UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

———————

KOIOS PHARMACEUTICALS LLC

Petitioner

v.

MEDAC GESELLSCHAFT FUER KLINISCHE SPEZIALPRÄPARATE MBH

Patent Owner

———————

IPR2016-01370
Patent No. 8,664,231
Title: Concentrated Methotrexate Solutions

PETITION FOR *INTER PARTES* REVIEW

Table of Contents

Table of Authorities

Cases

List of Exhibits

Exhibit 1001	U.S. 8,664,231 to Heiner Will, titled, "Concentrated Methotrexate Solutions," filed on March 4, 2009, and issued on March 4, 2014 ("the '231 Patent").
Exhibit 1002	Excerpts from File History for U.S. Patent No. 8,664,231.
Exhibit 1003	U.S. 6,544,504 to Paul Grint et al., titled, "Combined Use of Interleukin 10 and Methotrexate for Immunomodulatory Therapy," filed on June 26, 2000, and issued on April 8, 2003 ("*Grint*").
Exhibit 1004	Hoekstra et al. (2004) J. Rheumatol. 31(4):645-47 ("*Hoekstra*").
Exhibit 1005	Jørgensen et al. (1996) Ann. Pharmacother. 30:729-32 ("*Jørgensen*").
Exhibit 1006	Alsufyani et al. (2003) J. Rheumatol. 31:179-82 ("*Alsufyani*").
Exhibit 1007	Declaration of Dr. Elena Massarotti, dated June 2, 2016, in support of Medac's Preliminary Response in IPR2016-00649.
Exhibit 1008	Brooks et al. (1990) Arthritis and Rheum. 33(1):91-94 ("*Brooks*").
Exhibit 1009	Medac's Preliminary Response in IPR2016-00649, dated June 2, 2016.
Exhibit 1010	Zackheim (1992) J. Am. Acad. of Derm. 23(6) p. 1008 ("*Zackheim*").
Exhibit 1011	Müller-Ladner (2010) The Open Rheumatology Journal 4:15-22. ("*Müller-Ladner*").
Exhibit 1012	Weinblatt Declaration; Dated June 17, 2014 ("Weinblatt Decl.").
Exhibit 1013	Gammon Declaration; Dated June 27, 2014 ("Gammon Decl.").
Exhibit 1014	Pincus et al. (2003) Clin. Exp. Rheumatol. (Suppl. 31):S179-S185 ("*Pincus*").
Exhibit 1015	Insulin Administration, Diabetes Care, 26:1 S121-S124 (2003) ("*Insulin Admin*").
Exhibit 1016	Complaint in *Medac Pharma, Inc. v. Antares Pharma, Inc.*, Nos. 1:14-cv-01498-JBS-KMW.
Exhibit 1017	Portion of EPO prosecution for EP Application No. 07 786 239.9 and Certified English Translation of the same.
Exhibit 1018	Weinblatt (1993) "Methotrexate," in Textbook of Rheumatology, 4th Edition, Chapter 47, (Kelley et al., eds. 1993) ("*Weinblatt 1993*").
Exhibit 1019	Schiff et al., "Head-to-head, randomized, crossover study of oral versus subcutaneous methotrexate in patients with rheumatoid arthritis," Ann. Rheum. Dis. 0:1-3 (2014) ("*Schiff*").
Exhibit 1020	Weinblatt (1995) Efficacy of Methotrexate in Rheumatoid Arthritis, Br. J. Rheum. 34(suppl. 2):43-48 ("*Weinblatt 1995*").
Exhibit 1021	Product Label for the "Methotrexate Sodium for Injection" product by Wyeth, Date of First Authorization August 10, 1959, Date of

	Supplement Approval January 27, 2004, Obtained from Archive.org as of April 29, 2005 ("*Wyeth*"), and Internet Archive Affidavit.
Exhibit 1022	2003 Ed. of Physician's Desk Reference for "Methotrexate Sodium for Injection" by Wyeth ("*the PDR for Wyeth*").
Exhibit 1023	Arthur et al. (2002) A Study of Parenteral Use of Methotrexate in Rheumatic Conditions, J. Clinical Nursing 2002;11:256-63 ("*Arthur*").
Exhibit 1024	Arthur et al. (2001) Self-Injection of Gold and Methotrexate, J. Rheumatol. 2001;28(1):212 ("*Arthur 2001*").
Exhibit 1025	Moitra et al. (2005) Caveats to the use of parenteral methotrexate in the treatment of rheumatic disease, Rheumatology 2005;44:256-57 ("*Moitra*").
Exhibit 1026	Product Label for "Methotrexate For Injection, USP" by Bigmar, Date of First Authorization February 26, 1999, Obtained from Archive.org as of February 16, 2005 ("*Bigmar*").
Exhibit 1027	Feagan et al. (1995) Methotrexate for the Treatment of Crohn's Disease, N. Engl. J. Med. 332(5):292-97 ("*Feagan*").
Exhibit 1028	Furst et al. (1989) Increasing Methotrexate Effect with Increasing Dose in the Treatment of Resistant Rheumatoid Arthritis, J. Rheum. 16(3):313-20 ("*Furst*").
Exhibit 1029	Giannini et al. (1992) Methotrexate in resistant juvenile rheumatoid arthritis—results of the U.S.A.-U.S.S.R. double-blind, placebo-controlled trial. N. Engl. J. Med. 326(16):1043, 1045, 1048-49 ("*Giannini*").
Exhibit 1031	FDA Arthritis Advisory Committee.
Exhibit 1032	Results from Body Surface Area Calculator for Medication Doses ("*BSA Calculation*").
Exhibit 1033	Miller Declaration and Curriculum Vitae ("Miller Decl.").
Exhibit 1034	Schiff Declaration and Curriculum Vitae ("Schiff Decl.").
Exhibit 1035	Noroozi Declaration ("Noroozi Decl.").
Exhibit 1036	Kamholz Declaration ("Kamholz Decl.").

I. INTRODUCTION

Petitioner Koios Pharmaceuticals LLC ("Koios") requests *inter partes* review (IPR) of claims 1-22 of U.S. Patent No. 8,664,231. Ex. 1001.

Koios is a generic pharmaceutical company. Koios's mission is to increase Americans' access to affordable pharmaceuticals by promoting generic competition. Noroozi Decl. (Ex. 1035) ¶ 1. To that end, Koios challenges pharmaceutical patents that claim public knowledge for private profit. *Id.*

Patent Owner medac GMBH, and its U.S. subsidiary Medac Pharma, Inc. (collectively, "Medac" or "Patent Owner") produce and sell Rasuvo®. Rasuvo treats inflammatory autoimmune diseases, such as rheumatoid arthritis. Rasuvo contains a single active ingredient, methotrexate ("MTX"), which has been used to treat inflammatory diseases since the 1950s. Schiff Decl. (Ex. 1034) at ¶¶ 19-21.[1] Yet the '231 patent, granted in 2014, protects Rasuvo from generic competition until 2029. As a result, Rasuvo can cost $6,000 per patient per year. Koios seeks to introduce generic competition to Rasuvo.

[1] Medac agrees (as it must) that Dr. Schiff is at least one of ordinary skill in the art. *See* Ex. 1009 at 22 ("Dr. Schiff, one of ordinary skill in the art…."). Koios retained Dr. Schiff in October 2015.

II. GROUNDS FOR STANDING

Petitioner certifies that the '231 patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR of the '231 patent.

III. MANDATORY NOTICES

A. Real Party-In-Interest

Koios Pharmaceuticals LLC is the sole entity with authority to direct or control decisions or activities relating to this Petition or proceedings related to this Petition. Noroozi Decl. (Ex. 1035) ¶ 2.; 37 CFR § 42.8(b)(1). All of the costs associated with the Petition are expected to be borne by Koios. *Id.* Koios has entered into a partnership with a pharmaceutical company for the development and commercialization of a generic equivalent to Rasuvo. *Id*. This Petition, however, was not brought at the behest of any person or entity other than Koios, and is entirely under Koios's control. *Id.* Accordingly, Koios is the sole real party-in-interest. *See Hughes Network Sys., LLC et al v. California Institute of Tech.*, IPR2015-00059 (PTAB) (Paper 42) ("The key to a real party-in-interest inquiry is the relationship between the potential unnamed real party-in-interest and the proceeding. . . .").

B. Related Matters

The '231 patent was previously at issue in a district court action and IPR. *See Medac Pharma Inc. v. Antares Pharma, Inc.*, 1:14-cv-1498 (D.N.J.); *Antares*

Pharma, Inc. v. Medac Pharma Inc., IPR2014-01091 (PTAB). The Board instituted that IPR on January 6, 2015. *Id.* (Paper 7). The parties subsequently settled in April 2015 and jointly moved to terminate. *Id.* (Paper 17). The Board terminated on April 30, 2015, prior to a decision on the merits. *Id.* (Paper 21); 37 CFR § 42.8(b)(2).

The '231 patent has also been challenged by Frontier Therapeutics, LLC, IPR2016-00649 (PTAB). That petition is pending and had not received an institution decision as of this filing.

Koios has no relationship with either Antares or Frontier. Noroozi Decl. (Ex. 1035) at ¶ 2.

C. Lead and Back-Up Counsel, and Service Information

Lead counsel is Scott E. Kamholz, M.D., Ph.D., Reg. No. 48,543, of Foley Hoag LLP, 1717 K Street, N.W., Washington D.C. 20006-5350, Phone 202-261-7356, Fax 202-467-9656; skamholz@foleyhoag.com. Backup counsel is DeAnn F. Smith, Reg. No. 36,683, of Foley Hoag LLP, 155 Seaport Blvd., Boston MA 02210-2600, Phone 617-832-1230, Fax 617-832-7000; dsmith@foleyhoag.com. Koios consents to electronic service at ipr2016-01370@foleyhoag.com.

IV. PAYMENT OF FEES

The requisite fees have been submitted with this Petition in accordance with 37 C.F.R §§ 42.103(a) and 42.15(a). The Office may charge any additional fees required for this proceeding to Deposit Account No. 06-1448.

V. OVERVIEW OF THE CHALLENGE

A. Summary of the Challenge

The '231 patent claims priority to German Application No. DE 10 2006 033 837, filed July 21, 2006. Ex. 1001. It is titled "Concentrated Methotrexate Solutions." Ex. 1001. It describes and claims methods of treating inflammatory autoimmune diseases with "concentrated" MTX administered subcutaneously.[2] It contains 22 claims, with a single independent claim.

[2] It is critical here to emphasize the distinction between "concentration" and "dosage." The '231 patent describes the use of "highly concentrated" but "low dose" methotrexate solutions. Ex. 1001 at 1:56-60 ("Contrary to chemotherapy in the treatment of tumors, methotrexate as a basic therapeutic in the treatment of rheumatoid arthritis is dosed significantly lower, . . . which is why the antirheumatic therapy is also referred to as 'low-dosage methotrexate therapy.'"). The purported invention of the '231 patent was to administer the traditional "low dose" of MTX used for autoimmune therapy in a higher ***concentration*** solution,

Claim 1 recites a method for treating inflammatory autoimmune diseases via subcutaneous administration of a pharmaceutically acceptable solvent containing methotrexate at a concentration of more than 30 mg/ml. Ex. 1001. The remaining twenty-one dependent claims:

- cover various concentrations of methotrexate up to 100 mg/ml;
- specify solvents that constitute the "pharmaceutically acceptable solvent";
- specify that the "inflammatory autoimmune diseases" are RA, juvenile arthritides, psoriasis, and several other inflammatory autoimmune diseases; cover various dosage amounts; and
- cover various self-administration devices, including a ready-made syringe and pen injection device, as well as storage containers (such as a vial or carpule) for containing the medicament. *Id.*

---

thereby allowing the patient to receive the same dosage via less injection volume. Ex. 1001 at 5:14-18 ("The medicaments provided by the present invention on the other hand contain highly ***concentrated*** solutions of the active substance methotrexate which results in a reduction of the ***amount*** of liquid to be administered with a certain weekly active substance ***dosage***.") (emphasis added).

During prosecution, Medac identified the invention as the use of concentrated MTX for the treatment of inflammatory autoimmune diseases in subcutaneous form. Ex. 1002 at 20–22. In support, Medac wrongly asserted (without any evidence) that previously available high-concentration MTX solutions were "solely marketed and approved for treatment of cancer . . . ." *Id.* at 22. Medac further argued, without any evidence, that "it was not at all obvious at the time of the present invention that toxicity and bioavailability of methotrexate solutions with higher concentrations would be acceptable" and that "a person skilled in the art would have been very cautious to increase the concentration of the active agent in a subcutaneously administered solution." *Id.* at 21. Presumably relying on those representations, the Examiner issued a Notice of Allowance on January 7, 2014. *Id.* at 26.

As this Petition will demonstrate, Medac's assertions were false, and each of the claims of the '231 patent was either anticipated or obvious as of July 2006.

Since at least 1951, MTX has been a known treatment for inflammatory autoimmune diseases such as rheumatoid arthritis (RA) and psoriasis. Ex. 1001 at 1:28-32; Schiff Decl. (Ex. 1034) at ¶¶ 19-21; Ex. 1014 at S179-80.

The administration of MTX via subcutaneous injections at concentrations above 30 mg/ml was also both anticipated and obvious as of July 21, 2006.

It was anticipated by the *Grint* patent, issued in April 2003, which described methods for treating inflammatory autoimmune diseases via subcutaneous MTX injections at concentrations up to 40 mg/ml. See Section VI.A, *infra*; Schiff Decl. (Ex. 1034) at ¶¶ 48-71.

It was also anticipated by *Wyeth* (Ex. 1021, published prior to July 2006), the product insert for an FDA-approved product, which taught subcutaneous administration of a 50 mg/ml concentration MTX solution for the treatment of inflammatory autoimmune diseases. See Section VI.D, *infra*; Schiff Decl. (Ex. 1034) at ¶¶ 72-87.

The claimed subject matter of the '231 patent was also obvious because:

(1) The product disclosed in *Wyeth* (Ex. 1021) was FDA-approved for the intramuscular injection of a 50 mg/ml MTX concentration solution for treating rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriasis, Schiff Decl. (Ex. 1034) at ¶¶ 88-89; and

(2) *Brooks* (Ex. 1008) (1990) taught that subcutaneous injection of MTX is equal in safety and efficacy to, and more convenient than, intramuscular injection. Schiff Decl. (Ex. 1034) at ¶¶ 90-97.

Accordingly, skilled artisans would have had reason, with a reasonable expectation of success, to subcutaneously administer the MTX solution disclosed

in *Wyeth* to patients with inflammatory autoimmune diseases. Schiff Decl. (Ex. 1034) at ¶ 98; Miller Decl. (Ex. 1033) at ¶ 63.

The invention of the '231 patent was further obvious because:

(1) *Hoekstra* (Ex. 1004) (2004) taught treating inflammatory autoimmune diseases via subcutaneous MTX at dosages up to 40 mg using a 25 mg/ml concentration, Schiff Decl. (Ex. 1034) at ¶¶ 99-100; and

(2) *Jørgensen* (Ex.1005) (1996) taught that subcutaneously injected solutions should be less than 1 ml to reduce pain and increase compliance. Schiff Decl. (Ex. 1034) at ¶¶ 101-04; Miller Decl. (Ex. 1033) at ¶¶ 67-72.

Jørgensen's teachings would have led the skilled artisan to increase *Hoekstra*'s MTX concentration above 40 mg/ml to reduce subcutaneous injection volume below 1 ml. *Id.*[3]

Finally, there was nothing novel about the use of subcutaneous MTX self-administration devices in July 2006. *Arthur* (2002) (Ex. 1023) conducted a successful study in which "[p]atients were taught to self-administer their

[3] The skilled artisan would have understood, prior to 2006, how to optimize the relationship between concentration, dosage, and volume based on the following simple mathematical formula: dosage (in mg)/concentration (in mg/ml) = solution volume (in ml). Miller Decl. (Ex. 1033) at ¶ 40.

methotrexate subcutaneously" and were given "pre-filled syringes," which they used to "self-administer[ ] their MTX by the SC route at home for 3 consecutive weeks." Ex. 1023 at 256, 259. And *Moitra* (2005) reported 91 patients receiving subcutaneous MTX injections, of whom "77 had successfully been taught to self-inject." Ex. 1025 at 256. There was thus nothing inventive about placing the concentrated MTX of *Grint* or *Wyeth* into various self-injection devices. *See, e.g.*, Ex. 1001 at 6:60-67; Miller Decl. (Ex. 1033) at ¶¶ 42-44, 51-52.

Accordingly, this Petition demonstrates that Petitioner will prevail in showing that all claims of the '231 patent are unpatentable.

B. Claims Challenged and Asserted Grounds of Unpatentability

Petitioner challenges the patentability of claims 1-22 of the '231 patent on the following grounds:

References[4]	Basis	Claims Challenged
Grint (Ex. 1003)	§ 102(b)	1, 2, 4-6, 11-13, 17, and 22
Grint and *Arthur* alone, or further in view of either *Moitra* or *Insulin Admin*. (Exs. 1003, 1023, 1024, 1025, 1015)	§ 103(a)	7-10, 14-16, and 19-21
Grint and *Alsufyani* (Exs. 1003, 1006)	§ 103(a)	18
Wyeth (Exs. 1021, 1022)	§ 102(b)	1-6, 11-13, 17-18, and 22

[4] *See* Kamholz Decl. (Ex. 1036) concerning authentication of exhibits.

Wyeth and *Brooks* and *Arthur*, further in view of *Moitra*, or *Insulin Admin.* (Exs. 1021, 1022, 1008, 1023, 1024, 1025, 1015)	§ 103(a)	1-22
Hoekstra and *Jørgensen* (Exs. 1004 and 1005)	§ 103(a)	1-6, 11-13, 17, and 22
Hoekstra, *Jørgensen*, and *Arthur* in further view of *Insulin Admin*. (Exs. 1004, 1005, 1023, 1015)	§ 103(a)	7-10, 14-16, and 19-21
Hoekstra, *Jørgensen*, and *Alsufyani* (Exs. 1004, 1005, and 1006)	§ 103(a)	18

The challenges are supported by the expert declarations of Dr. Michael H. Schiff, M.D. (Ex. 1034) and Professor Donald Miller, Pharm.D. (Ex. 1033).

C. Claim Construction

In IPR proceedings, the Board gives claim terms "the broadest reasonable construction in light of the specification of the patent . . . ." 37 CFR § 42.100(b). Petitioner provides constructions for five claim terms of the '231 patent, and otherwise accepts, for purposes of this Petition only, that any other claim terms are presumed to take on the ordinary and customary meaning that they would have to one of ordinary skill in the art.

"Subcutaneously": Under the skin. Schiff Decl. (Ex. 1034) at ¶¶ 44-47; Ex. 1001 at 5:1-5.

"Pharmaceutically acceptable solvent": A solvent that is safe for administration to patients, including humans, that will not interfere with the active

pharmaceutical substance or other component in the solution. Miller Decl. (Ex. 1033) at ¶¶ 24-26; Ex. 1001 at 3:28-36.

"Injection device": A device that permits a medicament to be injected into a patient. Miller Decl. (Ex. 1033) at ¶¶ 28-30; Ex. 1001 at 4:19-39.

"Ready-made syringe": A device containing a medicament that permits the medicament to be injected into a patient. Miller Decl. (Ex. 1033) at ¶¶ 32-34; Ex. 1001 at 4:55-59; 5:28-40.

"Pen injector": A device that injects a dose of medicament into a patient via a powered or manually inserted hypodermic needle, wherein the device may be for single use or multiple uses, and may be disposable or reusable. Miller Decl. (Ex. 1033) at ¶¶ 36-38; Ex. 1001 at 6:55-7:27.

D. Level of Skill in the Art

The cited art demonstrates the level of skill in the art. Further, a person of ordinary skill in the art would have either a Pharm.D. or Ph.D. in pharmaceutical sciences, pharmacology, or a related discipline; an M.D. or D.O. with experience in using oral and injectable MTX to treat inflammatory autoimmune diseases; or a person with a lesser degree with several years of experience in formulating and/or administering methotrexate for injection, such as a nurse or pharmacy technician. Schiff Decl. (Ex. 1034) at ¶ 35; Miller Decl. (Ex. 1033) at ¶ 19. A person of

ordinary skill in the art would collaborate with others having expertise in, for example, methods of treating disease and administering medicines. *Id.*

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: *Grint* Anticipates Claims 1, 2, 4-6, 11-13, 17, and 22.

U.S. Patent 6,554,504 ("*Grint*," Ex. 1003) issued on April 8, 2003 and is prior art under § 102(b). *Grint* was not considered by the United States Patent and Trademark Office ("USPTO") during prosecution of the '231 patent.

Grint demonstrates that methods for treating inflammatory autoimmune diseases via subcutaneous injections of MTX at concentrations greater than 30 mg/ml were known before July 21, 2006, and anticipates claims 1, 2, 4-6, 11-13, 17, and 22—as the claim chart and discussion below show.

1. Anticipation Standard.

A prior art reference anticipates a claim if that reference discloses every limitation of the claimed invention, either explicitly or inherently. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987); 35 U.S.C. § 102(b). Moreover, "if granting patent protection on the disputed claim would allow the patentee to exclude the public from practicing the prior art, then that claim is anticipated, regardless of whether [the claim] also covers subject matter not in the prior art." *Atlas Powder Co. v. IRECO, Inc.*, 190 F.3d 1342, 1349 (Fed. Cir. 1999), citing *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 781 (Fed.Cir.1985).

2. Ground 1 Claim Chart.

Claim	Exemplary Citations in *Grint* (Ex. 1003)
1 [pre]. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	"The invention relates to a method for controlling autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and psoriasis." Ex. 1003 at 1:12-15. "The present invention provides a method for treating autoimmune disease . . . ." Ex. 1003 at 2:23-24. "Individuals suitable for treatment by the methods of the invention include any individual at risk (predisposed) for developing rheumatoid arthritis, or an individual exhibiting clinical symptoms." Ex. 1003 at 3:4-9. "As can be seen from the dosage regimens, the amount of methotrexate administered is to be sufficient to relieve the autoimmune disease symptoms prevalent in diseases such as arthritis and psoriasis." Ex. 1003 at 7:9-13. Schiff Decl. (Ex. 1034) at ¶¶ 49, 52, 58.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	"Methotrexate may also be administered parenterally . . . ." Ex. 1003 at 5:64. "The dose of MTX was 12.–25 mg/week (oral, subcutaneous or intramuscular) . . . ." Ex. 1003 at 7:56-57. "MTX (oral/intramuscular/SC) . . . ." Ex. 1003 at 8:1-2. Schiff Decl. (Ex. 1034) at ¶¶ 51, 59.
1b. in a pharmaceutically acceptable solvent at a	"Expressed in proportions, methotrexate is generally present in from about 0.1 to about 40

concentration of more than 30 mg/ml.	mg/ml of carrier." Ex. 1003 at 6:66-7:1. "Methotrexate is compounded for convenient and effective administration in effective amounts . . . ." Ex. 1003 at 6:60-63. "The pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions . . . . [That] carrier can be a solvent or dispersion medium containing, for example, water, ethyl alcohol, polyol . . . , suitable mixtures thereof, and vegetable oils." Ex. 1003 at 6:3-15. Schiff Decl. (Ex. 1034) at ¶¶ 49-50, 52, 60-61.
2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra,* at claim 1b. Schiff Decl. (Ex. 1034) at ¶¶ 62-63.
4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	"The carrier can be a solvent or dispersion medium containing . . . water, ethyl alcohol, polyol (for example, glycerol, propylene glycol, and liquid polyethylene glycol and the like), suitable mixtures thereof, and vegetable oils." Ex. 1003 at 6:11-15. "In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride." Ex. 1003 at 6:22-24. Schiff Decl. (Ex. 1034) at ¶ 64.
5. The method according to claim 1, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, brochial asthma,	"The invention relates to a method for controlling autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and psoriasis." Ex. 1003 at 1:12-15. "As can be seen from the dosage regimens, the amount of methotrexate administered is to be sufficient to relieve the autoimmune disease symptoms prevalent in diseases such as arthritis

Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.	and psoriasis." Ex. 1003 at 7:9-13. Schiff Decl. (Ex. 1034) at ¶ 65.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See, supra*, at claim 5.
11. The method according to claim 1, wherein the medicament is contained in a storage container.	"It is especially advantageous to formulate parenteral compositions in dosage unit form . . . . Dosage unit form as used herein refers to physically discrete units suited as unitary dosages for the mammalian subjects to be treated; each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect in association with the required pharmaceutical carrier." Ex. 1003 at 6:52-59. Miller Decl. (Ex. 1033) at ¶ 47.
12. The method according to claim 11, wherein the total storage container contains a total dosage amount of 5 to 5,000 mg.	"A unit dosage form can, for example, contain methotrexate in amounts ranging from about 0.1 to 400 mg, with from 1 to 35 mg being preferred, and 10 to 25 being most preferred." Ex. 1003 at 6:52-66. Miller Decl. (Ex. 1033) at ¶ 48.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	*Grint* teaches that MTX can be in "unit dosage form" containing MTX. A "unit dosage form" containing MTX would include an injection bottle, vial, bag, glass ampoule, or carpule. Miller Decl. (Ex. 1033) at ¶ 47.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	"In many cases, it will be preferable to include isotonic agents, for example, sugars or sodium chloride." Ex. 1003 at 6:22-24. Miller Decl. (Ex. 1033) at ¶ 49.
22. The method according	"Expressed in proportions, methotrexate is

to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	generally present in from about 0.1 to about 40 mg/ml of carrier." Ex. 1003 at 6:66-7:1. Schiff Decl. (Ex. 1034) at ¶ 67.

3. Ground 1 Detailed Analysis.

Claim 1: The preamble of claim 1 recites a "method for the treatment of inflammatory autoimmune diseases." Ex. 1001 at 8:43-44. *Grint* discloses "a method for treating autoimmune disease . . . ." Ex. 1003 at 2:23-24; claim chart, *supra*.

The first step of claim 1 is "subcutaneously administering to said patient a medicament comprising methotrexate." Ex. 1001 at 8:44-45. *Grint* discloses administering "methotrexate" or "MTX" "parenterally," including specifically "subcutaneously." Ex. 1003 at 5:64; 7:56-57; 8:1-2; claim chart, *supra*.

The second step of claim 1 is "in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml." *Grint* discloses a study in which MTX was administered subcutaneously on a weekly basis in dosages of 12.5 mg to 25 mg. Schiff Decl. (Ex. 1034) at ¶ 51; claim chart, *supra*. *Grint* further teaches that methotrexate should be "compounded for ***convenient*** and ***effective*** administration in ***effective*** amounts . . . ." Ex. 1003 at 6:60-63 (emphasis added); Schiff Decl. (Ex. 1034) at ¶¶ 50, 52. Given those disclosures, a skilled artisan would have understood *Grint* to disclose subcutaneous administration of MTX in

concentrations greater than 30 mg/ml for the treatment of inflammatory autoimmune diseases. Schiff Decl. (Ex. 1034) at ¶¶ 49-53. *Grint* also teaches administering MTX in a pharmaceutically acceptable solvent. Ex. 1003 at 6:3-15 ("pharmaceutical forms suitable for injectable use include sterile aqueous solutions or dispersions . . . containing, for example, water, ethyl alcohol, polyol . . . , suitable mixtures thereof, and vegetable oils."); Schiff Decl. (Ex. 1034) at ¶ 64. Accordingly, *Grint* anticipates claim 1.

In its response to IPR2016-00649, Medac argued that one of ordinary skill would not have understood *Grint* to teach the use of SC MTX in a concentration above 30 mg/ml. In support, Medac offered two arguments.

First, Medac relied on the opinions of Dr. Massarotti, who contended that some combinations of the dosages and concentrations disclosed in *Grint* could lead to formulation volumes that are either too small or too large for convenient and effective administration. Ex. 1009 at 31-32 (citing Ex. 1007 at ¶¶ 23, 27-41). On that basis, Dr. Massarotti (and Medac) concluded that a skilled artisan would not have understood *Grint* to teach the subcutaneous administration of MTX in concentrations above 30 mg/ml. *Id.*

As Koios's experts have explained, however, Medac's reasoning and conclusions in this regard are wrong. Schiff Decl. (Ex. 1034) at ¶¶ 53-55; Miller Decl. (Ex. 1033) at ¶ 46. *Grint* specifically teaches that methotrexate should be

"compounded for ***convenient*** and ***effective*** administration in ***effective*** amounts . . . ." Ex. 1003 at 6:60-63. Accordingly, an ordinarily skilled artisan would have known that the higher concentrations of MTX disclosed in *Grint*, such as 35 mg/ml, should be paired with the higher dosages of MTX disclosed in *Grint*, such as 35 mg, in order to administer MTX in "effective amounts," such as 1 ml. Schiff Decl. (Ex. 1034) at ¶¶ 53-55; Miller Decl. (Ex. 1033) at ¶ 46. Indeed, Dr. Massarotti's own opinions show the inherent flaw in her reasoning: while she acknowledges earlier in her declaration that it was "standard practice" to administer concentrations of 25 mg/ml prior to July 2006, she later stretches her misreading of *Grint* so far as to suggest that a skilled artisan would not have understood *Grint* to disclose the use of even a 20 mg/ml concentration solution. *Compare* Ex. 1007 ¶ 26 *with id.* ¶¶ 37-38; Schiff Decl. (Ex. 1034) ¶ 55.

Second, Medac argued that *Grint* merely teaches the use of MTX as "conventionally practiced," and that conventional practice prior to July 2006 did not include the use of SC MTX in concentrations above 30 mg/ml. Ex. 1009, 32-33 (citing Ex. 1003, 5:22-24).

That argument is also incorrect. *Grint*'s reference to "conventional practice" comes in the context of administration forms, not concentration levels, and would not have dissuaded the skilled artisan from subcutaneously administering the more than 30 mg/ml concentrations disclosed in *Grint*. Schiff Decl. (Ex. 1034) ¶ 56.

Moreover, as discussed later in this Petition, the FDA had already approved injectable MTX products in concentrations above 30 mg/ml for the treatment of inflammatory autoimmune diseases prior to July 2006. *See* Section VI.D, *infra*.

Claim 2 recites the method of claim 1, wherein the MTX "is present at a concentration of more than 30 mg/ml to 100 mg/ml." Ex. 1001 at 8:49-50. *Grint* discloses the method of claim 1 using MTX concentrations up to 40 mg/ml, *i.e.*, within the range claimed by claim 2. *See* claim 1 discussion, *supra*. Accordingly, *Grint* anticipates claim 2 because granting patent protection on the range in claim 2 "would allow the patentee to exclude the public from practicing the prior art . . . ." *Atlas Powder*, 190 F.3d at 1349 (Fed. Cir. 1999) (citing *Titanium Metals Corp.*, 778 F.2d at 781).

Moreover, the Federal Circuit has held that when the prior art discloses a range that overlaps with a range claimed by the patent at issue, the prior art anticipates unless there is evidence (and ultimately proof) that the claimed range is "critical to the ***operability*** of the claimed invention." *Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 871 (Fed. Cir. 2015) (emphasis added) ("when the prior art discloses a range, rather than a point, the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention."). Absent such evidence, an overlapping range disclosed in the prior art necessarily describes the claimed range with "sufficient specificity"

because all points within the claimed range are functionally the same, and thus even a single point of overlap between the prior art and claimed range anticipates. *Id.* at 869-70.

As the Federal Circuit has made clear, the touchstone is evidence and proof of criticality to the ***operation*** of the invention, and not simply evidence of some advantage conferred by the claimed range. *Id.* at 870-71. Thus in *Ineos*, the Federal Circuit rejected the relevance of patentee's argument that the claimed range was "critical to avoid unnecessary manufacturing costs and the appearance of undesirable blemishes" because "even if true, this ha[d] nothing to do with the operability or functionality of the claimed invention." *Id.* at 871.

Rather, to prove the criticality of the claimed range to the operability of the invention, the patentee must show that the invention would "***operate differently, or not at all,*** outside of the [ ] range claimed in the patent-in-suit." *Id*. at 869 (emphasis added); *Ex Parte Ravi Arora, Anna Lee Tonkovich, Dongming Qiu, & Laura J. Silva,* APPEAL 2013-004020, 2015 WL 5171024, at *1-2 (PTAB Aug. 28, 2015) (Rejecting claims over prior art because "[l]ike in *Ineos*, and unlike in *Atofina* [*v. Great Lakes Chemical Corp.*, 441 F.3d 991 (Fed. Cir. 2006)], Appellants have not shown that their claimed range of 'at least 0.03 inch' is critical to the operability of the invention.").

Here, the '231 patent on its face forecloses any possibility that the range of 30 mg/ml to 100 mg/ml is "critical to the operability of the claimed invention" or that the invention would "operate differently, or not at all" outside of that range. That is because the patent repeatedly states that the invention disclosed therein operates both ***below and above*** the range of claim 2. Schiff Decl. (Ex. 1034) at ¶¶ 36, 63. More specifically, the specification makes clear that the invention of the '231 patent operates at ***any concentration more than 25 mg/ml***, *i.e.*, including below the 30 mg/ml to 100 mg/ml range of claim 2. Ex. 1001 at 1:5-10 ("[T]he present invention relates to the use of methotrexate . . . at a concentration of more than 25 mg/ml."); Schiff Decl. (Ex. 1034) at ¶¶ 36, 63. Indeed, the '231 patent concedes that fact six more times. *See* Ex. 1001 at 3:1-21; 5:24-28; 6:49-54. And the '231 patent also admits that the invention would operate with MTX concentrations as high as 150 mg/ml, *i.e.*, above the 30 mg/ml to 100 mg/ml range of claim 2. Ex. 1001 at 3:19-21.

Accordingly, the 30 mg/ml to 100 mg/ml range of claim 2 is not "critical to the operability of the invention," Schiff Decl. (Ex. 1034) at ¶ 63, *id.* at ¶ 36, and the 0.1 to 40 mg/ml range disclosed in *Grint* thus anticipates claim 2.

Claim 4 limits the "pharmaceutically acceptable solvent" of claim 1 to "water, water for injection purposes, water comprising isotonization additives and

sodium chloride solution." Ex. 1001 at 8:54-56. *Grint* anticipates. *See* claim chart, *supra*.

Claim 5 limits claim 1 to certain types of inflammatory autoimmune diseases, and **Claim 6** specifies "rheumatoid arthritis." Ex. 1001 at 8:63-64. As of the publication of *Grint*, each disease identified in claims 5 and 6 was known to be an inflammatory autoimmune disease. Schiff Decl. (Ex. 1034) at ¶ 65. *Grint* thus anticipates claims 5 and 6. *Id.* at ¶¶ 65-66; s*ee* claim chart, *supra*. And *Grint* specifically teaches the treatment of rheumatoid arthritis. Ex. 1003 at 1:12-15.

Claims 11-13 and 17 are anticipated as stated in the above claim chart.

Claim 22 limits claim 1 to methotrexate concentrations of 40 to 80 mg/ml. *Grint* anticipates claim 22 for the same reasons as claim 2, *supra*.

B. Ground 2: Claims 7-10, 14-16, and 19-21 are Rendered Obvious by *Grint* in View of *Arthur*, or Further in View of *Moitra* or *Insulin Admin*.

Claims 7-10, 14-16, and 19-21 limit the method of claim 1 to various self-administration devices and dosages. As explained above, *Grint* anticipates claim 1. As demonstrated below, *Grint* in view of *Arthur* alone, or further in view of *Moitra* or *Insulin Admin.*, renders the administration and dosage claims obvious.

Arthur (2002), *Moitra* (2005), and *Insulin Admin*. (2003) were published in medical journals and were publicly available prior to July 21, 2006, and are thus

prior art. *Arthur* and *Moitra* are new art that was not previously cited in the Frontier Therapeutics or Antares IPR petitions or during prosecution.

1. Ground 2 Claim Chart.

Claim	Exemplary Citations in *Arthur* (Ex. 1023), *Moitra* (Ex. 1025), and *Insulin Admin.* (Ex. 1015)
7. The method according to claim 1, wherein the medicament is present in a form suitable for patient self-administration.	*Arthur*: "Patients were taught to self-administer their methotrexate subcutaneously and were then discharged to perform this task at home." Ex. 1023 at 256. "Three pre-filled syringes in a lockable box, needles, alcohol swabs and sharps disposal box were provided and participants were discharged for a month. . . . Participants self-administered their MTX by the SC route at home for 3 consecutive weeks." Ex. 1023 at 259. *Moitra*: "We analysed the notes of 102 of the 115 patients receiving parenteral MTX for a variety of conditions in the 3 months leading up to and including June 2002. Ninety-one patients were using the subcutaneous as opposed to the i.m. route and of these, 77 had successfully been taught to self-inject." Ex. 1025 at 256. Miller Decl. (Ex. 1033) at ¶¶ 44, 51-53.
8. The method according to claim 1, wherein the medicament is contained in an injection device for a single application.	*Arthur*: "Three pre-filled syringes in a lockable box, needles, alcohol swabs and sharps disposal box were provided and participants were discharged for a month." Ex. 1023 at 259. "Comprehensible written information sheets . . . about the . . . disposal of used syringes . . . were given to each participant." Ex. 1023 at 259. Miller Decl. (Ex. 1033) at ¶¶ 43-44, 51-52.

9. The method according to claim 8, wherein the injection device contains a dosage of 5 to 40 mg of methotrexate.	See above for claim 8; for dosages, see *Grint* claim chart for claim 12 at section VI.A.2 above.
10. The method according to claim 8 or 9, wherein the injection device is a ready-made syringe.	*Arthur*: "Three pre-filled syringes … were provided …." Ex. 1023 at 259. Miller Decl. (Ex. 1033) at ¶¶ 43-44.
14. The method according to claim 13, wherein the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device.	*Arthur*: "[T]he pen-type syringe" was "commonly used for SC injections." Ex. 1023 at 259. *Insulin Admin.*: "Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle." Ex. 1015 at S123. The '231 patent: "Carpules, also referred to as syringe cartridges, are well known in the art." Ex. 1001 at 6:35-36. Miller Decl. (Ex. 1033) at ¶¶ 44, 51-52, 57.
15. The method according to claim 14, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.	'231 patent: "[A] pen injector according to the present invention and the carpule contained therein are preferably designed such that multiple applications of single dosages can be carried out…. *Pen injectors with that type of structure are well known in the art*…." Ex. 1001 at 7:5-27. *Insulin Admin.*: "Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. In many patients (e.g., especially those who are neurologically impaired and those using *multiple daily injection regimens*), these devices have been demonstrated to improve accuracy of insulin administration and/or adherence. Low-dose pens that can deliver insulin in *half-unit increments* are also available." Ex. 1015 at S123.

	Arthur: "the pen-type syringe" was "commonly used for SC injections." Ex. 1023 at 259. Miller Decl. (Ex. 1033) at ¶¶ 44, 51-52, 57.
16. The method according to claim 15, wherein the single dosages per application can be adjusted to 5 to 40 mg each of methotrexate.	*See, supra*, at claim 15; for dosages, *see Grint* claim chart at claim 12 at section VI.A.2 *supra*.
19. The method according to claim 9, wherein the injection device contains a dosage selected from 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg of methotrexate.	*See, supra*, at claim 9.
20. The method according to claim 14, wherein the injection device is a pen injector.	*See, supra*, at claim 15.
21. The method according to claim 16, wherein the single dosages of methotrexate per application is adjusted to be 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg.	*See, supra*, at claim 15; for dosages, *see Grint* claim chart at claim 12 at section VI.A.2 *supra*.

2. Ground 2 Detailed Analysis.

Arthur discloses MTX packaged in forms suitable for subcutaneous self-administration, and subcutaneous self-administration of MTX using injection devices such as ready-made syringes and pen-injectors. *See* Ex. 1023 at 256, 259.

Arthur reports the findings of a study that taught "patients to self-administer methotrexate by the subcutaneous route." Ex. 1023 at 256. The study sought to determine "whether some patients could be safely discharged to self-administer their own [MTX] injections at home, with improved convenience for themselves and a reduction in hospital visits." *Id.* at 257. The study trained participants to safely self-administer MTX subcutaneously using disposable, pre-filled syringes, and also considered using "the pen-type syringe that is more commonly used for SC injections." *Id.* at 259. The study provided patients with three pre-filled syringes to use once per week over a three week period, *i.e.*, three single use syringes. *Id.* The study concluded: "Patients were able to administer safely methotrexate subcutaneously. Self-administration reduced hospital visits, was more convenient for patients and improved patient satisfaction." Ex. 1023 at 256-57.

Arthur thus discloses that, prior to July 2006, subcutaneous self-administration of MTX using various injection devices was known, safe, and highly desirable. Miller Decl. (Ex. 1033) at ¶¶ 51-52. Indeed, the authors reported

these findings in summary format in 2001, in a Letter to the Editor published in the *Journal of Rheumatology*. *Arthur 2001* (Ex. 1024); Schiff Decl. (Ex. 1034) at ¶ 96. A skilled artisan would have had reason, with an expectation of success, to combine the teachings of *Grint* with the teaching of *Arthur* to arrive at a highly concentrated MTX solution that could be self-administered by means of an injection device, ready-made syringe, or pen-injector—and it would have required merely routine effort to do so. Miller Decl. (Ex. 1033) at ¶¶ 42-44, 52. A skilled artisan would have further had reason to do so in view of *Moitra*, published in 2005 and thus prior art, which disclosed that 77 patients "had successfully been taught to self-inject" MTX subcutaneously. Ex. 1025 at 256; Miller Decl. (Ex. 1033) at ¶ 53. The combination of *Grint* and *Arthur* alone, or further in view of *Moitra*, thus renders claims 7-10, 14-16, and 19-21 obvious. Miller Decl. (Ex. 1033) at ¶¶ 52-53.

Patent Owner may argue that the "pen-type syringe . . . commonly used for SC injections" disclosed by *Arthur*, Ex. 1023 at 259, does not explicitly disclose the use of a carpule (claim 14) along with a pen injector device for the administration of multiple single dosages (claim 15). But the '231 patent admits on its face that there was nothing novel about the use of a carpule and pen injector device for multiple single dosage administration as of July 2006, and that fact would have been obvious to a skilled artisan. Ex. 1001 at 7:5-27 ("Pen injectors

with that type of structure are well known in the art, especially from the field of insulin injectors."); Miller Decl. (Ex. 1033) at ¶ 52.

And *Insulin Admin.* confirms the same. Ex. 1015 at S123 ("Several pen-like devices and insulin-containing cartridges are available that deliver insulin subcutaneously through a needle. In many patients (e.g., especially those who are neurologically impaired and those using multiple daily injection regimens), these devices have been demonstrated to improve accuracy of insulin administration and/or adherence. Low-dose pens that can deliver insulin in half-unit increments are also available."). It would have thus required merely routine effort for one of skill in the art to combine the teachings of *Grint* and *Arthur* with *Insulin Admin.* to arrive at the method of claims 14 and 15. Miller Decl. (Ex. 1033) at ¶¶ 52, 53, 60.

C. Ground 3: Claim 18 is Rendered Obvious by *Grint* in View of *Alsufyani*.

1. Ground 3 Claim Chart.

Claim	Exemplary Citations in *Alsufyani* (Ex. 1006)
18. The method according to claim 6, wherein rheumatoid arthritis is juvenile rheumatoid arthritis.	*See, supra*, at VI.A for claim 6. *Alsufyani* teaches subcutaneous administration of MTX to treat juvenile rheumatoid arthritis. "Objective. To describe the outcome of patients with juvenile idiopathic arthritis (JIA) treated with subcutaneous (Sc) methotrexate (MTX) . . . . Conclusion. . . . The use of SC MTX has a high likelihood of success with more than 70% of patients achieving clinically significant

	improvement, without clinically significant toxicity." Ex. 1006 at 179. "A commonly used initial dose is 10 mg/m^2 in a single weekly dose with doses up to 30 mg/m^2 being used subsequently." Ex. 1006 at 179. Schiff Decl. (Ex. 1034) at ¶¶ 68-71.

2. Ground 3 Detailed Analysis.

Grint teaches the use of highly concentrated MTX to treat "autoimmune diseases," and specifically teaches the treatment of rheumatoid arthritis. Ex. 1003 at 3:4-9, 1:12-15. A person of ordinary skill in the art would have understood *Grint*'s disclosure of "autoimmune diseases" and RA to include juvenile rheumatoid arthritis ("JRA") (also called "juvenile idiopathic arthritis"). Schiff Decl. (Ex. 1034) at ¶ 68.

Alsufyani (published in 2004 and thus prior art) teaches that subcutaneous MTX administration is effective for the treatment of JRA, and specifically teaches that the dose administered to children may reach 30 mg/m^2. *See* claim chart above; Schiff Decl. (Ex. 1034) at ¶¶ 68-71. As applied to a 56-inch tall child weighing 75 pounds, for instance, a 30 mg/m^2 dose translates to 35 mg of methotrexate. Schiff Decl. (Ex. 1034) at ¶¶ 70-71; Ex. 1032 at 1-2. One of ordinary skill in the art would thus have had reason, with a reasonable expectation of success, to apply the greater than 30 mg/ml concentrations disclosed in *Grint* to the treatment of JRA.

Id. For example, the skilled artisan would have understood that the 35 mg dose described above could be administered subcutaneously as a convenient and effective 1 ml solution if a 35 mg/ml concentration MTX solution were used. *Id.* Accordingly, *Grint* in view of *Alsufyani* renders claim 18 obvious. Schiff Decl. (Ex. 1034) at ¶ 71.

D. Ground 4: Claims 1-6, 11-13, 17-18, and 22 are Anticipated by *Wyeth*.

Wyeth and *the PDR for Wyeth* are the FDA-approved printed package insert for an injectable methotrexate product, available prior to July 2006, described as "Methotrexate Sodium for Injection, Lyophilized, Preservative Free, for Single Use Only." Ex. 1021 at 25; Ex. 1022 at 3420.

Wyeth teaches both subcutaneous and intramuscular administration of a 50 mg/ml MTX solution for treating inflammatory autoimmune diseases. Schiff Decl. (Ex. 1034) at ¶¶ 72-81; Miller Decl. (Ex. 1033) at ¶ 61.

Wyeth and the *PDR for Wyeth* are prior art. *Wyeth* was publicly available at the FDA's website as of April 2005. Ex. 1021 at p. 29 of 82 (Declaration of Internet Archive) [5]; Schiff Decl. (Ex. 1034) at ¶ 72; Miller Decl. (Ex. 1033) at ¶ 61.

[5] For a detailed explanation of Ex. 1021, *see* Kamholz Decl. (Ex. 1036) at ¶¶18-22.

The PDR for Wyeth was published in the Physician's Desk Reference as of 2003.[6] Ex. 1022. Moreover, *Wyeth* and *the PDR for Wyeth* are new prior art that was not previously cited by Frontier Therapeutics, Antares, or during prosecution.

1. Ground 4 Claim Chart.

Claim	Exemplary Citations in *Wyeth* (Ex. 1021) and *the PDR for Wyeth* (Ex. 1022)
1 [pre]. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*Wyeth* teaches administering MTX to treat an inflammatory autoimmune disease. Ex. 1021 at 8 (Identifying "Psoriasis" and "Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis" among the "Indications"); Ex. 1022 at 3417 ("Indications"). Schiff Decl. (Ex. 1034) at ¶ 74, 78, 82.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	*Wyeth* teaches that "children . . . may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or ***subcutaneously***." Ex. 1021 at 23; Ex. 1022 at 3420. Schiff Decl. (Ex. 1034) at ¶¶ 74-75.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*Wyeth* is an FDA-approved product label for an injectable methotrexate product to be reconstituted "with an appropriate sterile preservative free medium" to a concentration of 50 mg/ml. Ex. 1021 at 24; Ex. 1022 at 3420 ("Reconstitution of Lyophilized Powders").

[6] Each of the relevant disclosures in *Wyeth* is also found in the *PDR for Wyeth*. *See* Schiff Decl. (Ex. 1034) at ¶ 80. While the ensuing discussion generally refers to *Wyeth*, parallel citations for both references are provided.

	Schiff Decl. (Ex. 1034) at ¶ 76.
2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra,* at claim 1b.
3. The method according to claim 2, wherein the methotrexate is present at a concentration of 50 mg/ml.	*See, supra,* at claim 1b. Schiff Decl. (Ex. 1034) at ¶ 85.
4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	*Wyeth* teaches a pharmaceutically acceptable solvent that includes water and a sodium chloride solution. Ex. 1021 at 24; Ex. 1022 at 3420. Miller Decl. (Ex. 1033) at ¶ 62; Schiff Decl. (Ex. 1034) at ¶¶ 76, 86.
5. The method according to claim 1, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, brochial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.	*Wyeth* teaches administering MTX to treat an inflammatory autoimmune disease. Ex. 1021 at 7 (Identifying "Psoriasis" and "Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis" among the "Indications"); Ex. 1022 at 3417 ("Indications"). Schiff Decl. (Ex. 1034) at ¶¶ 74, 87.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See, supra*, at claim 5.
11. The method according	*Wyeth* teaches MTX in a storage container.

to claim 1, wherein the medicament is contained in a storage container.	Ex. 1021 at 25 ("1 g vial"); Ex. 1022 at 3420. Miller Decl. (Ex. 1033) at ¶ 62.
12. The method according to claim 11, wherein the total storage container contains a total dosage amount of 5 to 5,000 mg.	*Wyeth* teaches a 1000mg MTX vial. Ex. 1021 at 25; Ex. 1022 at 3420. Miller Decl. (Ex. 1033) at ¶ 62.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	*See* claim 12 *supra*.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	*Wyeth* teaches an isotonic sodium chloride solution. Ex. 1021 at 24; Ex. 1022 at 3420. Miller Decl. (Ex. 1033) at ¶ 62.
18. The method according to claim 6, wherein rheumatoid arthritis is juvenile rheumatoid arthritis.	*See, supra*, at claim 5, claim 1(a) and (b).
22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	*See* claim 2 *supra*.

2. Ground 4 Detailed Analysis.

Claim 1: *Wyeth* teaches the preamble of claim 1, a "method for the treatment of inflammatory autoimmune diseases." Schiff Decl. (Ex. 1034) at ¶¶ 74, 78, 82; claim chart, *supra*.

The rest of claim 1 recites: "subcutaneously administering to said patient a medicament comprising methotrexate in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml." Ex. 1001 at 8:44-47.

As shown in step 1(b) of the claim chart, *Wyeth* teaches administering methotrexate in a pharmaceutically acceptable solvent.

Moreover, *Wyeth* teaches administering methotrexate to children for the treatment of JRA in a concentration of 50 mg/ml via subcutaneous injection. Ex. 1021 at 23 ("children . . . may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or ***subcutaneously***.") (emphasis added); *id.* at 25; Ex. 1022 at 3420; Schiff Decl. (Ex. 1034) at ¶¶ 74-75. One of ordinary skill would have understood that teaching to apply equally to adults with other inflammatory autoimmune diseases such as RA. Schiff Decl. (Ex. 1034) at ¶ 75. Moreover, *Wyeth* was the FDA-approved label for an FDA-approved product available prior to July 2006, demonstrating that the FDA had deemed it safe for a skilled artisan to administer the MTX product disclosed in *Wyeth* in a 50 mg/ml concentration. Miller Decl. (Ex. 1033) at ¶ 63.

Medac may seek to argue otherwise by pointing to language in *Wyeth* stating that the 20 mg vial product (as opposed to the 1 g vial product) should only be reconstituted to a concentration of 25 mg/ml. That language, however, relates to a different product and is irrelevant. Schiff Decl. (Ex. 1034) at ¶ 79. That fact is

demonstrated, for instance, by *Bigmar*—the FDA-approved label for a generic equivalent to the 1 gram vial product of *Wyeth*—which reiterates that the "**1 gram vial should be reconstituted with 19.4 mL to a concentration of 50 mg/ml.**" Ex. 1026 at 6 (emphasis original); Schiff Decl. (Ex. 1034) at ¶ 79.

RECONSTITUTION OF LYOPHILIZED POWDER
Reconstitute immediately prior to use.

Methotrexate for Injection should be reconstituted with an appropriate sterile preservative free medium such as 5% Dextrose Solution or Sodium Chloride Injection. **The 1 gram vial should be reconstituted with 19.4 mL to a concentration of 50 mg/mL.** When high doses of methotrexate are administered by IV infusion, the total dose is diluted in 5% Dextrose Solution.

For intrathecal injection, reconstitute to a concentration of 1 mg/mL with an appropriate sterile, preservative free medium such as Sodium Chloride Injection.

Bigmar also instructs the user to "discard" any "unused portion" of the formulated solution, reinforcing that the solution was to be administered in a 50 mg/ml concentration and not to be further diluted. Schiff Decl. (Ex. 1034) at ¶79.

METHOTREXATE
FOR INJECTION USP

1 g

Lyophilized
PRESERVATIVE FREE

1 g Single Dose Vial Sterile

See package insert for routes of administration.

Pharmaceuticals Bigmar

Store between 15° - 30°C (59° - 86°F). **PROTECT FROM LIGHT.** Retain in carton until time of use. Discard unused portion.

Reconstitute immediately prior to use with 19.4 mL of an appropriate sterile, preservative-free medium to a concentration of 50 mg/mL.

WARNING: SEE PACKAGE INSERT FOR FULL PRESCRIBING INFORMATION AND BOXED WARNINGS.

Manufactured by:
Bigmar Pharmaceuticals SA
Barbengo, Switzerland

Manufactured for:
Bigmar, Inc.
Johnstown, OH 43031

Accordingly, *Wyeth* teaches each element of claim 1 and anticipates.

Claims 2, 3, and 22 cover the method of claim 1, wherein the MTX "is present at a concentration of" (1) "more than 30 mg/ml to 100 mg/ml," (2) "50 mg/ml" and (3) "40 mg/ml to 80 mg/ml," respectively. Ex. 1001 at 8:49-50, 52; 10:19-20. *Wyeth* thus anticipates claims 2, 3, and 22 for the same reasons as claim 1. *See* claim 1 discussion, *supra*. Moreover, the '231 patent on its face precludes any argument that the invention disclosed therein operates differently at any concentration greater than 25 mg/ml and up to 150 mg/ml. *See* Section VI.A.3 (claim 2), *supra*. Accordingly, claims 2, 3, and 22 are also unpatentable in view of *Wyeth*.

Claim 4 limits the "pharmaceutically acceptable solvent" of claim 1 to "water, water for injection purposes, water comprising isotonization additives and sodium chloride solution." Ex. 1001 at 8:54-56. **Claim 17** further specifies, "the sodium chloride solution is isotonic sodium chloride solution." Ex. 1001 at 10:4-5. *Wyeth* discloses a "Sodium Chloride Injection." Ex. 1021 at 24. It also teaches the use of "an appropriate sterile, preservative free medium," which a skilled artisan would have understood to include water. Miller Decl. (Ex. 1033) at ¶ 62. *Wyeth* thus anticipates Claim 4. Moreover, a skilled artisan would have understood *Wyeth*'s reference to "'an appropriate sterile preservative free medium such as . . . Sodium Chloride Injection' to include an isotonic sodium chloride solution,

meaning a 0.9% sodium chloride solution having the same salt concentration as blood *i.e.*, 'normal saline.'" Miller Decl. (Ex. 1033) at ¶ 62. Accordingly, *Wyeth* would inform a skilled artisan that an isotonic sodium chloride solution or other pharmaceutically acceptable solvents could be used to make a 50 mg/ml MTX solution. Miller Decl. (Ex. 1033) at ¶ 62. Claim 17 is thus also anticipated.

Claim 5 limits claim 1 to certain types of inflammatory autoimmune diseases, and **Claim 6** specifies "rheumatoid arthritis." Ex. 1001 at 8:57-64. Each disease identified in claims 5 and 6 was an established inflammatory autoimmune disease prior to July 2006. Schiff Decl. (Ex. 1034) at ¶ 65. Moreover, *Wyeth* specifically identifies "rheumatoid arthritis" among the approved indications for the product disclosed therein. Schiff Decl. (Ex. 1034) at ¶ 74. *Wyeth* thus anticipates claims 5 and 6. Schiff Decl. (Ex. 1034) at ¶¶ 81, 87.

Claims 11-13 are anticipated by *Wyeth*, which discloses a product that was offered in a 1 g vial (*i.e.*, a storage container containing 1000 mg). Miller Decl. (Ex. 1034) at ¶ 62.

Claim 18: *Wyeth* teaches that the 50 mg/ml MTX solution disclosed therein was indicated for the treatment of JRA and specifically teaches that "children . . . may have better absorption and fewer gastrointestinal side effects if methotrexate is administered either intramuscularly or ***subcutaneously***." Ex. 1021 at 23

(emphasis added); *id.* at 25; Ex. 1022 at 3420; Schiff Decl. (Ex. 1034) at ¶¶ 74-75. *Wyeth* thus anticipates claim 18.

Accordingly, *Wyeth* anticipates claims 1-6, 11-13, 17-18, and 22.

E. Ground 5: Claims 1-22 are Obvious Over *Wyeth* in View of *Brooks* and *Arthur*, Further in view of *Moitra* or *Insulin Admin.*

All of the claims of the '231 patent are obvious over *Wyeth* (2005) and *the PDR for Wyeth* (2003) in view of *Brooks* (1990) and *Arthur* (2002), further in view of *Moitra* (2005) or *Insulin Admin.* (2003). As noted, *Wyeth*, *the PDR for Wyeth*, *Arthur*, and *Moitra* are all new prior art that was not previously cited by Frontier Therapeutics, Antares, or during prosecution.

Critically, while Dr. Massarotti reviewed *Brooks* and *Moitra*, her declaration contained ***no criticisms or disagreements*** with either publication. Ex. 1007 at 73; Schiff Decl. (Ex. 1034) at ¶ 96.

1. Ground 5 Claim Chart.

Claim	Exemplary Citations in *Wyeth* (Ex. 1021), *the PDR for Wyeth* (Ex. 1022), *Brooks* (Ex. 1008), *Arthur* (Ex. 1023), *Moitra* (Ex. 1025) and *Insulin Admin.* (Ex. 1015)
1 [pre]. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*Wyeth* teaches administering MTX to treat an inflammatory autoimmune disease. Ex. 1021 at 7 (Identifying "Psoriasis" and "Rheumatoid Arthritis including Polyarticular-Course Juvenile Rheumatoid Arthritis" among the "Indications"); Ex. 1022 at 3417 ("Indications"). As does *Brooks*. Ex. 1008 at 91 ("Methotrexate

	(MTX), a folic acid antagonist, has recently been approved by the Food and Drug Administration for use in patients with severe rheumatoid arthritis that is refractory to conventional therapy."). *Arthur* discloses the same. *See* Ex. 1023 at 260, table 1 (identifying study subjects as suffering from rheumatoid arthritis, Wegener's granulomatosis, psoriatic arthritis, and polymyositis). As does *Moitra*. Ex. 1025 at 256 ("methotrexate (MTX) remains the most widely prescribed of the disease-modifying anti-rheumatic drugs (DMARDs) . . . ."). Schiff Decl. (Ex. 1034) at ¶¶ 74, 78, 82, 93, 96.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	*Brooks* teaches subcutaneous administration of MTX. Ex. 1008 at 91 ("IM and SQ are interchangeable routes of administration."). *Moitra* also teaches subcutaneously administering methotrexate for the treatment of various rheumatic diseases. Ex. 1025 at 256 ("We analysed the notes of 102 of the 115 patients receiving parenteral MTX for a variety of conditions in the 3 months leading up to and including June 2002. Ninety-one patients were using the subcutaneous as opposed to the i.m. route and of these, 77 had successfully been taught to self-inject."). *Arthur* also teaches subcutaneously administering methotrexate for the treatment of various inflammatory autoimmune diseases. "Participants self-administered their MTX by the SC route at home for 3 consecutive weeks." Ex. 1023 at 259. "In the future parenteral MTX should be prescribed

	by the SC [subcutaneous] route instead of the IM [intramuscular] route." Ex. 1023 at 262. *See* Ex. 1023 at 260, table 1 (identifying study subjects as suffering from rheumatoid arthritis, Wegener's granulomatosis, psoriatic arthritis, and polymyositis). Schiff Decl. (Ex. 1034) at ¶¶ 90-97.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*Wyeth* is an FDA-approved product label for an injectable methotrexate product to be reconstituted "with an appropriate sterile, preservative free medium" to a concentration of 50 mg/ml. Ex. 1021 at 24; Ex. 1022 at 3420 ("Reconstitution of Lyophilized Powders"). *Brooks* concluded that "IM and SQ are interchangeable routes of administration." Ex. 1008 at 91. *Arthur* compared "the safety and efficacy of methotrexate administered by intramuscular and subcutaneous injection" and concluded "there is no difference in the safety and efficacy of methotrexate given by either parenteral route." Ex. 1023 at 256. *Moitra* teaches that 91 of 102 patients "receiving parenteral MTX for a variety of conditions . . . were using the subcutaneous as opposed to the i.m. route . . . ." Ex. 1025 at 256. Schiff Decl. (Ex. 1034) at ¶¶ 90-98; Miller Decl. (Ex. 1033) at ¶ 63.
2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra*, at claim 1b.

3. The method according to claim 2, wherein the methotrexate is present at a concentration of 50 mg/ml.	*See, supra*, at claim 1b. Schiff Decl. (Ex. 1034) at ¶ 85.
4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	*See*, Section VI.D.1, *supra.* Miller Decl. (Ex. 1033) at ¶ 62.
5. The method according to claim 1, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, brochial asthma, Alzheimer's disease, multiple sclerosis, Bechterew's disease, joint arthroses, or psoriasis.	*See*, Section VI.D.1, *supra.* *Brooks* teaches: "Methotrexate (MTX), a folic acid antagonist, has recently been approved by the Food and Drug Administration for use in patients with severe rheumatoid arthritis that is refractory to conventional therapy." Ex. 1008 at 91. *Moitra* also teaches that "methotrexate (MTX) remains the most widely prescribed of the disease-modifying anti-rheumatic drugs (DMARDs) . . . ." Ex. 1025 at 256. *Arthur* teaches subcutaneous administration of methotrexate to treat rheumatoid arthritis. *See* Ex. 1023 at 260, table 1 (identifying study subjects as suffering from rheumatoid arthritis, Wegener's granulomatosis, psoriatic arthritis, and polymyositis). Schiff Decl. (Ex. 1034) at ¶¶ 93, 96.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See, supra*, at claim 5.
7. The method according to	*See* Section VI.B.1, *supra.*

claim 1, wherein the medicament is present in a form suitable for patient self-administration.	Miller Decl. (Ex. 1033) at ¶¶ 44, 51-53.
8. The method according to claim 1, wherein the medicament is contained in an injection device for a single application.	*See* Section VI.B.1, *supra.* Miller Decl. (Ex. 1033) at ¶¶ 44, 51-52.
9. The method according to claim 8, wherein the injection device contains a dosage of 5 to 40 mg of methotrexate.	See above for claim 8. The '231 patent: "In Germany, a dosage range of 5.0 to 30.0 mg per week is common for antirheumatic therapy, in other European countries, dosages of up to 40.0 mg per week are administered." Ex. 1001 at 1:56-65. *Arthur* teaches MTX dosages ranging from 7.5 mg to 25 mg. Ex. 1023 at 260 (Table 1). *Wyeth* teaches dosages of "10 to 25 mg." Ex. 1021 at 24; Ex. 1022 at 3420. Miller Decl. (Ex. 1033) at ¶¶ 52, 62.
10. The method according to claim 8 or 9, wherein the injection device is a ready-made syringe.	*See* Section VI.B.1, *supra.* Miller Decl. (Ex. 1033) at ¶¶ 43, 44.
11. The method according to claim 1, wherein the medicament is contained in a storage container.	*See*, Section VI.D.1, *supra.*
12. The method according to claim 11, wherein the total storage container contains a total dosage amount of 5 to 5,000 mg.	*See*, Section VI.D.1, *supra.*
13. The method according to claim 11, wherein the	*See*, Section VI.D.1, *supra.*

storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	
14. The method according to claim 13, wherein the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device.	*See* Section VI.B.1, *supra.* Miller Decl. (Ex. 1033) at ¶¶ 44, 51-52, 57.
15. The method according to claim 14, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.	*See* Section VI.B.1, *supra.* Miller Decl. (Ex. 1033) at ¶¶ 44, 51-52, 57.
16. The method according to claim 15, wherein the single dosages per application can be adjusted to 5 to 40 mg each of methotrexate.	*See, supra*, at claim 15; for dosages *see* claim 9, *supra*.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride solution.	*See*, Section VI.D.1, *supra.*
18. The method according to claim 6, wherein rheumatoid arthritis is juvenile rheumatoid arthritis.	*See*, Section VI.D.1, *supra.*
19. The method according to claim 9, wherein the injection device contains a dosage selected from 5.0,	*See, supra*, at claim 9.

7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg of methotrexate.	
20. The method according to claim 14, wherein the injection device is a pen injector.	*See, supra*, at claim 15.
21. The method according to claim 16, wherein the single dosages of methotrexate per application is adjusted to be 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg.	*See, supra*, at claim 15; for dosages, *see* claim 9, *supra*.
22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	*See, supra*, at claim 2.

2. Ground 5 Detailed Analysis.

Claim 1: *Wyeth* (2005), *the PDR for Wyeth* (2003), *Brooks* (1990), *Moitra* (2005), and *Arthur* (2002) each teach the preamble of claim 1, a "method for the treatment of inflammatory autoimmune diseases." Schiff Decl. (Ex. 1034) at ¶¶ 70-71, 78; claim chart, *supra*.

The rest of claim 1 recites: "subcutaneously administering to said patient a medicament comprising methotrexate in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml." Ex. 1001 at 8:44-47.

Wyeth teaches administering methotrexate for the treatment of RA, JRA, and psoriasis in a concentration of 50 mg/ml via intramuscular injection. Ex. 1021 at 24; Ex. 1022 at 3420; Schiff Decl. (Ex. 1034) at ¶¶ 88-89. *Brooks* teaches that "IM and SQ are interchangeable routes of [MTX] administration" and that "SQ administration may be a more convenient and less painful way of administering low-dose MTX." [7] Ex. 1008 at 91; Schiff Decl. (Ex. 1034) at ¶¶ 90-95. And the teachings of *Brooks* were widely adopted and implemented prior to July 2006. Schiff Decl. (Ex. 1034) at ¶ 96. For instance, *Moitra*, published in *Rheumatology*, cited *Brooks* for the proposition that "there are no significant differences in bioavailability between MTX administered subcutaneously and I.M., making the two routes interchangeable." *Id.*; Ex. 1025 at 256. And *Moitra* specifically disclosed that 91 out of 102 patients observed in that analysis "were using the subcutaneous as opposed to the i.m. route . . . ." *Id.*; Schiff Decl. (Ex. 1034) at ¶ 96. As another example, *Arthur* independently confirmed the findings of *Brooks* and concluded "there is no difference in the safety and efficacy of methotrexate given by either parenteral route [*i.e.*, intramuscular or subcutaneous injection]." Ex. 1023 at 256; Schiff Decl. (Ex. 1034) at ¶ 96. These findings were not limited to

[7] Note that the invention of the '231 patent (like *Brooks*) is directed to a more convenient and less painful way of administering "low-dose MTX." Fn. 1, *supra*.

the treatment of RA, but also included a variety of other autoimmune diseases. Schiff Decl. (Ex. 1034) at ¶ 96.

Accordingly, a skilled artisan reviewing *Wyeth* and *Brooks and Arthur*, further in view of *Moitra*, prior to July 2006, would have understood that the 50 mg/ml MTX solution of *Wyeth* could be administered subcutaneously with success. Schiff Decl. (Ex. 1034) at ¶ 97. Nothing in *Wyeth*, *Brooks*, *Arthur*, or *Moitra* cautions against using highly concentrated MTX solutions subcutaneously to treat inflammatory autoimmune diseases. *Id.* at ¶ 97.

Moreover, the skilled artisan would have been motivated to administer the 50 mg/ml MTX solution of *Wyeth* subcutaneously. Schiff Decl. (Ex. 1034) at ¶¶ 96-97. Because *Wyeth* is the FDA-approved product label for an FDA-approved product, a skilled artisan would have understood that intramuscular administration of the 50 mg/ml methotrexate injection disclosed in *Wyeth* had been demonstrated to be safe and effective for treating RA, JRA, and psoriasis. Miller Decl. (Ex. 1033) at ¶¶ 9, 63. But intramuscular injections are painful and most often must be administered in the hospital or physician's office by the physician or staff. Schiff Decl. (Ex. 1034) at ¶¶ 29, 92. And *Brooks* and subsequent publications like *Arthur* teach that subcutaneous administration is equally as safe and effective as IM administration, while conferring important advantages, including less pain, Ex. 1023 at 257 (citing *Brooks* (Ex. 1008)), and the ability to self-administer

injections at home, *id.*, which reduces hospital visits, is more convenient for patients, and improves patient satisfaction. *Id.*; Schiff Decl. (Ex. 1034) at ¶¶ 90-97. Indeed, subcutaneous administration of MTX was frequently practiced prior to July 2006. Ex. 1025 at 256 (reporting in 2005 that 91 patients had received subcutaneous MTX injections within a three month period).

Accordingly, *Wyeth* in view of *Brooks* renders claim 1 obvious.

Claims 2, 3, and 22 cover the method of claim 1, wherein the MTX "is present at a concentration of" (1) "more than 30 mg/ml to 100 mg/ml," (2) "50 mg/ml" and (3) "40 mg/ml to 80 mg/ml," respectively. Ex. 1001 at 8:49-50, 52; 10:19-20. *Wyeth* in view of *Brooks* and in further view of *Arthur* or *Moitra* renders claim 1 obvious for an MTX concentration of 50 mg/ml. *See* claim 1 discussion, *supra*. Moreover, the '231 patent on its face precludes any argument that the invention disclosed therein operates differently at any concentration greater than 25 mg/ml and up to 150 mg/ml. *See* Section VI.A.3 (claim 2), *supra*. Accordingly, claims 2, 3, and 22 are also unpatentable in view of *Wyeth* combined with *Brooks* further in view of *Arthur* or *Moitra*.

Claims 4-6 and 17-18 are unpatentable over *Wyeth* for the same reasons explained in Section VI.D.2, *supra*. *See also* Ex. 1023 at 260 (Table 1) (disclosing subcutaneously administered MTX as an effective treatment for rheumatoid arthritis, Wegener's granulomatosis, psoriatic arthritis, and polymyositis).

Claims 7-16, 19-21 would have been obvious for the reasons set forth in the claim chart and discussion in Section VI.B, *supra.*

Accordingly, claims 1-22 are thus unpatentable.

F. Ground 6: Claims 1-22 are Obvious Over *Hoekstra* and *Jørgensen* in View of *Arthur* and/or *Insulin Admin.*

1. Ground 6 Claim Chart.

Claim	Exemplary Citations in *Hoekstra* (Ex. 1004), *Jørgensen* (Ex. 1005), *Arthur* (Ex. 1023), and *Insulin Admin.* (Ex. 1015)
1 [pre]. A method for the treatment of inflammatory autoimmune diseases in a patient in need thereof, comprising	*Hoekstra* teaches the use of MTX to treat rheumatoid arthritis. Ex. 1004 at 645 ("Methotrexate (MTX) is commonly used in weekly single-dose regimens in the treatment of rheumatoid arthritis (RA)."). Schiff Decl. (Ex. 1034) at ¶ 99.
1a. subcutaneously administering to said patient a medicament comprising methotrexate	*Hoekstra* teaches subcutaneous administration of MTX to treat rheumatoid arthritis. Ex. 1004 at 646 ("we performed a crossover pharmacokinetic study in adult patients with RA, comparing the bioavailability of oral and subcutaneous MTX at doses ≥ 25 mg weekly."). Schiff Decl. (Ex. 1034) at ¶ 99.
1b. in a pharmaceutically acceptable solvent at a concentration of more than 30 mg/ml.	*Hoekstra* teaches providing doses of MTX as high as 40 mg. *Jørgensen* teaches reducing the volume of subcutaneously injected solutions below 1 ml. "Our data suggest that doses between 25 and 40 mg MTX per week, administered orally, result in limited bioavailability. Bioavailability is enhanced by the subcutaneous route of administration . . . ." *Hoekstra* (Ex. 1004) at 647.

	"The pain of subcutaneous injection is related to the injection volume . . . . In order to optimize patient convenience in relation to subcutaneous administration, the results from this study should be considered in relation to the formulation of injection fluids. The volume should generally be less than 1.0 mL . . . ." *Jørgensen* (Ex. 1005) at 731. Schiff Decl. (Ex. 1034) at ¶¶ 100, 102-03.
2. The method according to claim 1, wherein the methotrexate is present at a concentration of more than 30 mg/ml to 100 mg/ml.	*See, supra*, at claim 1b.
3. The method according to claim 2, wherein the methotrexate is present at a concentration of 50 mg/ml.	*See, supra*, at claim 1b.
4. The method according to claim 1, wherein the pharmaceutically acceptable solvent is selected from water, water for injection purposes, water comprising isotonization additives and sodium chloride solution.	*Hoekstra*'s MTX solution was administered to human patients, and was therefore present in a pharmaceutically acceptable solvent. Miller Decl. (Ex. 1033) at ¶ 66.
5. The method according to claim 1, wherein the inflammatory autoimmune disease is selected from rheumatoid arthritis, juvenile arthritides, vasculitides, collagenoses, Crohn's disease, colitis ulcerosa, brochial asthma, Alzheimer's disease, multiple sclerosis,	*Hoekstra* teaches the use of MTX to treat rheumatoid arthritis. Ex. 1004 at 645 ("Methotrexate (MTX) is commonly used in weekly single-dose regimens in the treatment of rheumatoid arthritis (RA).").

Bechterew's disease, joint arthroses, or psoriasis.	Schiff Decl. (Ex. 1034) at ¶ 99.
6. The method according to claim 5, wherein the inflammatory autoimmune disease is rheumatoid arthritis.	*See, supra*, at claim 5.
7. The method according to claim 1, wherein the medicament is present in a form suitable for patient self-administration.	*See* Section VI.B.1, *supra.*
8. The method according to claim 1, wherein the medicament is contained in an injection device for a single application.	*See* Section VI.B.1, *supra.*
9. The method according to claim 8, wherein the injection device contains a dosage of 5 to 40 mg of methotrexate.	See above for claim 8. The '231 patent: "In Germany, a dosage range of 5.0 to 30.0 mg per week is common for antirheumatic therapy, in other European countries, dosages of up to 40.0 mg per week are administered." Ex. 1001 at 1:56-65. *Hoekstra* teaches providing doses of MTX as high as 40 mg. Ex. 1004 at 647 ("Our data suggest that doses between 25 and 40 mg MTX per week, administered orally, result in limited bioavailability. Bioavailability is enhanced by the subcutaneous route of administration . . . .") *Arthur* teaches MTX dosages ranging from 7.5 mg to 25 mg. Ex. 1023 at 260 (Table 1).
10. The method according to claim 8 or 9, wherein the injection device is a ready-made syringe.	*See* Section VI.B.1, *supra.*
11. The method according	*Hoekstra* teaches an injectable solution of MTX,

to claim 1, wherein the medicament is contained in a storage container.	which is necessarily stored in a container. Miller Decl. (Ex. 1033) at ¶ 66.
12. The method according to claim 11, wherein the total storage container contains a total dosage amount of 5 to 5,000 mg.	*See, supra*, at claim 1b.
13. The method according to claim 11, wherein the storage container is an injection bottle, a vial, a bag, a glass ampoule, or a carpule.	*Hoekstra* teaches an injectable solution of MTX, which is necessarily stored in a container, including an injection bottle, a vial, a bag, a glass ampoule, or a carpule. Miller Decl. (Ex. 1033) at ¶ 66.
14. The method according to claim 13, wherein the storage container is a carpule and wherein said carpule is suitable for administering the medicament by means of an injection device.	*See* Section VI.B.1, *supra.*
15. The method according to claim 14, wherein the carpule and the pen injector are provided such that multiple applications of single dosages can be administered.	*See* Section VI.B.1, *supra.*
16. The method according to claim 15, wherein the single dosages per application can be adjusted to 5 to 40 mg each of methotrexate.	*See, supra*, at claim 15; for dosages, *see* claim 9, *supra*.
17. The method according to claim 4, wherein the sodium chloride solution is isotonic sodium chloride	*Hoekstra* teaches an injectable solution of MTX for administration to patients, which is commonly an isotonic sodium chloride solution.

solution.	Miller Decl. (Ex. 1033) at ¶ 66.
18. The method according to claim 6, wherein rheumatoid arthritis is juvenile rheumatoid arthritis.	*See* Section VI.C, *supra*. Schiff Decl. (Ex. 1034) at ¶¶ 105-06.
19. The method according to claim 9, wherein the injection device contains a dosage selected from 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg of methotrexate.	*See, supra*, at claim 9.
20. The method according to claim 14, wherein the injection device is a pen injector.	*See, supra*, at claim 15.
21. The method according to claim 16, wherein the single dosages of methotrexate per application is adjusted to be 5.0, 7.5, 10.0, 12.5, 15.0, 17.5, 20.0, 22.5, 25.0, 27.5, 30.0, 32.5, 35.0, 37.5 or 40.0 mg.	*See, supra*, at claim 15; for dosages, *see* claim 9, *supra*.
22. The method according to claim 1, wherein the methotrexate is present at a concentration of from 40 mg/ml to 80 mg/ml.	*See, supra*, at claim 1b.

2. Ground 6 Detailed Analysis.

Hoekstra (published in 2004 and thus prior art) teaches that high dosages of MTX (up to 40 mg) can be successfully subcutaneously administered to treat RA.

Schiff Decl. (Ex. 1034) at ¶¶ 99-100. The Examiner considered *Hoekstra* and cited it as a basis for rejection of the claims under § 103(a). Ex. 1002 at 7, 12/21/11 OA. During prosecution, Patent Owner conceded that *Hoekstra* "disclose[s] methotrexate solutions to be administered subcutaneously for treating inflammatory autoimmune diseases with a concentration of 25 mg/ml," and in dosages up to 40 mg per week. Ex. 1002 at 10, 20, 22, 3/21/12 OA Response.

Jørgensen (1996) teaches that subcutaneously injected solutions should be formulated in volumes less than one milliliter (mL) because such volumes reduce injection pain and increase patient comfort. Ex. 1005 at 729, 731; Schiff Decl. (Ex. 1034) at ¶ 103. Medac knew of *Jørgensen* and its materiality to the prosecution of the '231 patent, yet did not provide the reference to the USPTO. *See* Certified English Translation of Portion of EPO prosecution for EP Application No. 07786239.9 (Ex. 1017) at 36 ("[*Jørgensen*] is prima facie relevant for the assessment of inventive step.").

Based on *Hoekstra* and *Jørgensen*, prior to July 2006, one of skill in the art would have had reason to formulate higher concentration MTX solutions (at least up to 40 mg/ml) in order to deliver the dosage volumes taught by *Hoekstra* while achieving the pain reduction benefits taught by *Jørgensen*. Schiff Decl. (Ex. 1034) at ¶ 104; Miller Decl. (Ex. 1033) at ¶¶ 69-72. A skilled artisan would have faced no technical impediment to doing so. Miller Decl. (Ex. 1033) at ¶ 70, 72. And

success was predictable, since successful administration of subcutaneous MTX is *dosage*-dependent, and not concentration-dependent. Schiff Decl. (Ex. 1034) at ¶¶ 104, 107-110. Accordingly, claims 1-6, 11-13, 17, and 22 are unpatentable as obvious over the combination of *Hoekstra* and *Jørgensen*.

The remaining claims are likewise unpatentable in further view of *Arthur* or *Insulin Admin*, and *Alsufyani*, as demonstrated in the claim chart in section VI.F.1 and in previous sections. *See also* Schiff Decl. (Ex. 1034) at ¶¶ 105-06.

G. Secondary Considerations Do Not Rebut Obviousness.

Secondary considerations (or "objective indicia of non-obviousness"), such as unexpected results or evidence of "teaching away" from the claimed invention, can rebut a *prima facie* case of obviousness under certain circumstances. Medac presented arguments and purported "evidence" of secondary considerations during prosecution of the '231 patent, but neither overcomes Petitioner's *prima facie* case of obviousness here.

1. MTX Toxicity from Subcutaneous Injection is Dose, Not Concentration, Dependent.

Medac argued during prosecution that highly concentrated MTX solutions were used "solely" to treat cancer, and that "persons skilled in the art would have been very cautious to increase the concentration of the active agent in a subcutaneously administered solution" because it would not have been obvious

that higher-concentration MTX solutions would have acceptable toxicity. Ex. 1002 at 21, 3/21/12 OA Response. Medac cited no evidence in support.

Those contentions were false. As explained in Sections VI.D and VI.E, *Wyeth* taught injecting MTX subcutaneously and intramuscularly in a concentration of 50 mg/ml to treat rheumatoid arthritis, juvenile rheumatoid arthritis, and psoriasis—not cancer. Since *Wyeth* reflected the FDA-approved product label for an FDA-approved product, skilled artisans would have known that the product disclosed therein had been demonstrated to be safe and effective. Miller Decl. (Ex. 1033) at ¶¶ 9, 63. And *Brooks* and *Arthur* both taught that subcutaneous injection is as safe and effective as, and more convenient than, the IM route. *See* Section VI.E. Moreover, the toxicity associated with SC or IM MTX is ***dose***, not concentration dependent, and changing the concentration of MTX simply changes the volume administered, but does not change the ***dose*** administered. Schiff Decl. (Ex. 1034) at ¶¶ 107-110.

The skilled artisan prior to July 2006 would have read *Arthur* and *Brooks* and concluded that the highly concentrated MTX solution described in *Wyeth* could be safely administered subcutaneously, without creating issues of toxicity or bioavailability. Schiff Decl. (Ex. 1034) at IX.A and IX.B. And the skilled artisan faced with adverse events would reduce the dosage (in mg) of methotrexate, or cease its administration, but would not reduce its *concentration*. Schiff Decl.

(Ex. 1034) at ¶ 33. Finally, folic acid supplementation was commonly used to reduce or eliminate potentially toxic side-effects. *Id.*; *Pincus* (Ex. 1014) at S-181.

Accordingly, the evidence contradicts and refutes Medac's assertion that subcutaneous injections of highly *concentrated* MTX would have been non-obvious to a skilled artisan because of toxicity concerns.

2. MTX Bioavailability from Subcutaneous Injection is Dose, Not Concentration, Dependent.

Medac also argued it was non-obvious that the bioavailability of higher concentration MTX solutions would be acceptable. Ex. 1002 3/21/12 at 21, OA Response. Again, Medac provided no evidence in support.

At least two studies publicly published before July 2006 refute Medac's argument. Both *Arthur* and *Brooks* compared bioavailability of intramuscularly and subcutaneously administered MTX and concluded there was no difference. Ex. 1023 at 260 ("There was no significant difference in blood serum levels between IM and SC MTX injections."); Ex. 1008 at 93 ("The results of this study suggest that the SQ route achieves serum concentration versus time curves similar to the IM route. . . . No statistically significant differences were observed for any response variable."). A skilled artisan would not have been concerned about a different outcome with highly concentrated solutions, because the availability of MTX to the patient after SC injection is *dosage*, not *concentration* dependent.

Schiff Decl. (Ex. 1034) at ¶¶ 111-12. For example, a 25 mg dose is a 25 mg dose, regardless of the solution concentration that is used to administer it. *Id.* at ¶ 111. Indeed, Dr. Massarotti reviewed *Brooks* and *Moitra* but did not express any criticism of the findings and conclusions in either publication. *Id.* at ¶ 112. Thus, the evidence refutes Medac's bioavailability argument.

3. Medac's Reliance on *Müller-Ladner* to Show Unexpected Results is Specious.

During prosecution, Medac cited the 2010 *Müller-Ladner* paper to show unexpected results. Ex. 1002 at 21, 3/21/12 OA Response. According to Medac, this reference demonstrated that a 50 mg/ml concentration of MTX was better tolerated than a 10 mg/ml, and thus showed "surprising technical effect which was unexpectedly observed for the high methotrexate concentration underlying the present invention." *Id.* Medac's reliance on *Müller-Ladner* fails for two reasons. Schiff Decl. (Ex. 1034) at ¶¶ 113-18.

First, *Müller-Ladner* does not compare the purported invention to the closest prior art, and thus cannot provide relevant evidence of unexpected results. In order to demonstrate that the invention of the '231 patent provided unexpected results over the prior art, Medac would need to compare its purported invention against the closest prior art. Schiff Decl. (Ex. 1034) at ¶ 115.

The '231 patent repeatedly states on its face that "the present invention" disclosed therein operates at any "concentration more than ***25 mg/ml***," and never asserts or even suggests that the invention operates differently at any particular concentration point or range. Ex. 1001 at 1:5-10 (emphasis added) ("[T]he present invention relates to the use of methotrexate . . . at a concentration of more than 25 mg/ml."); 3:1-21; 5:24-28; 6:49-54. Medac's purported invention is thus a MTX solution with a concentration of just above 25.0 mg/ml.

And during prosecution, Medac conceded that prior art (such as *Hoekstra*) taught the use of 25 mg/ml MTX concentrations. Ex. 1002 at 20, 22. Indeed, Medac identified *Hoekstra* as the "closest prior art." [8]

Thus to demonstrate unexpected results, Medac would need a comparison of an MTX solution of just above 25 mg/ml with an MTX solution of exactly 25.0 mg/ml. *Müller-Ladner* does not make such a comparison. Schiff Decl. (Ex. 1034) at ¶ 115. Instead, *Müller-Ladner* compared a ***50 mg/ml*** solution to a ***10 mg/ml*** solution, and thus cannot provide relevant evidence of "unexpected results."

[8] *See* Ex. 1002 at 20, 3/21/12 OA Response, (Medac referring to *Hoekstra*, which taught the use of 25 mg/ml MTX, as "clearly . . . the closest prior art") *and* Ex. 1001 at 5:24-27 (describing "the present invention" as MTX in any concentration above 25 mg/ml).

Second, one of skill in the art prior to July 2006 would ***not*** have found the results of *Müller-Ladner* to be surprising or unexpected. *Müller-Ladner* concedes that the reason patients preferred the highly concentrated MTX solution was "a smaller volume of administered drug, which improves the comfort of injection and may represent a psychological benefit for the patient." Ex. 1011 at 21; Schiff Decl. (Ex. 1034) at ¶ 117. But *Jørgensen* previously taught that very result. Ex. 1004 at 731; Schiff Decl. (Ex. 1034) at ¶ 117. And while *Müller-Ladner* claims that 79.7% of patients who received the 50 mg/ml solution "showed an absence of erythema" as compared to 71.1% for patients who received the 10 mg/ml solution, Ex. 1011 at 21, the data presented in *Müller-Ladner* contradicts that claim. Schiff Decl. (Ex. 1034) at ¶ 118. Specifically, Table 2 on page 20 of *Müller-Ladner* (Ex. 1011) reports the "Adverse Events" from the study and notes the incidence of erythema was zero out of 131 patients receiving the 10 mg/ml MTX solution, and one out of 131 patients receiving the 50 mg/ml MTX solution. Ex. 1011 at 20. Moreover, *Müller-Ladner* acknowledged that "[i]n general, quantity and quality of adverse events did not differ between the two formulations to a relevant extent." *Id.* at 21. Thus, it is unclear how the values of 79.7% and 71.1% were generated with virtually no reports of erythema in either test group. *Id*. In addition, many injection site reactions such as erythema and pain are due to the administrator's conduct, not the administered solution—a factor that *Müller-Ladner* does not appear to address.

Id. Accordingly, *Müller-Ladner* does not provide evidence of actual unexpected results. Schiff Decl. (Ex. 1034) at ¶ 118.

4. *Zackheim* Does Not Teach Away.

During prosecution, Medac argued that *Zackheim* taught away from the invention because that reference describes administering 50 mg of MTX using two 1 ml injections at concentrations of 25 mg/ml rather than a single 50 mg/ml injection. Ex. 1002 at 22, 3/21/12 OA Response.

That argument is false. "A reference does not teach away . . . if it merely expresses a general preference for an alternative invention but does not criticize, discredit, or otherwise discourage investigation into the invention claimed." *Galderma Labs v. Tolmar Inc.*, 737 F.3d 731, 738 (Fed. Cir. 2013). Here, *Zackheim* did not "criticize, discredit, or otherwise discourage" the use of higher concentration MTX solutions. Indeed, *Zackheim* was not directed to, and did not even consider, the question of formulating a higher concentration dosage of MTX. Schiff Decl. (Ex. 1034) at ¶¶ 119-121. Accordingly, *Zackheim* is not evidence of "teaching away." *Id.*

Moreover, *Zackheim* dates to 1992. Subsequent publications including *Grint, Wyeth*, and the combination of *Hoekstra* and *Jørgensen* all taught toward the use of highly concentrated MTX solutions.

5. *Schiff* does not show that the invention is "surprisingly advantageous" over the prior art.

In responding to the Frontier petition, Medac's lawyers also cited to a paper by Koios's expert, Dr. Michael Schiff, as purported evidence that the invention of the '231 patent is "surprisingly advantageous." *See* Schiff Decl. (Ex. 1034) at ¶ 122. As Dr. Schiff makes clear in his declaration, the cited paper shows no such thing. *Id.* Instead, the paper merely shows that there are dosage-specific advantages from using subcutaneous methotrexate rather than oral MTX—a finding that has no relevance to the patentability or novelty of the invention of the '231 patent. *Id.*

VII. THE FACTS AND EQUITIES SUPPORT INSTITUTION UNDER § 325(D)

Koios anticipates that Medac may seek a stay or denial of this Petition in light of the Frontier or the Antares Petitions. Those arguments should be denied.

Koios is not in privity with, and has no relation to, either Frontier or Antares. Noroozi Decl. (Ex. 1035) at ¶ 2. Koios filed this Petition in order to bring a generic equivalent to Rasuvo to market. A stay or denial of this Petition would prejudice Koios's ability to achieve that aim.

Moreover, this Petition introduces new legal and factual arguments, new prior art references (*Wyeth*, *Arthur*, and *Moitra*), and new declarations from different experts than those presented by past petitioners.

Finally, the Antares Petition was terminated via private settlement prior to a final decision, and the Board had not decided whether to institute the Frontier Petition as of the time of this filing. In other words, the Board has never previously adjudicated the merits of any of the arguments and references presented in this Petition, nor was it close to doing so at the time this Petition was filed. *See* IPR2014-01091 Paper 7, Paper 21 at 2 (terminating Antares proceeding while emphasizing the proceeding had "not yet been decided on the merits.").

Koios thus respectfully submits that the facts and equities of this Petition do not warrant a stay or denial under § 325(d). *See* 80 FR 50719 at 50735 (rejecting a "one and done" interpretation of § 325(d) and refusing to adopt a "rigid rule that would require denial and, in effect, bind all challengers to the outcome of a first-filed petition . . . .").

VIII. CONCLUSION.

For the reasons set forth in this Petition and accompanying exhibits, Petitioner respectfully requests *inter partes* review of all claims of the '231 Patent.

Respectfully submitted,

Dated: July 20, 2016

/SCOTT E. KAMHOLZ /
Scott E. Kamholz, M.D., Ph.D.
Registration No. 48,543
Foley Hoag LLP
Counsel for Petitioner

CERTIFICATE OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24 (d), I certify that the present paper contains 13,984 words as counted by the word-processing program used to generate the Petition. This total does not include the table of contents, a table of authorities, grounds for standing, mandatory notices, a certificate of service or word count, or appendix of exhibits or claim listings.

/SCOTT E. KAMHOLZ/
Scott E. Kamholz
Reg. No. 48,543

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. §§ 42.6(e) and 42.105(a) and (b), I certify that on July 20, 2016, a copy of this Petition for *Inter Partes* Review and every exhibit filed with this paper was served on the patent owner at the correspondence address of record (Scully Scott Murphy & Presser, PC, 400 Garden City Plaza, Suite 300, Garden City NY 11530) by email to Edward Grolz at egrolz@ssmp.com, as well as to James F. Haley at James.Haley@ropesgray.com, per Medac's prior consent.

/SCOTT E. KAMHOLZ/
Scott E. Kamholz
Reg. No. 48,543