UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SAMSUNG BIOEPIS CO., LTD., Petitioner,

v.

GENENTECH, INC., Patent Owner.

United States Patent No. 6,627,196
Title: Dosages for Treatment with Anti-ErbB2 Antibodies

Case No.: IPR2017-01958

PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 6,627,196

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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42, Petitioner Samsung Bioepis Co., Ltd. ("Bioepis" or "Petitioner") respectfully requests *inter partes* review ("IPR") of claims 1–3, 5, 7, 9–11, and 17–33 (the "Challenged Claims") of U.S. Patent No. 6,627,196 ("'196 patent"), which is attached to this Petition as Exhibit 1001.[1] Concurrently filed with the petition is a power of attorney pursuant to 37 C.F.R. § 42.10(b).

The Challenged Claims are directed to methods of treating patients diagnosed with cancer characterized by overexpression of the ErbB2 receptor with an anti-ErbB2 antibody given at certain time intervals. This petition shows, by a preponderance of the evidence, that the Challenged Claims are unpatentable as obvious over the prior art.

A motion for joinder with IPR2017-00804 is being filed concurrently with this petition. For the sake of completeness and efficiency, the present petition is a practical copy of the petition in IPR2017-00804.

USPTO assignment records indicate the '196 patent is assigned to Genentech, Inc. ("Genentech"). (Ex. 1004)

[1] All references to exhibits, *e.g.*, "Exhibit" or "Ex.," are to the table of exhibits attached hereto as Petitioner's Exhibit List.

II. MANDATORY NOTICES

A. Petitioner and Real Party in Interest (37 C.F.R. § 42.8(b)(1))

Bioepis is the Real Party in Interest. Bioepis is a corporation organized and existing under the laws of the Republic of Korea, having its principal place of business at 107, Cheomdan-daero, Yeonsu-gu, Incheon 21987, Republic of Korea.

B. Matters (37 C.F.R. § 42.8(b)(2))

Bioepis is unaware of any litigation related to the '196 patent.

Bioepis is aware of two previously filed IPR petitions related to the '196 patent. Hospira, Inc. filed IPR 2017-00804 on January 30, 2017, which was instituted on July 27, 2017. Celltrion, Inc. subsequently filed IPR2017-01139 on March 24, 2017, which is active and awaiting an institution decision.

Bioepis is also aware of two previously filed IPR petitions concerning the related 7,371,379 patent. Hospira filed IPR2017-00805 on January 30, 2017, which was instituted on July 27, 2017. Celltrion subsequently filed IPR2017-001140 on March 24, 2017, which is active and awaiting an institution decision.

The UK designation of European Patent 1 210 115 B1 ("EP '115") (Ex. 1005), a European counterpart to the '196 patent,[2] was recently invalidated in UK proceedings as obvious in light of one or more of the references asserted here; the

[2] The EP '115 patent and the '196 patent both claim priority to U.S. Provisional Application Nos. 60/213,822 and 60/151,018.

court's judgment was affirmed on appeal. (*See Hospira UK Ltd. v. Genentech Inc.*, Case No. HC12C03487 [2014] EWHC (CH) 1094 (Pat) (Apr. 10, 2014), Approved Judgment (Ex. 1006); *Hospira UK Ltd. v. Genentech Inc.*, Case No. A3 2014 1800, [2015] WECA (Civ) 57 (Feb. 6, 2015), Approved Judgment (Ex. 1007))

EP '115 was also invalidated and revoked across Europe by the EPO on the grounds that it failed to disclose the invention in a manner sufficiently clear and complete for it to be carried out by the skilled person. (*See* Eur. Patent No. EP 1 210 115 B1, Application No. 00 959 423.5, *Decision revoking the Eur. Patent* (May 4, 2012) (Ex. 1009) at 5, 18)

Bioepis is not aware of any other judicial or administrative matters that would affect, or be affected by, a decision in the proceeding.

C. Counsel and Service Information (37 C.F.R. § 42.8(b)(3) and (4))

Bioepis designates the following counsel:

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Dimitrios T. Drivas White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 ddrivas@whitecase.com USPTO Reg. No. 32,218	Scott T. Weingaertner White & Case LLP 1221 Avenue of the Americas New York, New York 10020 Tel: (212) 819-8200 Fax: (212) 354-8113 scott.weingaertner@whitecase.com USPTO Reg. No. 37,756

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III. FEES (37 C.F.R. § 42.15(a))

Bioepis authorizes the United States Patent and Trademark Office to charge the fees enumerated in 37 C.F.R. § 42.15(a) regarding this Petition and any additional fees that may be due in connection with this Petition from Deposit Account No. 50-3672.

IV. REQUIREMENTS UNDER 37 C.F.R. § 42.104

A. Grounds for Standing (37 C.F.R. § 42.104(a))

Bioepis certifies that the ’196 patent is available for IPR and that Bioepis is not barred or estopped from requesting IPR on the grounds identified herein. 35 U.S.C. § 315.

B. Statement of relief requested (37 C.F.R. § 42.104(b))

The application from which the ’196 patent issued was filed on August 25, 2000. Because the application was filed before March 16, 2013, this Petition is governed by pre-AIA 35 U.S.C. § 103. *See* MPEP 2159.01. Pursuant to 37 C.F.R. §§ 42.104(b)(1) and (2), Bioepis requests review of the Challenged Claims on the following ground:

Ground	Proposed Statutory Rejection of the '196 Patent
1	Claims 1–3, 5, 7, 9–11, and 17–33 are obvious based on the Herceptin Label in view of Baselga '96, Pegram '98, and the knowledge of a person of ordinary skill in the art under 35 U.S.C. § 103.

The cited prior art is as follows:

- **Herceptin Label**. The 1998 FDA approved label for rhuMAb HER2[3] (the "Herceptin Label") is attached as Exhibit 1008. The Herceptin Label is a printed publication that was accessible to the relevant public as of the earliest priority date (August 27, 1999). It is dated "September 1998," (*id.* at 2), and the FDA approved rhuMAb HER2 on September 25, 1998. (Ex. 1010; Ex. 1011 at 1) Further, as evidenced by Genentech's SEC filings, Genentech manufactured and marketed rhuMAb HER2 by at least 1998. (*See* Ex. 1012 at 4–5, 13, 36) In addition, the FDA's website makes available the Herceptin Label as well as a list of supplements and modifications to the label. (*See* Ex. 1010 and image below)

[3] rhuMAb HER2 is also known as Herceptin® or trastuzumab. This Petition will refer to these interchangeable terms as "rhuMAb HER2".

Action Date	Submission	Submission Classification	Letters, Reviews, Labels, Patient Package Insert
04/27/2017	SUPPL-5337	Labeling-Package Insert, Labeling-Package Insert	Label (PDF) Letter (PDF) Review (PDF)
03/17/2016	SUPPL-5330	Labeling-Package Insert	Label (PDF) Letter (PDF)
04/23/2015	SUPPL-5327	Labeling-Package Insert	Label (PDF) Letter (PDF)
06/30/2014	SUPPL-5318	Labeling	Letter (PDF)
06/30/2014	SUPPL-5313	Labeling	Letter (PDF)
03/07/2014	SUPPL-5311	Efficacy	Label (PDF) Letter (PDF) Review
11/20/2013	SUPPL-5305	Labeling	Label (PDF)
02/23/2012	SUPPL-5275	Manufacturing (CMC)	Review (PDF)
10/29/2010	SUPPL-5256	Labeling	Label (PDF) Letter (PDF)
10/20/2010	SUPPL-5250	Efficacy	Label (PDF) Letter (PDF)
04/08/2009	SUPPL-5213	Labeling	
05/22/2008	SUPPL-5189	Efficacy	Letter (PDF) Letter (PDF) Review
05/22/2008	SUPPL-5187	Efficacy	Letter (PDF) Letter (PDF) Review
01/18/2008	SUPPL-5175	Efficacy	Label (PDF) Letter (PDF)
11/16/2006	SUPPL-5150	Efficacy	Label (PDF) Letter (PDF)
10/16/2003	SUPPL-5046	S	Letter (PDF)
08/28/2002	SUPPL-5008	Efficacy	Label (PDF) Letter
12/11/2001	SUPPL-5004	Efficacy	Label (PDF) Letter
02/09/2000	SUPPL-1005	S	Label Letter

According to 21 U.S.C. § 352(b) (effective 1998), drugs like rhuMAb HER2, if intended for sale in the U.S., must include the FDA-approved label with their package. As shown above, the FDA did not approve changes to the label for rhuMAb HER2 until 2000, at the earliest. This means that the Herceptin Label must have been included with any package of rhuMAb HER2 sold or available for sale in the U.S. in 1998 and 1999. Further, during UK litigation involving EP '115 claiming priority to the same date of August 27, 1999, Genentech "accept[ed] the

[Herceptin Label] is prior art." (Ex. 1006 ¶ 13) For all of these reasons, the Herceptin Label is prior art to the '196 patent claims under 35 U.S.C. § 102(a) as of August 27, 1999. *See also Phigenix, Inc. v. Immunogen, Inc.*, IPR2014-00676, Paper 11 at 21–22 (P.T.A.B. Oct. 29, 2014) (instituting IPR based, in part, on the Herceptin Label). (Ex. 1006 ¶ 68 (invalidating EP '115 patent based, in part, on the Herceptin Label); Ex. 1002 ¶¶ 10, 36 (describing administering rhuMAb HER2 to patients including around the earliest possible priority date and reviewing the Herceptin Label)

- **Baselga '96**. Baselga, et al., Phase II Study of Weekly Intravenous Recombinant Humanized Anti-p185^{HER2} Monoclonal Antibody in Patients with HER2/neu-Overexpressing Metastatic Breast Cancer, 14(3) J. CLIN. ONCOL. 737–44 (1996) ("Baselga '96") is attached as Exhibit 1013. Baselga '96 is a printed publication that was accessible to the relevant public as of the earliest possible priority date of the '196 patent (August 27, 1999). The Journal of Clinical Oncology published Baselga '96 on March 1, 1996. (*See id.* at 737) Thus, Baselga '96 is prior art to the '196 patent claims under 35 U.S.C. § 102(b).

- **Pegram '98**. Pegram, et al., Phase II Study of Receptor-Enhanced Chemosensitivity Using Recombinant Humanized Anti-p185$^{HER2/neu}$ Monoclonal *Antibody Plus Cisplatin in Patients with HER2/neu-Overexpressing Metastatic*

Breast Cancer Refractory to Chemotherapy Treatment, 16(8) J. CLIN. ONCOL. 2659–71 (1998) ("Pegram '98") is attached as Exhibit 1014. Pegram '98 is a printed publication that was accessible to the relevant public as of the earliest possible priority date of the '196 patent. Pegram '98 was published in the *Journal of Clinical Oncology* in August 1998 and was available to the relevant public by at least August 12, 1998 as evidenced by the Health Sciences Libraries stamp bearing the same date. (*See id.* at Cover Page, Table of Contents) Thus, Pegram '98 is prior art to the '196 patent claims under 35 U.S.C. § 102(b) as of August 27, 1999.

Below is a detailed explanation of the statutory ground for the unpatentability of each of the Challenged Claims that identifies examples of where each element can be found in the cited prior art, and the relevance of that prior art.

Additional evidence is provided in the accompanying Declaration of Allan Lipton, M.D. (Ex. 1002), Declaration of William Jusko, Ph.D. (Ex. 1003),[4]

[4] The Lipton and Jusko Declarations are exact copies of the declarations submitted by Drs. Lipton and Jusko in IPR2017-00804. These declarations are cited in this petition to avoid unnecessary cost and to advance efficiency in this instance. As mentioned above, this petition is presented along with a motion to join IPR2017-00804, and by using the same declarations, Bioepis has eliminated the need for analysis of another declaration or a new expert report.

Declaration of Professor Hilary Calvert (Ex. 1039), and other supporting exhibits.[5] 37 C.F.R. § 1.68. Dr. Lipton, Dr. Jusko, and Dr. Calvert were all persons of ordinary skill in the art at the time of the alleged invention. (*See* Ex. 1002 ¶ 14; Ex. 1003 ¶ 15; Ex. 1039 ¶ 12)

Dr. Allan Lipton is a Professor of Medicine and Oncology at the Milton S. Hershey Medical Center of The Pennsylvania State University, with over 50 years of experience in the medical field and extensive experience in clinical oncology. (*See* Ex. 1002 ¶¶ 4, 6) Dr. Lipton has clinical experience prescribing rhuMAb HER2 in combination with chemotherapy, and participated in the administration of clinical trials that led to FDA approval of rhuMAb HER2. (*See id.* ¶¶ 7, 10)

Dr. William Jusko is a Distinguished Professor at the State University of New York at Buffalo in the Department of Pharmaceutical Science, with over 50 years of experience in the field including teaching and consulting for government

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To the extent Drs. Lipton or Jusko become unavailable in IPR2017-00804, however, Bioepis will rely upon the Declaration of Professor Hilary Calvert.

[5] Additional evidence authenticating various exhibits is provided in the Declaration of Scott T. Weingaertner (Ex. 1030), the Declaration of Christopher Lowden (Ex. 1031), and the Declaration of Simon Cohen (Ex. 1032). The Lowden and Cohen declarations are exact copies of the documents submitted in IPR2017-00804.

bodies as well as pharmaceutical companies. (*See* Ex. 1003 ¶¶ 4, 7, 9)

Dr. Hilary Calvert is an Emeritus Professor of Cancer Therapeutics at the University College London ("UCL") Cancer Institute. (*See* Ex. 1039 ¶ 5) Dr. Calvert has extensive clinical and research experience concerning the treatment of cancers, including serving as a Research Fellow at the Royal Marsden Hospital, where he conducted research on clinical administration of chemotherapeutic treatment and as a Professor of Medical Oncology and Clinical Director of the Northern Institute for Cancer Research at the University of Newcastle upon Tyne. (*Id.* ¶ 6)

V. THE LEVEL OF ORDINARY SKILL IN THE RELEVANT ART

A person of ordinary skill in the art at the time of the alleged invention ("POSA") could be a clinical or medical oncologist with several years of experience in breast cancer research or clinical trials, including an understanding of drug kinetics. That person may also work as a member of a team. (*See* Ex. 1002 ¶ 14; Ex. 1003 ¶ 15; Ex. 1039 ¶ 12; *see also* Ex. 1006 ¶ 32 (finding a person of ordinary skill would be a team of an oncologist and an expert in pharmacokinetics)) The Challenged Claims should be found unpatentable as obvious even if the level of ordinary skill were lower.

VI. THE SCOPE AND CONTENT OF THE PRIOR ART

A. Oncology and Pharmacokinetics

rhuMAb HER2 is an injectable drug. Patient safety, convenience and satisfaction were routine considerations and important factors in choosing injectable treatments for metastatic cancer at the time of the alleged invention. (*See* Ex. 1002 ¶ 38; Ex. 1039 ¶ 36; *see also* Ex. 1017 ¶¶ 51, 63–64)

A single visit to the oncologist to receive an infusion of the antibody and any additional chemotherapeutic agents takes several hours and depending on how far away the oncologist is, can take up to an entire day. (*See* Ex. 1002 ¶ 43; Ex. 1039 ¶ 37) POSAs recognized the difficulties this could present to patients. (*See* Ex. 1002 ¶ 44; Ex. 1019 (studying quality of life for cancer patients); Ex. 1020 (same);

Ex. 1021 (same))

A drug effect arises from a pharmacodynamic interaction between the drug and its target within the body. The effect generally depends on the concentration of the drug at the site of action. (*See* Ex. 1003 ¶ 36; Ex. 1039 ¶ 44) A commonly used pharmacokinetic parameter is half-life. (*See* Ex. 1003 ¶ 38; Ex. 1039 ¶ 46) Half-life is the time required for the serum concentration to drop by one half of any previously selected concentration. (*See* Ex. 1003 ¶ 38; Ex. 1039 ¶ 46) As named '196 patent inventor Sharon A. Baughman declared to the Board:

> [H]alf-lives are routinely used to develop the appropriate dosing frequency. For example, the half-life can be used informally to map out a treatment regimen and to predict what dosing intervals would likely be efficacious. It can also be used more formally, where appropriate data is available, to model the pharmacokinetics and pharmacodynamics of multiple-dose treatments.
>
> * * *
>
> *[T]he half-life reported . . . was 11.6 to 13.7 days . . . [which] would have supported dosing [] less frequently than weekly* because a substantial amount of antibody

> would still be circulating in the blood one week after the initial injection.

(Ex. 1017 ¶¶ 66–67)[6]

When a drug is administered repeatedly, the concentration in the body eventually approaches a steady-state. (*See* Ex. 1003 ¶ 40; Ex. 1039 ¶ 48) For drugs given by repeat dosing, an initial higher dose (loading dose) was a commonly used method to reach steady-state more rapidly. (*See* Ex. 1003 ¶¶ 41–42; Ex. 1039 ¶ 50; *see also* Ex. 1022–1:109–11)[7] Further, the serum concentration of the drug rises to a peak sometime after dosing and falls to a trough just before the next dose is given. (*See* Ex. 1003 ¶ 40; Ex. 1039 ¶ 48; Ex. 1022–1:111)

It is routine in drug development to assess the minimum trough serum concentration needed for the drug to be efficacious. (*See, e.g.*, Ex. 1013 at 10; Ex.

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[6] Dr. Baughman's Declaration was filed in an IPR for a patent with an alleged priority date of June 8, 2001. Her cited statements would have been true at the time of the alleged priority date for the '196 patent. (*See* Ex. 1003 ¶ 39; Ex. 1039 ¶ 47)

[7] Rowland, *et al.*, *Clinical Pharmacokinetics: Concepts and Applications* LIPPINCOTT WILLIAMS & WILKINS (3rd ed. 1995) (Ex. 1022). All citations to Ex. 1022 are in the format: Ex. 1022–volume: page.

1014 at 9 (using 10 µg/mL and 10–20 µg/mL, respectively, as the minimum trough serum concentration for rhuMAb HER2 phase II clinical trials)) For maximum efficacy, the typical aim of a dosing regimen is to keep trough serum concentration above the target minimum serum concentration. (*See* Ex. 1003 ¶ 52; Ex. 1039 ¶ 83)

As discussed below, for a drug analyzed using a one-compartment model like rhuMAb HER2, there are simple, textbook equations that pharmacokineticists use to calculate an appropriate loading dose for a desired dosing interval. These equations can be generally used to calculate a loading dose such that the maximum serum concentration (C_{max}) during the loading dose will only go as high as that at steady-state if one just administered the maintenance dose; such a dose would typically not raise toxicity concerns. (*See, e.g.*, Ex. 1003 ¶ 62 (Figure 2); Ex. 1039 ¶ 99)

B. Prior Art Cited in the Petition

1. The Herceptin Label

Prior to the earliest possible priority date of August 27, 1999, the availability, safety, and efficacy of rhuMAb HER2 were well publicized. rhuMAb HER2 was already *FDA-approved* and commercially sold in the U.S. by 1998. (*See* Ex. 1006 ¶ 68; Ex. 1008 at 2; Ex. 1010; Ex. 1011 at 1; Ex. 1012 at 4–5, 13, 36) By the end of 1998, Genentech had already made $30.5 million in rhuMAb

HER2 sales and licensing revenue. (*See* Ex. 1012 at 36)

Genentech did *not* submit the Herceptin Label to the USPTO during prosecution of the '196 patent. The label provides important pharmacokinetic data useful for determining dosing. For example, the Herceptin Label reports that "[s]hort duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics." (Ex. 1008 at 1) Further, the "[m]ean half-life increased ... with increasing dose level." *Id.* At the 10 mg dose, the half-life was 1.7 days, while the half-life was *12 days* at the 500 mg dose. (*See id.*)

In addition, the Herceptin Label indicates that when rhuMAb HER2 was co-administered with paclitaxel, serum trough concentrations were elevated. (*See id.*) This means that, when administered in combination with paclitaxel, rhuMAb HER2 took longer to dip below the blood concentrations deemed effective and, thus, its half-life was actually longer than when it was administered by itself. The Herceptin Label further teaches that rhuMAb HER2 *was FDA approved for administration in combination with paclitaxel*, and that paclitaxel was administered every three weeks. (*See id.*) The Herceptin Label also contemplates administration of rhuMAb HER2 in combination with other chemotherapeutic drugs (e.g., doxorubicin and epirubicin) that were administered every three weeks. Indeed, all of the chemotherapeutic agents mentioned in the Herceptin Label for administration with rhuMAb HER2 were administered tri-weekly.

As discussed below, the Herceptin Label would not only encourage a person of ordinary skill in the art at the time of the alleged invention (a "POSA") to try extending the dosing interval for rhuMAb HER2 with a reasonable expectation of success, but the disclosed half-life information could be used to determine—using well-known pharmacokinetics equations—the appropriate loading and maintenance doses for such an extended interval.

2. Baselga '96

Baselga '96 reports the results of a phase II clinical trial in which patients with ErbB2-overexpressing metastatic breast cancer were treated with rhuMAb HER2. (*See* Ex. 1013 at 9–10) The pharmacokinetic goal of the trial "was to achieve rhuMAb HER2 trough serum concentrations greater than 10 μg/mL, a level associated with optimal inhibition of cell growth in the preclinical model." (*Id.* at 10) Further, the "[s]erum levels of rhuMAb HER2 as a function of time were analyzed for each patient using a one-compartment model." (*Id*.)

The clinical trial was successful. (*See id.* at 11; *see also* Ex. 1001 at 3:54–60) Moreover, "[t]oxicity [from rhuMAb HER2] was minimal," and no immune response against the antibody was detected. (*See* Ex. 1013 at 9) rhuMAb HER2 was administered 768 times and "only 11 events occurred that were considered to be related to the use of the antibody." (*Id*. at 11)

Baselga ’96 also teaches that in preclinical studies (both *in vitro* and in xenografts), rhuMAb HER2 “*markedly potentiated the antitumor effects* of several chemotherapist agents, including cisplatin, doxorubicin, and paclitaxel, *without increasing their toxicity*.” (*Id.* at 15 (citations omitted))

3. Pegram ’98

Pegram ’98 reports the results of a phase II clinical trial using a combination of rhuMAb HER2 plus cisplatin. (*See* Ex. 1014 at 8) Pegram ’98 reports that a rhuMAb HER2 “target trough serum concentration of 10 to 20 μg/mL” was used. (*Id.*) Pegram ’98 also reports a toxicity profile of the combination that paralleled the toxicity of cisplatin alone. (*See id.* at 17) This led to the conclusion that rhuMAb HER2 did not increase toxicity. (*See id.*)

4. Pegram ’95 and Vogel ’98

Additional clinical data published years before the earliest possible priority date showed that rhuMAb HER2 “has no substantial toxicity at any dose level.” (Ex. 1015 at 5) In addition, clinical data published in 1998 showed rhuMAb HER2 was successfully administered to stage IV breast cancer patients at a front-loaded dose of 8 mg/kg followed by 4 mg/kg weekly. (Ex. 1016) Vogel ’98 reports that a control group received the FDA-approved 4 mg/kg initial dose followed by 2 mg/kg weekly. The results showed “[p]atients in the two dose groups were generally comparable,” but the “Response Rate (RR%)” for the higher dose (28%)

was higher than for the lower dose (21%). (*Id.*) "[rhuMAb HER2] was generally very well tolerated in both dose groups," and researchers concluded that "[rhuMAb HER2] is active, well-tolerated, and has a favorable safety profile." (*Id.*)

VII. THE '196 PATENT

The '196 patent is directed to the "treatment of disorders characterized by the overexpression of ErbB2" by administering "an antibody that binds ErbB2[8]." (Ex. 1001 at 1:11–35 ("Field of the Invention")) One such disorder is cancer. More specifically, the '196 patent is directed to "front loading the dose of antibody during treatment." (*Id.* at 1:18–23)

The '196 patent claims priority to August 27, 1999. By then, rhuMAb HER2, a breast cancer-treating anti-ErbB2 antibody, was already known. (*See id.* at 3:54–65) rhuMAb HER2 had been developed, FDA-approved for use in humans, and commercially sold in the U.S. for nearly a year. (*See* Ex. 1006 ¶ 68; Ex. 1008 at 2; Ex. 1010; Ex. 1011 at 1; Ex. 1012 at 4–5, 13, 36)

The prior, FDA-approved, "recommended" dosing for rhuMAb HER2 was front-loaded:[9] an initial loading dose of 4 mg/kg administered followed by a

[8] "[H]uman ErbB2 gene (erbB2, also known as her2, or c-erbB-2) . . . is overexpressed in about 25% to 30% of human breast cancer." (Ex. 1001 at 1:38– 48; *see also* Ex. 1008 at 1; Ex. 1013 at 9)

[9] In this Petition, "front-loaded" means use of a loading dose.

weekly maintenance dose of 2 mg/kg. (*See* Ex. 1008 at 1) The purported invention of the '196 patent was "*greater* front loading"—*i.e.*, providing a *greater* "initial dose or doses of anti-ErbB2 antibodies followed by subsequent doses of equal or smaller amounts of antibody." (*See* Ex. 1001 at 4:21–26[10]) According to the patent, "[t]he front loading drug treatment method of the invention has the advantage of increased efficacy by reaching a target serum drug concentration early in treatment." (*Id.* at 5:5–8; *see also* Ex. 1003 ¶¶ 41–42)

Although the alleged invention requires administering an initial dose of "at least approximately 5 mg/kg," the '196 patent includes no data or explanation as to how the amount of the initial dose was determined, or why it was surprising that a greater front-loaded dose would work. Similarly, although the claims require subsequent doses "separated in time from each other by at least two weeks," the '196 patent contains no data or explanation as to how this length of time was determined. The patent contains no experimental data from a dosing regimen in humans other than the prior art "weekly" regimen. (*See* Ex. 1001 at 8:33–39, Fig. 3)

Likewise, none of the patent's six examples include experiments conducted using dosing regimens other than an initial 4 mg/kg dose followed by 2 mg/kg weekly doses. (*See id.* at 35:25–48:4 (Examples 1–6)) Example 5 *proposes*

[10] All emphasis is added unless otherwise noted.

various dosing regimens, including an 8 mg/kg initial dose, followed by a 6 mg/kg dose every three weeks, and *predicts* that the regimen will maintain a desired "trough serum concentration." (*Id.* at 44:11–45:32) But as decided, and admitted by Genentech, in the UK proceedings, "Example 5 is entirely 'prophetic.'" (*See* Ex. 1006 ¶ 54) Example 6 similarly describes a *proposed* clinical trial in which 12 metastatic breast cancer patients would be administered an initial 8 mg/kg dose of rhuMAb HER2 followed by 6 mg/kg every three weeks, in combination with paclitaxel every three weeks. (*See* Ex. 1001 at 46:9–48:14) The '196 patent concludes by stating that "[i]t is *believed* that the above treatment regimen will be effective in treating metastatic breast cancer." (*Id.* at 48:1–4)

Summary of the Prosecution History of the '196 Patent

The '196 patent issued from Application No. 09/648,067, which was filed on August 25, 2000. (*See* Certified File History for U.S. Patent No. 6,627,196 (Ex. 1024 at 1:3)[11] The '196 patent purports to claim priority to Provisional Application No. 60/213,822, filed on June 23, 2000, and Provisional Application No. 60/151,018, filed on August 27, 1999. (*See id.*)

Genentech did not submit the Herceptin Label to the USPTO. (*See id.* 1:119 (Information Disclosure Statement ("IDS") dated January 25, 2001), 31:266 (IDS dated August 28, 2002)) As a result, the Herceptin Label had not been considered

[11] Citations to Ex. 1024 are in the format volume:page.

by the Examiner when the '196 patent issued. (*See id.*; Ex. 1001 ("References Cited"))

During prosecution of the '196 patent, the Examiner rejected the claims as obvious over prior art references that taught weekly rhuMAb HER2 dosing schedules. According to the Examiner, it would have been obvious to try to extend the dose regimen beyond the weekly dosing taught by the prior art in order to find the most effective dosing protocol. (*See* Ex. 1024–31:234)

Genentech argued that the cited art taught away from dosing greater than weekly dosing because the longest half-life cited by the examiner was 9.1 days:

> Even assuming arguendo that 9.1 days was the reported mean serum half-life for [rhuMAb HER2], this would not teach the skilled person to administer subsequent doses of the antibody 'separated in time from each other by at least two weeks' ... the skilled person wouldn't have wanted to increase the period of time between dosing beyond ... 9.1 days, for fear that insufficient levels of drug would remain in the patient to treat cancer.

(*Id.* 31:325; *see also id.* 32:22 (Reasons for Allowance)) Genentech did *not* disclose that a 500 mg dose had been shown to be safe or would have a 12-day half-life.

Summary of the UK Proceedings

During proceedings challenging EP '115, the United Kingdom High Court of Justice, Patents Court found Genentech's claimed invention invalid as obvious. (*See* Ex. 1006 ¶ 118)[12] The court determined that Genentech and Hospira had a common understanding that a person of ordinary skill in the art "looking at the [Herceptin Label] would find and consider" Baselga '96 and Pegram '98 because they "are part of the common general knowledge in the sense that they are things which the skilled person would find and consider." (*Id.* ¶ 87)

The court held that a three week dosing schedule for rhuMAb HER2 would have naturally occurred to a skilled clinician, and would have been obvious and desirable, particularly given the existing three week dosing schedule for paclitaxel. (*See id.* ¶¶ 71, 79)

Looking at Baselga '96 and Pegram '98, "the skilled person would see that the target trough serum concentrations ... for [rhuMAb HER2] were 10 μg/ml

[12] In the U.K., the standard for lack of inventive step is "obvious[ness] to a person skilled in the art." Patents Act, 37§ 3 (U.K.) ("An invention shall be taken to involve an inventive step if it is not obvious to a person skilled in the art.") A similar analysis to the *Graham* factors considered by U.S. Courts is performed. *See Pozzoli Spa v. BDMO SA & Anor.*, 2007 WL 1685192, [2007] EWCA Civ. 588 ¶ 23 (Jun. 22, 2007).

(Baselga) or 10–20 μg/ml (Pegram)." (*Id.* ¶ 88) This "key piece" of information could be used "to assess whether a proposed dosing regimen would be effective." (*Id.*) From Baselga '96, the court reasoned that one of ordinary skill in the art would understand that a "one-compartment model" had been used to estimate serum levels over time. (*See* Ex. 1013 at 10)

According to the court, a POSA would have estimated patient serum level over three weeks after a single dose of 500 mg rhuMAb HER2 based on the 12 day half-life taught by the Herceptin Label and would have compared the estimated serum level for that regimen with the minimum target trough concentration of 10–20 μg/mL:

> There is no doubt about the mathematics. Based on this calculation the trough serum concentration would be 48 μg/ml on day 21. In other words after three weeks, at the time the next dose would be due on a three weekly schedule, a 500 mg dose of [rhuMAb HER2] would produce more than double the target trough serum concentration.

(Ex. 1006 ¶ 93) As such, the court found the claimed tri-weekly rhuMAb HER2 regimen invalid as obvious in view of the Herceptin Label, Baselga '96, and Pegram '98. *See id.* ¶ 118. The Court of Appeal affirmed. (*See* Ex. 1007 ¶ 56)

A comparison of the claim at issue (and found exemplary) in the UK proceedings (claim 1) and claim 1 of the '196 patent is shown below:

TABLE 1

'196 patent	**EP '115**
1. [a] A method for the treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 receptor, comprising [b] administering an effective amount of an anti-ErbB2 antibody to the human patient, the method comprising: [c] administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and [d] 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, [e] wherein the subsequent doses are separated in time from each other by at least two weeks.	1. [b] Use of the anti-ErbB2 antibody 4D5-8 in the manufacture of a medicament for use in a [a] method for treating a human patient diagnosed with a breast cancer **characterized by** overexpression of ErbB2, said method comprising the steps of [c] administering to the patient an initial dose of 8 mg/kg of the anti-ErbB2 antibody; [d] and administering to the patient a plurality of subsequent doses of the antibody in an amount that is 6 mg/kg, [e] wherein the doses are separated in time from each other by three weeks.

As can be seen in Table 1, claim 1 of EP '115 is narrower than claim 1 of the '196 patent in all relevant respects.

VIII. CLAIM CONSTRUCTION

Bioepis assumes that the Challenged Claims possess their broadest reasonable construction. *See Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 2131, 2142 (2016).

Bioepis submits that the BRI of "ErbB2 receptor" in the '196 patent claims is, interchangeably, "HER2," "ErbB2," or "$p185^{HER2}$." This construction is supported by the patent specification, which states that "the human ErbB2 gene (erbB2, also known as her2, or c-erbB-2), which encodes a 185 kD transmembrane glycoprotein receptor ($p185^{HER2}$) related to the epidermal growth factor receptor (EGFR), is overexpressed in about 25% to 30% of human breast cancer," and uses the terms interchangeably. (*See, e.g.*, Ex. 1001 at 1:41–47; *see also* Ex. 1002 ¶ 23; Ex. 1003 ¶ 23; Ex. 1039 ¶ 21)

IX. DETAILED STATEMENT OF GROUNDS FOR UNPATENTABILITY

A patent claim is unpatentable under 35 U.S.C. § 103(a) if the differences between the patented subject matter and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the pertinent art. *KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007). In addition, "[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options

within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense." *See id*. at 421.

"Generally, differences in concentration ... will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration ... is critical." MPEP 2144.05. "[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation." *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295–96 (Fed. Cir. 2012) (internal citation omitted). Further, "[i]t is a settled principle of law that a mere carrying forward of an original patented conception involving only change of form, proportions, or degree, or the substitution of equivalents doing the same thing as the original invention, by substantially the same means, is not such an invention as will sustain a patent, even though the changes of the kin[d] [*sic*] may produce better results than prior inventions." *In re Williams*, 36 F.2d 436, 438 (CCPA 1929).

Claims 1–3, 5, 7, 9–11, and 17–33 are unpatentable under 35 U.S.C. § 103(a) as being obvious over the Herceptin Label in view of Baselga '96, Pegram '98, and the knowledge of a POSA.

The Herceptin Label teaches rhuMAb HER2 should be used "in combination with paclitaxel" for treatment of patients with metastatic breast cancer. (*See* Ex.

1008 at 1) This was an FDA-approved, safe and effective use. The FDA recommended dose of rhuMAb HER2 was administered by intravenous injection "weekly," whereas paclitaxel was given by intravenous injection "every 21 days." (*Id.*) As discussed above, the Herceptin Label also contemplates rhuMAb HER2 in combination with other tri-weekly chemotherapeutic agents such as doxorubicin and epirubicin.

It would have been obvious to a POSA to have tried decreasing the frequency of rhuMAb HER2 injections to every three weeks (tri-weekly) to match the schedule of chemotherapy. A POSA would have been motivated to do so to reduce injection frequency and trips to the hospital—thereby being more efficient and convenient, particularly for terminally ill patients—and to improve patient compliance and quality of life. (*See, e.g.*, Ex. 1002 ¶ 63; Ex. 1039 ¶ 73) In fact, named inventor Dr. Baughman has argued as much to the Board. (Ex. 1017 ¶ 64 ("It would have been desirable to reduce the frequency of injection to increase patient compliance. First, injections hurt. By reducing the frequency of dosing and as a result dosing-related pain, patient compliance and satisfaction may improve.")) Further, a triweekly regimen would have been an obvious choice because it aligns with paclitaxel and other chemotherapy's dosing schedule and administering the combined therapies on the same schedule would achieve further benefits. (*See* Ex. 1002 ¶¶ 42, 66; Ex. 1039 ¶¶ 36-39, 75)

The claimed tri-weekly dosing schedule for rhuMAb HER2 was merely a matter of routine calculation and optimization. (*See* Ex. 1002 ¶ 67; Ex. 1003 ¶ 67; Ex. 1039 ¶ 90) The Herceptin Label, particularly in view of Baselga '96 or Pegram '98 or both, provided all the information and motivation necessary for a POSA to try the claimed dosing regimens. The Herceptin Label itself shows rhuMAb HER2 dosing should be front-loaded, (*see* Ex. 1008 at 1), as do several other prior art references. (*See* Ex. 1013 at 9–10; Ex. 1014 at 8; Ex. 1015 at 5; Ex. 1016 at 27) And unlike the prior art cited during prosecution, the Herceptin Label teaches that the average half-life for rhuMAb HER2 was as long as 12.1 days, and that the half-life is even longer if rhuMAb HER2 is administered in combination with paclitaxel. (*See* Ex. 1008 at 1) Baselga '96 and Pegram '98 provide the target minimum trough concentration of 10–20 μg/mL. All three references confirm rhuMAb HER2 is safe and that doses up to at least 500 mg exhibited no serious side effects. (*See* Ex. 1008 at 1; Ex. 1013 at 9; Ex. 1014 at 8)

A POSA would have been motivated to combine the teachings of the Herceptin Label, Baselga '96, and Pegram '98 because all three references are directed to the same problem of treating HER2-overexpressing cancers with rhuMAb HER2, and indeed, Baselga '96 and Pegram '98 describe clinical trials that led to the approval of rhuMAb HER2 and the Herceptin Label by the FDA.

The case for obviousness here is even stronger than that presented in

Biomarin Pharm., Inc. v. Genzyme Therapeutic Prods., LP, IPR2013-00537, Paper 79 (P.T.A.B. Feb. 23, 2015) (Ex. 1025), *aff'd Genzyme Therapeutic Prods. LP v. Biomarin Pharm. Inc*., 825 F.3d 1360 (Fed. Cir. 2016). There, the Board declared claims directed to a particular dose of a biologic (at least 10 mg/kg body weight of enzyme) and dosing schedule ("biweekly") unpatentable. *See id.* at 23. In *Biomarin*, "human clinical trials were not initiated" before the relevant priority date. *Id.* at 17. Nevertheless, the Board found that a POSA "would have been motivated to pursue the clinical development of the therapy disclosed" in the prior art, and "what remained to be achieved to arrive at the claimed subject matter was the selection of a specific dose and dosing schedule for a treatment regimen." *Id.* at 18–19. The Board found that "the selection of the dose and dosing schedule would have been a routine optimization of the therapy outlined in [the prior art] which would have been achievable through the use of standard clinical trial procedures." *Id.* at 19. Indeed, "[t]he motivation to optimize the therapy disclosed in [the prior art] 'flows from the normal desire of scientists or artisans to improve upon what is already generally known.'" *Id.* at 20 (internal citations omitted).

In this case, clinical trials of rhuMAb HER2 *had* been performed successfully at various doses including up to a weekly dose of 500 mg. It was a matter of routine pharmacokinetic calculations to confirm a front-loaded dosing regimen for safely and effectively administering rhuMAb HER2 on a tri-weekly

basis. (*See* Ex. 1003 ¶ 67; Ex. 1039 ¶ 90)

The Challenged Claims are unpatentable.

A. Claims 1–3, 5, 7, 9–11, and 17–33 are Obvious Over the Herceptin Label in View of Baselga '96, Pegram '98, and the Knowledge of a Person of Ordinary Skill in the Art

1. Claim 1

Claim 1 is obvious over the Herceptin Label in view of Baselga '96, Pegram '98, and the knowledge of a POSA.

a. Claim 1, preamble: "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:"

The Herceptin Label teaches treatment of a human patient diagnosed with cancer characterized by overexpression of ErbB2 by administering an anti-ErbB2 antibody. For example, the Herceptin Label teaches that rhuMAb HER2, which is an anti-ErbB2 antibody, is "administ[ered]" in "dosage[s]" "for the treatment of [human] patients with metastatic breast cancer whose tumors overexpress the HER2 protein." (Ex. 1008 at 1–2; *see also id.* at 1 ("Indications and Usage"))

The Herceptin Label also teaches administering an "effective amount" of rhuMAb HER2. Depending on the level of HER2 overexpression in patients, the Herceptin Label says the overall response rate was 21–44% and the median time to disease progression was 4.4–7.1 months. (*See id.* at Table 2) A POSA would have

understood this response rate and median time to disease progression as an effective result.[13] (*See* Ex. 1002 ¶ 53; Ex. 1039 ¶ 63) As discussed below, a POSA also would have understood that the claimed amounts would be effective.

b. Claim 1, element [a]: "administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and"

The Herceptin Label teaches that rhuMAb HER2 doses of up to 500 mg had been successfully administered to patients. (*See* Ex. 1008 at 1 ("Short duration intravenous infusions of 10 to 500 mg once weekly demonstrated dose-dependent pharmacokinetics.")) Doses may be expressed as absolute or weight-based values. (*See* Ex. 1002 ¶ 54; Ex. 1039 ¶ 64) 500 mg is an absolute dose. To get a weight-based dose from an absolute dose, one divides the absolute dose by the weight of the particular patient. For example, if a patient weighs 70 kg (154 lbs), a weight-based dose for the 500 mg absolute dose taught by the Herceptin Label is: 500 mg / 70 kg = 7.14 mg/kg (*i.e.*, greater than 5 mg/kg). (*See* Ex. 1002 ¶ 55; Ex. 1039 ¶ 65)

[13] Genentech also obtained FDA approval of the Herceptin Label and included the Herceptin Label with its sales of rhuMAb HER2 (sold under trade name Herceptin®). A POSA would have been well aware that the FDA's drug review process, which includes a review of labeling, is for the purpose of ensuring safe and effective use of the drug. (*See* Ex. 1002 ¶ 35; Ex. 1039 ¶ 33)

Patient weight is unique to each individual patient, and 70 kg is used as a representative example. Indeed, there are necessarily patients for whom the 500 mg absolute dose taught by the Herceptin Label is greater than approximately 5 mg/kg including 70 kg patients. (*See* Ex. 1002 ¶ 56; Ex. 1039 ¶ 66) Additionally, 55–85 kg is a reasonable range that a POSA would assume for patient weight. (*See* Ex. 1002 ¶ 57; Ex. 1039 ¶ 67; Ex. 1026 at 3; Ex. 1027 at 334 (Table 7-2); *see also* Ex. 1003 ¶ 45) The Herceptin Label's disclosure of a 500 mg absolute dose converts to a weight-based dose of at least approximately 5 mg/kg across this entire weight range (5.88 mg/kg for 85 kg patient to 9.09 mg/kg for 55 kg patient). (*See* Ex. 1002 ¶ 65 (Table A); Ex. 1039 ¶¶ 65, 98) Furthermore, as discussed below, a POSA would know to use a front-loaded initial dose that is greater than 500 mg, and thus greater than 5.88–9.09 mg/kg for patients weighing 55–85 kg. (*See supra* Section IX.A.1.d (claim 1, element [c]))

In light of a POSA's knowledge about patient weights and the appropriate weight assumptions to apply when calculating doses, the claimed dose of at least approximately 5 mg/kg would be at minimum obvious to a POSA reviewing the Herceptin Label.[14] The obviousness of this element is further confirmed by the fact that the '196 patent contains no data showing that any of the claimed dosing

[14] This Petition is addressing obviousness to a POSA at the time of the alleged invention.

regimens, much less the full scope of claimed dosing regimens, were tested by the inventors, had any unexpected properties, or were critical. *See In re Woodruff*, 919 F.2d 1575, 1578 (Fed. Cir. 1990) ("The law is replete with cases in which the difference between the claimed invention and the prior art is some range or other variable within the claims. These cases have consistently held that in such a situation, the applicant must show that the particular range is *critical*, generally by showing that the claimed range achieves unexpected results relative to the prior art range.") (emphasis in original) (internal citations omitted).

c. Claim 1, element [b]: "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"

The Herceptin Label discloses "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." For example, the Herceptin Label teaches that rhuMAb HER2 doses should be front-loaded. (*See* Ex. 1008 at 1 (recommending "a loading dose of 4 mg/kg followed by" a lower "weekly maintenance dose of 2 mg/kg"; describing clinical "studies using a loading dose")) Baselga '96 and Pegram '98 confirm that rhuMAb HER2 regimens should be front-loaded. (*See* Ex. 1013 at 9 ("Patients received a loading dose of 250 mg of intravenous rhuMAb HER2, then 10 weekly doses of 100 mg each."); Ex. 1014 at 8 ("Patients received a loading dose of rhuMAb HER2 (250 mg IV) on day 0, followed by weekly doses of 100

mg IV for 9 weeks.")) Further, a POSA would have known from his or her ordinary education and experience that intravenous injectable antibodies like rhuMAb HER2 should be administered such that the repeated doses are approximately the same or less than the initial dose. (*See* Ex. 1003 ¶ 59; Ex. 1039 ¶ 69)

For these reasons, it would have been obvious to have administered a plurality of subsequent rhuMAb HER2 doses in an amount approximately the same or less than the initial dose.

d. Claim 1, element [c]: "wherein the subsequent doses are separated in time from each other by at least two weeks."

The Herceptin Label teaches weekly administration of rhuMAb HER2. (*See* Ex. 1008 at 1) A POSA would have arrived at the claimed dosing schedule by routine optimization of the therapy outlined by the Herceptin Label. (*See* Ex. 1025 at 19–20) Indeed, a POSA would have been motivated to decrease the frequency of rhuMAb HER2 injections for several reasons, as detailed below.

First, a skilled artisan would decrease the frequency of injections to improve efficiency, to provide a more convenient dosing regimen—particularly for terminally ill patients—and to improve patient compliance and quality of life. *See Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1329 (Fed. Cir. 2014) ("A relatively infrequent dosing schedule has long been viewed as a potential solution

to the problem of patient compliance[.]"), *cert. denied*, 135 S. Ct. 878 (2014). As discussed in Dr. Lipton's and Dr. Calvert's Declaration, a trip to the clinic for a single intravenous infusion can take a full day. (*See* Ex. 1002 ¶ 43; Ex. 1039 ¶¶ 36-39, 73) Further, travel time to and from the clinic can make the patient's day even longer. In addition, clinic visits can be emotionally taxing (for example, by being placed in an infusion room) and disruptive to a patient's life (for example, by missing work). (*See* Ex. 1002 ¶¶ 42–43; Ex. 1039 ¶¶ 36-39)

Dr. Baughman, one of the named inventors of the '196 patent, has also argued for the obviousness of decreasing the frequency of injections for many of the same reasons discussed here in a Declaration submitted in another *inter partes* review. (*See* Ex. 1017 ¶ 64 ("It would have been desirable to reduce the frequency of injection to increase patient compliance. First, injections hurt. By reducing the frequency of dosing and as a result dosing-related pain, patient compliance and satisfaction may improve."); *see also* Ex. 1002 ¶ 64; Ex. 1039 ¶ 74)

Second, a skilled artisan would decrease the frequency of injections in view of the teachings of the Herceptin Label, which describes administration of rhuMAb HER2 in combination with chemotherapeutic agents, administered once every three weeks:

> For those who had received prior anthracycline therapy in the adjuvant setting, *chemotherapy consisted of*

> *paclitaxel ... every 21 days* for at least six cycles); for all other patients, *chemotherapy consisted of anthracycline plus cyclophosphamide (AC: doxorubicin ... or epirubicin ... plus ... cyclophosphamide every 21 days* for six cycles).
>
> * * *
>
> INDICATIONS AND USAGE. ... *HERCEPTIN in combination with paclitaxel* is indicated for treatment of patients with metastatic breast cancer whose tumors overexpress the HER2 protein and who have not received chemotherapy for their metastatic disease.

(*See* Ex. 1008 at 1)

When decreasing the frequency of rhuMAb HER2 injections, a tri-weekly regimen would have been an obvious choice because it would have aligned with the tri-weekly dosing schedules of the chemotherapy. Administering the combined therapies on the same schedule would achieve even further benefits. For example, a patient would only have to make one trip to the clinic to receive both therapies (with the added benefit of improving patient compliance). As discussed above, all of the chemotherapeutic agents mentioned in the Herceptin Label for

administration with rhuMAb HER2 were administered tri-weekly.

It is also beneficial for the clinic to administer the combined therapies on the same schedule because they only have to prep the patient once. (*See* Ex. 1002 ¶¶ 42, 66; Ex. 1039 ¶¶ 36-39, 75) In addition, there is added cost to the patient's care for each visit to the clinic. (*See* Ex. 1002 ¶¶ 43, 66; Ex. 1039 ¶¶ 36-39, 75)

Finally, a skilled artisan would decrease the frequency of injections and use a tri-weekly dosing regimen in view of rhuMAb HER2's known pharmacokinetic properties. (*See* Ex. 1003 ¶ 67; Ex. 1039 ¶ 76) These properties are taught by the Herceptin Label and include rhuMAb HER2's average half-life (12.1 days for a weekly dose of 500 mg) and "volume of distribution" (44 mL/kg). (Ex. 1008 at 1) The skilled artisan would have also been aware of the target trough serum concentration for rhuMAb HER2 (10–20 µg/mL) in view of Baselga '96 and Pegram '98 (*see* Ex. 1003 ¶ 51; Ex. 1039 ¶ 82), and the type of pharmacokinetic model (one-compartment model) to use in view of Baselga '96 and the Herceptin Label. (*See* Ex. 1003 ¶ 35; Ex. 1039 ¶ 43)

More specifically, Baselga '96 discloses that serum levels were analyzed using a one compartment model. (*See* Ex. 1013 at 10) Further, because the Herceptin Label reports only a single half-life, a POSA would have understood that the pharmacokinetic data contained therein had been modelled by a one compartment model. (*See* Ex. 1008 at 1; Ex. 1003 ¶ 34; Ex. 1039 ¶ 42; *see also*

Ex. 1006 ¶ 101 ("the only model which could be used based on the [Herceptin Label] was a one compartment model. Indeed it is clear from the information in the [Herceptin Label] that a one compartment model was used.")).

Using data from the Herceptin Label, it would have been a matter of routine calculation for a POSA to determine that a tri-weekly rhuMAb HER2 dose regimen would have resulted in a serum concentration well above the target minimum trough concentration of 10–20 µg/ml. (*See, e.g.*, Ex. 1003 ¶¶ 57 (Figure 1), 62 (Figure 2); Ex. 1039 ¶¶ 88, 95) Specifically, a POSA would have known that the initial antibody serum concentration can be estimated by the following equation, wherein the "*Dose*" is weight-based and V_D is the volume of distribution, and solving for C_0:

$$V_D = \frac{Dose}{C_0}$$

(Ex. 1003 ¶ 47 (Equation (2)); Ex. 1039 ¶ 78;] Ex. 1022–1:33) Then, using a one compartment model, the drug concentration over time could have been approximated by:

$$Conc = C_0 \cdot e^{-k_{el} \cdot time}$$

(Ex. 1003 ¶ 46 (Equation (1); Ex. 1039 ¶ 77) In Equation (1), k_{el} is defined as follows, wherein $t_{1/2}$ is the half-life:

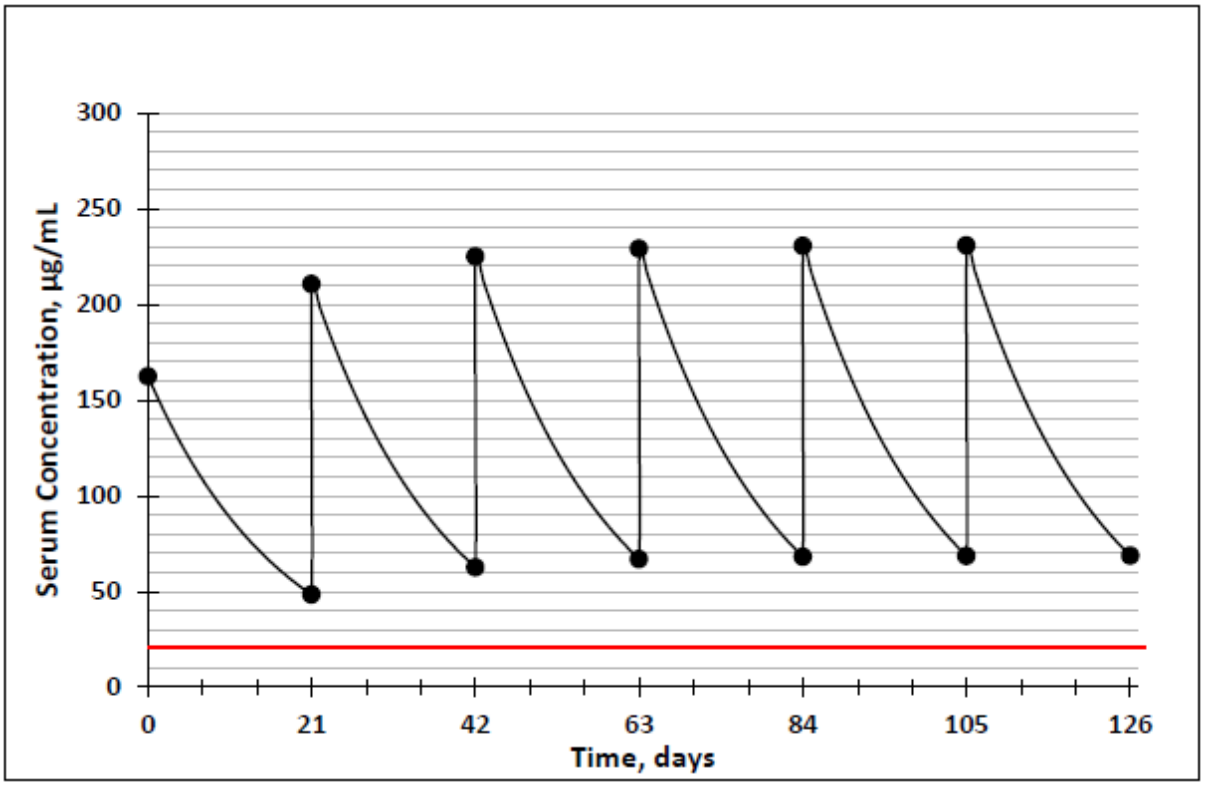
$$k_{el} = \frac{\ln(2)}{t_{1/2}}$$

(Ex. 1003 ¶ 49 (Equation (3)); Ex. 1039 ¶ 80; Ex. 1022–1:34)

Performing these routine calculations demonstrates that, after administering a 500 mg dose of antibody, the initial drug minimum concentration of a 70 kg patient after three weeks is 48.3 µg/mL, or at least double the target minimum trough concentration of 10–20 µg/ml. (Ex. 1003 ¶¶ 50–51; Ex. 1039 ¶¶ 81-82) After repeated 500 mg doses are administered, the steady-state trough concentration will eventually reach approximately 68.7 µg/mL. (Ex. 1003 ¶ 56; Ex. 1039 ¶ 87)

The expected concentration of antibody over time during this treatment regimen is illustrated in Figure 1.

Figure 1



(Ex. 1003 ¶ 57; Ex. 1039 ¶ 88) As can be seen in Figure 1, a POSA would have expected the rhuMAb HER2 serum concentration to stay well above the target minimum trough concentration of 10–20 µg/ml (20 µg/ml shown in red).

Based on these calculations, a pharmacokineticist would have had a reasonable expectation of success in trying tri-weekly 500 mg rhuMAb HER2 since 500 mg weekly doses had been safely administered and, based on routine calculations, a 500 mg tri-weekly regimen would have resulted in a serum concentration well above the target minimum trough concentration. (*See* Ex. 1003 ¶ 58; Ex. 1039 ¶ 89)

Further, to reach steady-state on the first administration of rhuMAb HER2, a POSA could have used other textbook equations to estimate an appropriate loading dose for a 500 mg repeating dose. (*See* Ex. 1003 ¶ 61; Ex. 1039 ¶ 94; Ex. 1022–1:101) Specifically, a loading dose can be estimated by either of:

$$D_L = C_{\max}(at\ steady - state) \times V_D$$

$$D_L = D_M \times R$$

(Ex. 1003 ¶ 59 (Equations (7) and (8), respectively); Ex. 1039 ¶ 92) In these equations, the *DM*, *R*, τ, and K_{el} are defined as follows:

D_M is the maintenance dose

$$R = \frac{1}{1 - e^{-k_{el} \cdot \tau}}$$

τ is the dose interval

$$k_{el} = \frac{\ln 2}{t_{1/2}}$$

In this case, the dose interval is three weeks, or 21 days, and the maintenance dose is 500 mg. Solving these equations results in an initial loading dose of approximately 712 mg. (*See* Ex. 1003 ¶ 61; Ex. 1039 ¶ 94]) This converts to the weight-based doses in Table A below:

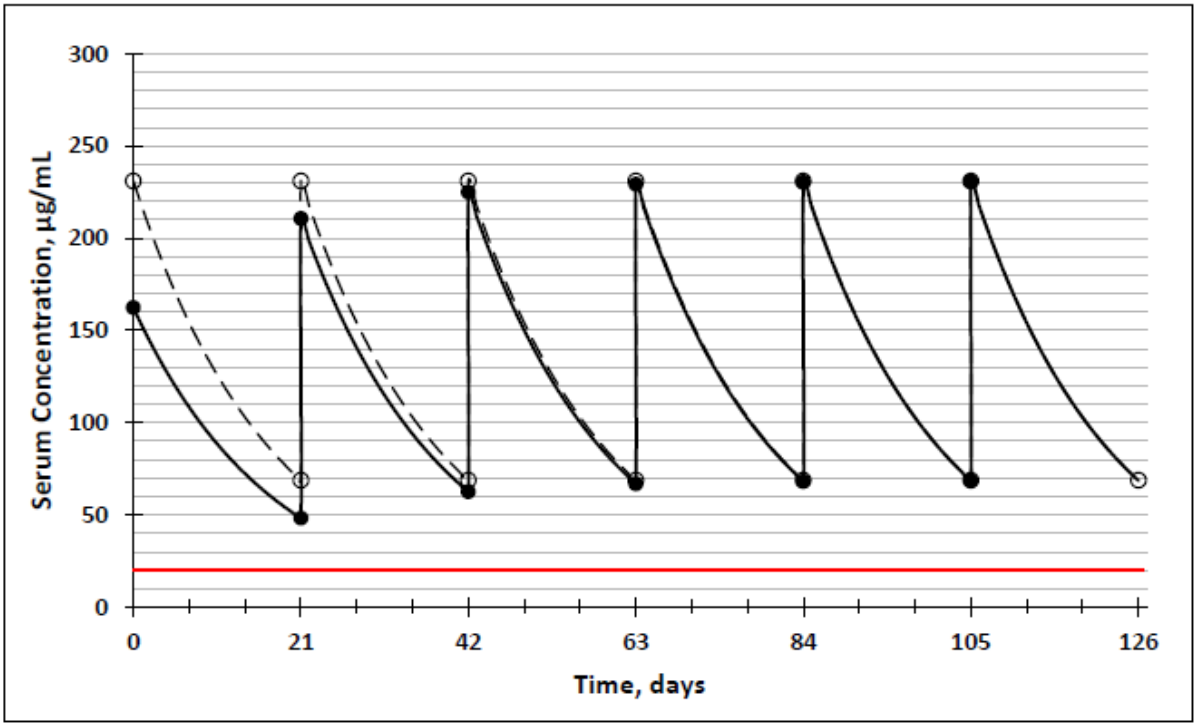
Table A

Patient Weight	712 mg Loading Dose	500 mg Maintenance Dose
55 kg	12.9 mg/kg	9.09 mg/kg
70 kg	10.2 mg/kg	7.14 mg/kg
85 kg	8.38 mg/kg	5.88 mg/kg

(Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

The concentration of rhuMAb HER2 over time during a treatment regimen of 712 mg followed by 500 mg every three weeks is illustrated in Figure 2 (dashed line):

Figure 2



(Ex. 1003 ¶ 62; Ex. 1039 ¶ 95) As shown in Figure 2, a 712 mg loading dose of rhuMAb HER2 followed by 500 mg/kg tri-weekly results in steady-state kinetics after the first dose administration. Just as in Figure 1, the rhuMAb HER2 serum concentration would have been expected to stay well above the target minimum trough concentration of 10–20 μg/ml (20 μg/ml shown in red line).

A POSA also would have known rhuMAb HER2 was generally well-tolerated, toxicity from the antibody was minimal, and that lower doses were effective. (*See, e.g.*, Ex. 1008 at 1; Ex. 1013 at 9; 1014 at 17; *see also* Ex. 1003 ¶ 55; Ex. 1039 ¶ 86; Ex. 1016 at 27 (Abstract 23) (describing safe administration of 8 mg/kg loading doses)) Therefore, a POSA at minimum would have had a reasonable expectation that a 712 mg loading dose followed by tri-weekly 500 mg doses would have worked.

In performing their calculations, Dr. Jusko and Dr. Calvert made three assumptions. First, Dr. Jusko and Dr. Calvert assumed that rhuMAb HER2 exhibits mono-exponential kinetics. (*See* Ex. 1003 ¶ 69; Ex. 1039 ¶ 135) Second, Dr. Jusko and Dr. Calvert assumed C_0 can be estimated by multiplying the dose by the volume of distribution and average mass of a patient. (*See* Ex. 1003 ¶ 70; Ex. 1039 ¶ 136; Ex. 1028 at 91 (describing the up-curve in plasma concentrations produced by the infusion process diminishes the influence of the early distribution process causing a bi-exponential curve to look more mono-exponential)) Last, Dr.

Jusko and Dr. Calvert assumed the kinetics of rhuMAb HER2 remain constant with multiple-dosing. (*See* Ex. 1003 ¶ 71; Ex. 1039 ¶ 137; Ex. 1029 at 77 (describing the pharmacokinetics of IgG))

2. Claim 2: "The method of claim 1, wherein the initial dose is at least approximately 6 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b) and [c] (*see supra* Section IX.A.1.d), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all the loading doses in Table A are at least approximately 6 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98])

3. Claim 3: "The method of claim 2, wherein the initial dose is at least approximately 8 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b) and [c] (*see supra* Section IX.A.1.d), and claim 2 (*see supra* Section IX.A.2), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all the loading doses in Table A are at least approximately 8 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

4. Claim 5: "The method of claim 1, wherein the subsequent doses are separated in time from each other by at least three weeks."

For at least the reasons discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill.

5. Claim 7: "The method of claim 1, wherein the initial dose is administered by intravenous injection, wherein at least two subsequent doses are administered, and wherein each subsequent dose is administered by a method selected from the group consisting of intravenous injection and subcutaneous injection."

For at least the reasons discussed above for claim 1, element [b] (*see supra* Section IX.A.1.c), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. In particular, the Herceptin Label teaches "[rhuMAb HER2] is a sterile, white to pale yellow, preservative-free lyophilized powder *for intravenous (IV) administration*." (Ex. 1008 at 1) Likewise, Baselga '96 and Pegram '98 teach intravenous administration of rhuMAb HER2. (*See* Ex. 1013 at 9; Ex. 1014 at 8)

Further, the Herceptin Label discloses an initial and at least two subsequent doses. For example, the Herceptin Label teaches weekly administration of rhuMAb HER2 for 32 weeks. (*See* Ex. 1008 at 1) Since the Herceptin Label teaches rhuMAb HER2 is *for* intravenous injection, it would have been obvious to

a POSA to have administered the initial and at least two subsequent doses via intravenous injection. (*See* Ex. 1002 ¶ 73; Ex. 1039 ¶ 103)

6. Claim 9: "The method of claim 1, wherein the initial dose is selected from the group consisting of approximately 6 mg/kg, 8 mg/kg, or 12 mg/kg, wherein the plurality of subsequent doses are at least approximately 2 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b), [b] (*see supra* Section IX.A.1.c) and [c] (*see supra* Section IX.A.1.d), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. In particular, and as discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d), a POSA could have calculated a 712 mg loading dose for a 500 mg tri-weekly repeating dose. (*See* Ex. 1003 ¶ 61; Ex. 1039 ¶ 94) There are necessarily patients for whom a 712 mg loading dose is approximately 8 mg/kg. (*See* Ex. 1002 ¶ 74; Ex. 1039 ¶ 104) For example, the weight based loading dose for an 89 kg patient would be 712 mg / 89 kg = 7.99 mg/kg. (*See id.*) Similarly, there are necessarily patients for whom a 712 mg loading dose is approximately 12 mg/kg. (*See id.*) For example, the weight-based loading dose for a 59 kg patient is 12.06 mg/kg. (*See id.*)

Additionally, 55–85 kg is a reasonable range that a POSA would assume for patient weight. (*See* Ex. 1002 ¶ 57; Ex. 1003 ¶ 45; Ex. 1039 ¶ 67; Ex. 1026 at 3; Ex. 1027 at 334 (Table 7-2)) A 712 mg loading dose converts to a weight-based

dose of 8.38 mg/kg for an 85 kg patient. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

In light of a POSA's knowledge about patient weight and the appropriate assumptions to apply when calculating doses, the claimed dose would be at minimum obvious to a POSA reviewing the Herceptin Label.

The obviousness of this element is further confirmed by the fact that the '196 patent contains no data showing that any of the claimed dosing regimens were tested by the inventors, were critical, or had any unexpected properties. *See Woodruff*, 919 F.2d at 1578.

7. Claim 10: "The method of claim 9, wherein the plurality of subsequent doses are separated in time from each other by at least three weeks."

For at least the reasons discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d) and claim 9 (*see supra* Section IX.A.6), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill.

8. Claim 11: "The method of claim 10, wherein the initial dose is approximately 8 mg/kg, and wherein at least one subsequent dose is approximately 6 mg/kg.

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b), [b] (*see supra* Section IX.A.1.c) and [c] (*see supra* Section IX.A.1.d), and claim 10 (*see supra* Section IX.A.7), the method of this claim

would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. In particular, and as discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d), 712 mg would have been an appropriate approximate loading dose for tri-weekly 500 mg rhuMAb HER2. (*See also* Ex. 1003 ¶ 61; Ex. 1039 ¶ 94) There are necessarily patients for whom a 712 mg loading dose is approximately 8 mg/kg and 500 mg subsequent doses are 6 mg/kg. For example, the loading dose for an 89 kg patient is 712 mg / 89 kg = 7.99 mg/kg, and the maintenance dose is 500 mg / 89 kg = 5.62 mg/kg.

Additionally, 55–85 kg is a reasonable range that a POSA would assume for patient weight. (*See* claim 1, element [a] (*see supra* Section IX.A.1.b); Ex. 1002 ¶ 57; Ex. 1003 ¶ 45; Ex. 1039 ¶ 109; Ex. 1026 at 3; Ex. 1027 at 334 (Table 7-2)) A 712 mg loading dose followed by 500 mg maintenance doses converts to an initial weight-based loading dose of 8.38 mg/kg followed by 5.88 mg/kg maintenance doses for an 85 kg patient. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98) These numbers round to the claimed dosing regimen of 8 mg/kg x 6 mg/kg. (*See also* Ex. 1003 ¶ 66 (discussing rounding for convenience); Ex. 1039 ¶ 99)

In light of a POSA's knowledge about patient weights and the appropriate assumptions to apply when calculating doses, the claimed dose would be at minimum obvious to a POSA reviewing the Herceptin Label. The obviousness of

this element is further confirmed by the fact that the '196 patent contains no data showing that any of the claimed dosing regimens were tested by the inventors, were critical, or had any unexpected properties. *See Woodruff*, 919 F.2d at 1578.

9. Claim 17: "The method of claim 1, wherein said cancer is selected from the group consisting of breast cancer, [and other cancers]."

The method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. As discussed above, the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill render obvious claim 1. (*See supra* Section IX.A.1) Further, the Herceptin Label discloses rhuMAb HER2 is indicated for the treatment of metastatic breast cancer. (*See, e.g.*, Ex. 1008 at 1 ("Both trials studied patients with *metastatic breast cancer* whose tumors overexpress the HER2 protein."); *id.* ("[rhuMAb HER2] in combination with paclitaxel is indicated for treatment of patients with *metastatic breast cancer* whose tumors overexpress the HER2 protein")) Baselga '96 and Pegram '98 also teach rhuMAb HER2 treats metastatic breast cancer. (*See* Ex. 1013 at 9; Ex. 1014 at 8)

10. Claim 18: "The method of claim 17, wherein said cancer is breast cancer."

For at least the reasons discussed above for claim 17 (*see supra* Section IX.A.9), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary

skill.

11. Claim 19: "The method of claim 18, wherein said cancer is metastatic breast carcinoma."

The method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. As discussed above, the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill render obvious claim 18. (*See supra* Section IX.A.10) Further, at least some of the patients in the clinical trials described in the Herceptin Label, Baselga '96, and Pegram '98 had carcinomas. (*See, e.g.*, Ex. 1013 at 9 ("We treated 46 patients with metastatic breast carcinomas that overexpressed HER2.")) Carcinoma is a common type of breast cancer. (*See* Ex. 1002 ¶¶ 83–84; Ex. 1039 ¶¶ 113-114)

12. Claim 20: "The method of claim 1, wherein said antibody binds to the extracellular domain of the ErbB2 receptor."

The method of this claim is disclosed by, inherent in, and at minimum obvious over the Herceptin Label, Baselga '96, and Pegram '98, in light of the POSA's ordinary skill. As discussed above, the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill render obvious claim 1. (*See supra* Section IX.A.1) Further, the Herceptin Label teaches "[rhuMAb HER2] is a recombinant DNA-derived humanized monoclonal antibody that selectively binds with high affinity in a cell-based assay (K_d = 5 nM) to the *extracellular domain of*

the human epidermal growth factor receptor-2 protein, HER2," and "[t]he antibody is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (4D5) that binds to HER2." (Ex. 1008 at 1) Since rhuMAb HER2 contains the complementarity determining regions of the 4D5 antibody, it will bind to the same epitope as the 4D5 antibody.

Baselga '96 further teaches that "[t]he murine monoclonal antibody (MAb) 4D5, *directed against the extracellular domai**n*** of $p185^{HER2}$ (ECD^{HER2}), is a potent inhibitor of growth, in vitro and in xenograft models, of human breast cancer cells that overexpress HER2." (Ex. 1013 at 9) Pegram '98 further discloses that the humanized rhuMAb HER2 "has improved binding affinity to the extracellular domain of HER2/*neu.*" (Ex. 1014 at 9; *see also* Ex. 1002 ¶ 86; Ex. 1039 ¶ 116; Ex. 1018 at 5–6 (describing the replacement of complementary determining regions in a human antibody with those from a mouse))

13. Claim 21: "The method of claim 20, wherein said antibody binds to epitope 4D5 within the ErbB2 extracellular domain sequence."

For at least the reasons discussed above for claim 20 (*see supra* Section IX.A.12), the method of this claim is disclosed by, inherent in, and at minimum obvious over the Herceptin Label, Baselga '96, and Pegram '98, in light of the POSA's ordinary skill. In particular, the Herceptin Label, Baselga '96, and

Pegram ’98 teach that rhuMAb HER2 binds to epitope 4D5. (*See, e.g.*, Ex. 1008 at 1 (“[rhuMAb HER2] is an IgG_1 kappa that contains human framework regions with the complementarity-determining regions of a murine antibody (*4D5*) that binds to HER2”); 1013 at 9 (“[t]he murine monoclonal antibody (MAb) *4D5* ... was humanized”); Ex. 1014 at 8 (rhuMAb HER2 is a humanized “murine monoclonal anti-HER2 antibody, *4D5*.”))

14. Claim 22: “The method of claim 21, wherein said antibody is a humanized 4D5 anti-ErbB2 antibody.”

For at least the reasons discussed above for claims 20 (*see supra* Section IX.A.12) and 21 (*see supra* Section IX.A.13), the method of this claim is disclosed by, inherent in, and at minimum obvious over the Herceptin Label, Baselga ’96, and Pegram ’98, in light of the POSA’s ordinary skill.

15. Claim 23: “The method of claim 1, wherein efficacy is measured by determining the time to disease progression or the response rate.”

The method of this claim is at minimum obvious over the Herceptin Label, Baselga ’96, and Pegram ’98, in light of the POSA’s ordinary skill. As discussed above, the Herceptin Label, Baselga ’96, Pegram ’98 and a POSA’s ordinary skill render obvious claim 1. (*See supra* Section IX.A.1) Further, the Herceptin Label discloses that efficacy is measured by time to disease progression as well as overall response rate. (*See* Ex. 1008 at 1 (“Compared with patients randomized to chemotherapy alone, the patients randomized to [rhuMAb HER2] and

chemotherapy experienced a significantly longer time to disease progression, a higher overall response rate (ORR), a longer median duration of response, and a higher one-year survival rate.”))

Baselga ’96 also discloses that efficacy is measured by the time to disease progression:

- “[O]ne patient had a complete remission and four had partial remissions”;
- “14 patients had stable disease at day 77. These patients entered a maintenance phase of weekly antibody administration until progression of disease”;
- “The median time to progression for the patients with either minor or stable disease was 5.1 months”;
- “One additional patient had a greater than 50% shrinking of her cancer that lasted more than 1 month”; and
- “[T]wo patients had regression of cancers in the liver and one patient achieved a pathologically-proven complete response of chest wall disease, which has persisted for 24 months.”

(*See, e.g.*, Ex. 1013 at 12–13)

Alternatively, efficacy may be measured by response rate. (*See id.* at 12–14

("Table 4. Response Rate Obtained With rhuMAb HER2 in 43 Assessable Patients"; Table 5; Fig. 2; "overall response rate of 11.6%"))

Pegram '98 further discloses that efficacy is measured by the time to disease progression, (*see* Ex. 1014 at 14 (Table 5)), or response rate. (*See id.* at 2659 ("*Conclusion*: The use of rhuMAb HER2 in combination with CDDP ... results in objective clinical response rates higher than those reported previously for CDDP alone, or rhuMAb HER2 alone.") (emphasis in original); s*ee also* Ex. 1002 ¶ 89; Ex. 1039 ¶ 119)

16. Claim 24

A comparison of claim 24 with claim 1 is shown below:

Claim 24	Claim 1
[preamble] A method for the treatment of cancer in a human patient comprising	[preamble] 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:
[a] administering to the patient a first dose of an anti-ErbB2 antibody	[a] administering to the patient an initial dose of at least approximately 5 mg/kg of the anti-ErbB2 antibody; and
[b] followed by two or more subsequent doses of the antibody,	[b] 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,
[c] wherein the subsequent doses are separated in time from each other by at least two weeks.	[c] wherein the subsequent doses are separated in time from each other by at least two weeks.

Applying the BRI, the scope of claim 24 is broader than that of claim 1. (*See* Ex. 1002 ¶ 93; Ex. 1039 ¶ 124]) Accordingly, claim 24 is unpatentable for at least all of the reasons described above for claim 1. Bioepis therefore incorporates by reference its analysis for claim 1. (*See supra* Section IX.A.1)

17. Claim 25: "The method of claim 24, wherein the first dose and a first subsequent dose are separated from each other in time by at least about three weeks."

For at least the reasons discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d) and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill.

18. Claim 26: "The method of claim 24, wherein the first dose and subsequent doses are each from about 2 mg/kg to about 16 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b), [b] (*see supra* Section IX.A.1.c) and [c] (*see supra* Section IX.A.1.d), and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all the doses in Table A are each "from about 2 mg/kg to about 16 mg/kg." (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

19. Claim 27: "The method of claim 26, wherein the first dose and subsequent doses are each from about 4 mg/kg to about 12 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b), [b] (*see supra* Section IX.A.1.c) and [c] (*see supra* Section IX.A.1.d), and claim 26 (*see supra* Section IX.A.18), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all the doses in Table A are each "from about 4 mg/kg to about 12 mg/kg." (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

20. Claim 28: "The method of claim 27, wherein the first dose and subsequent doses are each from about 6 mg/kg to about 12 mg/kg."

For at least the reasons discussed above for claim 1, elements [a] (*see supra* Section IX.A.1.b), [b] (*see supra* Section IX.A.1.c) and [c] (*see supra* Section IX.A.1.d), and claim 27 (*see supra* Section IX.A.19), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all the doses in Table A are each from about 6 mg/kg to about 12 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

21. Claim 29: "The method of claim 24, wherein from about two to about ten subsequent doses of the antibody are administered to the patient."

For at least the reasons discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d) and claim 24 (*see supra* Section IX.A.16), the method of this claim is at minimum obvious over the Herceptin Label, Baselga '96, and Pegram '98 in light of a POSA's ordinary skill. In particular, and as discussed above for claim 1, element [c] (*see supra* Section IX.A.1.d), it would have been obvious to modify the rhuMAb HER2 dosing schedule taught by the Herceptin Label to a tri-weekly regimen. The Herceptin Label discloses that paclitaxel was administered for at least six cycles. (*See* Ex. 1008 at 1) Since weekly rhuMAb HER2 was administered throughout the time that paclitaxel was administered during the clinical trial described in the Herceptin Label, a POSA would understand that rhuMAb HER2 should also be administered throughout the time that paclitaxel is administered under a three week dose regimen. (*See* Ex. 1002 ¶ 98; Ex. 1039 ¶ 129) For this reason, it would have been obvious to a POSA to administer rhuMAb HER2 for at least six cycles along with paclitaxel (i.e., loading dose followed by five maintenance doses).

22. Claim 30: "The method of claim 24, wherein the subsequent doses are separated in time from each other by at least about three weeks."

For at least the reasons discussed above for claim 1, element [c] (*see supra*

Section IX.A.1.d) and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill.

23. Claim 31: "The method of claim 24, wherein the two or more subsequent doses are each from about 2 mg/kg to about 16 mg/kg."

For at least the reasons discussed above for claim 1, element [b] (*see supra* Section IX.A.1.c) and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all of maintenance doses in Table A are each from about 2 mg/kg to about 12 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

24. Claim 32: "The method of claim 24, wherein the two or more subsequent doses are each from about 4 mg/kg to about 12 mg/kg."

For at least the reasons discussed above for claim 1, element [b] (*see supra* Section IX.A.1.c) and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all of maintenance doses in Table A are each from about 4 mg/kg to about 12 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

25. Claim 33: "The method of claim 24, wherein the two or more subsequent doses are each from about 6 mg/kg to about 12 mg/kg."

For at least the reasons discussed above for claim 1, element [b] (*see supra* Section IX.A.1.c) and claim 24 (*see supra* Section IX.A.16), the method of this claim would have been at minimum obvious to a POSA in light of the Herceptin Label, Baselga '96, Pegram '98 and a POSA's ordinary skill. For example, all of the maintenance doses in Table A are each from about 6 mg/kg to about 12 mg/kg. (*See* Ex. 1003 ¶ 65 (Table A); Ex. 1039 ¶ 98)

B. Secondary Considerations do not Support the Nonobviousness of the '196 Patent Claims

There is no evidence of secondary considerations of non-obviousness of the claims of '196 patent. (*See* Ex. 1002 ¶¶ 103–104; Ex. 1039 ¶¶ 138-139) During prosecution, Genentech argued that the prior art "taught away" from dosing greater than weekly. (*See* Ex. 1024–31:327) However, the prior art used in this Petition includes art that was not considered by the Examiner and does not teach away from the claimed subject matter. (*See id.*) Should Genentech make allegations regarding secondary considerations, Bioepis will respond.

CONCLUSION

For the foregoing reasons, Bioepis respectfully requests cancellation of claims 1–3, 5, 7, 9–11, and 17–33 of the '196 patent.

* * *

Date: August 25, 2017

Respectfully submitted,

/s/ Dimitrios T. Drivas

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. 42.24(d)

Pursuant to 37 C.F.R. §§ 42.24(a)(1)(i) and 42.24(d), I hereby certify that the number of words in this Petition is 12,526, excluding the Table of Contents, the Table of Authorities, the Mandatory Notices under § 42.8, Certificate of Service, Certificate of Word Count, signature block, and appendix listing of exhibits. In determining the number of words, Counsel relied upon Microsoft Word's word count feature.

Date: August 25, 2017

Signed,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6 and 42.105, I hereby certify that on this 25th day of August, 2017, the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 6,627,196 and accompanying exhibits referenced therein were served via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at the following correspondence address of record in PAIR:

Genentech, Inc.
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1 DNA Way
South San Francisco, CA 94080-4990

The foregoing Petition and accompanying exhibits referenced therein were also served on this 25th day of August, 2017 via PRIORITY MAIL EXPRESS® for single-day overnight delivery on the Patent Owner at an address known to the Petitioner as likely to affect service.

David L. Cavanaugh
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Date: August 25, 2017

Signed,

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