999." *Id.* As demonstrated in the declaration of Dr. Vinks, this analysis is incorrect. Ex. 2075 ¶¶17-19, 121.

a. The C_{min} values of an every-other-week dose would have been lower than those of a weekly dose

Both fundamental PK principles and the available PK data, including half-life, would have discouraged a POSA from the claimed dosing regimen because they would have suggested that a 40mg every-other-week dose would have delivered too low a dose of D2E7 to be safe and effective. *Id.* ¶123. In particular, a POSA would have expected that the C_{min} of the claimed invention would be substantially ***lower*** than the C_{min} of the prior art van de Putte regimens. *Id.* ¶¶43-45. This is significant. As explained by Petitioner's expert Dr. Jusko, C_{min} was regarded as "the most important factor" in dose determination for anti-rheumatic

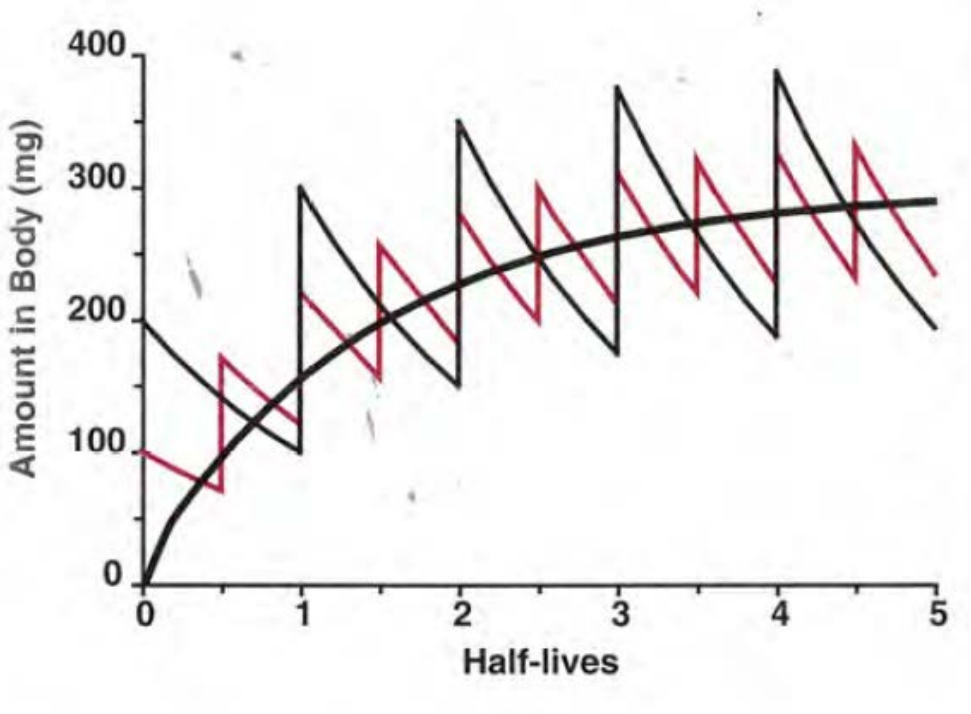
drugs because it is critical to maintain prolonged exposure at the site of action. Ex. 2052, 9.

The critical problem in Petitioner's analysis is its failure to consider and compare the PK profile of the two allegedly "equivalent" dosing regimens once a steady state has been reached.[10] Ex. 2075 ¶122. RA is not treated with a single dose. It is a chronic disease requiring long-term treatment. Ex. 2071 ¶25; Ex. 2093, 3; Ex. 2075 ¶38; Ex. 1003 ¶14; Ex. 2070, 239:20-240:8. This is why van de Putte analyzed efficacy at 3 months, not following a single administration. Ex. 2075 ¶123; Ex. 2069, 88:4-14. This is also why the claims expressly require dosing every-other-week "for a time period sufficient to treat the rheumatoid arthritis." Ex. 1001, 45:16-17. Indeed, claims 3 and 4 specifically require treatment for periods of at least 24 weeks. *Id*., 45:30-46:12. A POSA seeking to develop a method for treating RA would have focused on the profile of a drug over multiple administrations in which the course of treatment has reached a steady-state (in other words, when the trough (C_{min}) and peak (C_{max}) drug levels remain

[10] Steady-state concentrations are reached when the amount of drug eliminated from the body over each dosing interval is equal to the amount that was absorbed into the body after the previous dose. *E.g.*, Ex. 2069, 87:20-88:3; Ex. 2075 ¶39.

stable and are no longer increasing). Ex. 2075 ¶¶39-42; Ex. 2069,87:20-88:3; *see generally* Ex. 2091, 54-76.

Given the implications for Petitioner's obviousness theory, it is not surprising that the Petition fails to address steady-state concentrations. A basic PK principle is that increasing the dosing interval of a drug while maintaining the total exposure to the drug (*e.g.*, doubling both the dose amount and the interval between doses) will result in higher peaks and lower troughs of drug concentration at steady-state. Ex. 2075 ¶¶43-44, 123. The figure below, extracted from a well-known pharmacokinetics textbook, illustrates this principle. Ex. 2094, 11. The figure shows the PK profiles for a drug given either as 200mg once every half-life (black line) versus a drug given as 100mg twice every half-life (red line). Ex. 2075 ¶44. Administration of double the dose and double the dosing interval results in higher peak (C_{max}) and lower trough (C_{min}) concentrations. As explained by the authors, "the less frequent the administration, the greater is the fluctuation." Ex. 2094, 11.



Id., Fig. 11-3. This principle is shown in prior art textbooks and articles and is conceded by Petitioner's PK expert, Dr. Jusko. Ex. 2091, 57-58; Ex. 2098, 7; *see also* Ex. 2112, 13; Ex. 2094, 11; Ex. 2069, 125:5-16, 126:1-10. In light of this principle, a POSA would not have considered the claimed 40mg regimen and the 20mg weekly van de Putte regimen to be "equivalent," as Petitioner argues. Pet. 28. This alone is sufficient to overcome Petitioner's PK arguments.

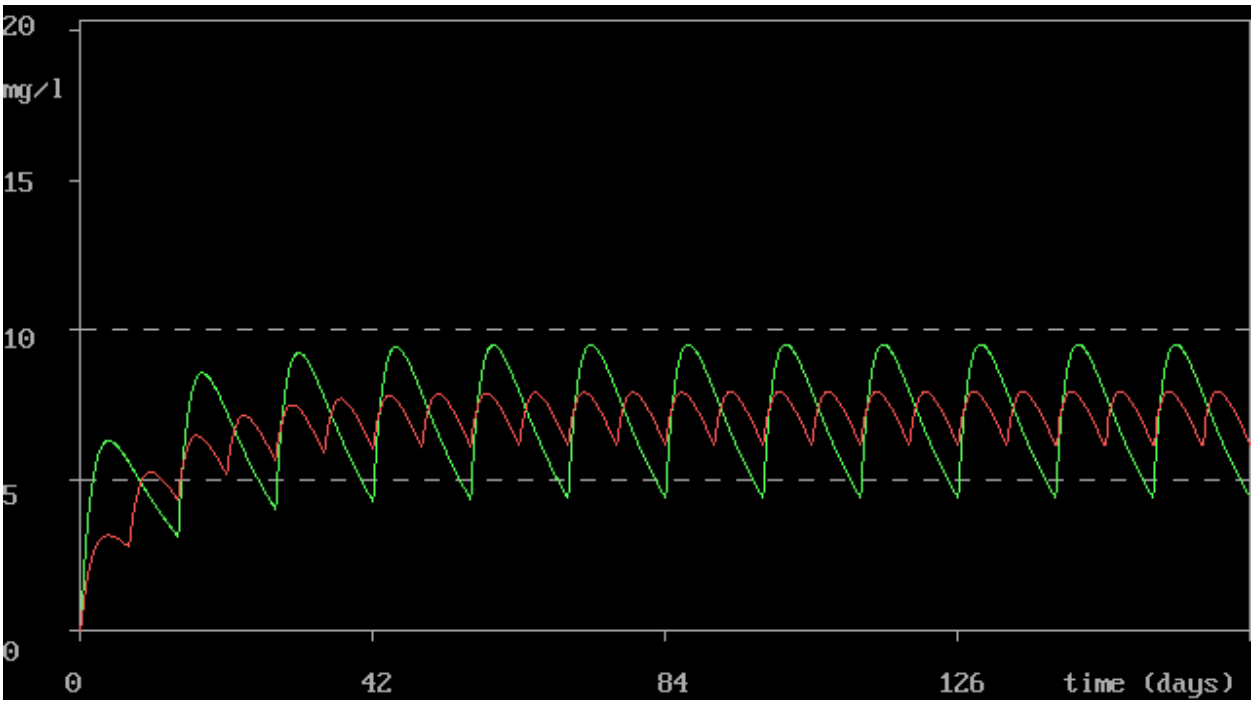
b. The difference in C_{min} values between a weekly 20mg dose and an every-other-week 40mg dose would have been significant

Dr. Jusko asserts that a POSA would have understood that the expected differences in steady-state C_{min} values between a weekly 20mg dose and an every-

other-week 40mg dose would be insignificant. Ex. 1004 ¶26. But modeling performed by Dr. Vinks indicates otherwise. Ex. 2075 ¶133.[11]

Using methods available to a POSA in June 2001 and certain conservative assumptions about the patient population and the rate of absorption, Dr. Vinks used the mean clearance (CL) and volume of distribution (Vd) information reported in Kempeni to model predicted concentrations over time for both the claimed invention and those resulting from the 20mg weekly regimen of van de Putte. *Id.* ¶¶134-138; *see* Ex. 2095; Ex. 2096. As expected, at steady-state, the claimed regimen (in green) shows ***higher peak concentrations*** and ***lower trough concentrations*** than the 20mg weekly van de Putte regimen (in red). Ex. 2075 ¶139.

[11] Dr. Vinks' modeling used the data available in the prior art. That data would have been viewed as insufficient to actually develop a predictable dosing regimen for D2E7 as of June 2001. Ex. 2075 ¶¶131-32. However, Dr. Vinks' modeling shows that the available PK data taught away from the claimed invention because it indicated that the steady-state trough concentrations for the claimed dosing regimen would have been too low. Ex. 2075 ¶¶140-147.



To address the effect of dose-stretching across the patient population, Dr. Vinks modeled multiple combinations of the mean clearances and distribution volumes reported in Kempeni (testing each possible combination using the high and low ends of the reported ranges). Ex. 2075 ¶143. At steady-state, every combination he modeled resulted in greater fluctuations for the 40mg every-other-week regimen versus the 20mg weekly van de Putte regimen. *Id.* ¶147. Further, at steady-state, ***every combination*** he modeled resulted in lower predicted C_{min} values for the claimed 40mg every-other-week regimen versus the 20mg weekly van de Putte regimen. *Id.* ¶144.

In each case, the predicted difference is substantial. *Id.* ¶145. For example, the percent difference in predicted steady-state C_{min} levels ranged up to 41%, meaning that certain patients could experience trough levels that were much lower

under the 40mg every-other-week regimen compared to the 20mg weekly regimen. Moreover, in each model, for four consecutive days out of the fourteen day dosing interval—more than half a week—patients receiving the 40mg every-other-week regimen would have less drug in their system than at any point in the 20mg weekly regimen. *Id*. ¶146. This could be the difference between a drug working and a drug not working. *Id.* ¶148-149, 168-171; Ex. 2098, 6; Ex. 2079, 9.

But even this substantially underrepresents the actual variability in C_{min} levels that would have been expected among different patients in the population for at least two reasons. First, Kempeni does not report standard deviations for these PK parameters (Ex. 1011, 4), so the variability is based only on estimated mean values and does not reflect the true variability among different patients in the population. Ex. 2075 ¶150.

Second, for subcutaneously administered D2E7, a POSA would have expected additional variability among different patients based on the rate of absorption and the extent of bioavailability (the Kempeni values are based on an intravenous dose). *Id.* ¶¶127-128, 150; *see also* Ex. 2077, 7, 9; Ex. 2018, 8-9. These additional sources of variability would have increased the distribution of values around the average C_{min} levels, particularly for the claimed 40mg regimen. *Id.* Consequently, more patients would experience lower than average C_{min} levels in the 40mg every-other-week regimen than in the 20mg weekly regimen. *Id.* This

would have been a particular concern for a fixed-dose regimen (as claimed), rather than a weight-based regimen.

The low C_{min} values expected for the claimed dosing regimen would have been a particular concern given the clinical data discussed in §IV.A1 above, including the evidence of up-dosing. In particular, doses that Petitioner asserts are equivalent to the claimed 40mg dose needed to be up-dosed to higher doses, strongly suggesting that the difference between the C_{min} values of a 20mg weekly dose and a 40mg every-other-week dose would have been expected to be clinically meaningful. Ex. 2075 ¶154-157. A POSA would have thus been deterred from administering 40mg every-other-week and would not have reasonably expected that the claimed dosing regimen would work. *Id*. 124, 158-159.

c. The lower C_{min} of an every-other-week regimen would have raised concerns about anti-drug antibodies

The lower expected trough levels for the 40mg every-other-week regimen would have been of particular concern to a POSA due to the risk of developing ADAs. Ex. 2071 ¶¶20, 35, 91-92; Ex. 2074 ¶¶10, 13-15; Ex. 2075 ¶¶61-62, 160-161. ADAs were known to cause a range of adverse effects, including serious reactions such as anaphylaxis. *See, e.g.*, Ex. 2075 ¶66; Ex. 2074 ¶¶20-21; Ex. 2137, 6; Ex. 2106, 38; *see also* Ex. 2138, 5. ADAs also have the potential to lessen or destroy a biologic's efficacy by increasing clearance of the administered biologic and/or interfering with the biologic's ability to bind to its target. Ex.

1022, 5, 14; Ex. 2074 ¶¶22-25, 28; Ex. 2075 ¶¶67, 72-74; Ex. 2024, 6; *see also* Ex. 2106, 37; Ex. 2109, 7; Ex. 2115, 9; Ex. 2139, 4; Ex. 2138, 5; Ex. 2034, 3; Ex. 2100, 10; Ex. 2069, 159:25-160:24. In other words, ADAs have the potential to abolish efficacy entirely.

It was known that the risk of developing ADAs increased as serum concentrations of the biologic decreased. Ex. 2074 ¶¶16-18; Ex. 2024, 12, 14; Ex. 2116, 6, 8; Ex. 2117, 4; Ex. 2100, 9; Ex. 2075 ¶¶68-69; *see also* Ex. 2115, 9. Clinical data with REMICADE®, for example, showed an ***inversely*** proportional relationship between dose and ADA formation, with lower doses resulting in higher levels of ADAs. Ex. 2024, 12; Ex. 2074 ¶16; Ex. 2071 ¶91. This inverse relationship is consistent with the immune system's typical response of producing antibodies after intermittent exposure to foreign antigens—lower antibody doses translate into lower serum concentrations, which mirror intermittent antigen exposure. *See, e.g.*, Ex. 2075 ¶70; Ex. 2074 ¶¶16-18. Because lengthening the dosing interval was known to cause lower trough concentrations, it carried an increased risk of developing ADAs. Ex. 2075 ¶161; Ex. 2074 ¶¶16-18; *see also* Ex. 2071 ¶93.

It was also appreciated that biological drugs administered subcutaneously often display greater immunogenicity than drugs administered intravenously. Ex. 2074 ¶19; Ex. 2075 ¶71; Ex. 2122, 3, 8; Ex. 2101, 14; *see also* Ex. 2123, 4, 17; Ex.

2124, 3; Ex. 2125, 9; Ex. 2081, 4, 10. This was believed to occur because subcutaneous administration exposes the drug to antigen-presenting cells in the extravascular space, which in turn stimulates ADAs. Ex. 2074 ¶19.

Drs. Weisman and Jusko acknowledge the issue of ADAs but dismiss any concern about them based on the lack of reports in the literature. Ex. 1003 ¶40 n.7; Ex. 1004 ¶25. The art, however, is replete with warnings about the risks posed by ADAs. In particular, the FDA had specifically identified the development of ADAs "following repeated courses of treatment" as a "particular concern with biological agents" used to treat RA. Ex. 1022, 14; Ex. 2075 ¶1664. Petitioner's suggestion that a POSA would not have been concerned about ADAs for D2E7 ignores the prior art's experience with REMICADE®, ENBREL®, and the anti-TNFα agent lenercept, which was abandoned as of June 2001 because of ADAs. Ex. 2024, 12, 14; Ex. 1011, 3; Ex. 2029, 7; Ex. 2100, 9-10; Ex. 2101, 20; Ex. 2060, 3; Ex. 2061, 3; Ex. 2099, 3; Ex. 2070, 233:3-24, 238:20-239:17. Ex. 2075 ¶¶63-64.

That the existing D2E7 literature did not report the actual detection of ADAs is both unsurprising and of no probative value. As an initial matter, the D2E7 prior art warned that allergic reactions could be caused by "idiotypical epitopes," which are portions of antibodies that differ among patients that can stimulate the body's immune response. Ex. 2074 ¶13; Ex. 2075 ¶65. More fundamentally, as of June

2001, the techniques for detecting ADAs were limited, typically requiring long washout periods to prevent the drug from interfering with the assays. Ex. 2074 ¶¶11, 29-36; Ex. 2104, 22; Ex. 2069, 169:13-18; *see also* Ex. 2024, 12; Ex. 2106, 37; Ex. 2107, 6-8; Ex. 2109, 19; Ex. 2058, 5; Ex. 1028, 3; Ex. 2070, 197:9-20. Because the D2E7 prior art trials were ongoing, there was no opportunity for the long washout periods needed to detect ADAs. Thus, a POSA would not have assumed from the meager record of prior clinical trials that ADAs did not pose a risk. Ex. 2074 ¶¶12, 37-39; Ex. 2075 ¶165; *see also* Ex. 2071 ¶¶77-78; Ex. 2038, 7; Ex. 2145, 1; Ex. 2060, 3; Ex. 2070, 231:25-233:25; 234:12-235:14 (acknowledging there was not enough information based on early studies of lenercept to state that ADAs would not be a problem).

Petitioner's reliance on the absence of evidence of ADAs in the D2E7 prior art is also illogical. The claimed dosing regimen is different from any regimen tested in the prior art, would have been expected to repeatedly produce lower trough levels, and consequently would have been expected to be more vulnerable

to development of ADAs. That less vulnerable regimens might have avoided the problem would not have ameliorated concern over this new treatment.[12]

3. Half-life does not provide sufficient information to design a dosing regimen

Concern about low blood levels is not the only consideration that would have counseled against relying on terminal half-life in devising a dosing regimen. Such reliance also would have been at odds with what was known in the art about the relevance of terminal half-life to developing a dosing regimen. Ex. 2075 ¶¶114-115, 126.

In particular, terminal half-life does not impart any information about drug concentration, the key determinant of safety and efficacy. *Id.* ¶37, 109. A POSA would have ideally designed a dosing regimen based on the concentration-response relationship of the drug in the body, taking into consideration the site of drug action. *Id.* ¶20-22, 45, 110, 116; Ex. 2112, 9 ("The aim of drug therapy is to achieve promptly and maintain a ***concentration of drug*** at the appropriate ***site(s) of action*** which is both clinically efficacious and safe for the desired duration of treatment.") (emphases added); Ex. 2069, 18:22-19:9 (admitting that in his own

[12] When studies of D2E7 were finally published in a peer-reviewed journal, they confirmed the existence of anti-D2E7 antibodies and their link to sub-therapeutic serum drug levels. Ex. 2119, 9; Ex. 2023, 5; *see also* Ex. 2111, 29.

work, Dr. Jusko designed dosing regimens based on "plasma concentrations over time" rather than half-life); *see also* Ex. 2070, 38:12-39:5; 224:3-225:19 (acknowledging C_{min}/trough levels are considered and used to guide dosing in drug development). Terminal half-life does not provide information about drug concentrations in the blood or at the site of action, nor does it provide any information as to how those concentrations correlate to safety and efficacy. Ex. 2075 ¶111. No information about drug concentrations in the blood or at the site of action, or the correlations of those concentrations to safety or efficacy, was publicly known at the relevant time.

Both the Federal Circuit and the Board have acknowledged the importance of complete PK/PD data when assessing the obviousness of a dosing regimen. *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) (claims to therapeutically effective dosage forms non-obvious because of the lack of a known PK/PD relationship); *see also Avanir Pharms., Inc. v. Actavis S. Atl., LLC*, 36 F. Supp. 3d 475, 487, 506 (D. Del. 2014) (stating that efficacy cannot be predicted "based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown"), *aff'd, Avanir Pharms. Inc. v. Par Pharm. Inc.*, 612 F. App'x 613 (Fed. Cir. 2015) (affirmance via Rule 36); *Dr. Reddy's Labs., Ltd. v. Galderma Labs., Inc.*, IPR2015-01782, Paper 10, 20-21 (Feb. 16, 2016) (denying institution despite prior

art's disclosure of drug half-life because petitioner failed to address the PK/PD relationship between peak drug levels and therapeutic effects).

Indeed, terminal half-life (what is reported in Kempeni) does not even tell a POSA how long the drug remains in the body. Ex. 2075 ¶¶110-112. It is a measure of drug elimination ***after*** the absorption and distribution phases—phases that can last days in the case of a subcutaneous administration. *Id.* ¶¶26-27, 33; Ex. 2017, 31; Ex. 2069, 101:1-13. And terminal half-life does not provide any information about how long a drug lasts ***at the site of action***. Ex. 2075 ¶117; *see also* Ex. 2069, 104:25-105:4 ("[t]erminal half-life doesn't tell you anything about the concentration of D2E7 in the joints"). In June 2001, it was uncertain whether, in treating RA, D2E7 would act on TNFα in the blood and/or at the site of inflammation, *e.g.*, in the synovial fluid of the joints. Ex. 2075 ¶118; *see also* Ex. 2113, 9; Ex. 2114, 2. It was also unknown whether measurements of drug levels in blood would correlate with concentrations in synovial fluid. Ex. 2075 ¶¶117-118. Thus, the terminal half-life values reported in Kempeni would not have informed a POSA about how long D2E7 would last in synovial fluid. *Id*. ¶119.

There is, moreover, no logical or scientific principle that would suggest that a dosing interval should be the same as or similar to the terminal half-life of a drug. Ex. 2075 ¶113; *see also* Ex. 2128, 6. On the contrary, in the absence of additional PK or PD data, designing a dosing regimen to be the same as a drug's half-life

ensures substantial fluctuations of drug concentrations, which are often undesirable. Ex. 2075 ¶44.

As of June 2001, the experience with other therapeutic antibodies also would have suggested that half-life alone could not be used as a surrogate or predictor for establishing dosing interval in any periodic dosing regimen. Ex. 2075 ¶¶114-115; *see also* Ex. 2128, 5. The lack of correlation between half-life and dosing interval, ignored entirely by Petitioner and its experts, is shown by these prior art FDA-approved antibodies:

- REMICADE® is dosed about once every 3 to 6 half-lives (Ex. 2029, 6, 8; Ex. 2069, 114:15-115:21);
- RITUXAN® is dosed about once every 2.8 half-lives (Ex. 2007, 1, 2;);
- MYLOTARG® is dosed about once every 5 half-lives (Ex. 2013, 3, 17); and
- ZENAPAX® is dosed about once every 0.6 half-lives (Ex. 2010, 1, 2).

Because these prior art therapeutic antibodies were dosed both more and less frequently than their half-lives, a POSA would have understood that other factors must be considered when determining dosing intervals for antibodies such as D2E7. Ex. 2075 ¶115.

4. Doubling both the dose and interval between doses can abolish efficacy irrespective of "linear pharmacokinetics"

Petitioner argues that the purported "linear pharmacokinetics" of D2E7 would have suggested that D2E7's half-life would not appreciably change across the 20, 40, and 80mg doses, and that accordingly enough D2E7 would remain in the body between every-other-week administration of 40mg doses. Pet. 30; Ex. 1004 ¶¶18-21.

As an initial matter, this ignores the substantially different steady-state peak and trough drug levels that would have been expected among these different multi-dose regimens. *See supra* §IV.A.2. It ignores clinical data teaching away from the claimed invention. *See supra* §IV.A.1. And it overstates the significance of terminal half-life in setting a dosing interval. *See supra* §IV.A.3. As Dr. Jusko wrote outside the context of this case, "[d]ose and interval selection" (not half-life) "control the magnitude of the peak and trough concentrations." Ex. 2051, 7.

Further, AbbVie's own experience with an 80mg monthly D2E7 dosing regimen demonstrates the unreliability of the analysis undertaken by Dr. Jusko. Under Dr. Jusko's "linear pharmacokinetics" analysis, 20mg weekly, 40mg every-other-week, and 80mg once every four weeks should produce equivalent results because the same total amount of drug is allegedly being delivered in each regimen. *See* Ex. 1004 ¶24. But in an actual clinical study, subcutaneous injection of 80mg D2E7 on a monthly basis was found to be no better than placebo for

ACR20, the primary outcome measure of the study. Ex. 2015, 6. Specifically, "***superiority*** of adalimumab [D2E7] 80 mg compared with placebo ***could not be claimed***" because no difference was observed in the primary efficacy endpoint (ACR20). *Id.*, 5 (emphasis added); Ex. 2071 ¶95; Ex. 2075 ¶170.

Although failed experiments and clinical results are frequently unreported, numerous examples of this sort of unpredictability exist in the art. For example, a 2000 publication authored by Dr. Vinks modeled the effect of two different dosing regimens of the same antibiotic on bacterial killing—5mg/kg administered every 12 hours versus 10mg/kg administered every 24 hours. Ex. 2075 ¶168-169; Ex. 2098, 6. The 5mg/kg dose administered every 12 hours resulted in bacterial eradication. Ex. 2075 ¶168. In contrast, the 10mg/kg dose administered every 24 hours permitted bacterial regrowth. *Id.* In other words, doubling the dose and interval between doses resulted in the study drug becoming ineffective. *Id.* ¶169.

Similarly, Dr. Jusko reported in 1999 that 4mg of a drug delivered twice daily produced superior results to once daily dosing of 8mg. Ex. 2053 ¶0091. He further reported that the concentration of drug remained above a particular critical threshold for 21 hours following twice daily dosing of 4 mg as compared to 14 hours for once daily dosing of 8 mg. *Id*. Notwithstanding purported linear pharmacokinetics, maintaining drug levels above a particular concentration was

represented to be more important than total exposure or AUC. Ex. 2054, 6; Ex. 2069, 158:23-159:20; Ex. 2140, 2; Ex. 2075 ¶171.

5. Patent Owner has never "admitted" equivalence between a 20 mg weekly dose and a 40 mg biweekly dose

Petitioner alleges that several non-prior art documents draw an equivalence between the weekly 20mg dosing regimen of van de Putte and the claimed regimen. Pet. 29. This attempt to bootstrap crop-quoted, non-prior art statements into its analysis, made with full knowledge of the claimed invention, is unavailing.

First, Petitioner misleadingly truncates a quote in suggesting that Patent Owner "admitted" the claimed dose and a 20 mg weekly dose would be considered equivalent in submissions to the European Patent Office ("EPO"). As Petitioner notes, Patent Owner informed the EPO of the truism that "over time," patients treated with a 40 mg every-other-week dose would receive the "same amount of D2E7 as those treated in the DE007 trial with [a] 20 mg flat dose weekly." Ex. 1023, 45; *see* Pet. 29. But in the very next sentence, which the Petition fails to quote, Patent Owner advised the EPO that "[e]xcept for the moments where the respective concentrations cross, for almost all of the time patients treated in the two different ways, 20 mg weekly versus 40 mg biweekly, have different amounts of bioavailable D2E7 remaining in their system." Ex. 1023, 45. Patent Owner further explained that the PK profiles would have been understood as "***completely different*** for 20 mg administered every week as compared to 40 mg administered

biweekly." *Id.*, 47 (emphasis added). As discussed above, not only would this difference in "respective concentrations" over time have led a POSA to understand that the two dosing regimens would have been non-equivalent, the difference would have affirmatively taught away from the claimed invention.

Petitioner also quotes from a table submitted to FDA (and thereafter reproduced by FDA) addressing the risk of tuberculosis and other opportunistic infections. Pet. 29; Ex. 1016, 2; Ex. 1017, 109. To make comparisons across different clinical trials, Patent Owner "assumed" that every-other-week doses were "similar to one-half the same dose given weekly." Ex. 1016, 2. This was not a broader admission about the comparability of these doses, but rather a post-hoc assumption made for the limited purpose of comparing infection rates reported in different clinical trials involving different dosing regimens.

B. The Claimed Invention Is Not Invalid Under An "Obvious To Try" Theory Or The Result Of "Routine Optimization"

As an alternative to its reliance on evidence of a reason or motivation to modify the prior art, Petitioner argues that "[a]t a minimum," the claimed invention would have been "obvious to try in view of the finite number of fixed dosing options (20, 40, and 80 mg) employed in van de Putte 1999 and a reasonable expectation of success based on one of ordinary skill's understanding of D2E7's

properties, including its long half-life." Pet. 30.[13] As an initial matter, it is fundamental patent law that an invention cannot be "obvious to try" where the prior art taught away from that invention. *Takeda*, 492 F.3d at 1359; *Leo*, 726 F.3d 1357. As explained in Section IV.A above, that is the case here.

Further, Petitioner's argument attempting to restrict the available options to van de Putte 1999 ignores the teachings of the prior art as a whole, while its reliance on D2E7's "long half-life" misconstrues what the available clinical and PK data would have taught.

Nothing in the Federal Circuit's precedent suggests that, in evaluating the options in the prior art, a POSA would be limited to the options in a single reference. For example, in *Hoffman-La Roche, Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331-32 (Fed. Cir. 2014), on which Petitioner relies, the Court examined two references disclosing six efficacious dosing regimens in the prior art in the context of teachings that efficacy depended only on the "total oral dose given rather than on the dosing schedule." Given this state of the art, the Court understandably found there were only a "finite number of identified, predictable solutions." *Id.* at 1332 (citing *KSR*, 550 U.S. at 421). Here, in contrast, a POSA seeking to develop

[13] Petitioner makes essentially the same argument with respect to Ground 2 (Pet. 45-46), and it fails for the same reasons.

a D2E7 dosing regimen would have been faced with numerous clinical trials in the prior art testing different doses, routes of administration, and dosing frequencies and a large range of different dosing regimens. The breadth of variables tested in the prior art demonstrates the complexity of the challenge skilled scientists faced in their attempts to treat RA with this novel drug. If one were to artificially restrict these variables to those reported in the prior art relied on by Petitioner (*i.e.*, route of administration: intravenous or subcutaneous; dose: 0.5mg/kg, 1mg/kg, 3mg/kg, 5mg/kg, 10mg/kg, 20mg, 40mg, 80mg; interval: weekly, every-other-week, when response status is lost; co-administration: with methotrexate or without), there are 96 dosing regimens possible. Ex. 2071 ¶75; *see also* Ex. 2070, 50:7-52:6; 53:9-54:17 (acknowledging various routes of administration, doses, and dosing intervals for D2E7 disclosed in the prior art). If one adds additional variables that actually would have confronted a POSA designing a new D2E7 dosing regimen, the options increase exponentially. These would have included doses and intervals other than those used in the references relied on by Petitioner, doses and intervals other than those previously reported, use of a loading dose, co-administration with agents other than MTX, or individualization based on disease severity or comorbidities. Ex. 2071 ¶75.

Moreover, even if the claimed invention would have been "obvious to try," it was not a "predictable solution," the second requirement of *KSR*'s formulation of

an obvious to try defense. *KSR*, 550 U.S. at 421 (express motivation to modify in the prior art may not be necessary where there are a "finite number of identified, predictable solutions"). For the reasons explained above, half-life would not have led a POSA to predict that the claimed regimen would work, while the available PK and clinical data would have suggested to a POSA that it would not. *See supra* §IV.A.1-3.

Petitioner also cannot avoid its burden of proving obviousness by resort to the claim that the invention is merely the result of "routine optimization." "Routine optimization" is not a legal test that can be relied on in lieu of evidence showing a reason or motivation to modify the prior art and a reasonable expectation of success. It is a label applied to the ultimate conclusion of obviousness after the issue has been analyzed under the standards enunciated in *KSR* and elaborated on by the Federal Circuit. *KSR*, 550 U.S. at 421; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364-66 (Fed. Cir. 2007) (first finding a motivation to modify the prior art and a reasonable expectation of success before discussing "routine optimization" in the context of "obvious to try").

Here, the Petition's discussion of "routine optimization" is devoted to arguing that all three doses disclosed in van de Putte were candidates for further experimentation. But this is just another version of Petitioner's obvious to try argument, which ignores both the evidence of other efficacious doses and dosing

regimens disclosed in the prior art and the evidence that teaches away in the prior art. Given the small number of patients involved and the minimal data reported in the prior art publications, as well as the preliminary nature of data reported in abstracts, a POSA would not have known which of the many tested regimens (involving different doses, intervals and routes of administration) would prove safe and efficacious across a larger patient population over extended periods of time or should be a candidate for further experimentation. Ex. 2071 ¶¶76-78.

Simply put, determining a safe and efficacious dosing regimen of a new biologic during clinical trials is not the result of routine experimentation. *See* Ex. 2072 ¶¶7-9, 11-17. Poor dose selection was ***the leading reason*** for delay and denial of FDA approval for new drug applications. Ex. 2080, 4, 6; Ex. 2072 ¶18. Sponsors are frequently forced to abandon once promising new biologics in the later stages of clinical trials even after years of development. Ex. 2072 ¶¶9, 19-20.

BioMarin Pharm. Inc. v. Genzyme Therapeutic Products Ltd., IPR2013-00534, Paper 81 (Feb. 23, 2015), relied on by Petitioner, is inapposite. Unlike *BioMarin*, where the Board determined that there were not "'numerous parameters' to try" (*id*. at 17), the dosing regimen claimed in the '135 patent involves multiple parameters, including the route of injection, the schedule, the amount dosed, and the period of time required, all of which were still being investigated and were unsettled in the prior art. Ex. 1001; *see* Ex. 2071 ¶75. And unlike *BioMarin*, the

available D2E7 clinical and PK/PD information taught away from the claimed invention. *See supra* §IV.A.1, 2.

C. Objective Indicia Support the Non-Obviousness of the Claims

Real-world evidence demonstrates the patentability of the challenged claims. Objective indicia "are not just a cumulative or confirmatory part of the obviousness calculus but constitute[ ] independent evidence of nonobviousness." *Leo*, 726 F.3d at 1358 (internal quotation omitted).

1. There was a long-felt but unmet need for new RA therapies

As of June 2001, there was an unmet need for new treatments for RA. Ex. 2071 ¶¶102-103; Ex. 2070, 143:9-21. Prior to the introduction of anti-TNFα biologics, traditional remedies were inadequate to treat moderate-to-severe RA. Ex. 2071 ¶¶26-30. The gold standard was methotrexate, an immunosuppressant with substantial side effects. *Id.* ¶29; *see also* Ex. 2083, 10. Few patients achieved complete remission using traditional therapies. Ex. 2071 ¶29; *see also* Ex. 2084, 25; Ex. 2085, 3

Anti-TNFα agents represented a breakthrough in treatment, but only two were approved as of 2001—ENBREL® and REMICADE®. Ex 2071 ¶¶31-33, 74. Both drugs were dosed, as Petitioner admits, in a manner with significant clinical disadvantages. *E.g.*, Pet. 31. ENBREL® required patients to inject themselves twice a week. Ex 2071 ¶39. REMICADE® was administered intravenously,

requiring patients to travel to a doctor's office for each administration of the drug. *Id.* Moreover, neither drug was effective in all patients. *Id.* A need thus existed for additional biologics with more advantageous dosing regimens. *Id*.

Others companies tried and failed to satisfy this need. Ex. 2071 ¶¶98-101; *see also* Ex. 2061, 2; Ex. 2087, 11; Ex. 2144, 3; Ex. 2034, 3-4; Ex. 2088, 4. Roche failed with an anti-TNFα fusion protein, lenercept, the dosing regimen of which generated unacceptable levels of ADAs. Ex. 2071 ¶99; Ex. 2144, 3; Ex. 2148, 8; Ex. 2061, 2; Ex. 2070, 235:21-239:17. Celltech failed with a humanized anti-TNFα antibody that also produced ADAs. Ex. 2071 ¶98; Ex. 2154, 2; Ex. 2087, 11 In contrast, D2E7 succeeded because the scientists who developed it designed a safe and effective dosing regimen for RA that has been successfully used to treat hundreds of thousands of patients. Ex. 2071 ¶¶96-97.

2. Despite low predicted trough levels, the claimed invention is unexpectedly effective

As detailed above, the available PK and clinical information would have suggested to a POSA that the claimed dosing regimen would have been insufficient to treat RA because the predicted steady-state trough concentrations (C_{min}) were substantially lower than those of the van de Putte regimens. Ex. 2075 ¶178. Given the predicted lower trough levels, a POSA also would have been concerned about the formation of ADAs and their associated effects on both safety and efficacy. *Id.* ¶¶72-74, 160-161. Inter-patient variability among the RA patient population

would have exacerbated these concerns. Ex. 2075 ¶¶48-51, 129; Ex. 2070, 141:10-143:7; 254:20-255:21; *see also* Ex. 2091, 13; Ex. 2130, 6.

The available PD information also taught away from any dosing regimen that would have been expected to produce trough levels lower than those predicted for the 20mg weekly van de Putte regimen. Ex. 2075 ¶152. Indeed, the PD data that was available highlighted the need for administering doses higher than 40mg or at intervals more frequent than once every-other-week. *Id.* As detailed above, every prior art trial that tested the purportedly comparable dose of 0.5mg/kg (*e.g.*, a dose of 40mg for an 80kg patient) reported up-dosing patients to higher doses such as 1mg/kg (equivalent to 80mg) and 3mg/kg (equivalent to 240mg). *See supra* §II.A. This up-dosing occurred in trials involving intravenous administration, where absorption and bioavailability would not have been concerns. Ex. 2075 ¶¶155-156.

Yet since its introduction in 2003, the claimed dosing regimen has unexpectedly been one of the most effective treatments for RA. Ex. 2075 ¶179; Ex. 2071 ¶¶96-97. HUMIRA® is indicated for reducing signs and symptoms of RA, including major clinical response, and improving physical function in adult patients with moderately to severely active disease. Ex. 1024, 1; Ex. 1022, 5-9. As explained by Dr. Gibofsky, the claimed methods, featuring a "one-size-fits-all" dose of 40mg every-other-week, works remarkably well for a wide variety of

patients. Ex. 2071 ¶¶96-97. Patients experience an improved overall health-related quality of life. *Id.*

3. The claimed invention was a commercial success as a result of its efficacious and safe dosing regimen

HUMIRA® is the most successful pharmaceutical product in the world. This is remarkable because when it launched in 2003, HUMIRA® was the third anti-TNFα biologic introduced into the RA market, coming several years after the market leaders, Amgen's ENBREL® and J&J's REMICADE®. Ex. 2073 ¶¶8-12.

The ability of HUMIRA® to break into an already-established market is attributable to at least (1) the safety and efficacy of the claimed RA treatment, *id.* ¶¶14-15, and (2) the features of the treatment that differentiate it from the established competition, *id.* ¶¶16-28. The safety and efficacy of HUMIRA's® dosing regimen, as well as its differentiation from ENBREL® and REMICADE®, are due to the claimed invention as a whole—a regimen that specifies the biological agent (D2E7), the method of administration (subcutaneous), the dose (40mg fixed dose) and the dosing interval (13-15 days). *Id*. ¶¶14-15, 26-28. Because the safety, efficacy, and dosing superiority of HUMIRA® for RA are attributable to all of these elements in combination, there is a "nexus" between the commercial success and the claimed invention. *See WBIP, LLC v. Kohler Co*., 829 F.3d 1317, 1330 (Fed. Cir. 2016) ("it is the claimed combination as a whole that serves as a nexus for the objective evidence").

Moreover, a nexus between the claimed invention and commercial success is presumed to exist where, as here, "the patentee shows both that there is commercial success, and that the thing (product or method) that is commercially successful is the invention disclosed and claimed in the patent." *Demaco Corp. v. F. Von Langsdorff Licensing, Ltd.*, 851 F.2d 1387, 1392 (Fed. Cir. 1988); *Innopharma Licensing, Inc. v. Senju Pharm. Co.*, IPR2015-00903, Paper 82, 17-18 (July 28, 2016).

Petitioner's discussion of blocking patents is insufficient to prove lack of nexus. Pet. 57. The Federal Circuit in *Merck* did not, as Petitioner suggests, broadly hold that commercial success has no probative value where there is another patent blocking market entry. Rather, in *Merck*, the claimed invention was a modification of an already-marketed dosage. *Merck & Co., v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1377 (Fed. Cir. 2005). Here, by contrast, there was no approved D2E7 dosage, there was fierce competition among competing anti-TNFα biologics, including prior market entrants, and HUMIRA® distinguished itself on the basis of a unique and superior treatment method for RA claimed in the '135 patent. *See* Ex. 2073 ¶¶12, 22-28.

V. GROUND 2: THE CHALLENGED CLAIMS WOULD NOT HAVE BEEN OBVIOUS OVER RAU 1998 IN VIEW OF SCHATTENKIRCHNER 1998 AND VAN DE PUTTE

Ground 2 of the Petition alleges that the challenged claims are obvious over Rau 1998 in view of Schattenkirchner 1998 and van de Putte 1999. Pet. 40 Ground 2 is entirely redundant of Ground 1. Rau 1998 and Schattenkirchner 1998 discuss the same trials as Kempeni 1999 while adding no additional information material to the issue of patentability. Notably, Dr. Weisman devotes just seven paragraphs of his declaration to this alternate theory, while Dr. Jusko devotes only one. Ex. 1003 ¶¶45-51; Ex. 1004 ¶28. Accordingly, Ground 2 is contrary to the evidence for the same reasons as Ground 1 and is otherwise factually erroneous. Ex. 2075 ¶¶172-174.

First, as discussed above and contrary to Petitioner's allegations, the DE003 trial discussed Rau 1998 (and Kempeni 1999) would not have demonstrated that every-other-week dosing of D2E7 is both effective and desirable, much less that a 40mg every-other-week subcutaneous dose would be effective. Indeed, the DE003 trial involved intravenous, not subcutaneous dosing, delivered weight-based, not fixed doses, and was not an every-other-week dosing schedule at all—patients were at most dosed on a biweekly basis for a limited period of time until they responded to the drug. *Supra* §II.A.1, 3.

Moreover, Rau 1998 and Schattenkirchner do not demonstrate the efficacy of a 40mg every-other-week dose; they suggest that such a dose would be inadequate. *Supra* §II.A.3, 4. As discussed in §IV.A.1.a above, in both the DE003 and DE004 trials evaluating the 0.5 mg/kg dose (purportedly corresponding to a fixed dose of 40 mg) patients had to be ***up-dosed*** to as high as 3 mg/kg (or ***240 mg***, by Petitioner's calculation) due to inadequate clinical response. Ex. 1006, 5; Ex. 1011, 4-5; Ex. 1007, 5.

Neither Schattenkirchner nor van de Putte 1999 provides information that would have led a POSA to completely revamp the parameters of the DE003 regimen, as Petitioner's obviousness theory would require. In particular, a POSA would not have equated subcutaneous and intravenous routes of administration based on undisclosed, "preliminary data" from the DE004 trial reported in Schattenkirchner, which also utilized weight-based dosing. Ex. 1007, 5; Ex. 1011, 4, 5. A POSA also would have had significant safety and efficacy concerns regarding a subcutaneous, fixed D2E7 dosing regimen, including in particular the formation of ADAs. *See* §IV.A.2.c; *see also* Ex. 2071 ¶¶19, 88-90.

In what appears to be the only argument specific to Petitioner's second ground, Petitioner contends that "Patent Owner argued during prosecution that Rau 1998 does not disclose *only* every-other-week dosing," but that the Examiner nevertheless concluded that "Rau 1998 teaches every-other-week dosing. . . ."

Pet. 46-47 (citing Ex. 1002 at 784-85, 1001-02) (emphasis in original). This argument is misleading. The abstract being discussed by both the Patent Owner and the Examiner (called Rau #1 during prosecution) ***is not Rau 1998***, but an ***entirely separate reference,*** published in a ***different year*** and ***journal***, discussing a ***different clinical trial*** (DE0010, not DE003). Ex. 1002 at 784-85, 1000-02; *compare* Ex. 1006, *with* Ex. 2020. Rau #1 and statements made about it in prosecution are irrelevant to Petitioner's second ground.

Finally, as explained above in connection with Ground 1, the objective indicia confirm the non-obviousness of the claims.

VI. THE CLAIMS REQUIRE A THERAPEUTICALLY MEANINGFUL LEVEL OF EFFICACY

Given the evidence before the Board, the proper interpretation of the claims and the level of efficacy they require is irrelevant to resolving the IPR. As shown above, the evidence does not support the theories advanced by Petitioner, and consequently Petitioner has failed to carry its burden of proving that the claims are unpatentable under the theory underlying the Petition.

In any event, the claim terms at issue necessarily require a therapeutically meaningful level of efficacy. No clinician would consider himself or herself to be "treating" RA if there were no therapeutically meaningful reduction in the patient's signs, symptoms, and disease progression. Ex. 2071 ¶¶21, 104-105; *see* Ex. 2025, 3 (fundamental goal as of 2001 was to eliminate disease activity or control it to the

fullest extent possible); Ex. 2070, 242:8-245:1. If that were the case, then anything that had any effect on a patient's symptoms, no matter how minimal or short-lived (for example, an analgesic or intoxicant), would constitute "treatment." Ex. 2071 ¶104. That is simply not how a physician seeking to reduce the signs, symptoms, and disease progression would understand his or her clinical objective (both then and now). *Id.*

Thus, to the extent the Board believes the claims do not require meaningful therapeutic efficacy, Patent Owner respectfully requests reconsideration of that construction. Instead of applying a claim construction that requires no level of efficacy whatsoever, the Board should adopt the construction originally proposed by Patent Owner—i.e., "for a time period sufficient to reduce significantly the signs and symptoms of rheumatoid arthritis." Paper 9, 6. A POSA would have recognized that the specification provides clinically meaningful outcome parameters for the treatment of RA. Ex. 2071 ¶¶104-105. Those same parameters are reported in the February 1999 FDA guidance for industry, which explained that new claims for treating RA could be established by reducing the signs and symptoms of validated composite endpoints such as ACR20. *See* Ex. 1022, 5-6; Ex. 2071 ¶104. Moreover, during prosecution, the Examiner acknowledged that the broadest reasonable interpretation of the claims encompassed "treating patients such that they achieve an ACR20 or a EULAR moderate response." Ex. 1002,

1541. Thus, Patent Owner's proposed construction is consistent with the teachings of the specification, as they would have been understood by a POSA in June 2001.

VII. CONCLUSION

For these reasons, Petitioner has not met its burden of showing, by a preponderance of the evidence, that claims 1-5 of the '135 patent would have been obvious. The Board should therefore order that claims 1-5 of the '135 patent have not been shown to be unpatentable.

Date: October 28, 2016

By: /Steven P. O'Connor/
Steven P. O'Connor, Reg. No. 41,225
Counsel for AbbVie Biotechnology Ltd.

CERTIFICATE OF COMPLIANCE

The undersigned hereby certifies that the foregoing PATENT OWNER'S RESPONSE contains 13,994 words, excluding those portions identified in 37 C.F.R. §42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: October 28, 2016

By: /Steven P. O'Connor/
Steven P. O'Connor
Reg. No. 41,225

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on October 28, 2016, in its entirety on the following:

Naveen Modi
Paul Hastings LLP
875 15th Street, N.W.
Washington, D.C. 20005

Eric W. Dittmann
Bruce M. Wexler
James T. Evans
Paul Hastings LLP
200 Park Avenue
New York, NY 10166

Petitioner has consented to electronic service by email to Boehringer-IPR-PH@paulhastings.com.

/Steven P. O'Connor/
Steven P. O'Connor
Reg. No. 41,225