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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CELLTRION, INC.,
Petitioner,

v.

GENENTECH, INC.,
Patent Owner.

Case IPR2017-01139
U.S. Patent 6,627,196

PATENT OWNER'S RESPONSE

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I. INTRODUCTION

The inventors of the '196 patent discovered that trastuzumab, the first antibody ever approved to treat breast cancer, could be administered on a three-week dosing regimen without compromising the safety or efficacy shown with weekly administration. Prior to trastuzumab's approval in September 1998, chemotherapy was the most common breast-cancer treatment. But for the estimated 25-30% of patients afflicted with virulent HER2-positive breast cancer, the prognosis was poor and life expectancy following a diagnosis was 12-18 months. Against this backdrop, oncologists welcomed the introduction of trastuzumab, which finally gave these patients hope.

Efforts to better understand and use this new therapy did not end when trastuzumab was first approved for weekly administration to treat metastatic breast cancer. Use of targeted antibody therapy to destroy or inhibit cancer cell growth was a novel approach that had been largely unsuccessful until the late 1990s. In addition, the biologic mechanism of trastuzumab differed dramatically from chemotherapy. With chemotherapy, clinicians sought to kill as many cancer cells as possible without causing side effects that were even worse than the cancer being treated. In contrast, trastuzumab was known to specifically target breast-cancer cells. Nevertheless, much remained to be studied and learned about this groundbreaking therapy.

The prior art relied upon by Petitioner reveals the extent to which skilled artisans were still learning about trastuzumab, and does not support the contention that the claimed dosing regimens would have been obvious. There is no dispute that the prior art only described weekly trastuzumab administration, and did not suggest an extended dose interval or the claimed regimens. Indeed, Petitioner has proffered no evidence that any skilled artisan ever suggested an extended dosing interval for trastuzumab before August 1999.

Petitioner bases its obviousness case on a single conclusory sentence in an expert declaration alleging that a generalized desire for "convenience" would have motivated a skilled artisan to administer trastuzumab less frequently to match three-week chemotherapy dosing regimens. But this alleged motivation is nowhere evident in the prior art. At the time of the invention, skilled artisans were focused on improving efficacy, not convenience. Rather than considering less frequent administration of trastuzumab to match three-week chemotherapy regimens, skilled artisans were considering the opposite. Inspired by the success of weekly trastuzumab, they were testing weekly administration of trastuzumab and the chemotherapy agent paclitaxel. In short, there is no contemporaneous evidence to support Petitioner's alleged motivation, but there is substantial evidence to contradict it.

Petitioner's proof of "reasonable expectation of success" is no more compelling. In the face of varied and conflicting data in the prior art, Petitioner's expert, Dr. Mark Ratain, admittedly oversimplified his analysis, and relied only upon the prior art data that would support his position while ignoring data that would not. For example, Petitioner's expert conceded that while the prior art taught that trastuzumab had dose-dependent kinetics (*i.e.*, that half-life varies with dose amount), he assumed a single half-life when performing his analysis and disregarded contrary information in the prior art. Petitioner's expert also admitted that his "back-of-the-envelope" calculations were "absolutely not" accurate and that the prior art did not disclose sufficient detail for a skilled artisan to accurately model an extended interval dosing regimen for a drug with non-linear kinetics. (Ex. 2026 (Ratain Dep. Tr.), 159:19-160:2; 169:10-13; 177:8-11.)

In sum, Petitioner's obviousness case does not properly account either for the seriousness of the disease condition at issue or the novelty of targeted cancer therapy at the time. With respect to "motivation," the prior art contains no indication that convenience was of concern to women with HER2-positive breast cancer or their physicians. On the contrary, effectively treating cancer was the driving force behind dosing regimens then being explored. Similarly, with respect to "reasonable expectation of success," there is no support for the proposition that a skilled artisan would rely on oversimplified analyses to predict pharmacokinetics

for a complex and novel cancer therapy where errors could have fatal consequences.

II. TECHNOLOGY BACKGROUND

A. Trastuzumab Opened the Door to Targeted Treatment of Breast Cancer

1. Trastuzumab offered hope to women with HER2-positive breast cancer

The '196 patent is directed to the treatment of "HER2-positive" cancers, a class of cancers characterized by the overexpression of human epidermal growth factor 2 receptor ("HER2") or human ErbB2. HER2-positive breast cancer is a particularly aggressive cancer, in which cancer cells grow and spread rapidly. HER2-positive status was associated with a high rate of tumor recurrence and spreading of the cancer to other areas of the body, as well as a shorter time to relapse. (Ex. 2029 at 433; Ex. 2030 at 1420; Ex. 2031 at 179-80); Ex. 2032 at 707.) The life expectancy of HER2-positive patients in 1996 was only 18 months post-diagnosis. (Ex. 2033 at 138; *see also* Ex. 2034 at 887; Ex. 2028 (Gelmon Decl.), ¶12).

In 1998, HER2-positive breast cancer made up 25-30% of the 180,000 yearly new breast cancer diagnoses. (*See* Ex. 2043 at 1, 5; *see also* Ex. 1007 at 3; Ex. 2028, ¶13.) As a result, even before FDA approval of trastuzumab, Genentech was "swamped" by demand for trastuzumab and teamed with patient advocacy

groups to design a lottery system to equitably distribute a limited supply to severely affected patients. (Ex. 2034 at 887.)

2. The biologic mechanisms of trastuzumab differed from traditional anti-cancer treatment

Until the approval of trastuzumab in September 1998, the treatment most commonly prescribed for breast cancer was chemotherapy. (Ex. 2028, ¶¶6, 29, 39.) Chemotherapy agents work by killing tumor cells, but they also kill healthy cells in the process and are thus considered non-targeted cancer treatments. (*Id.* at ¶58; Ex. 2026, 54:12-55:17.) Rapidly dividing cells—such as hair follicles, cells lining the intestine, and bone marrow cells—tend to be damaged the worst, leading to symptoms such as hair loss, gastrointestinal issues and myelosuppression.[1] (Ex. 2028, ¶¶30-31.) In 1999, the goal of most chemotherapy dosing was to kill the greatest number of tumor cells without causing life-threatening toxicity, such as severe myelosuppression and neutropenia.[2] (*Id.*) Typically, that was done by administering the largest tolerable dose, followed by a dosing interval that would allow a patient time to recover before the next dose. (*Id.* at ¶31; Ex. 2026, 57:8-

[1] Suppression of bone-marrow activity caused by the killing of bone marrow cells.

[2] Neutropenia occurs when a person has an abnormally low number of a particular white blood cell type. (Ex. 2028, ¶30.)

59:6 (a skilled artisan would use the maximally tolerated dose); 62:15-17 ("[T]here was a general belief [in the late 1990s] and there still is now that more is better.").)

The use of antibodies to treat cancer involved a radically different approach. Targeted cancer therapies interact with specific molecular targets involved in the growth, progression, and spread of cancer, providing a sharp contrast to the broad-based DNA-damaging activity of chemotherapeutic agents. (Ex. 2028, ¶¶30, 58.) At the time of the invention, although numerous antibodies had been tested in patients with different cancers (including breast cancer), consistent therapeutic efficacy had not been shown. (Ex. 2002 at 649, Table 2 (identifying failed antibody clinical trials for numerous cancers); Ex. 2028, ¶¶14, 16.) As one reviewer observed, "antibody therapy of cancer has become a story of unending failures." (Ex. 2009 at 732.) Indeed, prior to August 1999, the FDA had approved only one other antibody for use in treating cancer—Genentech's rituximab product, which was approved for non-Hodgkin's lymphoma treatment in 1997. (Ex. 2003 at 388.) Trastuzumab was the first antibody approved to target solid tumors and the first approved to treat breast cancer. (*Id.*)

At the time of the invention, most clinical investigators were well-aware of the distinction between the newer target-based agents and classical chemotherapy agents. (Ex. 2024 at 7-8; Ex. 2026, 55:12-56:1; 56:19-57:7.) As a consequence, they appreciated that trastuzumab worked differently from traditional

chemotherapy. (Ex. 1007 at 7 ("[T]he biologic action of [trastuzumab] … differs markedly from conventional anticancer agents."); Ex. 2026, 55:12-17 (agreeing that "chemotherapy is cytotoxic therapy" and "drugs like Herceptin are noncytotoxic therapy").) Trastuzumab binds to HER2 receptors on HER2 cancer cells. Once there, it inhibits tumor cell growth and induces cell death by flagging HER2-overexpressing tumor cells for destruction by the body's immune system. (*See, e.g.*, Ex. 1001 at 35:45-58; Ex. 1008 at 1.)

Skilled artisans also knew that for trastuzumab to be effective, adequate blood levels had to be maintained over the entire course of treatment. (Ex. 2028, ¶¶8, 36; Ex. 2027, ¶¶45-47.) Failure to maintain therapeutic serum concentrations could jeopardize clinical efficacy. (Ex. 2028, ¶36.) Pre-clinical studies of trastuzumab identified 10-20 µg/mL as the target trough concentration for clinical efficacy, and early clinical studies showed that failure to reach this target was associated with a lack of clinical response. (*Id.* at ¶¶36, 69; Ex. 1009 at 4; Ex. 1007 at 4; Ex. 1006 at 5.) Moreover, at the time of the invention, the weekly trastuzumab dosing regimens in the prior art resulted in mean trough concentrations higher than 10-20 mg/mL for the average patient. For example, the weekly regimen of Baselga '96 resulted in a mean trough concentration of 54 µg/mL. (Ex. 1009 at 8, Table 6.) The 1998 Herceptin® Label (Ex. 1008, "The

Label") reported that the approved weekly dosing regimen resulted in mean trough serum concentration levels of approximately 79 μg/mL. (Ex. 1008 at 1.)

B. Armed with a New Therapeutic Approach, Researchers Sought to Improve Treatment and to Learn More

1. At the time of the invention, researchers focused on improving efficacy

Trastuzumab's 1998 approval marked a breakthrough in the breast oncology field, providing patients with hope of treatment for a condition previously viewed as a death sentence. In the wake of the approval, skilled artisans seeking to maximize clinical outcomes for patients with HER2-positive breast cancer now focused on how trastuzumab could be used more effectively. (Ex. 2028, ¶¶24-25, 29, 39; Ex. 2021 at 27; Ex. 2035 at 76.) As one of the '196 patent inventors noted, trastuzumab's success prior to August 1999 offered "proof of principle," but further research was needed to improve patient outcomes. (Ex. 2035 at 76.) During the five years following trastuzumab's approval, hundreds of papers and abstracts were published in which researchers explored various ways to maximize the effective use of trastuzumab. (Ex. 2028, ¶29.)

For example, in the late 1990s, skilled artisans were actively investigating how to combine trastuzumab with chemotherapy, including paclitaxel, the chemotherapy agent administered with trastuzumab in the Phase III studies that led to trastuzumab's approval. (Ex. 2028, ¶¶7, 25, 37-38, 55; Ex. 2021 (Baselga

'2000) at 28.) Inspired by the favorable Phase III results reported in the Label, researchers—including coauthors of the prior art upon which Petitioner relies—studied administering paclitaxel more frequently than the then-standard three-week regimen to match weekly trastuzumab administration. (Ex. 2016 (Seidman 1998) at 3360; Ex. 2036 (Perez 1998) at 370; Ex. 2037 (Fornier 1999) at 482; *see also* Ex. 2026, 39:7-12 (conceding that some skilled artisans "were focusing on weekly paclitaxel with weekly trastuzumab.").)

This approach to more frequent dosing was supported by studies reporting that weekly paclitaxel administration had a remarkably favorable toxicity profile, with the same or better efficacy as compared to three-week schedules. (*See* Ex. 2016 (Seidman 1998) at 3353, 3357-58; Ex. 2038 at 24; Ex. 2026, 27:8-15.) Indeed, by 1999, studies showed that weekly paclitaxel was more effective than a three-week regimen. (Ex. 2018 at 432 (weekly paclitaxel study had the highest response rate in advanced breast cancer for single agent paclitaxel and suggesting further study); Ex. 2016 (Seidman 1998) at 3357-58 (weekly paclitaxel may have advantages over three-week dosing).) As described by a preeminent researcher in 1998, weekly paclitaxel was generating "much interest," given the high relative dose intensity and density and very modest side effects. (Ex. 2036 at 373, 375-76; *id.* at 385 ("Further investigation into the role of weekly paclitaxel … is ongoing."); *see also* Ex. 2038 at 15 ("The weekly administration of paclitaxel has

raised much interest in the last few years in view of the quite astonishing doses delivered with this schedule.").)

While Petitioner's expert could not recall "when the weekly [paclitaxel] regimen was developed" and did not consider the active interest in weekly paclitaxel in rendering his opinions, he acknowledged studying weekly paclitaxel himself. (Ex. 2026, 24:20-21; 33:17-34:1.) In a 2003 publication reporting these studies, he concluded that a weekly paclitaxel schedule improved the therapeutic index of paclitaxel in terms of toxicity and possibly in terms of effectiveness, and that the study results were "encouraging." (Ex. 2015 at 2486, 2480; Ex. 2026, 23:3-6.)

These studies reporting more frequent administration of chemotherapy, including with trastuzumab, show that efficacy, not convenience, was the primary concern of skilled artisans at the time of the invention. (Ex. 2028, ¶¶7, 39-41, 53-55, 60; Ex. 2016 (Seidman 1998); Ex. 2021 (Baselga 2000).) In contrast, nothing in the prior art reflects any motivation to extend the trastuzumab dosing interval to match three-weekly paclitaxel dosing for the sake of convenience.

2. The pharmacokinetic data in the prior art presented a complex picture

Although researchers had some understanding of how trastuzumab worked (and that it differed from chemotherapy), the experience and data available to

skilled artisans regarding trastuzumab pharmacokinetics were limited and varied. The prior art taught that trastuzumab was dose-dependent and that half-life increased with dose amount when the drug was dosed weekly. But at the time of the invention, the degree to which half-life varied, and the reasons for the variance were not known.

a. The prior art taught that trastuzumab exhibited dose-dependent (i.e., non-linear) pharmacokinetics

The prior art explicitly taught that trastuzumab exhibited dose-dependent pharmacokinetics over the dosing ranges tested. (Ex. 2026, 147:10-13; *see also* Ex. 2027 (Grass Decl.), ¶¶34-41.) For example, the Label reports, "Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics." (Ex. 1008 at 1.) Similarly, Baselga '96 reports: "The resulting recombinant humanized anti-p185HER2 monoclonal antibody (rhuMAb HER2) was found to be safe and to have dose-dependent pharmacokinetics in two prior phase I clinical trials." (Ex. 1007 at 3.) Further, Watanabe shows that trough plasma concentrations did not increase proportionally with 1 mg/kg to 8 mg/kg trastuzumab doses, data that Petitioner's expert conceded is consistent with dose-dependent kinetics. (Ex. 1006 at 5; Ex. 2026, 88:11-12; *see also* Ex. 2027, ¶35.) A skilled artisan would understand the prior art's teaching that trastuzumab

exhibited dose-dependent pharmacokinetics to mean that trastuzumab had non-linear kinetics. (Ex. 2027, ¶38; *see also* Ex. 2026, 76:11-14.)

In the case of drugs with linear kinetics, the half-life of a drug—*i.e.*, the time it takes for a drug's concentration in the body to decrease by half—remains constant over time, regardless of the drug's serum concentration. (Ex. 2006 at 145-46; Ex. 2027, ¶¶24-27; Ex. 2026, 66:16-18.) A drug with linear kinetics is thus eliminated at a rate proportional to the drug's plasma concentration. (Ex. 2027, ¶¶26-27.) In contrast, for drugs with non-linear kinetics, the drug's half-life changes as its concentration in the body changes—*i.e.*, the half-life is dependent on the drug's concentration in body. (*Id.* at ¶28.) That means that plasma concentrations do not change proportionally with dose or interval. (*Id.*) Thus, the pharmacokinetic parameters from one dose amount and interval cannot be reliably used to predict the effects of a different dose amount or interval. (*Id.* at ¶¶64-65, 75, 28-33, 56, 12.) More data is needed. (*Id.*)

While the prior art taught that trastuzumab had non-linear kinetics, it did not contain sufficient data from which to determine the specific characteristics or cause of the non-linearity. (Ex. 2027, ¶56.) One such potential source of non-linear kinetics was the presence of shed antigen. (*Id.* at ¶¶81-85.) "Shed antigen" refers to circulating extra cellular domain ECD^{HER2} "shed" from the tumor source that circulates in the bloodstream. (Ex. 2027, ¶¶65, 81-85; Ex. 1013 at 5.) The prior

art taught that 64% of patients with HER2-positive breast cancer had detectable levels of shed antigen and that the presence of shed antigen was correlated with lower trough serum concentrations, lower half-life values, and the lack of a clinical response. (Ex. 2027, ¶¶13, 81; *see also e.g.*, Ex. 1008 at 1; Ex. 1009 at 8; Ex. 1007 at 8.) Notwithstanding relatively poor efficacy of trastuzumab in patients with high circulating levels of shed antigen, researchers noted that those patients should continue to be studied. (Ex. 1007 at 8; *see also* Ex. 1009 at 12.)

b. The prior art did not contain data that a skilled artisan would need to predict the result of an alternative dosing regimen for trastuzumab

Whether a drug has linear or non-linear kinetics has significant implications for predicting the results of a proposed dosing regimen. (Ex. 2027, ¶11, 23). For drugs with linear pharmacokinetics, a pharmacokineticist can reasonably predict serum trough concentrations for different dose amounts and intervals by assuming that the drug's half-life remains constant. (Ex. 2027, ¶¶25-27, 29-30.) In contrast, for drugs with non-linear pharmacokinetics, pharmacokinetic parameters such as half-life do not have the same utility as they do in a linear system because half-life value is limited to the particular concentration of the drug in the system at that very moment. (Ex. 2027, ¶¶28, 30-31, 57, 64; Ex. 2006 at 124.) As Petitioner's expert has explained, "pharmacokinetic parameters are unpredictable" for non-linear, dose-dependent drugs. (Ex. 2001 at 130.) Alteration of the schedule of drugs that

display non-linear kinetics may unpredictably alter clinical effects. (Ex. 1025 at 15; Ex. 2026, 76:7-10; *see also* Ex. 2027, ¶30.)

The prior art contains insufficient information about the pharmacokinetics of trastuzumab for a skilled artisan to reliably predict the impact of a three-week dosing regimen on serum concentration. (Ex. 2027, ¶¶65-76, 6-12.) The cited prior art only provides limited pharmacokinetic data derived from weekly trastuzumab administration, and does not provide the breadth of serum-concentration vs. time data that a skilled artisan would need to reliably predict the results of a three-week dosing regimen. (*Id.* at ¶66.) In fact, Petitioner's expert readily conceded that there was insufficient data in the prior art to model the behavior of trastuzumab according to its demonstrated non-linear kinetics. (Ex. 2026, 159:19-160:2.)

III. THE '196 PATENT

A. The Invention

The '196 patent discloses and claims new regimens for treating cancer with trastuzumab. The new dosing regimens described in the patent feature less frequent dosing of trastuzumab as well as higher initial loading doses and higher maintenance doses. (Ex. 1001 at 1:34-35; 6:20-21; 44:29-37; 5:31-40; 34:10-27.)

The patent specification also provides important information about trastuzumab's pharmacokinetic properties that was not available in the prior art,

including information collected during a Phase III clinical trial of trastuzumab involving 213 patients. (Ex. 1001, 38:33-39:10; 39:11-31 (Table 2); 39:32-40:17, Fig. 3.) For example, Table 2 of the specification discloses weekly mean trough serum concentrations over seven weekly infusions. (Ex. 1001, 39:10-33.) Figure 3 provides additional information with respect to mean trough concentration over an even longer period of time—through 36 weeks of treatment. (*Id.* at Fig. 3.) This information about the pharmacokinetics of trastuzumab was not available in the prior art.

B. Challenged Claims

The Board instituted review of claims 1-3, 5, 7, 9-11, and 17-33.[3] (Paper 7 at 16.) Patent Owner opposes Petitioner's arguments regarding all the challenged claims, but will refer to claims 11, 18, and 22, which depend indirectly from independent claim 1, as exemplary for this response.

Claim 1 relates to a method for treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor. The initial loading dose is at least 5 mg/kg of an anti-ErbB2 antibody; subsequent maintenance doses,

[3] The Institution Decision did not address claims 13-15, despite their inclusion in Petitioner's proposed grounds for institution. (*Compare, e.g.*, Paper 2 at 4, 51-52, *with* Paper 7 at 16.)

comparable to or smaller than the loading dose, are separated in time "by at least two weeks." Dependent claims specify the cancer type, the loading dose amount, the maintenance dose amount(s), and the time interval between doses. For example, claim 11 requires the loading dose to be 8 mg/kg and at least one subsequent maintenance dose to be 6 mg/kg, and the interval between doses to be three weeks.[4] Written in independent form, claim 11 reads:

> A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising:
>
> administering to the patient ***an initial dose of approximately 8 mg/kg*** of the anti-ErbB2 antibody; and
>
> administering to the patient a plurality of subsequent doses of the antibody in an amount that is approximately the same or less than the initial dose, wherein at least one subsequent dose is ***approximately 6 mg/kg***, wherein the plurality of subsequent doses are separated in time from each other ***by at least three weeks***.

[4] Challenged claims 5, 10, 11, and 30 are directed to dose intervals of at least three weeks. The remaining challenged claims require dose intervals of at least two weeks.

IV. PETITIONER'S ASSERTED REFERENCES

The Board instituted review on a single ground, obviousness based on Slamon, Watanabe, Baselga '96, and Pegram '98. (Paper 7 at 16.)

A. Watanabe Does Not Disclose or Suggest the Claimed Regimen

Watanabe consists of two brief paragraphs reporting results of a Phase I dose escalation study of trastuzumab. (Ex. 1006 at 5.) Eighteen patients received a first trastuzumab dose of 1, 2, 4, or 8 mg/kg and then, after three weeks, received nine weekly doses. (*Id.*) Watanabe reports that the trough level of each tested dose ranged from 9 μg/mL for the 1 mg/kg dose amount to 248 μg/mL for the 8 mg/kg dose amount. (*Id.*) Watanabe reports that serum concentrations of 9 μg/mL did not demonstrate a therapeutic response. (Ex. 1006 at 5; Ex. 2026, 87:15-17.) Watanabe does not express any concerns regarding convenience or suggest a dosing interval of longer than one week. (Ex. 1006 at 5; *see also* Ex. 2026, 91:6-12.) On the contrary, Watanabe recommends that weekly administration of 2 mg/kg or 4 mg/kg of trastuzumab be investigated further. (Ex. 1006 at 5; Ex. 2028, ¶17.)

Although Watanabe does not explicitly state that trastuzumab exhibits dose-dependent pharmacokinetics, the reported data showing trough concentrations that did not rise proportionally with dose amount is consistent with dose-dependent

kinetics. (*See* Ex. 2026, 185:9-12.) Watanabe does not report any other pharmacokinetic information, such as half-life. (Ex. 2027, ¶35.) Indeed, Petitioner's expert expressly acknowledged Watanabe's deficiencies, stating that a skilled artisan reading Watanabe would not be able to say, "I know what's going on based on Watanabe." (Ex. 2026, 184:18-185:12.)

B. Slamon Does Not Disclose or Suggest the Claimed Regimen

Slamon consists of two brief paragraphs reporting preliminary Phase III clinical trial results of trastuzumab administered in conjunction with either doxorubicin-cyclophosphamide or paclitaxel, both chemotherapy agents. (Ex. 1005 at 5; Ex. 2028, ¶¶21-23.) Trastuzumab was administered as a 4 mg/kg loading dose followed by weekly 2 mg/kg maintenance doses, while chemotherapy was administered every three weeks. (Ex. 1005 at 5.) Slamon indicates that adding weekly trastuzumab to chemotherapy increases clinical benefit. (*Id.*) Slamon does not express any concerns regarding convenience or suggest extending the trastuzumab dosing interval to match the chemotherapy schedule. (*Id.*; Ex. 2026, 86:12-16.) Petitioner's expert admitted that Slamon is devoid of any pharmacokinetic data that a skilled artisan could have used to design or evaluate alternative dosing regimens, such as those claimed. (*Id.* at 86:7-11; Ex. 2027, ¶67.)

C. Baselga '96 Does Not Disclose or Suggest the Claimed Dosing Regimen

Baselga '96 reports the results of a Phase II clinical study designed to evaluate the efficacy and toxicity of weekly trastuzumab administration in patients with HER2-positive metastatic breast cancer. (Ex. 1007 at 3; Ex. 2028, ¶19.) Forty-six patients received a 250 mg trastuzumab loading dose followed by 100 mg weekly doses. (*Id.*) According to the authors, the weekly regimen was determined to be the "***optimal dose and schedule*** of rhuMAb HER2" based on two prior Phase I clinical trials. (*Id.* at 4.) Baselga '96 notes that trastuzumab has "documented dose dependent pharmacokinetics" and reports, for the weekly regimen tested, a mean serum half-life of 8.3 +/- 5.0 days. (*Id.* at 4-5.) Petitioner's expert testified that Baselga '96 contains "insufficient [data] for a POSA to calculate any pharmacokinetic parameters with any reasonable clarity" and includes "conflicting information." (Ex. 2026, 106:16-107:7; 105-5-6.)

Baselga '96 indicates that the weekly regimen did not work for 11% (5/45) of patients with high shed antigen levels, reporting that "no anticancer responses were observed in groups of patients with serum concentrations of $ECD^{HER2} \geq 500$ ng/mL." (Ex. 1007 at 8, 5.) Baselga '96 further cautions that interpretation of results of further trials of drugs like trastuzumab should take shed antigen into account. (*Id.*)

Baselga '96 does not reference or suggest administering trastuzumab at any dosing interval other than weekly. (Ex. 2026, 97:11-22.) Nor does Baselga '96 discuss patient convenience or the possibility of administering trastuzumab on a less frequent regimen. (*Id.* at 99:12-14.) Although Baselga '96 refers generally to preclinical studies administering trastuzumab with chemotherapy such as paclitaxel (Ex. 1007 at 9), there is no mention or hint as to the desirability of administering trastuzumab on the same schedule as chemotherapy. (Ex. 2026, 98:15-99:3.)

D. Pegram '98 Does Not Disclose or Suggest the Claimed Dosing Regimen

Pegram '98 describes the results of a Phase II clinical study in which 39 patients with metastatic breast cancer received trastuzumab in combination with the chemotherapeutic agent cisplatin. (Ex. 1009 at 2; Ex. 2028, ¶19.) Similar to Baselga '96, patients were treated with a 250 mg trastuzumab loading dose followed by 100 mg weekly doses for nine weeks. (*Id.*; *see also* Ex. 2026, 111:22-112:3.) Patients also received cisplatin about every four weeks, but not on the same day as trastuzumab. (Ex. 1009 at 2-4; Ex. 2026, 114:5-115:12.)

Pegram '98 provides only limited pharmacokinetic information on trastuzumab. Specifically, Table 6 of Pegram '98 reports a half-life of 11.0 ± 4.0 days for patients treated with trastuzumab and cisplatin. (Ex. 1009 at 8, Table 6.) Pegram '98 also includes results from Baselga '96, reporting that when

administered alone, trastuzumab had a mean half-life of 9.2 ± 5.3 days. (*Id.*) Pegram '98 further reports that mean maximum trough serum concentrations reached 54 µg/mL when trastuzumab was administered without chemotherapy, and 85 µg/mL when trastuzumab was administered with cisplatin. (*Id.*)

Pegram '98 reports that patients with any measurable detectable levels of shed antigen had mean trough concentrations 57% lower than those patients without detectable shed antigen (18.7 µg/ml vs. 43.6 µg/mL) and had lower mean trough concentrations across all time points. (Ex. 1009 at 9, Fig. 1.) Pegram '98 further reports that "there was an inverse relationship between [trastuzumab] serum half-life and serum shed HER2 ECD of 0.5 µg/mL or greater." (*Id.*) Indeed, the observed half-life of trastuzumab in patients with shed antigen of 0.5 µg/ml or greater was only 2.9 days for trastuzumab alone or 4.0 days for trastuzumab plus cisplatin. (*Id.* at 8.) Approximately 16% (13/82) of patients in the study had shed antigen levels greater than 0.5 µg/mL.

Pegram '98 does not reference or suggest administering trastuzumab at any dosing interval other than weekly. (Ex. 1009; Ex. 2026, 112:4-7; 115:18-21.) Nor does Pegram '98 mention convenience or suggest administering trastuzumab less frequently to match a chemotherapy regimen.

E. The 1998 Herceptin® Label Does Not Disclose or Suggest the Claimed Regimen

In its grounds for institution, Petitioner does not rely on the 1998 Herceptin® Label, which describes the initial FDA-approved indications and dosing regimen for trastuzumab. (Ex. 1008 at 1.) Indeed, Petitioner's expert dismissed the Label as providing little more information than an abstract (Ex. 2026, 132:15-133:8) and said that "by looking only at this [L]abel, one wouldn't know terribly much." (*Id.* at 142:17-143:11.) He nevertheless used the Label to estimate serum trough concentrations for three-week dosing of trastuzumab. (Ex. 1003, ¶¶107-109.)

The Label reports that short duration intravenous infusion of 10 to 500 mg of trastuzumab once weekly demonstrated "dose-dependent pharmacokinetics." (Ex. 1008 at 1.) In these dose-rising studies, 10 mg doses administered weekly had an average half-life of 1.7 days and 500 mg doses administered weekly had an average half-life of 12 days; the Label does not provide half-life information for any doses between 10 and 500 mg. (*Id.*; Ex. 2027, ¶¶10, 37, 53, 77.) Although there is insufficient information in the Label from which a skilled artisan could determine the scope and extent of that non-linearity, a skilled artisan would understand from the Label that trastuzumab has "non-linear" kinetics. (Ex. 2027, ¶11.) Petitioner's expert nevertheless disregarded the information about dose-dependent kinetics in the Label, testifying that he could not "make heads or tails

out of the … stuff in the [L]abel that talks about the half-life changing with dose…." (Ex. 2026, 165:6-21.)

Based on the Phase III clinical trials involving nearly 700 patients reported in the Label, the FDA approved a regimen of a 4 mg/kg loading dose followed by 2 mg/kg weekly maintenance doses to treat HER2 positive metastatic breast cancer. (Ex. 1008 at 1.) The Label reports an average observed half-life for trastuzumab of 5.8 days with a range of 1 to 32 days for patients administered this regimen. (*Id.*; Ex. 2027, ¶¶59, 83.)

The Label only refers to weekly dosing, and says nothing about the possibility of a three-week regimen. (Ex. 2026, 140:17-141:13.) Nor does the Label disclose or suggest a need for more convenient dosing regimens, or to dose trastuzumab on the same schedule as chemotherapy.

V. PERSON OF ORDINARY SKILL

Petitioner argues that a skilled artisan would have expertise in both oncology and pharmacokinetics. (Paper 2 at 14 (citing Ex. 1003, Ratain Decl. ¶44).) For the purposes of these proceedings, Patent Owner does not dispute the areas of substantive expertise, but disagrees with Petitioner's characterization of a skilled artisan insofar as it could be construed to exclude a clinical oncologist working ***in consultation with*** a pharmacokineticist. A skilled artisan would have had access to and worked on a team with a number of other individuals involved in drug

development with expertise in clinical pharmacology, including pharmacokinetics. (Ex. 2028, ¶¶9-11.) In any event, the challenged claims would not have been obvious under either definition.

VI. ARGUMENT

Petitioner falls short of proving obviousness in at least three key respects.

First, Petitioner's argument that a generalized desire for "convenience" would have motivated a skilled artisan to administer trastuzumab less frequently is unsupported by and is inconsistent with the prior art. Nothing in the prior art suggests that skilled artisans treating patients with HER2-positive cancer were concerned with convenience in August 1999. Given the seriousness of the disease condition at issue, skilled artisans were focused on improving clinical outcomes for these patients. And even if a skilled artisan were to have a general desire for convenience, that desire could not be viewed without taking into consideration the more important (and well-documented) concern that failure to reach therapeutic serum trough concentrations would reduce efficacy. Petitioner's myopic focus on convenience as a motivating factor in the absence of evidence that the extended dose interval would maintain efficacy ignores the realities of HER2-positive cancer treatment in the 1990s.

Second, nothing in the prior art supports the proposition that a skilled artisan would have been motivated to dose trastuzumab to match a three-week

chemotherapy regimen or use the chemotherapy-based concept of "dose intensity" to determine dose amounts for a targeted antibody treatment such as trastuzumab. The prior art contains no such suggestion, and a skilled artisan would not have been motivated to combine the teaching in the prior art in the manner Petitioner suggests. With regard to frequency of administration, the prior art suggests skilled artisans were motivated to dose chemotherapy more frequently to match the approved weekly trastuzumab schedule, not the other way around. In addition, skilled artisans would not have been motivated to use chemotherapy-dosing concepts to determine dose amounts or dose intervals for trastuzumab given known differences in mechanisms of action.

Third, even if a skilled artisan were motivated to try three-week dosing, the prior art contained insufficient pharmacokinetic data to reasonably predict whether such a regimen would have been clinically effective. At the time of the invention, trastuzumab was the first antibody approved to treat solid tumors, and marked the very start of targeted cancer therapy use. For skilled artisans, who had previously relied primarily on chemotherapy and had little experience with antibodies, fundamental questions remained to be addressed. Moreover, the prior art taught that trastuzumab had non-linear kinetics, which made developing a dosing regimen more challenging and uncertain. Petitioner improperly ignores the prior art's complexity, relying on simple estimations that do not account for non-linear

kinetics and cherry-picking only convenient data. A skilled artisan would not risk patient lives in reliance on Petitioner's admittedly over-simplified and "not accurate" analysis.

A. A Person of Ordinary Skill Would Not Have Been Motivated to Administer Trastuzumab on a Three-Week Schedule

1. A skilled artisan would not have been motivated to extend the dosing interval for the sake of convenience

a. The evidence shows that in August 1999 skilled artisans were not focused on convenience

In August 1999, trastuzumab had been FDA-approved for less than a year. While it offered tremendous promise to patients diagnosed with HER2-positive breast cancer, skilled artisans remained focused on improving efficacy. (Ex. 2028, ¶25; Ex. 2035 at 76.) Indeed, in the case of metastatic breast cancer—the only indication approved at the time of the invention—efficacy was critical because every day matters where untreated patients have a life expectancy of only 10-18 months. (Ex. 2033 at 138; *see also* Ex. 2034 at 887 ("[B]reast cancer patients who overproduce HER2 can now expect to live some 10 to 12 months after metastasis begins, a horribly rapid progression compared to six or seven years for HER2-normal patients."); Ex. 2028, ¶12.)

This is borne out by the prior art. All the references upon which Petitioner relies discuss safety and efficacy, whereas not a single one refers to convenience. (*See, e.g.*, Ex. 1005 at 5 (describing testing trastuzumab's ability to safely augment

chemotherapy activity); Ex. 1006 at 5 (describing a trastuzumab dose escalation study to determine dose levels/intervals for future clinical studies); Ex. 1009 at 3 (describing administration of cisplatin the day after trastuzumab, even when the two drugs were administered during the same week); Ex. 1007 at 4 (describing study objectives including investigating "the antitumor activity of rhuMAB HER2" and to "defin[ing] further the toxicity profile and pharmacokinetics of rhuMAb HER2").) This is because efficacy was the primary concern. (Ex. 2028, ¶¶34, 39-47, 50, 56-57, 60.)

In addition, studies at the time of the invention found that treatment with weekly trastuzumab could ***improve*** patient quality of life in comparison to treatment with chemotherapy regimens alone, despite the weekly regimen. (Ex. 2039 at 86-87.)[5] Osoba 1999 reports that the patients who received weekly trastuzumab reported no decline in quality in life over the course of treatment, in contrast to prior studies showing deteriorating quality of life scores while patients received chemotherapy treatment alone. (*Id.* at 86-87, 84; *see also* Ex. 2028, ¶¶48-49.) Even when weekly trastuzumab was added to a three-week paclitaxel

[5] Ex. 2039, Osoba 1999, while published shortly after the priority date, presents survey data that was collected prior to the priority date and therefore represents patient concern at the time of the invention.

regimen, quality of life scores of treated patients increased as compared to three-week chemotherapy alone. (Ex. 2039 at 87.) In sum, contrary to Petitioner's suggestion, the addition of two extra visits per treatment cycle to allow for the weekly administration of trastuzumab did not negatively impact patient quality of life, but appeared to improve it. (Ex. 2028, ¶¶48-49.)

b. The conclusory statements in Dr. Ratain's declaration are insufficient to establish a motivation to combine, particularly given contrary evidence

Petitioner's assertion that a skilled artisan would have been motivated to try three-week dosing of trastuzumab is based on a conclusory statement in Dr. Ratain's declaration in which he alleged that "a POSA would have been motivated to reduce the frequency of trastuzumab administration from weekly to an every three week schedule in order to improve patient convenience." (Ex. 1003, ¶¶118, 136, 90; Paper 2 at 27.) Dr. Ratain also alleged that skilled artisans would have been motivated to align the chemotherapy and trastuzumab dosing schedules. (*Id.* at ¶¶90-91, 136.) Dr. Ratain did not cite any evidence to support these assertions.

Moreover, Petitioner's expert conceded that in August 1999 and even today that "the optimal dose and schedule for [paclitaxel] have yet to be determined." (Ex. 1003, 20:17-21:4.) And he provided no explanation why a skilled artisan would have been motivated to extend trastuzumab's schedule to match the three-weekly paclitaxel that was not even known to be optimal. (Ex. 2026, 20:17-21:4.)

Dr. Ratain's opinion is not even supported by anecdotal evidence. Dr. Ratain, who does not focus on treatment of breast cancer, could not recall the extent to which he was treating breast cancer patients in the late 1990s. (Ex. 2026, 13:18-14:6 ("Q. So focusing on August 1999, approximately how many breast cancer patients had you treated before that date? A. … I can't recall."); 14:16-21 ("Q. So as you sit here today, you can't remember how many breast cancer patients you'd treated … Per year in 1999[?] A. No."); 50:9-18.) Indeed, Dr. Ratain could not recall a single instance in which a patient raised an issue about the inconvenience of weekly trastuzumab. (Ex. 2026, 50:9-18.) Dr. Ratain's declaration, expressing a generalized concern for "convenience" untethered to the specific patient population of the claims, is legally insufficient to carry Petitioner's burden. *See Rovalma, S.A. v. Bohler-Edelstahl GmbH & Co. KG*, 856 F.3d 1019, 1025-26 (Fed. Cir. 2017) (reversing PTAB decision finding a motivation to combine, and finding a general desire for "high thermal conductivities" was insufficient to find a motivation to increase thermal conductivity beyond levels previously achieved."); *Böhler-Edelstahl GmbH & Co. KG v. Rovalma S.A.*, IPR2015-00150, Paper 51 at 12-13 (Dec. 6, 2017) (Pollock, APJ) (finding challenged claims patentable on remand for same reason); *see also Innogenetics, N.V. v. Abbott Labs*., 512 F.3d 1363, 1373-74 (Fed. Cir. 2008); *see also Depomed, Inc. v. Actavis Elizabeth LLC,* No. CIV.A. 12-1358 JAP, 2014 WL 4215435, at *48

(D.N.J. Aug. 25, 2014) ("general motivation to … improve compliance and possibly reduce side effects" insufficient where "certain unique characteristics of [the claimed compound] … may have dissuaded a POSA" from creating the claimed invention.).

Moreover, the absence of any support for Dr. Ratain's opinions stands in stark contrast to evidence offered by Patent Owner's expert, Dr. Gelmon, who does specialize in treatment of breast cancer and was actively treating patients in the late 1990s. Dr. Gelmon has offered specific evidence regarding her experience with patients taking trastuzumab in 1999. Dr. Gelmon explains that, at the time of the invention, she did not receive any complaints about inconvenience from patients. (Ex. 2028, ¶¶42-47, 50, 57.)

This is hardly surprising in the context of breast cancer. As Dr. Gelmon explains, if the drug does not have its intended clinical effect, convenience simply does not matter. (*Id.* at ¶40.) Indeed, dozens of researchers at the time of the invention were testing dose-dense regimens, which involved administering chemotherapy more frequently than was standard. (Ex. 2028, ¶¶7, 32-33, 36, 53-54; *see supra* Section II.B.1.) It was believed that the shortened dosing intervals would increase efficacy due to lack of time for regrowth between cycles—despite the seemingly "inconvenient" regimen. (*Id.*)

c. A clinical oncologist would not have been motivated to dose trastuzumab on a three-week schedule like a chemotherapy agent

Petitioner also contends that a skilled artisan would have been motivated to dose trastuzumab on the same schedule as chemotherapy, and to use concepts developed for administration of chemotherapy to determine trastuzumab dose amounts. (Ex. 1003, ¶¶89-91.) Again, this opinion has no foundation in the prior art, despite numerous papers discussing combination therapy. (Ex. 2028, ¶¶56-60.)

At the time of the invention, skilled artisans were not extending trastuzumab's dosing interval, but were ***decreasing*** paclitaxel's dosing interval to match that of trastuzumab. In numerous clinical trials, oncologists were using weekly paclitaxel. (*See* Ex. 2028, ¶¶38, 54-55; Ex. 2016 at 3353, 3357-58; Ex. 2038 at 15, 24; Ex. 2036 at 370, 375-76; Ex. 2040 at 636; Ex. 2017 at 740; Ex. 2020 at 515; Ex. 2022 at 480; Ex. 2065 at 22; Ex. 2018 at 432; Ex. 2019 at 245.) These studies suggested that more frequent paclitaxel administration could have significant advantages. (*See, e.g.*, Ex. 2016 at 3353, 3357-58; Ex. 2038 at 24; *see also* 2042 at 576, 583 (stating that weekly paclitaxel is more effective than three-week paclitaxel).) Moreover, as discussed above, Dr. Ratain himself was involved in clinical trials involving weekly administration of paclitaxel aimed at improving efficacy. (*Supra* p. 10; Ex. 2015.)

Skilled artisans at the time of the invention were motivated by trastuzumab's Phase III results to explore the weekly co-administration of trastuzumab and paclitaxel—not extending trastuzumab to match paclitaxel. For example, one author wrote "[t]he recent observation of meaningful translation of preclinical synergy into clinical benefit for the combination of paclitaxel (3-hour infusion every 3 weeks) and Herceptin … ***has motivated us to explore the weekly co-administration of these two agents*** (paclitaxel via weekly 1-hour infusion) in a phase II trial that is well underway…." (Ex. 2016 (Seidman 1998) at 3360); *see also* Ex. 2021 at 29 ("The results of preclinical studies and the pivotal phase III study have led to the design of series of follow up studies with taxanes plus trastuzumab" including "a phase II study of weekly paclitaxel plus trastuzumab in patients with metastatic breast cancer.").) Indeed, consistent with the conclusion that weekly administration of trastuzumab was the "optimal" schedule, ***four*** co-authors of Baselga '96 investigated ***weekly*** administration of paclitaxel in conjunction with weekly trastuzumab, rather than attempting to extend the trastuzumab dose interval as suggested by Petitioner. (*Compare,* Ex. 1007 at 3, *with* Ex. 2016 at 3353.)

That skilled artisans, including the co-authors of the prior art relied on by Petitioner, were not applying chemotherapy-dosing regimens or concepts to trastuzumab is hardly surprising. In August 1999, very little had been published in

the literature about trastuzumab pharmacokinetics. (Ex. 2028, ¶¶53-54; *see supra* Section II.B.2.). Nevertheless, as Baselga '96 explains, "the biologic action of [trastuzumab] … differs markedly from conventional anticancer agents," like chemotherapy. (Ex. 1007 at 7; Ex. 2028, ¶¶51-55, 58.) Petitioner's expert has acknowledged that most clinical investigators and sponsors were well aware of the distinction between the newer target-based agents and classical chemotherapy agents. (*See* Ex. 2024 at 8; Ex. 2026, 55:12-56:1.) A skilled artisan would therefore have known that chemotherapy agents and targeted therapies like trastuzumab are dosed according to different principles, and would not have assumed a chemotherapy regimen could be used with trastuzumab. (*See id.*) Indeed, Dr. Ratain expressly conceded that "the rationale that would lead you to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks." (Ex. 2026, 59:13-18.)

d. Petitioner's generalized convenience argument is not supported by the caselaw

i. Motivation must be viewed in the context of the prior art at issue and the perspective of a skilled artisan

Whether a skilled artisan would have been motivated to combine the prior art to achieve the claimed invention is a case-specific inquiry that must be grounded in the evidentiary record. *Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d

1075, 1089 (Fed. Cir. 2008) ("The determination of obviousness is dependent on the facts of each case."); *see also Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1051 (Fed. Cir. 2016) (*en banc*) ("[W]hether a skilled artisan would have been motivated to combine references [is] a question[] of fact."). Importantly, Petitioner must identify a particularized motivation to combine the prior art to achieve the claimed invention. *Innogenetics, N.V.*, 512 F.3d at 1373 (Fed. Cir. 2008) (citations omitted) ("A generalized motivation to develop a method is not the kind of motivation required by the patent laws."). (*See supra* pp. 29-30.)

The need to identify a particularized motivation to solve a problem in the prior art is essential to avoid the pitfalls of hindsight bias. "[W]hile we understand that '[t]he obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation,' we also recognize that we cannot allow hindsight bias to be the thread that stitches together prior art patches into something that is the claimed invention." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017) (quoting *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 419, 421 (2007)).

ii. The Board's reliance on Hoffman-La Roche is misplaced

The Board's reliance on *Hoffman-La Roche Inc. v. Apotex, Inc.* for the proposition that "[a] relatively infrequent dosing schedule has long been viewed as

a potential solution to the problem of patient compliance" is misplaced. (Paper 7 at 13 (quoting *Hoffman-La Roche*, 748 F.3d 1326, 1329 (Fed. Cir. 2014).). *Hoffman-La Roche* does not hold that a desire for convenience or patient compliance will always provide motivation to extend dosing intervals. *Hoffman-La Roche* addressed the specific issue of whether once monthly administration of 150mg of the bisphosphonate ibandronate was obvious in view of prior art teaching that monthly administration of bisphosphonates (including ibandronate) improved patient compliance. *Hoffman-La Roche*, 748 F.3d at 1330 (identifying three prior art references disclosing monthly administration of ibandronate). The Federal Circuit's statement regarding convenience was clearly grounded in the specific facts of that case:

> A relatively infrequent dosing schedule has long been viewed as a potential solution to the problem of patient compliance ***stemming from the inconvenience of oral bisphosphonate regimens***. Fosamax®, a prior art bisphosphonate product sold by Merck & Co., was administered weekly, and several prior art references taught once monthly oral dosing of ibandronate or other bisphosphonates.

Hoffman-La Roche, 748 F.3d at 1329.

The facts that supported a finding of motivation in *Hoffman-LaRoche* have no bearing upon this case, which involves a first-in-class therapeutic, a fatal disease condition, and a completely different set of prior art. At the time of the

invention, trastuzumab was the only antibody approved for the treatment of solid tumors and one of the first targeted cancer treatments. (Ex. 2003 at 388.) In contrast, the drug at issue in *Hoffman-La Roche*, ibandronate, was a member of a well-characterized class of drugs, bisphosphonates, in which other members of the class had already been efficaciously administered over the claimed dosing interval. *Hoffman-La Roche*, 748 F.3d at 1327-28, 1330.

Convenience considerations that may be applicable in the context of treatments to prevent osteoporosis have little relevance in the context of treating HER2-positive breast cancer. (Ex. 2028, ¶¶42-47.) Failure to take osteoporosis medication may increase the risk of bone injury many years later, but has no short-term impact on patients. Doctors therefore must oftentimes coax patients into taking this type of preventative medication, including by making treatment regimens convenient and easy to remember. (*Id.* at ¶45.) In contrast, failure to take medication for HER2-positive breast cancer will typically result in death within months. (*Id.* at ¶42.) Patients thus need little additional convincing in the form of convenience to take trastuzumab. (*Id.*; *see also id.* at ¶¶42-47, 50, 57 (compliance was not likely to be an issue for breast-cancer patients).) In short, factual findings relevant to the motivations applicable to dosing of bisphosphonates have no relevance to motivations relating to dosing regimens for novel antibodies targeting breast cancer.

2. The available pharmacokinetic data would not have motivated a skilled artisan to administer trastuzumab in accordance with the claimed regimen

a. The pharmacokinetic data in the prior art would not have motivated a skilled person to extend the dosing interval of trastuzumab

The pharmacokinetic data in the prior art would not have motivated a skilled artisan to extend the dosing regimen interval for these reasons.

First, the prior art's statements that weekly dosing of trastuzumab was "optimal" (Ex. 1007 at 4) and "warranted" (Ex. 1006 at 5) would have pointed a skilled artisan away from three-week dosing. Watanabe's recommendation that weekly administration be pursued and the uniform focus on weekly dosing in concurrent and subsequent clinical trials (Baselga '96, Pegram '98, Slamon, and the Label) is strong evidence of non-obviousness. This is particularly so given that several of the extraordinarily skilled artisans in Baselga '96 later conducted trials increasing the frequency of paclitaxel administration to match the weekly trastuzumab administration. (Ex. 2016 (Seidman 1998) at 3353; Ex. 2021 (Baselga 2000) at 29.)

Second, a skilled artisan would have known from the prior art's report of trastuzumab's non-linear kinetics that seemingly small changes in dose amount or interval could unpredictably alter clinical effects. (Ex. 2027, ¶¶11, 14-15, 30-32, 42-44, 77-80.) Pharmacokineticists and oncologists have observed that it can be

exceedingly difficult to design dosing regimens for drugs with such behavior. Dr. Ratain has written that "[i]n contrast to drugs with linear pharmacokinetics, alteration of the schedule of drugs that display nonlinear kinetics may … potentially alter clinical effects." (Ex.1025 at 15-17; *see also* Ex. 2067 at 519, 522 ("Drugs that demonstrate nonlinear pharmacokinetic behavior can prove difficult in terms of designing dosage regimens and determining correlations between drug concentrations and effects (efficacy and toxicity).").) Given this unpredictability, a skilled artisan would not have been motivated to alter trastuzumab's dosing regimen.

Third, the unpredictability generally associated with drugs having non-linear kinetics was compounded for trastuzumab given the prior art's reporting of widely varied half-life data and the potential impact of shed antigen on serum trough concentrations. (*See supra* Sections IV.C-E (describing half-life variability).) This would have been particularly concerning given the Label reports that 64% of patients studied had detectable levels of shed antigen and that "[p]atients with higher baseline shed antigen were more likely to have lower serum trough concentrations." (Ex. 1008 at 1.) Likewise, Pegram '98 reported that circulating shed antigen was inversely related to half-life and that for patients with high levels of shed antigen, trastuzumab had a half-life of only 2.9 days. (Ex. 1009 at 8.) While the Label reports that "most patients with elevated shed antigen levels

achieved target serum concentrations of Trastuzumab by week 6," (Ex. 1008 at 1), *i.e.*, after six weekly doses, a skilled artisan would have been concerned that a three-week dosing regimen would not achieve the same results. Given the data in the prior art regarding the effect of shed antigen on half-life and trough serum concentration data, a skilled artisan would have been cautious in designing a new dosing regimen for trastuzumab. (Ex. 2027, ¶¶14-15, 83-85, 77-80.)

Lastly, independent of trastuzumab's non-linear kinetics and the prevalence of shed antigen, a skilled artisan would have known that extending the dosing interval for trastuzumab would have increased peak concentrations while lowering trough concentrations. (Ex. 2027, ¶46; Ex. 2028, ¶59; Ex. 1003, ¶57 ("as the intervals between doses increase, the fluctuation increases, with higher peaks and lower trough concentrations.").) A skilled artisan would have been concerned that a three-week dosing interval would have resulted in plasma trough concentrations below those previously shown to have been clinically effective. (Ex. 2027, ¶¶46-47; Ex. 2028, ¶¶69-71.)

A skilled artisan would not have risked patients' lives by tinkering with a proven regimen for a life-saving drug like trastuzumab without more information about the pharmacokinetics of the drug. (Ex. 2028, ¶¶7-8, 63, 65-68, 71.)

b. The pharmacokinetic data in the prior art would not have motivated a skilled person to apply dose intensity principles to trastuzumab

The claimed loading and weekly dose amounts in combination with three-week dosing interval are found nowhere in the prior art. To fill this gap, Petitioner has asserted that a skilled artisan would apply the chemotherapy dosing strategy of "dose intensity" to determine dose amounts for a three-week regimen. (Paper 2 at 28; Ex. 1003, ¶91.) But Petitioner has failed to articulate ***why*** a skilled artisan would apply a chemotherapy dosing strategy to trastuzumab, a targeted antibody treatment. (*See* Paper 2 at 28 (citing Exs. 1024, 1029); Ex. 1024 at 1 (describing dosing of doxorubicin, a chemotherapy agent); Ex. 1029 at 6 (same); Ex. 2028, ¶58.) Nor did Petitioner cite any evidence that skilled artisans would have applied the concept of "dose intensity" to antibody treatment, let alone trastuzumab. Indeed, Petitioner's expert conceded that the "the rationale that would lead [a skilled artisan] to dose chemotherapy every three weeks would not apply to dosing trastuzumab every three weeks." (Ex. 2026, 59:13-18.)

Chemotherapy dosing regimens seek to administer the highest tolerable dose (typically resulting in a high peak concentration) followed by sufficient time for recovery (and very low troughs); the goal is not to maintain a therapeutic minimum concentration over the entire dose interval. (Ex. 2028, ¶31.) In contrast, at the time of the invention, skilled artisans believed that trastuzumab should be dosed to

maintain a minimum trough concentration over the entire dose interval. (*Id.* at ¶36.) A skilled artisan would also have known that increasing the dose amount while extending the dosing interval would result in higher peak and lower trough concentrations, an approach that would be desired for chemotherapy but not necessarily when administering a drug such as trastuzumab where lower trough concentrations could compromise efficacy. (Ex. 2005 at 171 (greater dosing interval corresponds to greater percent fluctuation in plasma concentration); Ex. 2027, ¶46; Ex. 1003, ¶57.)

Given that the goal of maintaining dose intensity during chemotherapy is fundamentally different from the goal of maintaining minimum trough concentrations, it is unsurprising that all the articles cited by Dr. Ratain in support of his dose-intensity approach relate to chemotherapy dosing; none teaches the use of "dose intensity" for administration of targeted antibodies or for drugs dosed to maintain therapeutic minimum concentrations. (*See* Ex. 1003, ¶91 (citing Exs. 1024, 1029).) In fact, Dr. Ratain conceded at deposition that there "were not enough publications about trastuzumab for – for those [dose intensity] analyses to be presented." (Ex. 2026, 64:5-10.)

Petitioner's failure to identify a credible reason to select the claimed dose amounts is fatal. *See Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1072 (Fed. Cir. 2012) ("Evidence of obviousness,

especially when that evidence is proffered in support of an 'obvious-to-try' theory, is insufficient unless it indicates that … skilled artisans would have had a reason to select the route that produced the claimed invention." (citing *Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc*., 520 F.3d 1358, 1364 (Fed. Cir. 2008))). Indeed, the Federal Circuit and the Board have repeatedly rejected obviousness challenges that lack a basis in the prior art. *See, e.g., Eli Lilly & Co. v. Teva Parenteral Meds., Inc.*, 845 F.3d 1357, 1374-75 (Fed. Cir. 2017); *Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00654, Paper 69 at 26-27 (Sept. 21, 2015).

B. Petitioner Has Failed to Show that a Skilled Artisan Would Have a Reasonable Expectation of Success

Petitioner has the burden of establishing that a skilled artisan would have a reasonable expectation of success that extending the trastuzumab dosing regimen to three weeks with the claimed loading and maintenance doses would be safe and effective. The reasonable-expectation-of-success inquiry is firmly rooted in the facts of the case, the context of the problem to be solved, and the claims. *See Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (the "expectation-of-success analysis" must match the problem to be solved); *see also Arctic Cat Inc. v. Bombardier Recreational Prod. Inc.,* No. 2017-1475, --- F.3d ----, 2017 WL 6044237, at *5 (Fed. Cir. Dec. 7, 2017) (reasonable expectation of success is a question of fact). In the context of a

cancer-treatment regimen, an analysis that is admittedly "oversimplified," produces estimates that are "[a]bsolutely not" accurate, and is based on "back-of-the-envelope" calculations cannot provide a reasonable expectation of success. (Ex. 2026, 189:12-190:1; 177:8-11; 169:10-13.)

The pharmacokinetic calculations upon which Petitioner relied to demonstrate reasonable expectation of success are fatally flawed in two key respects. First, Dr. Ratain incorrectly assumes that the half-life of trastuzumab measured over the course of a weekly interval will remain constant over the course of a three-week interval. (Ex. 1003, ¶¶103-109; Ex. 2026, 192:22-193:6; *see also* Ex. 2027, ¶¶22, 31-33, 42-44, 54-55.) This assumption—that trastuzumab has linear pharmacokinetics—is directly contradicted by the teachings of the prior art and results in a fundamentally unreliable calculation. Second, Petitioner's expert impermissibly cherry-picked the data used in his calculations, ignoring data that would not support a reasonable expectation of success, while selecting only the data that would most strongly support his opinions. These errors further undermine his conclusions.

1. Dr. Ratain's analysis contradicts fundamental teachings of the prior art

a. Petitioner's assumption of linear kinetics to support its position is erroneous

The core of Petitioner's oversimplified reasonable-expectation-of-success argument is Dr. Ratain's unjustified assumption that the half-life of trastuzumab measured over the course of a ***weekly*** interval will remain constant over the course of a ***three-week*** interval. (Ex. 1003, ¶¶103-109; Ex. 2026, 192:22-193:6; *see also* Ex. 2027, ¶¶22, 31-33, 42-44, 54-55.) This assumption—that trastuzumab has linear pharmacokinetics—is directly contradicted by the teachings of the prior art.

i. The prior art does not support application of linear kinetics

Petitioner's expert conceded that the prior art teaches that trastuzumab has dose-dependent, *i.e.*, non-linear pharmacokinetics. (Ex. 1003, ¶¶51-55; Ex. 2026, 76:11-14; 88:5-12; *see also* Ex. 2027, ¶¶11, 22; Ex. 1006 at 5; Ex. 1008 at 1.) Textbooks and review articles—including those written by Dr. Ratain—teach that for drugs with dose-dependent, non-linear pharmacokinetics, pharmacokinetic parameters such as half-life change as the concentration of the drug changes in the bloodstream. (*See* Ex. 2005 at 179, 181-82; Ex. 2006 at 120-21; Ex. 2008 at 9; Ex. 1025 at 15; *see also* Ex. 2027, ¶¶16, 64.)

Indeed, Dr. Ratain admitted at deposition that when half-life is measured from peak and trough data—as was the case in Pegram '98 and Baselga '96—half-

life will change with concentration because of the nonlinearities of the system. (Ex. 2026, 157:13-158:13; 105:2-108:19 (Baselga '96 does not report terminal half-life, only estimate of half-life); 118:14-17 (Pegram '98 used the same method as Baselga '96); Ex. 1007 at 4 (pharmacokinetic samples were taken within an hour after an infusion and just before each infusion).) Likewise, Dr. Ratain acknowledged that the elimination rate of trastuzumab will change over time: once enough of a "high dose" is eliminated from the blood stream to match the initial concentration of a comparatively lower dose, the drug will be cleared at the same rate as if the patient had been administered a lower dose. (*See* Ex. 2026, 80:18-81:4.) Dr. Ratain further admitted that for "a constant dose and assuming nonlinear pharmacokinetics, if you change the schedule, you can change the clearance of the drug." (*Id.* at 81:14-17.) Dr. Ratain's admissions are at odds with his assumption of linear kinetics.

What little "support" for Dr. Ratain's assumption of linear kinetics that can be found in Dr. Ratain's declaration—a citation to Baselga '96—is misplaced. (*Cf.* Ex. 1003, ¶79 (citing Ex. 1007 at 4); *see also* Ex. 2027, ¶¶39-41.) Baselga '96's use of a one-compartment linear model to describe the data collected from the weekly administration of 100 mg of trastuzumab cannot be read in isolation from its statement that trastuzumab has dose-dependent pharmacokinetics. *See, e.g.*, *W.L. Gore & Assocs., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1550 (Fed. Cir. 1983)

(a prior art reference must be considered in its entirety); M.P.E.P. § 2141.02(VI) (same.) A skilled artisan reading Baselga '96 in its entirety would understand that while the one-compartment linear model may have been descriptive of the data collected over a weekly dosing interval of a single dose amount, it could not be used to reliably predict what would happen over a longer dosing interval or a different dose amount. (Ex. 2027, ¶¶72-74, 76, 39-41.) Lastly, Dr. Ratain's reliance on Baselga '96 here should be given little weight given his conclusion that "what Baselga writes is in conflict with itself." (Ex. 2026, 105:5-6; 106:16-107:7; *cf. id.*, 107:17-19.)

ii. Application of a linear kinetic model likely overestimates trough concentration

A skilled artisan would not assume, as Dr. Ratain did, that the half-life derived from weekly administration of trastuzumab would accurately predict the concentration of a different dose amount at a different dosing interval. (Ex. 2027, ¶¶70-71, 76.) Dr. Ratain even conceded that one could not determine the half-life of drug over a particular interval "***unless you measure the drug over*** [that interval]." (Ex. 2026, 120:13-18 ("[U]nless you measure the drug over a period of two weeks, you can't explicitly determine" the half-life over two weeks.).)

Because the half-life of trastuzumab depends upon the concentration of the drug in the body, changes to dose amount or dosing interval will also change half-

life. (Ex 2027, ¶30.) As a result, pharmacokinetic data from one dose amount—for example, the half-life for a 250 mg loading dose, followed by weekly 100 mg doses, reported in Pegram '98 and Baselga '96 and selected by Petitioner's expert for one of his calculations—will not be the same for the half-life of a different dose amount, *e.g.*, 4 mg/kg or 6 mg/kg. (*Id.* at ¶31.) Similarly, one cannot reasonably assume that the half-life of a 4 mg/kg dose of trastuzumab measured after weekly administration could be extrapolated out to three weeks because the plasma drug concentration is continually changing as the drug is eliminated. (Ex. 2027, ¶¶31, 43, 64; *see also* Ex. 2026, 80:18-81:4 (agreeing that the trastuzumab concentration in the blood changes as the drug is eliminated.)) As a consequence, the mean half-life measured between days 1 to 7 will be different from the mean half-life measured from days 8 to 14, which will be different from the mean half-life measured from days 15 to 21. (*See id.*; Ex. 2027, ¶¶43, 57, 64; *Cf.* Ex. 2026, 193:1-6.)

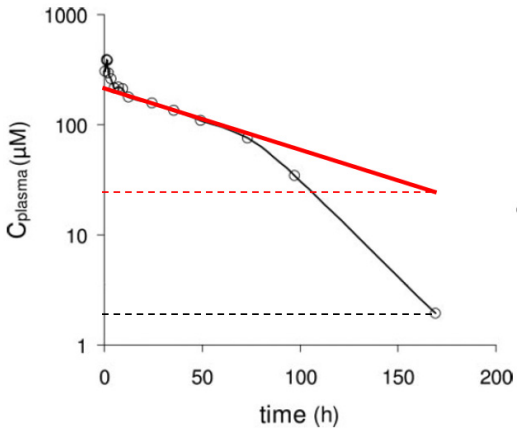
A skilled artisan would also know that applying linear kinetics to data from weekly administration of a dose-dependent drug such as trastuzumab to predict a three-week dosing regimen would likely overestimate serum trough concentrations—not underestimate as suggested by Dr. Ratain. (Ex. 2027, ¶¶16-17, 31-32, 48-55, 76.) A skilled artisan would understand the Label's statement that "[m]ean half-life increased and clearance decreased with increasing dose

level" (Ex. 1008 at 1) to mean that as the concentration of trastuzumab decreased in the blood stream, the rate of clearance also increased, such that the trastuzumab would be eliminated from the blood stream at a rate higher than would be expected if trastuzumab exhibited linear kinetics. (Ex. 2027, ¶¶50-52; Ex. 2026, 82:12-17.)

This is consistent with the prior art's reporting of shorter half-lives for smaller doses of trastuzumab. (*See, e.g.*, Ex. 1008 at 1 (reporting 1.7-day half-life for 10 mg dose, 5.8-day half-life for 4 mg/kg loading dose and 2 mg/kg maintenance doses, and 12-day half-life 500 mg doses.) In other words, where lower dose amounts are associated with shorter half-lives, the rate at which the drug is eliminated increases as the concentration of the drug in bloodstream is reduced. (Ex. 2027, ¶¶50-52.) Thus, a skilled artisan would know that applying linear kinetics to data from weekly administration of a dose-dependent drug such as trastuzumab to predict the results of a three-week dosing regimen would likely overestimate serum trough concentrations. (*Id.* at ¶¶16-17, 31-32, 48-55, 76.)

The anti-cancer agent indisulam provides a real-world example of how incorrectly assuming a constant half-life measured over a short interval could greatly overestimate the predicted serum concentration over a longer interval. (Ex. 2027, ¶32; Ex. 2041, at 1041.) The graph below shows a plasma concentration vs. time profile of indisulam. If a skilled artisan were to predict the serum concentration of indisulam after 175 hours using only the data collected from the

first 50 hours and assuming the half-life would remain constant (*i.e.*, assume linear kinetics as depicted by the red line), the predicted serum concentration would be an overestimate of the measured serum concentration by at least an order of magnitude:



(*See id*. at 1045, Fig. 6 (edited for clarity, red and dotted lines added); Ex. 2027, ¶32.) It is for this very reason that a skilled artisan would not have assumed that application of linear kinetics could reliably predict how trastuzumab would be eliminated over a three-week period absent additional information not found in the prior art.

For these reasons, Petitioner's suggestion that applying linear kinetics would result in a conservative estimate (Paper 2 at 35 n.8; Ex. 1003, ¶102) has no basis in the prior art. (Ex. 2027, ¶¶47-55.) The lynchpin of Dr. Ratain's argument is his assumption—again without any evidentiary support—that the half-life of trastuzumab could ***never*** decrease as the concentration of the drug changes in the

body as long as the concentration is in therapeutic range. (Ex. 2026, 191:22-193:6.) But the evidence of record shows that is not the case. (*See supra* pp. 10-13, 46-49.) Further, Dr. Ratain admitted that the purported "understand[ing] that the nonlinearity goes away … as the dose goes up … ***was not apparent*** back in 1999." (Ex. 2026, 77:7-10.) There was no information in the cited prior art to support Dr. Ratain's belief that the half-life of trastuzumab could not be shorter than the values he used in his calculations.

In addition, the Label points out that the half-life of trastuzumab increased as the weekly dose amount increased. (Ex. 1008 at 1.) While an increase in dose amount—***while holding constant the interval—***may have increased the half-life during that interval, Dr. Ratain's analysis extended the dosing interval three-fold, while expecting the measured half-life to remain the same. This is error. (Ex. 2027, ¶¶42-44, 54.)[6]

[6] Dr. Ratain argued for the first time in deposition that his half-life estimates are "conservative" because he applied a one-compartment model instead of a two-compartment model. (Ex. 2026, 119:20-120:3; 101:19-102:18; *see also id*., 68:2-21.) Dr. Ratain's conviction that the half-life is going to be longer "if it's not a one-compartment linear model" can only be explained by prior knowledge of when the distribution phase for trastuzumab ends, and when the elimination phase

Further, Dr. Ratain's own writings confirm that his calculations are speculative at best. Dr. Ratain has warned that "[e]xtrapolation of models outside the known time points must be done with great caution." (Ex. 1025 at 15.) Notwithstanding such prior admonishments, Dr. Ratain proceeded with anything but caution. He applied linear equations based only on isolated data points to a drug that exhibits non-linear kinetics. Petitioner also modified the prior art's dose amount and dose schedule without his own prior cautions that "pharmacokinetic parameters are unpredictable" for drugs with highly nonlinear behavior (Ex. 2001 at 130; Ex. 2026, 76:3-6) and that, "[i]n contrast to drugs with linear pharmacokinetics, alteration of the schedule of drugs that display nonlinear kinetics may markedly affect [drug exposure] and potentially alter clinical effects." (Ex. 1025 at 15; *see also* Ex. 2026, 76:7-10.)

Lastly, Petitioner's reliance on Pegram '98's statement that the Phase I trials showed that trastuzumab had "predictable" kinetics is misplaced. (Paper 2 at 16-17 (citing Ex. 1009 at 3); *id.* at 24-25.) Because the prior art showed that trastuzumab had non-linear kinetics, a skilled artisan would not interpret Pegram

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begins. (Ex. 2027, ¶¶72, 75.) But he concedes this information was not known at the time of the invention. (Ex. 2026, 207:6-16; 102:15-20, 106-107:7; *see also* 106:6-107:7, 108:14; 118:14-17.)

'98's statement to mean that the half-life values from weekly dosing could be used to reliably predict the trastuzumab concentrations of a dosing regimen different from the weekly schedule reported in Pegram '98. (Ex. 2027, ¶¶61-62.) Baselga '96 reports that the Phase I trials showed that trastuzumab had "documented dose-dependent pharmacokinetics" and that a weekly regimen was "optimal." (Ex. 1007 at 4.) Pegram '98 thus does not stand for the proposition that modifying the dosing regimen would be predictable.

iii. Petitioner's calculated serum concentrations leave no room for error

Petitioner's expert candidly admitted his calculations were "oversimplified," "back-of-the-envelope" calculations and do not provide an accurate estimation of the trough concentration of trastuzumab after three weeks. (*See* Ex. 2026, 169:6-18; 189:4-190:3; 177:8-11, 174:12-175:3 ("[T]his probably got simplified a little too much.").) He also admitted that his calculations may lead to a regimen that "didn't work," alleging that if that were the case it would "probably" work at a dosing regimen involving higher doses. (Ex. 2026, 199:4-7 ("If it didn't work for 8-6-6, it would work at 8-8-8 probably. If it didn't work at 8-8-8, it might work at 10-8-8.").) Nevertheless, he asks the Board to assume that his calculations are overestimates because he applied "conservative" assumptions. But his failure to properly account for the effects of non-linear kinetics that would have been

expected based on the disclosure in the prior art undermines the predictive value of Petitioner's estimated serum concentration values.

Given the teaching that trastuzumab demonstrated dose-dependent pharmacokinetics, the danger of assuming linear kinetics to extrapolate a dosing regimen involving a different dose amount and a different dosing interval was particularly acute. Petitioner's expert predicted trough serum concentrations of 10.9 to 21.1 μg/mL. These admittedly inaccurate results are just barely above the targets of 10-20 μg/mL established by the preclinical studies, and far below the levels reached in clinical studies like Baselga '96 and Pegram '98, and those reported in the Label. (*See, e.g.*, Ex. 1009 at 8, Table 6; Ex. 1008 at 1; *cf.* Ex. 1007 at 7-8 (no clinical response for patients that did not achieve "adequate serum concentrations").) The uncertainty associated with trastuzumab's variable half-life and non-linear kinetics further cautions against relying on predictions that are admittedly oversimplified and barely above therapeutic targets. (*See* Ex. 1021 at 49 ("Variability in half-life will influence variability in time above any specific plasma concentration. This is becoming increasingly well-recognized as an important factor in both toxicity and response.").) Petitioner failed to explain why a skilled artisan would ignore the prior art's warnings, including warnings from Petitioner's own expert, and administer a speculative dosing regimen based on oversimplified calculations that ignore the complexities of the prior art.

Further, given Watanabe's report that no tumor response was observed at a trough concentration of 9 µg/ml, a skilled artisan concerned about treating patients with deadly cancer would have not have had a reasonable expectation of success for a regimen that resulted in a trough concentration of 10.9 µg/ml. (Ex. 1006 at 5; Ex. 2028, ¶¶69-71; *see also* Ex. 1007 at 7-8.) A skilled artisan would not administer an alternative dosing regimen to treat a life-threatening disease such as metastatic breast cancer unless she was reasonably certain that the claimed protocol reached therapeutic serum levels. (Ex. 2028, ¶¶69-71.) Here, uncertainty and risk preclude a skilled artisan from having the requisite reasonable expectation of success that every three-week dosing of trastuzumab would be effective based on the cited prior art.

In sum, a skilled artisan would not have applied linear kinetics to predict how a drug with non-linear kinetics like trastuzumab would be eliminated over a three-week period. Nor would a skilled artisan assume that Dr. Ratain's simplified analysis was "conservative." Based on the prior art, a skilled artisan would have been concerned that Dr. Ratain's assumption of linear kinetics for trastuzumab could overestimate trough serum concentrations.

b. There is insufficient data in the prior art to accurately predict whether a three-week dosing regimen would be clinically effective

Although the prior art disclosed that trastuzumab had dose-dependent kinetics, it did not provide enough information from which a skilled artisan could reliably predict whether a three-week dosing regimen would have been effective. (Ex. 2027, ¶¶56-64.) Dr. Ratain conceded that there "were not sufficient data" in the prior art to apply a non-linear model for trastuzumab, (Ex. 2026, 159:19-160:2), and that if it were possible to build a model, a skilled artisan would have done so. (*Id.* at 172:12-20.) Here, the only available data in the prior art was isolated, aggregated serum concentration data from weekly administration of different dose amounts. (Ex. 2027, ¶¶58-64, 66-71, 76.) A skilled artisan could not have reliably predicted the results of an alternative dosing regimen based on this data. (*Id.* at ¶¶65-76.)

The lack of sufficient information in the prior art to reliably predict alternative dosing regimens is not a valid reason to apply an oversimplified analysis. (*Id.* at ¶¶66, 76.) A skilled artisan would have known that without the appropriate data, applying linear pharmacokinetics to predict a three-week dosing regimen for trastuzumab could have overestimated the predicted serum trough concentration or could have had other unintended consequences. (*Id.*; Ex. 2028, ¶¶61-68.)

2. Dr. Ratain's cherry-picking of data in the prior art is pure hindsight and should be rejected

Despite acknowledging the dearth of pharmacokinetic information available in the prior art, Dr. Ratain retraced the path to a three-week dosing regimen by choosing only the data points that lead to a trough serum concentration above the 10-20 μg/mL pre-clinical target. In doing so, he selected pharmacokinetic data from across five references ignoring data that did not fit into his theory and oftentimes criticizing the very prior art that reported the data upon which Petitioner's obviousness case rests.

Dr. Ratain acknowledged that there was insufficient information in either primary reference—Slamon or Watanabe—to understand trastuzumab's pharmacokinetics. (Ex. 2026, 85:17-86:11; 184:16-185:12.) He questioned the reliability of the data in Watanabe and stated that there is not enough information from which a skilled artisan would "know what's going on" with regard to trastuzumab. (*See id.*) Regarding Baselga '96, Dr. Ratain opined there was "insufficient [data] for a POSA to calculate any pharmacokinetic parameters with any reasonable clarity." (*Id.* at 106:16-107:7; *see also id.* at 105:5-6.) He nonetheless used the 8.5-day half-life reported in Baselga '96 while expressly giving "zero" weight to Baselga '96's statement that prior Phase I studies had

shown that optimal dosing regimen was weekly. (*See, e.g.*, Ex. 1003, ¶¶102-03; Ex. 2026, 95:4-16.)

Dr. Ratain's analysis regarding the Label—a reference both he and Petitioner rely on to support the obviousness case (Ex. 2026, 132:4-8; Ex. 1003, ¶¶107-09)—is even more baffling. He argued that a skilled artisan "would ordinarily treat a patient based on what's in the [L]abel and/or potentially based on other published studies" but he nevertheless explicitly disregarded the pharmacokinetics section of the Label. (Ex. 2026, 169:19-170:6; *see also id.* at165:6-21 ("I can't make heads or tails out of the stuff in the [L]abel that talks about the half-life changing with dose…."); 166:10-15 (agreeing that he is "disregarding the half-lives reported in the [L]abel at the 10-milligram dose and the 500-milligram dose").) Instead he used only the calculated 5.8-day half-life reported for the Phase III studies and disregarded all other pharmacokinetic information in the Label. (*See id.*) And despite his reliance on the Label, Dr. Ratain freely admitted that "by looking only at this [L]abel, one wouldn't know terribly much." (*Id.* at 142:17-143:11; *see also id.* at 132:15-133:8.)

An obviousness analysis that recreates the steps of the invention through hindsight—and ignores the complexities of the prior art when inconvenient for the analysis—must be rejected. *See Endo Pharm. Inc. v. Depomed, Inc.*, IPR2014-00654, Paper 69 at 26-27 (Sept. 21, 2015) (finding that Petitioner's obviousness

challenge to a dosage form patent reflected impermissible hindsight by picking and choosing certain preferred attributes of the various references and combining them to yield the claimed invention); *see also Ortho-McNeil Pharm.*, 520 F.3d at 1364 (An analysis that "simply retrace[s] the path of the inventor with hindsight [and] discount[s] the number and complexity of the alternatives … is always inappropriate for an obviousness test based on the language of Title 35 that requires the analysis to examine 'the subject matter as a whole' to ascertain if it '*would have been obvious at the time the invention was made*.'" (quoting 35 U.S.C. § 103(a)) (emphasis in original).

Yet, this is precisely what Dr. Ratain did here: he only considered the data points that would support his conclusions and ignored the rest. *See also Zoltek Corp. v. United States*, 815 F.3d 1302, 1311-13 (Fed. Cir. 2016) (rejecting an obviousness analysis where defendant's expert cherry-picked data from the prior art and plugged that data into an equation derived by the expert to reconstruct the claimed invention.).

C. This Proceeding is Unconstitutional

The Board should terminate this proceeding because it violates Patent Owner's constitutional rights. Because patents are private property rights and disputes concerning their validity were traditionally decided by courts, patent validity must be litigated in an Article-III court, not before an executive branch

agency. *McCormick Harvesting Mach. Co. v. C. Aultman & Co.*, 169 U.S. 606, 609 (1898). Adversarial challenges to an issued patent—like *inter partes* reviews—are also "Suits at common law" for which the Seventh Amendment guarantees a jury trial. U.S. Const. amend. VII; *Markman v. Westview Instruments, Inc.*, 517 U.S. 370, 377 (1996). Moreover, even if *inter partes* review is constitutional in other circumstances, it is unconstitutional for patents—like the '196 patent—that issued before passage of the America Invents Act.

The Supreme Court is currently considering the constitutionality of *inter partes* reviews in *Oil States Energy Services, LLC v. Greene's Energy Group, LLC*, No. 16-712. Patent Owner presents this constitutional challenge now to preserve the issue pending the Supreme Court's decision.

VII. CONCLUSION

For the reasons set forth above, the Board should confirm the patentability of the challenged claims 1-3, 5, 7, 9-11, 13-15, and 17-33 of the '196 patent.

Respectfully submitted,

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CERTIFICATE OF COMPLIANCE

I hereby certify that the foregoing Patent Owner's Response, contains 12,865 words as measured by the word processing software used to prepare the document, in compliance with 37 C.F.R. § 42.24(d).

Respectfully submitted,

Dated: December 21, 2017

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CERTIFICATE OF SERVICE

I hereby certify that, on December 21, 2017, I caused a true and correct copy of the following materials:

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- Patent Owner's Exhibit List
- Exhibits 2015-2059, 2061-2062, 2065-2068

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PATENT OWNER'S EXHIBIT LIST
IPR2017-01139

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2012	Declaration of Lisa J. Pirozzolo in Support of Motion for *Pro Hac Vice*
2013	Declaration of Kevin S. Prussia in Support of Motion for *Pro Hac Vice*

Patent Owner's Exhibit Number	**Exhibit Name**
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2060	RESERVED

Patent Owner's Exhibit Number	**Exhibit Name**
2061	Cynthia Campbell-Baird et al., *Incidence of Acute Phase Adverse Events Following Denosumab or Intravenous Bisphosphonates: Results from a Randomized, Controlled Phase II Study in Patients with Breast Cancer and Bone Metastases*, 7 COMMUNITY ONCOLOGY 85 (2010)
2062	PierFranco Conte & Valentina Guarneri, *Safety of Intravenous and Oral Bisphosphonates and Compliance with Dosing Regimens*, 9 (Suppl. 4) THE ONCOLOGIST 28 (2004)
2063	RESERVED
2064	RESERVED
2065	Andrew D. Seidman, *One-Hour Paclitaxel Via Weekly Infusion: Dose-Density with Enhanced Therapeutic Index*, 12 (SUPPL. 1) ONCOLOGY 19 (1998)
2066	David Spiegel, *Psychosocial Aspects of Breast Cancer Treatment*, 24 (SUPPL. 1) SEMIN. ONCOLOGY (1997)
2067	Donald E. Mager & William J. Jusko, *General Pharmacokinetic Model for Drugs Exhibiting Target-Mediated Drug Disposition*, 28 J. PHARMACOKINETICS & PHARMACODYNAMICS 507 (2001)
2068	CLINICAL PHARMACOKINETICS: CONCEPTS AND APPLICATIONS (Malcolm Rowland & Thomas N. Tozer eds., 3d ed. 1995) (Chapters 1, 3, & 19)