IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES HOLDINGS LTD., and ROYALTY PHARMA COLLECTION TRUST,	)	
Plaintiffs,	)	
v.	)	Civ. No. 13-1602-SLR (Consolidated)
MYLAN INC., and MYLAN PHARMACEUTICALS INC.,	)	
Defendants.	)	

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OPINION

Dated: July 11, 2016
Wilmington, Delaware

ROBINSON, District Judge

I. INTRODUCTION

This action arises out of the filing of an Abbreviated New Drug Application ("ANDA") by defendants Mylan Pharmaceuticals, Inc. and Mylan, Inc. (collectively, "Mylan") seeking to market generic versions of Savella®, a selective serotonin and norepinephrine reuptake inhibitor ("SNRI") indicated for the management of fibromyalgia. Plaintiffs Forest Laboratories Holdings, Ltd. ("Forest") and Royalty Pharma Collection Trust ("Royalty Pharma") (collectively, "plaintiffs") filed suit against Mylan, alleging infringement of U.S. Patent Nos. 6,602,911 ("the '911 patent"), 7,888,342 ("the '342 patent"), and 7,994,220 ("the '220 patent") (collectively, "the patents-in-suit"). The patents-in-suit are currently assigned to Royalty Pharma (D.I. 1 at ¶¶ 23-25) and Forest is the exclusive licensee (*Id.* at ¶ 27). New Drug Application ("NDA") No. 022256 is directed to the use of Savella® in the management of fibromyalgia and was approved by the FDA on January 14, 2009. (D.I. 1 at ¶ 26) The patents-in-suit are listed in the Food and Drug Administration's ("FDA's") publication titled "Approved Drug Products with Therapeutic Equivalence Evaluations" (known as the "Orange Book") for Savella®. (*Id.*) Plaintiff Forest is the exclusive distributor of Savella® tablets containing 12.5 mg, 25 mg, 50 mg, and 100 mg of the active ingredient milnacipran hydrochloride in the United States. (D.I. 1 at ¶ 27)

Pursuant to 21 U.S.C. § 355(j), Mylan submitted ANDA No. 205367, seeking approval to commercially manufacture, use, and sell generic milnacipran hydrochloride tablets in 12.5 mg, 25 mg, 50 mg, and 100 mg dosage strengths with a paragraph IV certification stating that the patents-in-suit are invalid and not infringed. (Civ. No. 13-

1605, D.I. 1 at ¶¶ 25-26) On August 27, 2013, Mylan informed plaintiffs that an ANDA had been filed and alleged non-infringement and invalidity of claims 1-7 of the '911 patent, claims 1-10 of the '342 patent, and claims 1-7 of the '220 patent. (Civ. No. 13-1604, D.I. 1 at ¶ 27) Plaintiffs responded on September 23, 2013 by filing this suit for infringement of the '911, '342, and '220 patents.

On December 15, 2015, the court held a claim construction hearing and a final pretrial conference. The court subsequently held a six-day bench trial from January 19-26, 2016 on the issues of infringement and validity, and the parties have since completed their post-trial briefing. The 30-month stay of FDA final approval expires on July 14, 2016. The court has jurisdiction over this matter pursuant to 28 U.S.C. §§ 1331, 1338(a), and 1400(b). Having considered the documentary evidence and testimony, the court makes the following findings of fact and conclusions of law pursuant to Federal Rule of Civil Procedure 52(a).[1]

II. FINDINGS OF FACT AND CONCLUSIONS OF LAW

A. The Technology at Issue

1. Technical background and treatments of fibromyalgia

Fibromyalgia, also referred to as fibromyalgia syndrome or "FMS" and previously referred to as fibrositis,[2] is a complex, systemic disorder characterized by widespread musculoskeletal pain, a reduced threshold for pain at specified tender points, fatigue,

[1] To the extent that any findings of fact may be construed as conclusions of law, the court hereby adopts them as such. To the extent that any conclusions of law constitute findings of fact, the court adopts them as such.

[2] The term fibrositis was coined in the early 20th century to describe a chronic musculoskeletal pain condition that was felt to be related to inflammation in peripheral fibrous tissue. (D.I. 276 at 236:22-237:5)

sleep disturbance, cognitive dysfunction, and additional comorbidities to include irritable bowel syndrome and depression. (D.I. 276 at 76:22-77:17, 433:10-14, JTX 099; JTX 101) Patients suffering from FMS are marked by hypersensitivity to external influences and everyday sensations, to include physical contact, clothing, and scents that may not bother individuals without the disorder, leading not only to pain, but the inability of patients to function normally in everyday life. (D.I. 276 at 78:5-16, 76:22-78:1; D.I. 281 at 965:25-966:11) This hypersensitivity also makes treating FMS difficult, as patients with fibromyalgia are particularly susceptible to the side effects associated with drug therapy, typically resulting in the need to start medications on a low dose and slowly increase the dose over time to achieve a therapeutically effective dose. (D.I. 276 at 77:9-78:1; D.I. 278 at 668:7-669:25; D.I. 281 at 965:25-966:24; 978:8-17; 987:2-989:2; 1037:6-20; 582:8-19; JTX 079 at 659, 664; JTX 038 at 104)

By 2001, FMS was well described, but the etiology and pathophysiology of the disease were poorly understood. (D.I. 277 at 434:2-15; D.I. 278 at 682:4-18) Some considered fibromyalgia as "a psychological disorder, or perhaps, a local myofascial pain syndrome," while others believed that fibromyalgia results from dysregulation of pain processing within the central nervous system ("CNS"). (JTX 99 at 161) "This disarray in construct has led to a blurring of the margins of the disorder and the consequent idea that fibromyalgia means something different to every observer." (D.I. 276 at 76:22-78:16; D.I. 278 at 666:8-669:25; JTX 071 at 1-2; JTX 038 at 104)

The lack of a known etiology of fibromyalgia made diagnosing and studying the disorder very difficult. It is not uncommon for patients to seek help from a variety of specialists, including gastroenterologists, neurologists, oral surgeons, and urologists

seeking a diagnosis, with each specialist citing a different condition. (D.I. 278 at 668:11-670:4) It may be years later when a patient seeks help from a pain specialist who diagnoses the patient with fibromyalgia. (*Id.*) The first diagnostic criteria for FMS were established in 1990 by the American College of Rheumatology. (D.I. 277 at 434:2-15) These criteria require: (1) a history of widespread pain for at least three months; and (2) pain in at least 11 of 18 defined tender point sites.[3] (D.I. 277 at 434:16-435:1) Additionally, patients with FMS typically experience a variety of other symptoms, including sleep disturbance, fatigue, stiffness, cognitive dysfunction (fibrofog), and depression. (D.I. 277 at 302:17-22, 344:19-345:2)

Treatment of FMS is tailored to the individual patient and their individual symptoms. Although all FMS patients have pain, physicians must also assess and treat patients' other potential symptoms such as fatigue, cognitive dysfunction, insomnia, nonrestorative sleep, depression, anxiety, and stiffness in order to successfully manage a patient's FMS. (D.I. 277 at 315:3-317:21, 411:2-13) Although there are currently three drugs specifically approved to treat FMS, no single treatment is effective to treat all symptoms of FMS, and individual FMS patients respond differently to treatments. (D.I. 277 at 315:3-317:21, 411:2-13; D.I. 280 at 795:21-23)

Before 2001, physicians were successfully treating FMS patients' symptoms with a variety of compounds. (D.I. 277 at 440:7-17) Antidepressants, particularly tricyclic antidepressants ("TCAs"), were commonly prescribed by doctors. (D.I. 277 at 310:3-10, 316:14-317:17, 440:7-17, 441:5-442:11; D.I. 278 at 730:2-7) Doctors prescribed

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[3] The tender point exam is administered by pressing until blanching in the fingernail bed is achieved, resulting in about 4 kg/cm^2 of pressure. (D.I. 276 at 80:8-19)

TCAs such as amitriptyline, newer compounds such as selective serotonin reuptake inhibitors ("SSRIs"), and the first-approved serotonin and norepinephrine reuptake inhibitor ("SNRI"), venlafaxine. (D.I. 277 at 440:7-17, 764:15-765:19) Amitriptyline, at the time, was the most commonly prescribed drug for the treatment of FMS. (D.I. 277 at 240:24-241:18, 440:7-17)

The majority of studies evaluating pharmacological treatments of FMS focused on antidepressants. (JTX 79; JTX 38) Studies suggested that patients taking antidepressants were four times more likely to improve compared to patients taking placebo and that about 25 percent of all patients taking antidepressants improved. (JTX 79 at 663) Studies of antidepressants for the treatment of FMS recognized improvements in fatigue, sleep, and overall well-being, as well as pain severity. (*Id.* at 664) Amitriptyline and cyclobenzaprine, tricyclic medications that inhibit both serotonin and norepinephrine reuptake, were two of the most studied drugs for the treatment of FMS, and about 33 percent of patients had a clinically meaningful response to the use of these compounds.[4] (D.I. 277 at 446:21-447:3) Given the success of TCAs like amitriptyline, the prior art suggested that "certain symptoms of [FMS] may respond

[4] Serotonin ("5-HT") and norepinephrine (sometimes referred to as "noradrenaline," "NE" or "NA," referred to herein as "NE") are neurotransmitters found in the CNS. The body uses neurotransmitters to send signals between neuronic gaps called synapses (the space between two neurons where neurotransmitters pass from one neuron to the other). When an electrical signal reaches a terminus of a neuron, neurotransmitters are released which migrate the synapse and are recognized on receptors on the post-synaptic neuron. (D.I. 277 at 435:10-437:12) Compounds that inhibit the reuptake of 5-HT and/or NE prevent the clearance of neurotransmitters from the synapse and were known to impact diseases such as depression, anxiety, and FMS. (*Id.*)

better to drugs that primarily affect serotonin, whereas drugs that affect norepinephrine uptake may improve other symptoms." (JTX 62 at 1852; D.I. 277 at 447:17-448:1)

Currently, three drugs are FDA-approved for the management of FMS: (1) Lyrica (pregabalin) was approved in June 2007; (2) Cymbalta (duloxetine) was approved in June 2008; and (3) Savella® (milnacipran) discussed below, was approved in January 2009. Physicians, however, continue to prescribe other drugs off-label to treat the specific symptoms of FMS. (D.I. 277 at 316:14-317:17; DTX 64 at 402-405)

2. Savella® and the development of milnacipran

As previously discussed, plaintiffs' product is known as Savella®. According to plaintiffs, there were no FDA approved treatments for the disease at the time of the filing of the asserted patents, and Savella® was only the third drug approved for the treatment of fibromyalgia in the United States. (D.I. 94 at 1; D.I. 276 at 37:2-7) While milnacipran was approved in Europe for the treatment of depression, it was not approved in the United States for depression or any other indication until the work of the inventors of the patents-in-suit. For this reason, Savella® is designated by the FDA as a new chemical entity ("NCE").

a. Development of milnacipran for depression in France

Milnacipran was originally developed by Pierre-Fabre in France during the 1980s for use as an antidepressant and as a potential replacement for TCAs and SSRIs. (D.I. 277 at 475:11-476:2) SSRIs were originally developed to replace TCAs with the idea of removing receptor interactions associated with TCAs' adverse effects, while maintaining the ability to inhibit the reuptake of 5-HT. (D.I. 277 at 476:3-479:8) As a result of their selectivity, SSRIs exhibit lower rates of adverse events compared to the

TCAs. (JTX 50 at 137; D.I. 277 at 476:17-479:8) However, without the ability to inhibit the reuptake of NE, SSRIs failed to match the TCAs in antidepressant efficacy. (JTX 50 at 137; D.I. 277 at 476:17-479:8) "Milnacipran was thus developed as a new specific 5-HT and norepinephrine reuptake inhibitor (SNRI) with the intention of providing greater antidepressant efficacy than the SSRIs without the side effects of the TCAs." (JTX 50 at 137) By 2001, milnacipran was one of the three SNRIs (with venlafaxine and duloxetine) that were known to be in development or being commercially marketed for depression. (JTX 197)

During the 1990s, Pierre-Fabre conducted numerous clinical trials on milnacipran for depression. (JTX 125 at FOR000278390) Milnacipran was first approved for marketing in France in December 1996 and was approved in 22 other countries between December 1996 and July 2000. (JTX 125 at FOR000278419; D.I. 277 at 324:2-325:5, 475:15-22) By October 2000, milnacipran had been launched in France, Austria, Portugal, Lebanon, Argentina, Russia, Israel, and Japan. (JTX 125 at FOR000278419-20) By late 2001, over 400,000 patients worldwide had been treated with milnacipran, but milnacipran was not approved in the U.S. for depression. (JTX 125 at FOR000278420; D.I. 277 324:2-325:5)

b. Development of milnacipran for FMS

Cypress was a "one-product company" that was "solely dependent" on a product sold for the treatment of rheumatoid arthritis. (DTX 176 at FOR002426897-98) Faced with a declining stock price, Cypress decided to pursue treatments of FMS "with the goal of owning the first product(s) to be approved for this indication." (*Id.* at FOR002426902-03) In October 2000, Dr. Kranzler, the CEO, informed the Board of

Directors that he believed Cypress should pursue FMS treatments. (*Id.*) Dr. Kranzler believed that FMS was an "attractive opportunity" because even if a drug's efficacy was "similar to the drugs that are already out there," an approved drug had "enormous potential" because the drugs being prescribed for FMS, like amitriptyline, were generic with no marketing efforts behind them. (*Id.* at FOR002426904) Similarly, Dr. Kranzler emphasized that there was "no need to invent drugs de novo, as there are simple strategies to develop substances that can be proprietary, yet have already been used for many years, some even for FMS!" (*Id.*) Cypress believed that milnacipran was a good candidate for use in FMS because it could modulate both 5-HT and NE. (JTX 178 at FOR002462034)

c. The labels

i. Savella®

Upon approval of Savella®, the FDA also approved a package insert ("label") that provides guidance and instructions to physicians, pharmacists, and patients on how to use the approved drug, including the indications approved by the FDA, dosage titration schedules, recommended dosage amounts, side effects the patient might experience, contraindications, and results from the clinical trials showing safety and efficacy. (D.I. 276 at 90:16-91:25)

Based on the record, the Savella® label was last revised in January 2015. (JTX 149) The FDA-approved label provides the best and most up-to-date information for safely and effectively using milnacipran. (D.I. 276 at 90:1691:25) The label for Savella® indicates that Savella® contains "milnacipran hydrochloride," which is a "selective norepinephrine and serotonin reuptake inhibitor; it inhibits norepinephrine

uptake with greater potency than serotonin." (JTX 149 at FOR003621963, FOR003621980)

Section 1 of the Savella® label, "Indications and Usage," informs the physician that Savella® is used for the "management of fibromyalgia." (*Id.* at FOR003621963; D.I. 276 at 88:6-15) This is the only FDA-approved indication for milnacipran and physicians understand that the "management of fibromyalgia," as recited in the Savella® label, encompasses treating the symptoms of fibromyalgia presented in a patient, including the chronic pain and fatigue associated with fibromyalgia. (*Id.* at FOR003621963; D.I. 276 at 96:3-97:3)

Section 2.1 of the Savella® label, "Recommended Dosing," recites the following:

> The recommended dose of Savella is 100 mg/day (50 mg twice daily).
>
> Based on efficacy and tolerability dosing may be titrated according to the following schedule:
>
> Day 1: 12.5 mg once
> Days 2-3: 25 mg/day (12.5 mg twice daily)
> Days 4-7: 50 mg/day (25 mg twice daily)
> After Day 7: 100 mg/day (50 mg twice daily)
>
> Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily).
>
> Doses above 200 mg/day have not been studied.

(JTX 149 at FOR003621963; D.I. 276 at 132:8-12) Savella® is available in 12.5 mg, 25 mg, 50 mg, and 100 mg dosages. (JTX 149 at FOR003621961, 65) Additionally, the "FDA Approved Medication Guide" in the label states "[t]ake Savella exactly as your healthcare provider tells you," and the "health care provider will slowly increase your dose . . . . On the first day of treatment, you will take 1 dose of Savella as prescribed." (JTX 149 at FOR003621994; D.I. 276 at 137:1-138:1)

The Savella® label contains data from two pivotal Phase III studies, FMS-031 and MD-02, supporting the safety and efficacy of milnacipran. (JTX 149 at FOR003621984-6; JTX 071; JTX 055; JTX 117; JTX 121; D.I. 276 at 98:21-103:24, 104:21-107:25) Both studies used the dosage escalation schedule found in section 2.1 of the label. (JTX 149 at FOR003621963; JTX 117 at FOR002199012; JTX 121 at FOR003618568) The label reports that both of these studies demonstrate that a greater number of patients taking milnacipran (100 mg/day up to 200 mg/day) showed a statistically significant greater improvement in pain from baseline compared to those receiving placebo. (JTX 149 at FOR003621984-6; JTX 121 at FOR003618545-46; JTX 117 at FOR002198986; D.I. 276 at 98:21-100:5; 973:21-974:11) These studies also demonstrate that the recommended dosing listed in the label (100 mg up to 200 mg) comprise amounts of milnacipran effective to treat the pain associated with fibromyalgia. (D.I. 276 at 98:15-100:5) In addition to assessing pain, the FMS-031 and MD-02 studies assessed the efficacy of milnacipran, as a monotherapy, for the treatment of fatigue in the fibromyalgia patients through the use of the Multidimensional Fatigue Inventory (MFI), and the Patient Global Impression of Change ("PGIC") scale. (JTX 149 at FOR003621985; JTX 121 at FOR003618645-47, FOR003618583; JTX 117 at FOR002199090-92, FOR002199032; D.I. 276 at 226:17-228:13) These studies showed that the patients' fatigue associated with fibromyalgia was improved upon administration of the doses of milnacipran listed in the label (100 mg up to 200 mg). (*Id.*) Plaintiffs, therefore, assert that clinicians reviewing defendants' labels would understand that a reported improvement in "fibromyalgia" includes overall improvement

of the symptoms of the condition, including pain and fatigue, if present. (D.I. 276 at 100:6-12)

ii. Defendants' labels and the accused ANDA product

Defendants seek to market their own generic versions of milnacipran as outlined in Mylan's ANDA, No. 205367. As part of their ANDA, defendants submitted to the FDA their proposed product labels,[5] which provide instructions for the intended use of their products, the recommended dosages, and a titration schedule for administering their generic milnacipran products to patients. (JTX 144) Specifically, defendants' labels state that their "Milnacipran Hydrochloride Tablet is a selective serotonin and norepinephrine reuptake inhibitor (SNRI) indicated for the management of fibromyalgia." (JTX 144 at MYLANMILN-00006077; D.I. 276 at 95:14-96:2) Additionally, defendants' product is directed to human use. (D.I. 276 at 97:4-9) The labels also indicates that the "[r]ecommended dose is 100 mg/day" and that the drug "[m]ay be increased to 200 mg/day based on individual patient response." (JTX 144 at MYLANMILN-00006077; D.I. 276 at 97:19-98:1)

3. The asserted patents

Plaintiffs initially asserted claims 1-3 and 5-7 of the '911 patent, claims 1-10 of the '342 patent, and claims 1-7 of the '220 patent. Post-trial briefing only discusses claims 1, 2 and 7 of the '911 patent, claims 1, 2 and 6 of the '342 patent, and claim 1 of the '220 patent pursuant to the parties' stipulations (D.I. 260). The court will likewise limit its discussion.

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[5] While the Mylan defendants are the sole remaining defendants, the court will refer to defendants' labels in this litigation as plural because multiple defendants were present through trial and post-trial briefing.

a. The '911 patent

The '911 patent, filed December 19, 2001 and issued August 5, 2003, is titled "Methods of Treating Fibromyalgia," and is directed to using milnacipran in treating fibromyalgia syndrome ("FMS") and chronic fatigue syndrome ("CFS"). ('911 patent at Abstract) Specifically, the '911 patent is directed to "administering a therapeutically effective amount of a dual serotonin norepinephrine reuptake inhibitor compound or a pharmaceutically acceptable salt thereof ... characterized by a non-tricyclic structure and an equal or greater inhibition of norepinephrine reuptake than serotonin reuptake." (*Id.*) The specification discusses two distinct concepts, providing a "therapeutic benefit" as opposed to administering the drug "prophylactically." ('911 patent at 8:20-21) As to "therapeutic administration," milnacipran "typically will be administered to a patient already diagnosed with the particular indication being treated." ('911 patent at 8:53-54) In contrast, for "prophylactic administration," the specification makes clear the distinction that milnacipran "may be administered to a patient at risk of developing FMS, CFS, or pain or to a patient reporting one or more of the physiological symptoms of FMS or CFS, even though a diagnosis of FMS or CFS may not have yet been made. Alternatively, prophylactic administration may be applied to avoid the onset of the physiological symptoms of the underlying disorder, particularly if the symptom manifests cyclically." ('911 patent at 8:55-63)

The '911 patent teaches that milnacipran can be administered to FMS patients at a dose of 100 mg/day without titration. ('911 patent at 13:46-50; D.I. 277 495:24-496:16, D.I. 281 at 1033:17-1034:3) In contrast, the '911 patent also provides a titration

schedule for the treatment of diabetic neuropathy in which the dose of milnacipran is increased by 25 mg every three days, reaching 100 mg/day on day 10 as follows:

Day	1	2	3	4	5	6	7	8	9	10	11	12
Dose (mg/day)	25	25	25	50	50	50	75	75	75	100	100	100

('911 patent at 14:35-41; D.I. 277 at 503:8-504:7)

Claim 1 of the '911 patent recites:

> A method of treating fibromyalgia syndrome (FMS) comprising administering to an animal subject suffering from FMS, a composition wherein the active ingredient consists of milnacipran, or a pharmaceutically acceptable salt thereof in an amount effective to treat the chronic pain and fatigue associated with FMS.

('911 patent at 15:13-18) Claim 2 depends from claim 1 and further requires that "the animal subject is a human." ('911 patent at 16:1-2) Claim 7 depends from claim 1 and further requires that "the amount of milnacipran administered is between 100 and 250 mg per day." ('911 patent at 16:14-15)

b. The '342 patent

The '342 patent, filed December 22, 2009 and issued February 15, 2011, is titled "Methods of Treating Fibromyalgia Syndrome, Chronic Fatigue Syndrome and Pain." The '911 and '342 patents are from the same family, share the same effective filing date of November 5, 2001, and contain nearly identical specifications. Like the '911 patent, the '342 patent is directed to the use of milnacipran in treating FMS and CFS. ('342 patent at Abstract)

Claim 1 of the '342 patent recites:

> A method of treating fibromyalgia, the method consisting essentially of administering to a patient in need thereof an effective amount of at least one compound selected from milnacipran, a pharmaceutically acceptable

salt of milnacipran, or a combination thereof, with the proviso that the method excludes administering phenylalanine, tyrosine, or tryptophan.

('342 patent at 19:2-8) Claims 2 and 6 are nearly identical to claim 1, except they specify that doses of 100 and 200 mg per day, respectively, should be used.

c. The '220 patent

The '220 patent, filed September 26, 2006 and issued August 9, 2011, is titled "Milnacipran for the Long-Term Treatment of Fibromyalgia Syndrome," and is directed to the long-term treatment of fibromyalgia, claiming a method of administering milnacipran to patients according to an escalated dose or titration schedule. ('220 patent at Abstract, 14:3-10)

Claim 1 of the '220 patent recites:

A method of treating fibromyalgia in a patient suffering from fibromyalgia comprising administering milnacipran, or a pharmaceutically acceptable salt thereof, to the patient according to the following schedule:

a) administering 12.5 mg milnacipran/dayto the patient for 1 day; then

b) administering 25 mg milnacipran/day to the patient for 2 days; then

c) administering 50 mg milnacipran/day to the patient for 4 days; then

d) administering 100 mg milnacipran/day.

('220 patent at 13:25-26-14:1-10)

B. Claim Construction

1. Standard

Claim construction is a matter of law. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1330 (Fed. Cir. 2005) (en banc). Claim construction focuses on intrinsic evidence - the claims, specification, and prosecution history - because intrinsic evidence is "the most significant source of the legally operative meaning of disputed claim language."

Vitronics Corp. v. Conceptronic, Inc., 90 F.3d 1576, 1582 (Fed. Cir. 1996); *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979 (Fed. Cir. 1995) (en banc), *aff'd*, 517 U.S. 370 (1996). Claims must be interpreted from the perspective of one of ordinary skill in the relevant art at the time of the invention. *Phillips*, 415 F.3d at 1313. In some cases, "the district court will need to look beyond the patent's intrinsic evidence and to consult extrinsic evidence in order to understand, for example, the background science or the meaning of a term in the relevant art during the relevant time period." *Teva Pharm. USA, Inc. v. Sandoz, Inc.*, _ U.S. _, 135 S. Ct. 831, 841 (2015) (citation omitted).

Claim construction starts with the claims and remains centered on the words of the claims throughout. *Interactive Gift Express, Inc. v. Compuserve Inc.*, 256 F.3d 1323, 1331 (Fed. Cir. 2001). In the absence of an express intent to impart different meaning to claim limitations, "the words of a claim are generally given their ordinary and customary meaning," which is "the meaning that the term would have to a person of ordinary skill in the art in question at the time of the invention." *Phillips*, 415 F.3d at 1312-13 (quoting *Vitronics*, 90 F.3d at 1582). "The ordinary meaning may be determined by reviewing various sources, such as the claims themselves, the specification, the prosecution history, dictionaries, and any other relevant evidence. Ultimately, '[t]he only meaning that matters in claim construction is the meaning in the context of the patent.'" *Ruckus Wireless, Inc. v. Innovative Wireless Sols., LLC*, Civ. No. 2015-1425, _ F.3d. _, 2016 WL 3065024, at *3 (Fed. Cir. May 31, 2016). The specification is often "the single best guide to the meaning of a disputed term." *Phillips*, 415 F.3d at 1315.

2. Issues at bar[6]

a. "Comprising administering . . . a composition wherein the active ingredient consists of milnacipran:"[7] "Excludes combination therapy with any other compound that provides a therapeutic benefit whether in the same or a separate dosage form." A review of the prosecution history reveals that the patentees disclaimed combination therapy to obtain allowance of the asserted claims. While claim terms "are generally given their ordinary and customary meaning . . . the prosecution history can often inform the meaning of the claim language by demonstrating how the inventor understood the invention and whether the inventor limited the invention in the course of prosecution, making the claim scope narrower than it would otherwise be." *Phillips*, 415 F.3d at 1312, 1317 (citing *Vitronics*, 90 F.3d at 1582-83) "[W]hen the patentee unequivocally and unambiguously disavows a certain meaning to obtain a patent, the doctrine of prosecution history disclaimer narrows the meaning of the claim consistent with the scope of the claim surrendered." *Biogen Idec, Inc. v. GlaxoSmithKline LLC*, 713 F.3d 1090, 1095 (Fed. Cir. 2013) (citations omitted). "Such statements can take the form of either amendment or argument." *Id.*; *Computer Docking Station Corp. v. Dell, Inc.*, 519 F.3d 1366, 1374 (Fed. Cir. 2008) ("Statements made during prosecution may also affect the scope of the claims."). "The entirety of a patent's file history captures the public record of the patentee's representations concerning the scope and meaning of the claims." *Biogen*, 713 F.3d at 1095.

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[6] The parties indicated at the claim construction hearing that an agreement was reached regarding term 1, "treating fibromyalgia syndrome (FMS)" or "treating fibromyalgia."

[7] Found in claims 1-3 and 5-7 of the '911 patent.

During prosecution, patentee's draft claims included combination therapy. For instance, draft claim 5 read as follows:

> Claim 5: The method according to claim 1, wherein the compound is adjunctively administered with an antidepressant, analgesic, muscle relaxant, anorectics, stimulants, antiepileptic drug, sedatives, hypnotics.

(D.I. 94, Ex. 6 at FOR00000033) Similarly, draft claim 6 included adjunctive administration[8] with "neurontin, pregabalin, pramipexole, 1-DOPA, amphetamine, tizanidine, clonidine, tramadol, morphine, codeine, carbamazepine, sibutramine, amphetamine, valium, or trazodone." *Id.* The examiner, however, rejected these claims in view of PCT Publication No. WO 01/26623 ("WO '623").[9] (D.I. 94, Ex. 7 at FOR000000168-171) In response, patentee cancelled claims 2-6 and amended the remaining claims to remove all forms of combination therapy, stating "[c]laim 1 has been amended to be specific to the administration of a composition containing as the sole active ingredient, milnacipran," and that "[t]he claims to combination therapy have been deleted solely to facilitate prosecution and will be pursued in a continuation application."[10] (D.I. 94, Ex. 8 at FOR000000275)

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[8] The court equates combination therapy and adjunctive administration as both terms relate to the treatment of a disease with multiple therapies.

[9] As discussed infra, defendants proffer U.S. Patent No. 6,441,038 ("the '038 patent" or "Horrobin") as prior art in support of their anticipation and obviousness arguments. The court notes that Horrobin and WO '623 contain substantially the same disclosure. (D.I. 94, Ex. 5; DTX-8) Essentially, WO '623 and Horrobin describe the co-administration of an SNRI with a neurotransmitter precursor. (D.I. 94, Ex. 5 at 1:25, 1:29-2:2)

[10] The continuation application eventually issued as the '342 patent, which disavows combination therapy with neurotransmitters, but includes other forms of combination therapy.

Following an interview with the examiner on March 4, 2003, the patentee further amended the claims and explained that "[a]s discussed at the interview, the claims have been narrowed to define administration of a composition comprising only milnacipran as the active ingredient to treat the pain and fatigue associated with fibromyalgia." (D.I. 94, Ex. 10 at FOR000000308) The examiner then allowed the claims, as amended, in a Notice of Allowability. (D.I. 94, Ex. 11 at FOR000000326) In no way could it be interpreted that the claims as prosecuted and issued include combination therapy. This disavowal in claim scope is unequivocal and unambiguous. *Biogen*, 713 F.3d at 1095.

b. "milnacipran:"[11] "milnacipran or a pharmaceutically acceptable salt thereof." The specification expressly provides for the inclusion of pharmaceutically acceptable salts in the definition of milnacipran as follows:

> Unless otherwise indicated, **milnacipran can include all** stereosisomeric forms, mixtures of stereoisomeric forms, diastereoisomeric forms, and **pharmaceutically acceptable salts** thereof, including both enantiomerically pure forms of milnacipran as well as mixtures of milnacipran enantiomers.

('220 patent at 6:21-25) (emphasis added) This provision is itself dispositive. *Phillips*, 415 F.3d at 1315; *Vitronics*, 90 F.3d at 1582 ("The specification acts as a dictionary when it expressly defines terms used in the claims.").

c. "in an amount effective to treat the chronic pain and fatigue associated with FMS:"[12] "An amount of milnacipran that is effective to treat the

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[11] Found in claim 1 of the '220 patent.

[12] Found in claim 1 of the '911 patent. During expert discovery, defendants' expert, Dr. Zizic, raised a non-infringement argument that implicated a new issue concerning the proper construction of claim 1 of the '911 patent. The parties agreed to submit supplemental briefing and the court agreed to this procedure in its oral order on October 5, 2015.

symptoms of chronic pain and fatigue that are associated with fibromyalgia in a subject that presents with chronic pain, fatigue, or both." According to the claim language, not every patient suffering from fibromyalgia must present with symptoms of both chronic pain and fatigue. Rather, the phrase "in an amount effective to treat the chronic pain and fatigue associated with FMS" indicates that the claimed method is to treat the patient population suffering from FMS, not chronic pain and fatigue. ('911 patent at claim 1)

This is also apparent from the criteria necessary to diagnose FMS as described in the specification. Specifically, FMS "involves the presence of pain for over 3 months duration in all four quadrants of the body, as well as along the spine. In addition, pain is elicited at 11 out of 18 'tender points' upon palpation." ('911 patent at 1:24-29) These criteria do not require the presence of fatigue. Instead, the specification recognizes fatigue as one of the "[o]ther associated symptoms" of FMS along with nonrestorative sleep and memory difficulties. ('911 patent at 1:29-30) Moreover, the specification postulates that "administration of milnacipran to a patient suffering from FMS provides therapeutic benefit not only when the underlying FMS indication is eradicated or ameliorated, but also when the patient reports decreased fatigue, improvements in sleep patterns, and/or a decrease in the severity or duration of pain." ('911 patent at 1:24-29) This "and/or" language indicates that fatigue is not necessarily present in every patient suffering from FMS. In accordance with the specification and claim language, all patients diagnosed with FMS must have chronic pain, but they do not need to have fatigue.

C. Infringement

1. Standard

a. Direct infringement

A patent is infringed when a person "without authority makes, uses or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). To prove direct infringement, the patentee must establish that one or more claims of the patent read on the accused device literally or under the doctrine of equivalents. *See Advanced Cardiovascular Sys., Inc. v. Scimed Life Sys., Inc.*, 261 F.3d 1329, 1336 (Fed. Cir. 2001). A two-step analysis is employed in making an infringement determination. *See Markman*, 52 F.3d at 976. First, the court must construe the asserted claims to ascertain their meaning and scope, a question of law. *See id.* at 976-77; *see also Teva*, 135 S. Ct. at 837. The trier of fact must then compare the properly construed claims with the accused infringing product. *See Markman*, 52 F.3d at 976. This second step is a question of fact. *Spectrum Pharm., Inc. v. Sandoz Inc.*, 802 F.3d 1326, 1337 (Fed. Cir. 2015) (citing *Bai v. L & L Wings, Inc.*, 160 F.3d 1350, 1353 (Fed. Cir. 1998)).

"Direct infringement requires a party to perform each and every step or element of a claimed method or product." *Exergen Corp. v. Wal-Mart Stores, Inc.*, 575 F.3d 1312, 1320 (Fed. Cir. 2009) (quoting *BMC Res., Inc. v. Paymentech, L.P.*, 498 F.3d 1373, 1378 (Fed. Cir. 2007)). "If any claim limitation is absent . . ., there is no literal infringement as a matter of law." *Bayer AG v. Elan Pharm. Research Corp.*, 212 F.3d 1241, 1247 (Fed. Cir. 2000). If an accused product does not infringe an independent claim, it also does not infringe any claim depending thereon. *Ferring B.V. v. Watson Labs., Inc.-Florida*, 764 F.3d 1401, 1411 (Fed. Cir. 2014) (citing *Wahpeton Canvas Co.,*

Inc. v. Frontier, Inc., 870 F.2d 1546, 1552 (Fed. Cir. 1989) ("One who does not infringe an independent claim cannot infringe a claim dependent on (and thus containing all the limitations of) that claim.")). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Monsanto Co. v. Syngenta Seeds, Inc.*, 503 F.3d 1352, 1359 (Fed. Cir. 2007) (quoting *Wahpeton Canvas*, 870 F.2d at 1552) (internal quotations omitted). The patent owner has the burden of proving literal infringement by a preponderance of the evidence. *Octane Fitness, LLC v. ICON Health & Fitness, Inc.*, _ U.S. _, 134 S. Ct. 1749, 1758 (2014).

b. Indirect infringement

To establish indirect infringement, a patent owner has available two theories: active inducement of infringement and contributory infringement. *See* 35 U.S.C. § 271(b) & (c). Liability for indirect infringement may arise "if, but only if, [there is] ... direct infringement." *Limelight Networks, Inc. v. Akamai Technologies, Inc.*, _ U.S. _, 134 S. Ct. 2111, 2117 (2014) (citing *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 365 U.S. 336, 341 (1961) (emphasis omitted)). The patent owner has the burden of proving infringement by a preponderance of the evidence. *Octane Fitness,* 134 S. Ct. at 1758.

Under 35 U.S.C. § 271(b), "whoever actively induces infringement of a patent shall be liable as an infringer." "To prove induced infringement, the patentee must show direct infringement, and that the alleged infringer knowingly induced infringement and possessed specific intent to encourage another's infringement." *Toshiba Corp. v. Imation Corp.*, 681 F.3d 1358, 1363 (Fed. Cir. 2012) (quoting *i4i Ltd. P'ship. v. Microsoft Corp.*, 598 F.3d 831, 851 (Fed. Cir. 2010) (internal quotation marks omitted)).

"[I]nduced infringement under § 271(b) requires knowledge that the induced acts constitute patent infringement." *Global-Tech Appliances, Inc. v. SEB S.A.*, 563 U.S. 754, 766 (2011). The knowledge requirement can be met by a showing of either actual knowledge or willful blindness. *See id.* "[A] willfully blind defendant is one who takes deliberate actions to avoid confirming a high probability of wrongdoing and who can almost be said to have actually known the critical facts." *Id.* at 769 (citation omitted). "[I]nducement requires evidence of culpable conduct, directed to encouraging another's infringement, not merely that the inducer had knowledge of the direct infringer's activities." *DSU Medical Corp. v. JMS Co., Ltd.*, 471 F.3d 1293, 1306 (Fed. Cir. 2006) (en banc in relevant part) (citations omitted).

To establish contributory infringement, the patent owner must demonstrate the following: (1) an offer to sell, sale, or import; (2) a component or material for use in a patented process constituting a material part of the invention; (3) knowledge by the defendant that the component is especially made or especially adapted for use in an infringement of such patents; and (4) the component is not a staple or article suitable for substantial non-infringing use. *See Fujitsu Ltd. v. Netgear Inc.*, 620 F.3d 1321, 1326 (Fed. Cir. 2010) (citing 35 U.S.C. § 271(c)). Defendant "must know 'that the combination for which his component was especially designed was both patented and infringing.'" *Global-Tech*, 563 U.S. at 763 (citing *Aro Mfg. Co. v. Convertible Top Replacement Co.*, 377 U.S. 476, 488 (1964)).

2. Induced infringement

a. The '911 patent

Defendants assert that they do not induce infringement of the asserted claims of the '911 patent because they do not instruct physicians to use milnacipran only as a monotherapy treatment. The court disagrees. Milnacipran is the only drug listed in defendants' labels for the management of fibromyalgia. The clinical studies described in the labels were performed using milnacipran as a monotherapy. Neither plaintiffs nor defendants could instruct doctors that milnacipran was approved for combination therapy because no such studies were submitted to the FDA and no such approval has been obtained. Consequently, the court finds that defendants' labels will "inevitably lead some consumers to practice" the label's recommended use of milnacipran for the monotherapy treatment of fibromyalgia." *AstraZeneca LP v. Apotex, Inc.*, 633 F.3d 1042, 1060 (Fed. Cir. 2010) (holding generic defendant liable for induced infringement where label would "inevitably lead some consumers to practice the claimed method"); *Eli Lilly & Co. v. Actavis Elizabeth LLC*, 435 F. App'x 917, 926 (Fed. Cir. 2011) ("We have long held that the sale of a product specifically labeled for use in a patented method constitutes inducement to infringe that patent, and usually is also contributory infringement."). In sum, defendants have the requisite intent to induce infringement of claims 1, 2, and 7 of the '911 patent.

b. The '342 patent

Turning to the '342 patent,[13] defendants' labels recommend "100 mg" or "200 mg" of "milnacipran," which is an "effective amount" for "treating fibromyalgia" in "a patient in need thereof." (JTX 144 at MYLANMILN00006077; D.I. 276 at 122:8-123:2,

[13] Defendants have stipulated that if they are found to infringe claims 1, 2, and 6 of the '342 patent, they will stipulate to infringement of claims 3-5 and 7-10. (D.I. 260)

126:17-127:18) The dispute between the parties pertains to the proviso that the method excludes administering phenylalanine, tyrosine, or tryptophan. Unlike the '911 patent, the '342 patent is not limited to monotherapy. Rather, the '342 patent allows for both monotherapy and combination therapy for treatment of fibromyalgia, so long as the other drug used in combination is not phenylalanine, tyrosine, or tryptophan. (D.I. 94 at 3-8, 11-19; D.I. 112 at 2-5, 6-10; D.I. 282 at 16:1-32:14, 39:4-41:16, 43:14-18, 43:20-50:18, 62:6-23)

Defendants suggest that their products will be used with these amino acids and that their labels do not specifically instruct to avoid these amino acids; therefore, they cannot be held liable for inducing infringement of the asserted claims. In reality, defendants' labels specifically warn against the co-administration of serotonergic agents such as "triptans, tricyclic antidepressants, fentanyl, lithium, tramadol, tryptophan, buspirone and St. John's Wort," and with drugs that impair metabolism of serotonin. (JTX 144 at MYLANMILN-00006077; D.I. 276 at 123:11-125:11) Moreover, defendants' labels actually warn against using milnacipran with phenylalanine, tyrosine, or tryptophan, stating that such combinations could lead to potentially life-threatening side effects and such combinations could be potentially very dangerous for fibromyalgia patients. (JTX 144 at MYLANMIILN00006084 (§ 5.2 "Serotonin Syndrome"), MYLANMILN-00006093 (§ 7.4 "Catecholamines"); D.I. 276 at 123:13-126:13)

Dr. Argoff, plaintiffs' expert, explained that the co-administration of phenylalanine or tyrosine, both of which are norepinephrine precursors (DTX 8 at 7:42-53), with milnacipran could cause "terrible adverse consequences" due to the increases in norepinephrine. (D.I. 276 at 125:12-126:8) Defendants' labels in section 7.4

"Catecholamines," warn that concomitant use of milnacipran with norepinephrine "may be associated with paroxysmal hypertension and possible arrhythmia." (JTX 144 at § 7.4 MYLANMILN00006093) Dr. Argoff testified that he did not prescribe milnacipran with phenylalanine, tyrosine, or tryptophan, nor was he aware of any other physician to have knowingly prescribed any of these combinations. (D.I. 276 at 125:6-14, 126:3-8) Given the explicit warnings of potentially life-threatening side effects if milnacipran were combined with phenylalanine, tyrosine, or tryptophan, defendants' labels cannot be read to condone such combinations.[14]

c. The '220 patent

Defendants contend that they do not instruct physicians or patients to follow the titration schedule on their labels because the titration schedule is preceded by the following sentence: "Based on efficacy and tolerability, dosing **may** be titrated according to the following schedule."[15] (JTX 144 at MYLANMILN00006079; D.I. 276 at 266:5-19) (emphasis added) However, both defendants' labels and plaintiffs' Savella® label include the very titration schedule recited in claim 1 of the '220 patent. Claim 1 of the '220 patent recites the following titration schedule:

> a) administering 12.5 mg milnacipran/dayto the patient for 1 day; then

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[14] Indeed, defendants presented no credible evidence that patients do in fact use milnacipran with amino acids to treat their fibromyalgia. Dr. Zizic's testimony that "a lot" of his patients use nutraceuticals, including these amino acids, in the treatment of their fibromyalgia is not supported by any objective evidence and does not provide a sufficient or credible basis to allow defendants to avoid liability for induced infringement. (D.I. 277 at 377:20-379:20)

[15] Defendants stipulated that if they are found to infringe claim 1 of the '220 patent, they will stipulate to infringement of claims 2-7. (D.I. 290)

b) administering 25 mg milnacipran/day to the patient for 2 days;
then
c) administering 50 mg milnacipran/day to the patient for 4 days;
then
d) administering 100 mg milnacipran/day.

('220 patent at 13:25-26-14:1-10), whereas defendants' labels recite the following titration schedule:

> **2.1 Recommended Dosing**
> The recommended dose of milnacipran hydrochloride tablets is 100 mg/day (50 mg twice daily).
>
> Based on efficacy and tolerability dosing may be titrated according to the following schedule:
>
> **Day 1:** 12.5 mg once
>
> **Days 2 to 3:** 25 mg/day (12.5 mg twice daily)
>
> **Days 4 to 7:** 50 mg/day (25 mg twice daily)
>
> **After Day 7:** 100 mg/day (50 mg twice daily)
>
> Based on individual patient response, the dose may be increased to 200 mg/day (100 mg twice daily).

(JTX 144 at MYLANMILN00006077; D.I. 276 at 129:21-130:6, 133:9-136:2) The titration schedule reflected on defendants' labels is the only schedule the FDA evaluated and has deemed safe and effective for the initiation of treatment with milnacipran.[16] (D.I. 276 at 132:16-133:8) This is particularly important due to the increased susceptibility of fibromyalgia patients to the side effects of drug therapy, further warranting the use of the labeled titration schedule. (D.I. 276 at 130:10-25, 965:25-966:11)

[16] Of note, the FDA, in reviewing two Phase III clinical trials for milnacipran in the treatment of fibromyalgia, concluded that the safe and efficacious treatment of fibromyalgia using milnacipran required inclusion of the titration schedule on the Savella® label. (D.I. 276 at 138:15-20; 130:22-25; 145:11-146:5)

The Federal Circuit has established that "[t]he pertinent question is whether the proposed label instructs the users to perform the patented method. If so, the proposed label may provide evidence of [the generic's] affirmative intent to induce infringement." *AstraZeneca*, 633 F.3d at 1060. The Federal Circuit has also explained that it is irrelevant that some users may not specifically perform the patented method. *Id.* In this regard, the Federal Circuit held:

> Even if Apotex were correct that the downward-titration language[17] may be applied to other dosing regimens, the language is still applicable to the recommended starting doses and, as correctly determined by the district court, would inevitably lead some consumers to practice the claimed method.

Id. The Federal Circuit rejected Apotex's argument that it lacked specific intent because it was required by the FDA to include the downward-titration language, explaining that Apotex's decision to proceed with distributing its product, despite the label presenting infringement problems, reflects Apotex's intent to induce, as Apotex could have submitted a Paragraph III certification and waited for the asserted patents to expire.[18] *Id.* "The question is not ... whether a user following the instructions may end

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[17] The label stated " '[i]n all patients, it is desirable to downward-titrate to the lowest effective dose once asthma stability is achieved' and '[o]nce the desired clinical effect is achieved, consideration should be given to tapering to the lowest effective dose." *AstraZeneca*, 633 F.3d at 1047.

[18] The Hatch-Waxman Act requires each ANDA applicant to certify that (1) the Orange Book contains no patent information relevant to their ANDA ("Paragraph I certification"), (2) the listed patents have expired ("Paragraph II certification"), (3) the applicant will not enter the market until the listed patents expire ("Paragraph III certification"), or (4) the applicant believes that the listed patents are invalid or will not be infringed by the applicant's generic compositions ("Paragraph IV certification"). 21 U.S.C. § 355(j)(2)(A)(vii)(I)-(IV) (2006). The Act specifies that filing an ANDA containing a Paragraph IV certification constitutes an act of infringement. 35 U.S.C. § 271(e)(2) (2006); *AstraZeneca,* 669 F.3d at 1374 (citation omitted). Where the Orange Book lists a method of use patent that "does not claim a use for which the applicant is seeking approval," an applicant may instead submit a statement under 21 U.S.C. §

up using the device in an infringing way. Rather, it is whether [the] instructions teach an infringing use of the device such that we are willing to infer from those instructions an affirmative intent to infringe the patent." *Vita-Mix Corp. v. Basic Holding, Inc.*, 581 F.3d 1317, 1329 n.2 (Fed. Cir. 2009); *Bayer Schering Pharma AG v. Lupin, Ltd.*, 676 F.3d 1316, 1322 (Fed. Cir. 2012) ("The question to be answered, then, is whether the FDA has approved the use of Yasmin to achieve the combination of the three effects claimed in the '652 patent.").

Defendants attempt to distinguish the use of the word "may" in its labels from the "consideration should be given to" language on the label at issue in *AstraZeneca.* But in the context of induced infringement, it is a distinction without a difference. Defendants are essentially advancing the same argument that was rejected in *AstraZeneca,* namely, that permissive language in the labels allows them to escape induced infringement. The crux of induced infringement is that defendants have included the exact titration schedule as claimed in the '220 patent and have made no effort to remove the titration schedule from the labels or submit a Paragraph III certification and wait for the asserted patents to expire. (D.I. 277 at 386:25-387:13)

Like the defendant in *AstraZeneca*,[19] there is no evidence that defendants at bar made any efforts to contact the FDA in an attempt to remove or modify their labels.

355(j)(2)(A)(viii) averring that the ANDA excludes all uses claimed in the patent ("Section viii statement"). *Id.* (citing *Warner-Lambert*, 316 F.3d 1348, 1360-61 (Fed. Cir. 2003)).

[19] AstraZeneca's label for its drug Pulmicort Respules® (budesonide), indicated that the drug may be administered once or twice daily. AstraZeneca's patents, however, were directed to "once daily" treatment. *AstraZeneca*, 633 F.3d at 1047. For this reason, Apotex submitted an ANDA to sell generic budesonide along with a "section viii statement" indicating that it was **not** seeking approval for the once daily method of use claimed in AstraZeneca's patents, "and that its proposed generic label

(D.I. 277 at 386:25-387:13) There is also no evidence in the record that defendants sought permission to sell only the 50 mg and 100 mg dosage strengths. (D.I. 277 at 388:6-9) To the contrary, it appears defendants intend to sell 12.5 mg, 25 mg, 50 mg, and 100 mg tablets of milnacipran, the very dosage strengths needed to follow the titration schedule claimed in the '220 patent and reflected on defendants' labels. (JTX 144 at MYLANMILN00006077, 78; D.I. 276 at 136:3-21) The experts agreed that physicians and patients could follow the labeled titration schedule using the dosage forms defendants intend to sell.[20] (D.I. 276 at 136:3-21, 145:21-146:9, 147:15-151:9, D.I. 277 at 391:9-392:12) According to Federal Circuit precedent, therefore, defendants induce infringement of the '220 patent because doctors and patients will inevitably follow the titration schedule on defendants' labels using defendants' available dosage strengths according to the claimed method.

3. Contributory infringement

a. The '911 patent

Defendants contend that there are several substantial non-infringing uses, including the use of their milnacipran products in combination with another drug to treat fibromyalgia. As discussed above, however, the use of milnacipran in combination with

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would contain no explicit mention of once-daily administration." *Id.* Nevertheless, Apotex's label kept in language from AstraZeneca's label that "[o]nce the desired clinical effect is achieved, **consideration should be given** to tapering to the lowest effective dose." *Id.* at 1047. (emphasis added) This language was presumably there to avoid any adverse effects from excessive use of the medication. Apotex's label also included two strengths, 0.25 mg and 0.5 mg per 2 mL vial. *Id.*

[20] Dr. Zizic, defendants' expert and a physician who has never published on fibromyalgia nor considered the condition to be a focus of his practice, testified that there was "no sound medical reason" to use the titration schedule. (D.I. 276 at 278:3-7) Even if such testimony were credible, the labels belie his opinion.

another drug for the management of fibromyalgia would be an off-label use that cannot constitute a substantial non-infringing use. Notably, both Dr. Zizic and Dr. Argoff agreed that neither plaintiffs nor defendants would be permitted to market milnacipran in combination therapy. (D.I. 276 at 109:2-110:2; 112:1-113:24; 355:10-24; 371:3-9); *Eli Lilly*, 435 F. App'x at 927. Defendants presented no credible evidence concerning the extent to which milnacipran is actually used in combination with another drug.[21]

b. The '342 patent

Defendants contend that they do not contribute to the infringement of the asserted claims because their products can be used in combination with phenylalanine, tyrosine, or tryptophan. Here again, such use would be off-label and, thus, cannot constitute a substantial non-infringing use. (D.I. 277 at 355:18-24, 368:6-370:1, 371:3-9, 374:1-14); *Eli Lilly*, 435 F. App'x at 927. Moreover, no evidence has been presented that milnacipran has ever been combined with phenylalanine, tyrosine, or tryptophan. To this point, Dr. Zizic testified that his approximately 30-40 fibromyalgia patients also take nutraceuticals, including essential amino acids, leading Dr. Zizic to conclude that "it has to be a lot" of patients taking milnacipran in combination with phenylalanine, tyrosine, or tryptophan. (D.I. 277 at 377:20-379:20) In contrast, Dr. Argoff testified that

[21] DTX 77, relied on by Dr. Zizic, is a slide presentation dated March 3, 2009, which was prior to the approval date of Savella®. This exhibit, then, cannot provide information as to the prevalence of using milnacipran in combination therapy. (DTX 077; D.I. 277 at 362:4-363:12) Dr. Zizic also relied on Dr. Mease's publication (JTX 071), a report regarding one of the Phase III clinical trials of milnacipran. This paper, however, reports the results of the FMS-031 clinical trial in which milnacipran was not used in combination with other drugs. (JTX 071 at 3; JTX 121A at Title, FOR003618540; D.I. 276 at 100:18-101:19) The paper provides no information as to the actual use of milnacipran in combination with another drug, but merely suggests that such studies may be conducted in the future. (D.I. 277 at 366:14-370:1)

he has not combined milnacipran with these three compounds, nor is he aware of any physicians prescribing such a combination. (D.I. 276 at 125:6-126:8) Dr. Zizic's conclusory testimony falls far short of establishing that the combination of milnacipran with phenylalanine, tyrosine, or tryptophan constitutes a substantial non-infringing use.

c. The '220 patent

Defendants' labels indicate that patients using the products are to be titrated and that treatment should be initiated with the exact titration schedule found in claim 1 of the '220 patent. (JTX 144 at MYLANMILN-00006077, 79, 109) There is no other titration schedule on the labels, and the basis for approval was solely based on the two pivotal Phase III clinical trials (FMS-032 and MD-02) that used the titration schedule claimed in the '220 patent. (D.I. 276 at 132:4-133:8; 139:18-19) Accordingly, and contrary to defendants' assertions, the use of any other titration schedule would be considered an "off-label" use. Dr. Argoff testified that, although physicians "have always had-have the ability to prescribe in a manner he or she feels is best for the interests of the person he or she is treating," defendants' labels nevertheless provide instruction for use of only one titration schedule and, therefore, any other use "would be an off-label titration." (D.I. 276 at 138:21-141:21)

Defendants rely on testimony from William Kane, a Forest employee in his personal capacity, regarding what and what does not constitute an off-label titration schedule. According to plaintiffs, his testimony was directed to whether clinicians "can make their own choices as to how they use the drug." (D.I. 283 at 1250:15-23; D.I. 276 at 69:2-3, 69:5-11) Plaintiffs assert that Mr. Kane specifically testified that Forest representatives could not promote titration schedules different from the labels. (*Id.*)

Accordingly, this falls squarely within the reasoning of *Eli Lilly*, where the Federal Circuit held that uses that could not be marketed or promoted by the company cannot be considered a substantial non-infringing use. *Eli Lilly*, 435 F. App'x at 927 (citing 21 C.F.R. § 202.1(e)(4)). Defendants fail to offer any evidence that the FDA considered alternative schedules to be safe and effective, or that plaintiffs would be permitted to instruct physicians to use a different schedule. Consequently, an alternative titration schedule cannot constitute a substantially non-infringing use. *Eli Lilly*, 435 F. App'x at 927.

D. Invalidity

Defendants argue that Horrobin anticipates and, therefore, invalidates the asserted claims of the '911 and '342 patents as it discloses each and every asserted limitation. Along with asserting the '911 patent as prior art to the '220 patent, defendants offer 10 prior art references in support of their obviousness arguments. As to the '911 and '342 patents, defendants rely on two combinations: (1) the Horrobin, Dwight, Barkin, and WO '223 references; and (2) the Goldenberg and Fishbain references combined with Briley II and Kasper. Regarding the '220 patent, defendants argue the asserted claim would have been obvious in combination with the '691 publication, the '911 patent, and Ansseau.

Plaintiffs argue that rather than providing a coherent explanation supported by sufficient evidence, defendants present a "shotgun approach," relying on a variety of different theories based on multiple prior art publications.[22] Defendants sought to use

[22] The court characterizes defendants' invalidity arguments as throwing spaghetti at the proverbial post trial wall, noodling together snippets from a plethora of prior art hoping that something will stick.

the inventors' own thought processes and later post-filing publications to provide a road map to the prior art. Plaintiffs contend that this approach is forbidden by the Patent Act, where an inventor's own thought process cannot be used to show the obviousness of a claimed invention. *Life Techs., Inc. v. Clontech Labs., Inc.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) (citing 35 U.S.C. § 103(a)) ("[T]he path that leads an inventor to the invention is expressly made irrelevant to patentability by statute."); *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) ("The inventor's own path itself never leads to a conclusion of obviousness; that is hindsight. What matters is the path that the person of ordinary skill in the art would have followed, as evidenced by the pertinent prior art.").

The court recognizes at the outset that the record demonstrates that in 2001 and continuing through today, fibromyalgia is a complex disease treated by various medications with different mechanisms of action. At this time, there appears to be no concrete understanding of the cause(s) of fibromyalgia, let alone a clear course of treatment. At best, the teaching of the art was and is multidirectional, with no clear motivation to pursue milnacipran as an effective treatment for fibromyalgia. Notably, there were no FDA-approved treatments for fibromyalgia at the time of the patents-in-suit. Consequently, the inventors' development of treating fibromyalgia with milnacipran was the antithesis of anticipation and obviousness as discussed in more detail below.

1. Anticipation

a. Standard

Under 35 U.S.C. § 102(b), "[a] person shall be entitled to a patent unless the invention was patented or described in a printed publication in this or a foreign country . . . more than one year prior to the date of the application for patent in the United States." The Federal Circuit has stated that "[t]o anticipate a claim, a single prior art reference must expressly or inherently disclose each claim limitation." *Finisar Corp. v. DirecTV Grp. Inc.*, 523 F.3d 1323, 1334-35 (Fed. Cir. 2008) (quoting *Celeritas Techs., Ltd. v. Rockwell Int'l Corp.*, 150 F.3d 1354, 1361 (Fed. Cir. 1998)). "Anticipation requires that the reference describe not only the elements of the claimed invention, but also that it describe those elements arranged as in the claim." *Enfish, LLC v. Microsoft Corp.*, _ F.3d _, Civ. No. 2015-1244, 2016 WL 2756255, at *11 (Fed. Cir. May 12, 2016) (internal quotations omitted).

"The explicit claim limitations must be considered in [the] determination of anticipation." *In re Schreiber*, 128 F.3d 1473, 1481 (Fed. Cir. 1997). In determining whether a patented invention is explicitly anticipated, "the proponent must show 'that the four corners of a single, prior art document describe every element of the claimed invention,'" "arranged or combined in the same way as in the claim." *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1370 (Fed. Cir. 2008). The claims are read in the context of the patent specification in which they arise and in which the invention is described. *Glaverbel Societe Anonyme v. Northlake Mktg. & Supply, Inc.*, 45 F.3d 1550, 1554 (Fed. Cir. 1995). The prior art need not be ipsissimis verbis (i.e., use identical words as those recited in the claims) to be anticipating. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716 (Fed. Cir. 1984).

"A reference may anticipate inherently if a claim limitation that is not expressly disclosed is necessarily present, or inherent, in the single anticipating reference." *In re Montgomery*, 677 F.3d 1375, 1379-80 (Fed. Cir. 2012) (internal quotations omitted). The Federal Circuit has explained that an inherent limitation is one that is necessarily present and not one that may be established by probabilities or possibilities. *Id.* at 1379 (citations omitted). "The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Bettcher Indus., Inc. v. Bunzl USA, Inc.*, 661 F.3d 629, 639 (Fed. Cir. 2011) (quotation omitted). The Federal Circuit has also observed that "[i]nherency operates to anticipate entire inventions as well as single limitations within an invention." *Schering Corp. v. Geneva Pharms. Inc.*, 339 F.3d 1373, 1380 (Fed. Cir. 2003). Moreover, recognition of an inherent limitation by a person of ordinary skill in the art before the critical date is not required to establish inherent anticipation. *Id.* at 1377.

An anticipation inquiry involves two steps. First, the court must construe the claims of the patent in suit as a matter of law. Second, the finder of fact must compare the construed claims against the prior art. *In re Montgomery*, 677 F.3d at 1379. Anticipation, an invalidity defense, must be proven by clear and convincing evidence. *Microsoft Corp. v. i4i Ltd. P'ship.*, 564 U.S. 91, 95 (2011).

b. Discussion

i. Horrobin

U.S. Patent No. 6,441,038 (DTX 8) ("Horrobin"), filed on October 12, 2000[23] and issued on August 27, 2002, is titled "Treatment of Fatigue, Head Injury, and Stroke" and generally teaches and claims the use of noradrenergic drugs, including milnacipran, in combination with the noradrenaline precursors, phenylalanine and tyrosine, to treat neurologic diseases, including FMS. (DTX 8 at 3:20-27; D.I. 277 at 472:1-474:7) Horrobin states that the noradrenergic drug and the noradrenaline precursor may be combined in one dosage form or may be prepared in separate dosage forms. (DTX 8 at 8:38-42) Although Horrobin focuses on improving the use of noradrenergic compounds with the co-administration of the precursors, Horrobin also teaches that the "noradrenergic compounds," including milnacipran, demonstrate some efficacy when administered alone. (DTX 8 at 6:36-40; D.I. 277 at 474:8-475:10) Specifically Horrobin states:

> [The] effects of noradrenergic compounds alone are important but relatively modest. Our concept of combining a noradrenergic drug like lofepramine or desipramine, together with a noradrenaline precursor such as phenylalanine or tyrosine, is much more effective.

(DTX 8 at 6:36-40; D.I. 277 at 474:18-475:10) Horrobin additionally teaches and claims the use of the two other known SNRIs, venlafaxine and duloxetine, in combination with the noradrenaline precursors for the treatment of neurologic diseases such as FMS. (DTX 8 at Abstract, claim 10; D.I. 277 at 473:12-474:7)

ii. Analysis

[23] As it was filed prior to the unopposed earlier date of invention asserted by plaintiffs for the '911 and '342 patents, Horrobin is considered prior art pursuant to 35 U.S.C. § 102(e).

The court notes as an initial matter that Horrobin was extensively considered by the U.S. Patent and Trademark Office ("PTO") during prosecution of the '911 and '342 patents. (JTX 004 at FOR000000168-71, 236-41, 275-83, 288-90, 308-15, JTX 005 at FOR000000558-85) Not only do defendants have to overcome the presumption of validity with clear and convincing evidence, but "ha[ve] the added burden of overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents." *Shire LLC v. Amneal Pharm., LLC*, 802 F.3d 1301, 1307 (Fed. Cir. 2015) (quoting *PowerOasis, Inc. v. T–Mobile USA, Inc.*, 522 F.3d 1299, 1304 (Fed. Cir. 2008)). Nonetheless, defendants designate Horrobin as the most important piece of prior art for the court's consideration.

Defendants' anticipation argument rests on the sentence in Horrobin that states "[t]hese effects of noradrenergic compounds alone are important but relatively modest," and relies on the testimony of a chemist with no experience in fibromyalgia or with treating patients. (DTX 8 at 6:36-37; D.I. 277 at 429:2-6, 473:8-475:10, 481:6-484:17) This argument encompasses several flaws: (1) Horrobin teaches away from using any drug unless used in combination with certain amino acids; (2) the '342 patent recites a method of treating FMS in a patient without disclosing the specific amino acids described in Horrobin ('342 patent at claim 1; JTX 5 at FOR000000557-586); and (3) as per the court's claim construction, the '911 patent applicants reached an agreement with the examiner that the asserted claims are limited to monotherapy, or the "exclusion

of a second compound."[24] (*See also* JTX 4 at FOR000000290, D.I. 94 at 11-17; D.I. 112 at 6-10; D.I. 282 at 18:4-22:19; '911 patent at claim 1)

Moreover, the sentence relied on by defendants does not relate to the treatment of fibromyalgia. Rather, the sentence at issue relates to the "effects" of the "noradrenergic compounds" on stroke and brain injury. (D.I. 278 at 726:2-728:8) "Case History No. 1" is instructive where Horrobin reports that the patient in question

> developed multiple aches and pains throughout her body, characteristic of fibromyalgia, and an irritable bowel in which painful spasms alternated with constipation. She was given almost all conceivable treatments over the years, including many types of non-steroidal anti-inflammatory drugs, both tricyclic and serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants, and even steroids. Some of these treatments produced transient effects but these never lasted.

(DTX 8 at 5:51-59) Consequently, Horrobin states that treatment with certain drugs, including monotherapy with TCAs as well as serotonin reuptake inhibiting and noradrenaline reuptake inhibiting antidepressants, were unsuccessful for fibromyalgia and irritable bowel. (D.I. 278 at 566:19-567:17) In other words, the use of the compounds identified in Case History No. 1 alone did not work to treat the patient's fibromyalgia.

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[24] This agreement was reached to overcome the portion of Horrobin that specifically discloses that the active drug and amino acid can either be in one pill or two pills. (JTX 4 at FOR000000290; DTX 8 at 8:37-44) Following the agreement, and as discussed in the claim construction analysis, Forest submitted the following amendment: "As discussed at the interview, the claims have been narrowed to define administration of a composition comprising **only milnacipran** as the active ingredient to treat the pain and fatigue associated with fibromyalgia. The combination claims will be pursued in a continuation application." (JTX 4 at FOR000000308)

Regarding the statement that "[t]he implications are important in stroke and brain injury which have remained depressingly resistant to the development of pharmacological interventions" (DTX 8 at 5:66-6:1), Horrobin explains:

> Treatment with noradrenaline facilitates recovery in animals from such lesions and there is preliminary evidence that there may be beneficial effects in humans . . . . Of particular interest, desipramine, which is a metabolite of lofepramine, is able to enhance LC function and recovery of motor function after brain lesions: in contrast, drugs acting on the serotonin system have much smaller effects . . . .These effects of noradrenergic compounds alone are important but relatively modest. Our concept of combining a noradrenergic drug like lofepramine or desipramine, together with a noradrenaline precursor such as phenylalanine or tyrosine, is much more effective.

(*Id.* at 6:8-40 (citations omitted)) Accordingly, when read in context, the phrase "these effects" refer to the effects in brain lesions discussed in the previous sentences, not the effects in fibromyalgia. (D.I. 278 at 726:6-728:8) More importantly, an effective treatment involves the combination of a noradrenergic drug like lofepramine or desipramine, **together** with a noradrenaline precursor such as phenylalanine or tyrosine.[25] In other words, Horrobin teaches that norepinephrine reuptake inhibiting drugs must be given in combination with certain amino acids to be effective. Consequently, Horrobin does not describe milnacipran as being effective as a monotherapy treatment for fibromyalgia in accordance with the claimed method.

The court also notes that the asserted claims of the '911 and '342 patents require an effective treatment for fibromyalgia in a patient suffering from the disease,

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[25] Further, when Horrobin refers to "noradrenergic compounds," it is very likely referring to compounds such as "desipramine" and "lofepramine," particularly as these are the two compounds specifically discussed in the preceding and immediately following text. (DTX 8 at 6:21-22, 6:36-40) Horrobin states that these compounds have an effect on norepinephrine "ten times" larger than for serotonin and are taught to be the most effective.

i.e., that actually treats the disease in a meaningful way. ('911 patent at claim 1; '342 patent at claim 1) Both patents refer to an effective treatment as one that actually treats the underlying fibromyalgia and its associated symptoms. ('911 patent at 2:40-42, 8:19-34; '342 patent at 2:46-58, 8:35-50) "Relatively modest" effects are not an "effective" treatment within the meaning of the asserted claims and, therefore, cannot anticipate.

Lastly, the court will address defendants' contention that the sentence discussing the modest effects of "noradrenergic compounds alone" was overlooked by the PTO. During prosecution of the '342 patent, applicants conducted an interview with the examiner and submitted a declaration of co-inventor Dr. Rao addressing this issue, informing the examiner that Horrobin was referring to the effects in stroke and brain injury: "Moreover, Dr. Rao clarified the record explaining that Loder [Horrobin] was referring to improvements in motor function in stroke/brain injury models, not fibromyalgia or pain, when it stated that noradrenergic compounds could have relatively modest effects in patients." (JTX 5 at FOR000000559-560, FOR000000563-585) Therefore, it appears that the examiner considered the very same argument now raised by defendants but nevertheless allowed the patent to issue.

Overall, defendants fail to present clear and convincing evidence that Horrobin anticipates, particularly in light of the enhanced burden as a result of Horrobin having been considered by the PTO during prosecution of the '911 and '342 patents. The court concludes that defendants' proffered arguments and evidence are neither credible nor persuasive. Consequently, defendants have not demonstrated that the '911 and '342 patents are invalid as anticipated by Horrobin.

2. Obviousness

a. Standard

"A patent may not be obtained . . . if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art." 35 U.S.C. § 103(a). Obviousness is a question of law, which depends on underlying factual inquiries.

> Under § 103, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented.

KSR Int'l Co. v. Teleflex Inc., 550 U.S. 398, 406 (2007) (quoting *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 17-18 (1966)).

"[A] patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art." *KSR*, 550 U.S. at 418. Likewise, a defendant asserting obviousness in view of a combination of references has the burden to show that a person of ordinary skill in the relevant field had a reason to combine the elements in the manner claimed. *Id.* at 418-19. The Supreme Court has emphasized the need for courts to value "common sense" over "rigid preventative rules" in determining whether a motivation to combine existed. *Id.* at 419-20. "[A]ny need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420. In addition to showing that a person of

ordinary skill in the art would have had reason to attempt to make the composition or device, or carry out the claimed process, a defendant must also demonstrate that "such a person would have had a reasonable expectation of success in doing so." *PharmaStem Therapeutics, Inc. v. ViaCell, Inc.*, 491 F.3d 1342, 1360 (Fed. Cir. 2007).

A combination of prior art elements may have been "obvious to try" where there existed "a design need or market pressure to solve a problem and there [were] a finite number of identified, predictable solutions" to it, and the pursuit of the "known options within [a person of ordinary skill in the art's] technical grasp" leads to the anticipated success. *Id.* at 421. In this circumstance, "the fact that a combination was obvious to try might show that it was obvious under § 103." *Id.*

A fact finder is required to consider secondary considerations, or objective indicia of nonobviousness, before reaching an obviousness determination, as a "check against hindsight bias." *See In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1079 (Fed. Cir. 2012). "Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Graham*, 383 U.S. at 17-18.

"Patents are presumed to be valid, and overcoming that presumption requires clear and convincing evidence." 35 U.S.C. § 282; *Spectrum*, 802 F.3d at 1333 (citing *Microsoft Corp.*, 564 U.S. at 95 (holding that an invalidity defense must be proved by clear and convincing evidence)). In conjunction with this burden, the Federal Circuit has explained that,

> [w]hen no prior art other than that which was considered by the PTO examiner is relied on by the attacker, he has the added burden of

> overcoming the deference that is due to a qualified government agency presumed to have properly done its job, which includes one or more examiners who are assumed to have some expertise in interpreting the references and to be familiar from their work with the level of skill in the art and whose duty it is to issue only valid patents.

PowerOasis, Inc. v. T-Mobile USA, Inc., 522 F.3d 1299, 1304 (Fed. Cir. 2008) (citations omitted).

b. Discussion

Defendants offer ten prior references[26] in support of their obviousness arguments. As to the '911 and '342 patents, defendants rely on two combinations: (1) the Horrobin, Dwight, Barkin, and WO '223 references[27] for the proposition that these references teach the use of SNRIs to treat FMS; and (2) the Goldenberg and Fishbain references that teach the use of TCAs to treat FMS combined with the Briley II and Kasper references which teach that milnacipran is an SNRI and a suitable replacement for TCAs. As to the '220 patent, defendants argue the asserted claim would have been obvious in combination with the '691 publication, the '911 patent, and Ansseau.[28]

i. The person of ordinary skill in the art

Defendants argue that a person of ordinary skill in the art could include a medical doctor ("M.D.") with at least a few years of experience in treating patients with

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[26] Defendants additionally assert the '911 patent as prior art in reference to the '220 patent.

[27] Horrobin, Dwight, and Barkin discuss venlafaxine while WO '223 discusses duloxetine.

[28] Generally, the '681 application discusses the phase II trials using milnacipran to treat fibromyalgia while the '911 patent and Ansseau discuss using milnacipran to treat other conditions.

FMS or other chronic pain syndromes (D.I. 277 at 429:25-432:8),[29] someone specializing in drug development with a Ph.D. in medicinal chemistry, organic chemistry or a related discipline and at least a few years of experience in drug development to include either the development of CNS drugs or knowledge regarding the molecular mechanisms and pathways of neuropathic and nociceptive pain, or someone with a lesser degree but with commensurately more experience. (D.I. 277 at 429:25-432:8) More specifically, defendants argue that plaintiffs' expert, Dr. Argoff, improperly limits the person of ordinary skill to "an M.D. or someone who has experience taking care of patients with at least a few years of experience in treating patients with fibromyalgia or other chronic pain syndromes . . . ." (D.I. 278 at 664:3-11) because the definition ignores the reality that M.D.'s in the U.S. could not prescribe milnacipran to patients during the relevant time frame. Defendants also argue that under plaintiffs' definition, Drs. Gendreau and Kranzler would not have been persons of ordinary skill because they never treated FMS patients in practice.

Plaintiffs' experts, Dr. Charles Argoff and Dr. Philip Mease, are specialists in the field of fibromyalgia and have published extensively on the disease. Dr. Argoff is a board-certified neurologist and pain medicine specialist. (JTX 020; D.I. 276 at 70:20-71:1) His primary area of practice is pain medicine, including the treatment of fibromyalgia, and he holds various leadership positions in a number of professional organizations directed to the treatment of pain, is the neuropathic pain section co-editor

[29] Dr. Fortunak testified the time frame for a person of ordinary skill in the art for the '911 and '342 patents would have been in 2001 and 2005 for the '220 patent. (D.I. 277 at 430:3-6)

of the journal Pain Medicine, and has won numerous awards for his work in pain management. (D.I. 276 at 70:11-19, 71:2-72:19) Dr. Argoff has written numerous papers on the treatment of pain and has participated in at least 15 to 20 clinical trials, including at least three for fibromyalgia. (JTX 020; D.I. 276 at 72:20-73:23; 74:19-75:5) Dr. Argoff is also a Professor at the Albany Medical College where he instructs students on the proper diagnosis of pain disorders, including fibromyalgia, and treats approximately 300 fibromyalgia patients each year. (*Id.* at 73:24-74:18, 76:11-14)

Dr. Mease is Director of Clinical Rheumatology Research at Swedish Medical Center, Clinical Professor at the University of Washington, and has a clinical practice at Seattle Rheumatology Associates where he sees approximately 100 patients in an average week, of which 15 to 20 percent have fibromyalgia. (D.I. 277 at 950:16-24, 950:25-951:15; JTX 021) As for leadership positions, Dr. Mease is on the steering committee and co-chair of the psoriatic arthritis and chronic pain working groups of OMERACT, an international research organization that determines in a valid and reliable way the outcomes of clinical trials, and has published over 300 peer-reviewed articles, numerous book chapters, and is an editor for medical publications, including Rheumatic Disease Clinics of North America, which specifically addressed fibromyalgia in 2013. (JTX 021; D.I. 281 at 952:10-25, 953:1-953:15) Dr. Mease has additionally been involved in numerous clinical trials directed to drug treatments for fibromyalgia, including milnacipran. (D.I. 281 at 954:1-17) Consequently, Dr. Mease is considered to be a leader in the treatment of fibromyalgia. (D.I. 277 at 366:14-22; D.I. 281 at 954:18-955:9)

Defendants' infringement expert, Dr. Zizic, has over 40 years in practice, but has never authored a paper on fibromyalgia, spoken at a national conference regarding fibromyalgia, or conducted research on fibromyalgia. He additionally did not identify fibromyalgia as a specialty focus of his practice, but testified that he treats approximately 30-40 fibromyalgia patients per year. (D.I. 281 at 337:23-341:18, 342:14-22, 236:22-237:11) Defendants' invalidity expert, Dr. Fortunak, is a chemist who has never treated patients for fibromyalgia, nor designed nor conducted clinical trials for any drug. Because this case concerns the pharmacological and medical treatment aspects of the claims for the treatment of fibromyalgia (rather than principles of medicinal chemistry), Dr. Fortunak's chemistry background gives him limited experience in the context of the dispute at bar. This is confirmed by the literature at trial that was written by either M.D.s (*see e.g.* JTX 038; JTX 092; JTX 099; JTX 101) or Ph.Ds in pharmacology (*see e.g.* JTX 081; JTX 057; JTX 083; JTX 094). *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (discussing how the prior art typically informs the question of the level of one of ordinary skill).

In sum, plaintiffs' experts have the more relevant and extensive expertise. Therefore, plaintiffs have offered the more credible evidence.

ii. Horrobin with Dwight, Barkin, and WO '223

(a) Dwight

Dwight, a prior art article published in 1998 and titled "An Open Clinical Trial of Venlafaxine Treatment of Fibromyalgia," focuses on the use of venlafaxine for the treatment of FMS. (DTX 28; D.I. 281 at 459:8-460:19) Specifically, Dwight conducted an open label trial "to assess whether venlafaxine, a potent inhibitor of both

norepinephrine and serotonin reuptake, is well tolerated and efficacious in the treatment of fibromyalgia." (DTX 28 at 14) The treated patients showed improvements in fatigue and pain, as well as other FMS symptoms, specified as follows:

> These preliminary data suggest that venlafaxine may be effective in alleviating the symptoms of fibromyalgia in some patients. Venlafaxine was well tolerated by most patients despite the report of persistent insomnia by some patients. Most patients completing the study reported an improved quality of sleep, an increased feeling of restfulness upon awakening, a decrease in day-time fatigue, decrease in pain and morning stiffness, and an improved global assessment of the fibromyalgia, as well as a significant improvement in their quality of life, as measured by the PAIS-SR.

(DTX 28 at 16; D.I. 281 at 461:16-462:3) Dwight also recognized that venlafaxine's action as a dual 5-HT and NE inhibitor was likely the reason for its effectiveness:

> Both norepinephrine and serotonin may play a role in the pathophysiology of fibromyalgia. Prior studies have suggested that blockade of both norepinephrine and serotonin reuptake is more effective in treating fibromyalgia than blockade of either neurotransmitter alone. The ability of venlafaxine to exert effects on both the noradrenergic and serotonergic systems may explain its effectiveness in this preliminary trial.

(DTX 28 at 16-17; D.I. 277 at 462:4-21) Dwight notes that TCAs are often used to treat FMS patients, but their side effect profile may limit giving higher doses to patients who do not respond to low doses. (DTX 28 at 14; D.I. 277 at 459:8-460:19)

(b) Barkin

Barkin, a prior art article published in 2000 and titled "The Management Challenges of Chronic Pain: The Role of Antidepressants," recognizes that TCAs' analgesic properties were not fully understood, but notes that "[t]he impact of the TCAs on both NE and 5-HT, the two monoamines believed to be key in the etiology of depression, is also important to their effects on chronic pain." (DTX 29 at 38; D.I. 277

at 464:6-466:3) Because SSRIs only impact 5-HT, Barkin teaches that they may be less effective for the management of chronic pain. (DTX 29 at 38) Barkin suggests SNRIs as an ideal class of antidepressants for the management of chronic pain as follows, "[a]n ideal antidepressant agent for the management of chronic pain would be characterized by modulation of both NE and 5-HT, but would lack the nontherapeutic acute synaptic effects associated with the TCAs." (DTX 29 at 38; D.I. 277 at 466:4-467:3) Barkin additionally notes "particular efficacy" for venlafaxine in the treatment of FMS based on the authors' "clinical experience" and reports that pain relief seen with venlafaxine was "equal to or greater than that achieved with TCAs or SSRIs." (DTX 29 at 39; D.I. 277 at 466:15-467:21) Of note, Barkin also cites Dwight as providing support for venlafaxine's effectiveness in treating FMS. (DTX 29 at 39; D.I. 277 at 467:4-21)

(c) WO '223

PCT Publication No. WO 2000/15223 ("WO '223"), titled "Treatment of Persistent Pain," discloses and expressly claims the administration of duloxetine for the treatment of persistent pain, including pain from FMS. (JTX 195 at 1:3-6, 7:10-29, 22:14-16, 23:15-16; D.I. 277 at 468:6-24)[30] Duloxetine, the other known SNRI, was still in development in 2001, but the prior art disclosed that duloxetine could be used for the treatment of FMS due to its ability to inhibit the reuptake of both 5-HT and NE. (D.I. 277 at 468:6-470:1) WO '223 teaches that duloxetine is an SNRI and that it was being developed due to the drawbacks of TCAs and the need for drugs with a superior safety

[30] WO '223 was published on March 23, 2000, prior to the earlier date of invention asserted by plaintiffs and is, therefore, considered prior art under 35 U.S.C. § 102(b).

and tolerability profile. (JTX 195 at 1:17-19, 4, 10:17-24; D.I. 277 at 437:13-21, 468:25-470:1)

(d) Analysis

In view of the teaching of Horrobin[31] and the above-mentioned disclosures of Dwight, Barkin, and WO '223,[32] defendants maintain that a person of ordinary skill in the art would have been motivated to use, and would have had a reasonable expectation of successfully using, milnacipran without the neurotransmitter precursors, or any other compounds, to treat the pain and fatigue associated with FMS. (D.I. 277 at 429:7-12: 484:12-485:23) Given that milnacipran was one of only three SNRIs, and the other two SNRIs were already known to be effective by themselves for FMS, defendants conclude that milnacipran was one of a "finite number of identified, predictable solutions." *KSR,* 550 U.S. at 421.[33]

Defendants, however, fail to offer any meaningful explanation as to why one skilled in the art would have made this particular combination of references. The record is devoid of any such explanation. *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) (stating that "[w]here, as here, the necessary reasoning is absent, we cannot simply assume that 'an ordinary artisan would be awakened to modify prior art in such a way as to lead to an obviousness rejection.'"); *Mintz v. Dietz & Watson, Inc.*,

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[31] That "venlafaxine, duloxetine, milnacipran, and certain TCAs, are effective for the treatment of . . . FMS . . . when administered in combination with neurotransmitter precursors such as phenylalanine, tyrosine and/or tryptophan" ('911 patent at 7:26-32)

[32] Teaching the use of venlafaxine and duloxetine without precursors.

[33] Defendants improperly make invalidity arguments under 35 U.S.C. §§ 101 and 112 that the court will not consider as these arguments were not raised at any time prior to post-trial briefing.

679 F.3d 1372 (Fed. Cir. 2012); *Proctor & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 995 (Fed. Cir. 2009) ("[A] court must determine whether, at the time of invention, a person having ordinary skill in the art would have had 'reason to attempt to make the composition'. . . and 'a reasonable expectation of success in doing so.'") (citation omitted)). This is especially true where the alleged modification specifically contradicts the very teaching of the reference. *Daiichi Sankyo Co., Ltd. v. Matrix Labs., Ltd.*, 679 F.3d 1346, 1356 (Fed. Cir. 2010) ("[A] person of ordinary skill in the art would not select the '902 patent compounds as lead only to disregard one of their distinguishing characteristics . . . .") (internal citations omitted); *Plas-Pak Industries, Inc. v. Sulzer Mixpac AG*, 600 Fed. App'x. 755, 758 (Fed. Cir. 2015) (rejecting obviousness findings where the necessary alterations to a first reference would fundamentally change its "principle of operation").

Here, the "invention" or improvement disclosed in Horrobin "is the combination, the drug plus a neurotransmitter precursor," and there is no basis in the record for ignoring the alleged inventive feature of Horrobin and using venlafaxine, duloxetine, or milnacipran in monotherapy. (D.I. 277 at 475:7-10) More specifically, Dwight was published in 1998, a year before the 1999 foreign priority date of Horrobin. (DTX 028 at 14; DTX 008 at front cover) A skilled artisan reviewing the later filed Horrobin reference, in view of the earlier published Dwight reference, would understand that the authors of Horrobin concluded that the monotherapy use of venlafaxine in Dwight was ineffective and that combination therapy with venlafaxine and amino acid supplementation should be pursued for the treatment of fibromyalgia. There is no basis

for the proposition that Dwight in combination with Horrobin would lead to an effective monotherapy treatment with milnacipran.

Moreover, the teachings of Dwight and Barkin concerning monotherapy with venlafaxine contradict the teaching of Horrobin, and do not provide a basis for the combination proffered by defendants. As discussed above, Horrobin states that norepinephrine is the key in treating certain conditions, and only norepinephrine reuptake inhibiting drugs in combination with certain amino acids. One skilled in the art reading Dwight/Barkin would understand that serotonin was the neurotransmitter primarily implicated in the treatment of fibromyalgia. In this regard, it was initially believed that serotonin was the key mechanism involved in treating fibromyalgia, and the candidates for treating fibromyalgia were drugs that were biased towards inhibiting the reuptake of serotonin, including fluoxetine. (JTX 038 at 104-105; JTX 203; JTX 062 at 1852) The experimentation with venlafaxine then followed, as venlafaxine at most therapeutic doses behaves as a drug that selectively inhibits the reuptake of serotonin, or SSRI. (JTX 081 at 1305-1322; JTX 092 at 238; D.I. 280 at 845:6-846:3; 854:11-856:22; 859:24-861:16) However, it takes large doses, close to 225 mg per day, for venlafaxine to begin to implicate the reuptake of norepinephrine and to function like a dual inhibitor of serotonin and norepinephrine, or SNRI. (D.I. 280 at 861:8-22)

Turning to the expert testimony on this point, plaintiffs' expert, Dr. Blier, testified regarding how these drugs behave pharmacologically in humans, looking at both in vitro and in vivo data concerning venlafaxine. (D.I. 280 at 851:9-865:15; JTX 081 at Table 3; JTX 057; JTX 058; JTX 092) In terms of in vitro data, Dr. Blier relied on a 1997 publication, written by Dr. Owens and titled "Neurotransmitter Receptor and

Transporter Binding Profile of Antidepressants and Their Metabolites." (JTX 081) Dr. Blier testified regarding the excellent reputation of the authors[34] in the field and that the article was based on their experiments with numerous compounds that were conducted at the same time, at the same laboratory, and under the same conditions. (D.I. 280 at 851:22- 852:2) In contrast, defendants relied on a publication that reports earlier obtained rat data from different laboratories. (DTX 156; D.I. 280 at 923:6-924:6) Consequently, Dr. Blier testified that Dr. Owens' data was much more reliable. (D.I. 280 at 942:15-943:9; 848:14-849:24; 851:22-852:2)

Based on the experiments, Dr. Owens reported that the inhibition ratio for venlafaxine was 16:1 in favor of serotonin. (JTX 081 at Table 3, 1309; D.I. 280 at 851:9-17) Dr. Owens concluded that "[a]lthough marketed as a 'dual uptake inhibitor' . . . venlafaxine and [its metabolite] are not potent NET antagonists in vitro, although they do show activity in vivo." (JTX 081 at 1320; D.I. 280 at 853:13-854:10)

As to in vivo studies with venlafaxine, Dr. Blier testified that his laboratory performed studies which were reported in a 1998 abstract titled "Comparison of the Effect of Low and High Doses of Venlafaxine on Serotonin and Norepinephrine Reuptake Processes in Patients with Major Depression and Healthy Volunteers."[35] (JTX 057; D.I. 280 at 854:11-861:22) In this study, Dr. Blier used two tests (blood serotonin 5-HT content and the tyramine pressor test) to measure the ability of

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[34] Four authors are listed in the publication, but Dr. Blier generally referred to Dr. Owens throughout his testimony.

[35] Dr. Blier also lectured about these results in 1998 at the International College of Psychopharmacology and later published the same data in a full journal article. (JTX 058; 857:3-14; 861:23-862:12) These results were also referred to in other of Dr. Blier's papers by 2001. (JTX 094 at 519)

venlafaxine at different doses to inhibit the reuptake of serotonin and norepinephrine. (D.I. 280 at 855:22-863:24) The tyramine pressor test is a functional in vivo assay to determine how effective the test drug is in inhibiting the reuptake of norepinephrine. (D.I. 280 at 856:17-858:25) After explaining the mechanisms of how the tests work and how the studies were properly controlled, Dr. Blier testified concerning the results of the studies, explaining that at both 75 mg and 225 mg, venlafaxine was inhibiting the reuptake of serotonin and was functioning as a "potent SSRI." (D.I. 280 at 859:1-861:22) In contrast, venlafaxine only meaningfully inhibited the reuptake of norepinephrine once the dose reached 225 mg per day. (D.I. 280 at 860:22 to 861:22; JTX 094 at 519 (noting a tyramine pressor response at 225 mg/day))

Dr. Blier also relied on a 2001 publication by Dr. Michael Thase titled "Remission Rates During Treatment with Venlafaxine or Selective Serotonin Reuptake Inhibitors." (JTX 092) In the article, Dr. Thase stated "[i]t appears that relatively higher doses of venlafaxine may be necessary to achieve significant noradrenergic effects, as inferred from in vitro, animal, and human studies." (*Id.* at 239 (citations omitted)) Of note, Barkin confirms these properties of venlafaxine as it identifies venlafaxine as an "ideal antidepressant" that should be considered for the treatment of chronic pain. However, Barkin notes that venlafaxine "may be characterized as 'three drugs in one'" due to its "unique dose-related receptor mediated events." (DTX 029 at 39; D.I. 278 at 604:16-605:25) At low doses, Barkin states venlafaxine inhibits serotonin reuptake, i.e., it acts as an SSRI. (*Id.*)

Dwight does not disclose the individual doses taken by each of the 11 patients, but instead provides a "mean final dose" of 167 mg/day, and a range of 37.5 mg/day to

300 mg/day. (DTX 029 at 15) Accordingly, one skilled in the art would understand that, to the extent venlafaxine is even working to treat fibromyalgia in Dwight, it is doing so as an SSRI. (D.I. 280 at 881:7- 882:10) A person of ordinary skill in the art, therefore, would not have been motivated to combine Horrobin with the references asserted by defendants discussing venlafaxine and somehow be motivated to use milnacipran in monotherapy. Further, as discussed in detail below, milnacipran has the "opposite" pharmacology of venlafaxine, in that it works as a selective norepinephrine drug at low doses. (D.I. 280 at 865:8-15) As such, the teachings of Dwight/Barkin would not motivate one skilled in the art towards monotherapy with milnacipran with a reasonable expectation of success. (D.I. 280 at 882:5-15)

Even if one were to combine the teachings of Horrobin and the publications concerning venlafaxine, there is still a leap in logic that must be made before arriving at milnacipran. Barkin, which fails to mention milnacipran as a possible drug to treat pain and/or fibromyalgia, states that venlafaxine (not SNRIs generally) is the ideal agent because of its "unique" properties. (DTX 029 at 38-39) One of venlafaxine's "unique" properties is that, at doses lower than 225 mg, venlafaxine primarily works as an SSRI. In direct contrast, the record shows that it was well known in 2001 that milnacipran at lower doses inhibits the reuptake of norepinephrine, and it is only at higher doses that milnacipran begins to inhibit serotonin, i.e., it has the "opposite" pharmacology of venlafaxine. (D.I. 280 at 865:8-15; 875:5-11; 879:3-880:2) Overall, as described by Dr. Blier at trial, milnacipran has the opposite pharmacology as venlafaxine in that it is more potent for norepinephrine reuptake inhibition than serotonin. Even the Sanchez

reference relied on by defendants shows that in vitro, venlafaxine and milnacipran have the opposite pharmacology. (DTX 156 at 478)

Aside from the fact that venlafaxine and milnacipran are pharmacologically different, as of 2001, one skilled in the art would not have been motivated to combine Horrobin with Dwight with a reasonable expectation that monotherapy treatment with milnacipran would be effective for the treatment of fibromyalgia because, contrary to defendants' assertions, Dwight does not establish that venlafaxine is effective in treating fibromyalgia. Dwight was an open label study, without the use of a placebo control and consisting of only 11 patients who completed the study, many of whom had current (or past) concurrent depression. (DTX 028 at 15; D.I. 278 at 607:18-613:5) As discussed by Dr. Argoff, small, open-label, non-placebo controlled trials, such as Dwight, would not be accepted by persons of ordinary skill in the art as establishing the efficacy of a drug for the treatment of fibromyalgia for many reasons, including the introduction of patient and doctor bias, false positives due to a placebo response, and lack of sufficient patients.[36] (D.I. 278 at 671:22-681:6) Dwight also recognized the limitations of the study by specifically noting the lack of a placebo control (preventing assessment of the placebo response), the "homogencity and small size" of the study, patient selection bias, and the inclusion of patients with lifetime Axis I disorders, including depression (which did correlate to a positive response to the antidepressant

[36] Dr. Argoff is not alone in recognizing these problems. In a study assessing amitriptyline or placebo in patients with fibrositis (the predecessor name of fibromyalgia), Dr. Carette noted that 50 percent of patients taking placebo believed their symptoms decreased overall, and that this improvement could have simply been a result of the increased attention given to the patients in the clinical trial, when their disease was previously not taken seriously. (JTX 051 at 658-59)

venlafaxine), leading Dwight to conclude that "[c]ontrolled studies are needed to further examine this issue." (DTX 028 at 16-17; D.I. 278 at 731:16-24, 596:22-597:22, 599:5-19, 608:11-610:2) Importantly, Dwight acknowledged that the "open nature of this exploratory study limits drawing firm conclusions about the efficacy of venlafaxine in the treatment of fibromyalgia" and, thus, Dwight could only suggest that venlafaxine "may be useful for the treatment of fibromyalgia patients with comorbid lifetime Axis I disorders." (DTX 028 at 17)

The limitations of Dwight were confirmed in a randomized, placebo-controlled, double-blind trial of venlafaxine in patients with fibromyalgia conducted by Wyeth, the proprietor of venlafaxine. (JTX 103[37] at S105; D.I. 278 at 703:6-21) ("Zijlstra abstract" or "Wyeth study")[38] The Zijlstra abstract, published in September 2002, reported studies conducted in Europe and designed to assess "the effect of venlafaxine in FM [fibromyalgia] in a randomized, placebo-controlled design." (JTX 103) The Wyeth study included 90 subjects that met the 1990 ACR criteria for fibromyalgia, but (unlike Dwight) excluded patients with severe depression and included a placebo control. (*Id.*) Patients were then randomized to either 75 mg/day of venlafaxine or placebo and treated for 6 weeks. (*Id.*) After analyzing the data, Dr. Zijlstra[39] concluded that

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[37] The objection to admissibility because this reference is not prior art was overruled as the opposing party had admitted a similar exhibit. (D.I. 278 at 614:1-19)

[38] Because the authors of the abstract are ambiguous on the face of the exhibit as submitted, the naming convention is based on Dr. Fortunak's testimony that Dr. Zijlstra was among the authors at Wyeth when the study was completed. (D.I. 278 at 615:3-12)

[39] While it is not outcome determinative, the court cannot determine whether it was Dr. Zijlstra himself or in conjunction with the other authors of the Wyeth study that arrived at this conclusion.

"[v]enlafaxine 75 mg/day is not effective in reducing pain and other symptoms of FMS." (*Id.*; D.I. 278 at 613:9-617:11) The fact that 75 mg was used is telling, because Wyeth, the originator of venlafaxine, understood what an effective dose of venlafaxine was and choose this for its study. (D.I. 278 at 703:2-5) The Zijlstra abstract confirms Dr. Argoff's opinion that Dwight's small, open label, non-placebo controlled study in fibromyalgia patients with a lifetime Axis I disorder does not provide any expectation that venlafaxine is actually effective in treating fibromyalgia. (D.I. 278 at 703:22-704:23; 796:1-798:20) Moreover, and contrary to defendants' argument, the Zijlstra abstract confirms that Dwight does not evidence efficacy in fibromyalgia, but instead only showed improvement due to positive effects on lifetime Axis I disorders. (DTX 028 at 17; DTX 54) Dwight, therefore, provided no reasonable expectation that venlafaxine could be effective in treating fibromyalgia as opposed to improving the patients' condition due to a positive improvement of depression. Dwight did not provide any reasonable expectation of successfully treating fibromyalgia using a different drug, milnacipran, with different pharmacological properties, and in a manner different from the combination therapy disclosed in Horrobin.

The same problem applies to defendants' arguments regarding WO '223's discussion of duloxetine, another compound that has the potential to be an SNRI depending on the dose. (JTX 195) As Dr. Blier testified, there would have been no reason or motivation to combine Horrobin with duloxetine to arrive at milnacipran for monotherapy because, like venlafaxine, duloxetine functions primarily as an SSRI at most therapeutic doses. (D.I. 280 at 883:5-15) In this regard, Dr. Blier relied on a paper titled "Blockade of the Serotonin and Norepinephrine Uptake Processes by

Duloxetine: In Vitro and In Vivo Studies in the Rat Brain," published in 1996 by Dr. Blier himself. (JTX 106) This paper discusses both in vitro data (inhibition ratios) and in vivo data (decrease in the firing rates of neurons) for duloxetine. In terms of in vitro data, Dr. Blier's paper reports that, like venlafaxine, duloxetine has a preference for the inhibition of serotonin reuptake. (*Id.*) Dr. Blier testified that in his laboratory, the inhibition ratio for duloxetine was 2:1 in favor of serotonin, and in Dr. Wong's laboratory (the inventor of duloxetine), the inhibition ratio for duloxetine was 3:1 in favor of serotonin. (D.I. 280 at 884:11-885:13; JTX 106 at 282) Further explaining the results of the firing rate experiments, the paper states that the "fact that duloxetine is five times less potent for suppressing the firing activity of NE neurons than for inhibiting that of 5-HT neurons is consistent with the present electrophysiological experiments in the hippocampus, both of which indicate the preferential selectivity of the duloxetine in blocking 5-HT uptake than NE uptake." (JTX 106 at 285) Dr. Blier testified this meant that at "lower doses or concentration, you have a potent serotonin reuptake reaction, and then you need to push up the dose to engage the norepinephrine transporter." (D.I. 280 at 886:3-10)

Dr. Blier performed similar in vivo experiments as he had previously performed on venlafaxine. (D.I. 280 at 887:3-23) These experiments were reported in a 2001 paper, titled "Assessment of the Serotonin and Norepinephrine Reuptake Blocking Properties of Duloxetine in Healthy Subjects." (JTX 094) This paper reported that duloxetine, like venlafaxine, had a strong preference for the inhibition of serotonin reuptake in vivo as follows: "Duloxetine, at doses of 20, 40 and 60 milligrams per day, significantly interfered with the 5-HT reuptake processes, as demonstrated by the

decrease in blood 5-HT concentrations. However, the same doses of duloxetine failed to impede the usual increase in blood pressure that follows a tyramine intravenous infusion, indicating that this drug did not alter the NE reuptake process." (*Id.* at 517) Dr. Blier concluded that duloxetine, at most therapeutic doses, functions much more like an SSRI than an SNRI. (D.I. 280 at 888:2-17)

Dr. Blier also testified that duloxetine has a different pharmacology than milnacipran because, as discussed above, milnacipran is more selective towards norepinephrine reuptake inhibition. At trial, Dr. Blier created a chart that summarized the differences between the pharmacological properties of the two compounds. (D.I. 280 at 890:7-892:24) Dr. Blier went through each column in the chart and explained the differences between milnacipran and duloxetine. (*Id.*) In particular, Dr. Blier noted that the in vitro inhibition ratios for the two compounds were reversed, and that duloxetine failed to inhibit the tyramine presser response at doses up to 60 mg, that duloxetine is 57 more times potent than milnacipran in terms of suppressing the firing rate of serotonin neurons; in contrast, milnacipran was much more potent in suppressing the firing rate of norepinephrine neurons. (*Id.*) Dr. Blier further explained that all the data demonstrated that "duloxetine at low doses or low concentration is very effective in . . .inhibiting the transport system for serotonin, but you need higher doses to block to have a corresponding effect on the norepinephrine transporter, whereas basically milnacipran is the opposite."[40] (D.I. 280 at 892:17-24) Based on all the

[40] Further, in his 2009 chapter, Dr. Blier specifically wrote about the differences between duloxetine and milnacipran citing to many of the same papers discussed above, and explained that neither duloxetine nor milnacipran are "balanced" inhibitors. (D.I. 280 at 892:25-894:3; JTX 108 at 461)

above, Dr. Blier testified that duloxetine would not have "rendered obvious the use of milnacipran to treat fibromyalgia in 2001," because "the selectivity ratio is opposite, totally reversed." (D.I. 280 at 894:1-11)

Finally, there is no evidence of record that duloxetine was effective in treating fibromyalgia in 2001. As the sole basis for asserting that duloxetine worked against fibromyalgia, defendants rely on the WO '223 application (JTX 195). But this application contains nothing more than the suggestion that duloxetine may be used in a multitude of completely unrelated pain conditions, including tension type headache, musculoskeletal pain, pain associated with somatoform disorders, visceral pain, back pain, shoulder pain, cancer pain, pain associated with AIDS, post-operative pain, post-burn pain, multiple chemical sensitivity, sick building syndrome, repetitive stress injury, chronic whiplash, chronic lyme disease, side effects of silicone breast implants, Gulf War syndrome, food allergies, and hypoglycemia. (JTX 195 at 5:34-10:4; D.I. 278 at 617:12-619:19; 620:4-9) While fibromyalgia is identified as one of the multitude of pain conditions, there is not a single example in the WO '223 reference using duloxetine for fibromyalgia. (JTX 195 at 7:15-29; D.I. 278 at 621:7-9) As explained by Dr. Argoff, the scientific community would not consider the WO '223 applications' laundry list of pain conditions as "being proof of anything." (D.I. 278 at 732:6-9)

The court concludes that defendants' proffered arguments and evidence are not persuasive. Consequently, defendants have not demonstrated, by clear and convincing evidence, that the '911 and '342 patents are invalid as obvious in light of Horrobin with Dwight, Barkin, and the WO '223 application.

iii. Fishbain and Goldenberg with Briley II and Kasper

As described in more detail below, the Fishbain and Goldenberg references teach the use of TCAs to treat FMS. Briley II and Kasper teach that milnacipran is an SNRI that defendants argue is a suitable replacement for TCAs.

(a) Fishbain

Fishbain, a prior art article published on March 23, 2000 and titled "Evidence-based data on pain relief antidepressants," teaches that dual 5-HT and NE reuptake inhibitors, including TCAs, are more effective in FMS treatment than SSRIs. (D.I. 262 at 17; DTX 27) Specifically, Fishbain notes that "antidepressants vary according to their specificity for noradrenaline or serotonin [and it] has been postulated that if antidepressants do indeed have an anti-nociceptive (analgesic) effect, it relates to one or both of these neurotransmitters." (DTX 27 at 305; D.I. 277 at 448:23-450:6) Fishbain's review of placebo controlled trials concludes that TCAs with a balanced effect on NE and 5-HT, and in particular amitriptyline, demonstrated better efficacy in treating FMS than SSRIs, which only impacted 5-HT. (DTX 27; D.I. 277 at 448:2-450:6) Fishbain's review of FMS studies led him to conclude that the data "indicate that serotonergic-noradrenergic antidepressants are consistently effective for [FMS] pain whereas serotonergic antidepressants are not." (DTX 27 at 309; D.I. 277 at 448:23-450:6)

(b) Goldenberg

Goldenberg, a prior art article published in 1996 and titled "A Randomized, Double-Blind Crossover Trial of Fluoxetine and Amitriptyline in the Treatment of Fibromyalgia," notes that TCAs such as amitriptyline, which inhibit the reuptake of both 5-HT and NE, are among the most commonly studied agents for the treatment of FMS;

about 33 percent of all patients taking such TCAs see "clinically meaningful" improvement to their FMS. (JTX 62 at 1852; D.I. 277 at 446:21-447:3) Additionally, Goldenberg notes that "[i]t has been suggested that certain symptoms of [FMS] may respond better to drugs that primarily affect serotonin, whereas drugs that affect norepinephrine uptake may improve other symptoms." (JTX 62 at 1852; D.I. 277 at 447:17-448:1) Goldenberg describes results of an independent study using amitriptyline (a TCA) and fluoxetine (an SSRI), both alone and in combination with each other. (JTX 62; D.I. 277 at 444:7-445:17) The study determined that both compounds improved patients' FMS and "were associated with significantly improved scores on the FIQ and on the VAS for pain, global well-being, and sleep disturbances." (JTX 62 at 1852; D.I. 277 at 447:7-16) Goldenberg suggests that the improved efficacy of the combination of amitriptyline and fluoxetine may relate to a "more ideal balance" of NE and 5-HT reuptake inhibition. (JTX 62 at 1858)

(c) Briley II

Briley II, a prior art article published in 1998 and titled "Milnacipran, a Well-Tolerated Specific Serotonin and Norepinephrine Reuptake Inhibiting Antidepressant," states that milnacipran and other SNRIs were developed "with the intention of providing greater antidepressant efficacy than the SSRIs without the side effects of the TCA." (JTX 50 at 137; D.I. 277 at 478:21-479:8) Briley II teaches that milnacipran and other SNRIs demonstrate superior efficacy to SSRIs, and that "[t]his suggests that a simultaneous double action on serotonin and norepinephrine may be associated with superior efficacy compared with the more selective action on serotonin alone." (JTX 50 at 146 (internal citations omitted))

Briley II also discloses that milnacipran is well-tolerated by patients and exhibits a side effect profile superior to TCAs. (JTX 50 at 147; D.I. 277 at 478:21-479:8) Briley II teaches the administration of 25 mg, 50 mg and 100 mg of milnacipran, dosed twice daily. (JTX 50 at 141) Finally, Briley II notes that milnacipran is a "useful alternative to TCAs" and its "low side effect profile make it a drug of choice in most situations." (*Id.* at 147)

(d) Kasper

Kasper, a prior art article published in 1996 and titled "Comparative studies with milnacipran and tricyclic antidepressants in the treatment of patients with major depression: a summary of clinical trial results," discloses that milnacipran, like TCAs, inhibits reuptake of both 5-HT and NE. (DTX 36 at 35; D.I. 277 at 479:9-480:15) Kasper recognizes that some TCAs are used to treat depression and "a range of other syndromes, including . . . chronic pain," but that "new antidepressants have been and are being developed in an attempt to overcome the limitations of TCAs, particularly their adverse event profile." (DTX 36 at 35; D.I. 277 at 480:1-481:5) Kasper discloses that milnacipran and TCAs have similar mechanisms of action as follows:

> The mechanisms of action of TCAs and milnacipran are similar: both inhibit the reuptake of 5-HT and noradrenaline. TCAs also interact, however, with various neurotransmitter receptors, such as adrenergic, muscarinic and histaminergic receptor sites. . . . By contrast, milnacipran does not interact with post-synaptic receptors and this is thought to be responsible for its favourable [sic] tolerance profile.

(DTX 36 at 35) Kasper notes that the adverse effect profile of TCAs can lead to a significant rate of patient withdrawal and, thus, milnacipran demonstrates equivalent efficacy to TCAs, but produces fewer side effects. (*Id.* at 37-38; D.I. 277 at 480:1-

481:5) Table IV of Kasper indicates that patients treated with milnacipran see a lower incidence of fatigue and somnolence as compared to a placebo. (DTX 36 at 38; D.I. 277 at 480:19-481:5) In contrast, Table IV indicates that fatigue and somnolence occurred approximately four times as frequently with TCAs as compared to milnacipran (combined incidence of 4.8% for patients dosed with milnacipran vs. combined incidence of 19.4 percent with TCAs). (*Id.*)

(e) Analysis

Defendants argue that the asserted claims of the '911 and '342 patents would have been obvious in view of the prior art related to the use of TCAs in FMS, such as Goldenberg and Fishbain, in combination with the knowledge in the art (as reflected by Briley II and Kasper) that milnacipran was a safe and effective replacement for TCAs. (D.I. 277 at 429:13-20, 484:24-487:17) Given that TCAs that inhibited the reuptake of 5-HT and NE were known to be effective in treating FMS, and milnacipran was developed as a substitute for TCAs, defendants assert that a person of ordinary skill in the art would have been motivated to use milnacipran for the treatment of FMS. (D.I. 277 at 466:4-467:3, 477:17-479:8) Because milnacipran has the same mechanism of action as attributed to the TCAs' efficacy in FMS (dual inhibition), one skilled in the art would also have a reasonable expectation of success in using milnacipran to treat FMS, including the chronic pain and fatigue associated with FMS. (D.I. 277 at 480:1-15)

Defendants also argue that those of ordinary skill in the art were not focused on TCAs' other mechanisms of action. Specifically, although TCAs have other mechanisms of action, the art shows that by 2001, those of skill believed that the primary mechanism of action by which TCAs (such as amitriptyline) worked for the

treatment of chronic pain was the dual inhibition of 5-HT and NE reuptake. (D.I. 277 at 451:19-452:9) That is why researchers such as Goldenberg, Fishbain, Barkin, and Dwight focused on this mechanism of action. Defendants assert that Barkin is illustrative because, although Barkin fully recognized that TCAs have numerous mechanisms of action, their impact on both NE and 5-HT was "important to their effects on chronic pain" and expressly states that "[a]n ideal antidepressant agent for the management of chronic pain would be characterized by modulation of both NE and 5-HT." (DTX 29 at 38; D.I. 277 at 464:24-466:14) Importantly, defendants continue, those of ordinary skill in the art recognized that dual inhibition of 5-HT and NE was the reason TCAs were effective for treating FMS, and correspondingly focused on SNRIs which shared that essential mechanism of action. (D.I. 277 at 477:17-478:13, 451:19-452:9)

Plaintiffs counter that: (1) TCAs interact with a number of receptors that modulate their analgesic response; (2) post-filing publications demonstrate continued confusion as to the mechanism concerning how tricyclics work; and (3) neither Fishbain nor Goldenberg establish that TCAs worked to treat fibromyalgia through a dual inhibition mechanism. Plaintiffs assert that, while the reported literature contains an indication that TCAs exhibited some efficacy in treating fibromyalgia, the mechanism(s) by which certain TCAs worked was, and still is, unknown. (D.I. 277 at 520:15-522:1; D.I. 278 at 640:18-655:17, 697: 2-21; D.I. 280 at 894:12-904:16; D.I. 281 at 956:25-957:18) The fundamental assumption underlying defendants' invalidity assertion, that the TCAs were known to work through dual reuptake inhibition, is overly stated. What was known as of 2001 was that TCAs interact with many different receptors that may

result in efficacy, but also cause many undesirable side effects impacting patient tolerability. (D.I. 277 at 520:15-522:1; D.I. 281 at 959:4-15) These non-selective interactions led to TCAs being considered "dirty drugs." (JTX 085; JTX 038; D.I. 277 at 520:15-522:1; D.I. 281 at 959:4-15)

Prior to 2001, persons having ordinary skill in the art acknowledged the uncertainty as to how TCAs impart efficacy in fibromyalgia. (D.I. 277 at 520:15-522:1; D.I. 278 at 696:6-697:21) For example, Barkin notes that, although "[TCAs] have the longest history of use in general, and, consequently, most extensive record in the treatment of chronic pain[,]" "[t]heir mechanism of action in chronic pain is incompletely understood but implicates substance P." (DTX 029 at 38; D.I. 278 at 697:12-21) Barkin also states that "[s]ome evidence suggests an interaction between antidepressant agents and opioid receptors, and this may be the mechanism by which antidepressants provide antinociception." (*Id.*; D.I. 278 at 696:25-697:11) While some TCAs, depending on the dose, can inhibit the reuptake of both serotonin and norepinephrine, persons of ordinary skill postulated that TCAs might impart efficacy in fibromyalgia via different mechanisms, including interactions with substance P and/or opioid receptors. (D.I. 278 at 696:6-697:21)

Due to the antihistaminergic effects of TCAs, several investigators suggested that TCAs are efficacious in treating fibromyalgia because they help improve sleep. For example, Dr. Arnold published a meta-analysis and review of the use of antidepressants, including TCAs and SSRIs, for the treatment of fibromyalgia in 2000. (JTX 038) Contrary to defendants' allegations that by 2001 those skilled in the art had determined sleep was not connected to fibromyalgia, this reference makes clear that

the "largest effect" TCAs had on fibromyalgia "was found in measures of sleep quality," and that "the most consistently observed improvement in these studies may have been attributed, in part, to the sedative properties of these agents." (JTX 038 at 110; D.I. 278 at 653:7-654:23, 681:7-684:11)

Evidence that the TCAs do not treat fibromyalgia through the inhibition of serotonin and norepinephrine reuptake is further demonstrated by the doses of TCAs, such as amitriptyline, typically used to treat fibromyalgia. (D.I. 280 at 894:12-896:10) As Dr. Blier testified, such doses are simply too low to obtain a rigorous inhibitory effect on the serotonin or norepinephrine transporters and demonstrate that another mechanism is responsible for the TCAs' analgesic effect. (*Id.*) This was recognized in the placebo-controlled crossover study by Goldenberg (JTX 062), wherein patients were given 25 mg/day amitriptyline, a dose well below what is necessary to treat depression. (JTX 062 at 1371; D.I. 280 at 899:9-900:2) At such low doses, and based on the published prior art, including the paper published by Dr. Owens referred to above (JTX 081), it was likely that it was amitriptyline's interaction with the 5-HT_{2a} receptor that was responsible for its analgesic effect. (D.I. 280 at 896:14-899:7) This is because amitriptyline has a much higher affinity to the 5-HT_{2a} receptor than it does for either the serotonin or norepinephrine transporters. (*Id.*) Thus, at low doses, it is likely only having a meaningful effect on the 5-HT_{2a} receptor. (*Id.*) As plaintiffs point out, this was not a litigation derived theory. Dr. Blier published this theory by 2001 in a series of papers admitted into evidence. (JTX 032; JTX 033; JTX 049; D.I. 280 at 901:7-15) In the last paper in the series, Dr. Blier specifically wrote that "it is striking that the most effective antidepressant drugs for the control of chronic pain (e.g., amitriptyline and

mianserin [mirtazapine]) are potent 5-HT_2 antagonists." (JTX 049; D.I. 280 at 903:2-14) Taken as a whole, these articles demonstrate that: (1) 5-HT_{2a} antagonists are effective against pain; (2) amitriptyline is a potent 5-HT_{2a} antagonist; and (3) this property could be the reason why amitriptyline has demonstrated efficacy against chronic pain. At a minimum, these facts would lead one of ordinary skill in the art to believe that amitriptyline's interaction with the 5-HT_{2a} receptor is "a very important aspect" responsible for amitriptyline's mechanism in fibromyalgia. (D.I. 280 at 904:5-16) On the other hand, milnacipran does not have activity against the 5-HT_{2a} receptor. (*Id.*) In 2001, therefore, those of ordinary skill in the art would find it unlikely that milnacipran would work as an effective agent in managing pain.[41]

Turning to the Fishbain reference relied on by defendants, neither Fishbain nor Goldenberg establish that TCAs worked to treat fibromyalgia through a dual inhibition

[41] Even after the 2001 filing date of the asserted patents, clinicians expressed doubt concerning how the TCAs treated pain. (D.I. 278 at 642:4-645:20; 697:2-21) For example, a 2007 paper titled "Sodium Channel Blockade May Contribute to the Analgesic Efficacy of Antidepressants" stated that there have been "numerous randomized, placebo-controlled human trials that support the analgesic efficacy of TCAs and suggest that it is independent of the antidepressant action." (JTX 122 at 319) The paper further explains that "the mechanism by which antidepressants assert their analgesic effect is poorly understood." (*Id.*; D.I. 278 at 642:4-644:8) "Tricyclic antidepressants interact with several molecular targets, and, as such, their ability to relieve pain may not be attributable to a singular molecular mechanism." (JTX 122 at 322) The paper then emphasized that "the block of sodium channels" may contribute to the analgesic efficacy of TCAs. (JTX 122 at 315, 316, 322) This paper suggests that as late as 2007, persons having ordinary skill in the art still did not know the precise mechanism by which TCAs treated pain. It is well-established that such post-filing references can be used to show confusion in the art as of the filing date of the patent. *In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993) (relying on art published five years after filing date to show what was "sufficiently unpredictable" as of filing date); *Plant Genetics Systems v. DeKalb Genetics Corp.*, 315 F.3d 1335, 1344 (Fed. Cir. 2003) (using later published art to establish difficulty as of filing date).

mechanism. Fishbain discusses many different pain conditions and is not limited to fibromyalgia. (DTX 027) Table 7 of Fishbain lists multiple studies that have been performed with amitriptyline, which the table identifies as an "(S-NA)" or a "serotonergic-noradrenergic" drug. (*Id.* at 309) However, as discussed above, while amitriptyline has the potential to inhibit the reuptake of both serotonin and norepinephrine, the doses used in the studies listed in the table are too low for amitriptyline to meaningfully interact with the serotonin norepinephrine and transporters. (D.I. 280 at 894:12-896:10) Thus, it is likely that amitriptyline at those doses are interacting with the 5-HT_{2a} receptor, a receptor that milnacipran does not interact with. (D.I. 280 at 896:11-904:16) As set forth above, there was significant confusion in the art, both as of the filing date and after, concerning the precise mechanism of how amitriptyline worked to treat fibromyalgia. There was no consensus that its analgesic properties were due to dual reuptake inhibition. Further, as also shown by Dr. Owens' paper, which contained the most accurate data and also used human as opposed to rat transporters, amitriptyline had a 3:1 ratio favoring serotonin reuptake inhibition. (JTX 081 at 1309) This would not have led a person of ordinary skill in the art to milnacipran which is much more biased towards norepinephrine reuptake inhibition. Fishbain's inclusion of amitriptyline would not have motivated a person of ordinary skill to use milnacipran to treat fibromyalgia with any reasonable expectation of success.

Table 7 in Fishbain also lists S-Adenosylmethionine (SAMe) as a drug used to treat fibromyalgia patients. However, this drug does not inhibit the reuptake of serotonin or norepinephrine. (DTX 027 at 309; D.I. 280 at 906:5-9) Similarly, Table 7 lists cyclobenzaprine; cyclobenzaprine, which is approved as a muscle relaxant rather

than an antidepressant, does not inhibit the reuptake of norepinephrine and is not a dual inhibitor. (D.I. 280 at 908:6-15) Instead, cyclobenzaprine actually increases the firing of NE neurons in the locus coereleus, a result which is the opposite of what one would expect with NE reuptake inhibition. (JTX 056; D.I. 280 at 908:16-909:24)

Table 7 identifies fluoxetine, a SSRI. The table indicates that fluoxetine was tested in two studies for fibromyalgia, a "Wolfe" study where it was not effective, and a later "Goldenberg" study where efficacy was found. (DTX 027 at 309) Defendants rely on Goldenberg as further evidence that dual reuptake inhibition was the key. (JTX 062) Dr. Goldenberg conducted a randomized, double-blind, placebo controlled crossover trial assessing fluoxetine (an SSRI) and amitriptyline (a TCA) alone, and in combination, for the treatment of fibromyalgia. He concluded that fluoxetine's individual ability to improve a patient's fibromyalgia was equal to that of amitriptyline's. (*Id.* at 1852, 1858) More specifically, Dr. Goldenberg determined that "improvement in FM pain resulting from treatment with 20 mg of [fluoxetine] was comparable to that with 25 mg of [amitriptyline]. The level of pain improvement was also similar to that with various tricyclic antidepressants in prior FM clinical trials." (*Id.* at 1858) Based on these results, Goldenberg stated that "[c]linical observations and some basic investigations have suggested that neurotransmitters, such as serotonin, are important in FM." (*Id.*) Goldenberg's focus on fluoxetine would have taught one skilled in the art that serotonin was the key to the successful treatment of fibromyalgia and would have affirmatively taught away from using a drug like milnacipran, which is a dual inhibitor that is much more selective for norepinephrine at most therapeutic doses. (D.I. 280 at 907:16-908:5) Accordingly and contrary to Dr. Fortunak's opinion, those skilled in the

art as of the filing date would have understood that Goldenberg taught that fluoxetine was effective in treating fibromyalgia, which would lead a person of ordinary skill away from milnacipran. Similarly, given the wide variety of possible mechanisms for the different drugs listed in Table 7 of Fishbain (amitriptyline, SAMe, cyclobenzaprine, and fluoxetine), persons having ordinary skill in the art would not have understood that a dual inhibition mechanism was responsible for the treatment of fibromyalgia. The literature discussing the TCAs do not provide the necessary reason or motivation to use milnacipran with the requisite expectation of success.[42]

The court concludes that defendants' proffered arguments and evidence are not persuasive. Consequently, defendants have not demonstrated, by clear and convincing evidence, that the '911 and '342 patents are invalid as obvious in light of Fishbain and Goldenberg with Briley II and Kasper.

iv. The '681 application, '911 patent, and Ansseau

Turning to the '220 patent, defendants argue that the most relevant prior art to the invalidity of the '220 patent in relative order of importance includes: (1) U.S. Publication No. 2004/0106681 ("the '681 application"); (2) the '911 patent; and (3) Ansseau.

(a) The '681 application

U.S. Patent Application No. 10/678,767, titled "Dosage Escalation and Divided Daily Dose of Anti-Depressants to Treat Neurological Disorders," published on June 3, 2004 as Publication No. US 2004/0106681 ("the '681 application") (JTX 197). The '681

[42] The fact that Briley and Kasper state that milnacipran is safe for use in depression does not alter this analysis.

application includes the results of Cypress'[43] Phase II trials and relates to the treatment of neurological disorders (such as FMS) using antidepressants, including "milnacipran, administered in an escalating dosage to minimize undesirable side effects." (JTX 197 at ¶¶ [0002]-[0003]) While the '681 application references other antidepressants, milnacipran is repeatedly referenced in the specification and is the only compound discussed in all three working examples. (*Id.* at ¶¶ [0002]-[0011], [136-7], [0162]-[0204]; D.I. 281 at 1020:25-1021:18)

The Phase II trials were successful in establishing that milnacipran was effective for the treatment of fibromyalgia in well-controlled placebo controlled trials. This was the first time milnacipran was shown to be effective in treating fibromyalgia (D.I. 281 at 969:21-24), and was one of the earliest demonstrations that a drug could be proven effective in FDA placebo-controlled clinical trials in treating fibromyalgia. In addition to the '681 application, the results of this study were also published in an article (JTX 060) titled "Efficacy of Milnacipran in Patients with Fibromyalgia." (JTX 197 at ¶¶ [117-120]; D.I. 277 at 536:1-538:2; D.I. 281 at 971:1-24, 990:15-18)

The '681 application teaches that titration of milnacipran can improve tolerance relative to an unescalated dose. (JTX 197 at ¶ [0117]; D.I. 277 at 498:15-499:12, D.I. 281 at 1029:3-7) Moreover, the '681 application defines improved tolerance as the patient experiencing: (1) no side effects; (2) fewer side effects; and/or (3) a reduction in the severity of side effects. (JTX 197 at ¶ [0117]) The '681 application also discloses

[43] Anticipating that milnacipran was a good candidate for use in FMS because it could modulate both 5-HT and NE, Cypress is the company that initially developed milnacipran for the treatment of FMS in the United States. (JTX 178 at FOR002462034)

that milnacipran can be safely and effectively administered without titration. (*Id.* at ¶¶ [0162], [0169], [0119]) For instance, the '681 application discloses that patients who received an unescalated dose of 100 mg/day of milnacipran experienced side effects, but that such side effects decreased as treatment progressed and did not cause the patients to discontinue treatment. (*Id.* at ¶ [0169]; D.I. 277 at 497:12-498:1)

Example 1 of the '681 application titled "Gradual or Dosing Escalation, and the Effect of Milnacipran for Treatment of Fibromyalgia," describes the Phase II trial to assess milnacipran for the treatment for fibromyalgia. (JTX 197 at ¶¶ [0162]-[0169]; D.I. 281 at 969:25-970:10) Example 1 states that one of the objectives was "to determine whether gradual escalation of dosage could increase the tolerated dose of milnacipran." (JTX 197 at ¶ [0162]; D.I. 281 at 969:25-970:25) The '681 publication explains, "[i]n previous studies, patients were given initial daily dosages of milnacipran of 50 mg, 100 mg, or 200 mg, and the adverse event profile with 200 mg was substantially worse than with 100 mg or 50 mg. In this study, daily dosages were gradually escalated." (JTX 197 at ¶ [0162]) Example 1 provides a 4-week titration schedule used in the Phase II clinical trial of milnacipran for the treatment of FMS as follows: 25 mg/day for week 1, 50 mg/day for week 2, 100 mg/day for week 3, and 200 mg/day for week 4. (JTX 197 at Example 1, at ¶ [0164]; D.I. 281 at 1021:21-23) Utilizing this schedule, the patient received a dose of 100 mg/day on day 15. (D.I. 277 at 500:12-501:19) The '681 application discloses that this schedule was safe and effective for the treatment of FMS. (JTX 197 at Example 1; D.I. 277 at 501:16-19) Specifically, the '681 application concluded that "[s]ide effects for patients given an unescalated initial dose of 100 mg milnacipran were worse in the first week of treatment and subsided to lower levels by weeks 2-4," suggesting "that the

slower escalation of dose was responsible for greater patient tolerance of a 200 mg daily dosage of milnacipran." (JTX 197 at ¶ [0169]) This 100 mg unescalated dose is reflected in Example 3 of the '911 patent, which is directed to the treatment of fibromyalgia. ('911 patent at 13:46-50) The '681 application teaches that dose titration is flexible and can be carried out in multiple ways. (JTX 197 at ¶¶ [0118]-[0124]; D.I. 277 at 500:7-11) For example, the '681 application teaches 4-step titration schedules, starting at doses up to 100 mg/day, with a minimum of 3 days at each step. (JTX 197 at ¶¶ [0119], [0120]; D.I. 277 at 498:2-14, 501:23-502:6)

Defendants assert that a person of ordinary skill in the art reading the '681 application would have understood that there is a balance between tolerability of the drug and reaching an effective dose as quickly as possible. (D.I. 277 at 499:13-500:2, 502:7-14) Consequently, a person of ordinary skill in the art would have been motivated to shorten the weekly titration schedule of Example 1 using the disclosed 3-day escalation. (D.I. 277 at 501:23-503:7) A patient using the resulting titration schedule would have achieved a dose of 100 mg/day of milnacipran on day 7 as follows:

Day	1	2	3	4	5	6	7	8	9	10	11	12
Dose (mg/day)	25	25	25	50	50	50	100	100	100	200	200	200

(b) Ansseau

Ansseau, a prior art article published in 1989 titled "Controlled comparison of two doses of milnacipran (F 2207) and amitriptyline in major depressive inpatients," discloses a multicenter study that compares the antidepressant efficacy and tolerability of two doses of milnacipran (50 mg/day (the "50 Group") and 100 mg/day (the "100

Group")) to amitriptyline (150 mg/day). (DTX 12 at 163; D.I. 277 at 505:23-506:7) Ansseau discloses a 5-day titration schedule for both the 50 and 100 Groups as follows:

Ansseau 50 Group:

Day	1	2	3	4	5	6	7	8
Dose (mg/day)	12.5	25	25	50	50	50	50	50

Ansseau 100 Group:

Day	1	2	3	4	5	6	7	8
Dose (mg/day)	25	50	75	75	100	100	100	100

(DTX 12 at 164; D.I. 277 at 506:8-20)

(c) Analysis

The fast titration schedule contained in the '220 patent was directly contrary to the prior art, namely, Forest's own previously published Phase II clinical trial that described a slow multi-week titration schedule as medically necessary for patients to tolerate the medicine and reach an effective dose. Plaintiffs' expert, Dr. Mease, testified how one skilled in the art would understand that a "start low-go slow approach" was essential to obtaining effective treatment. (D.I. 281 at 971:1-8) Dr. Mease further testified that, based on the published successful results of the Phase II trials, those skilled in the art would not have been motivated to use a fast titration schedule with a reasonable expectation of success. (D.I. 281 at 973:5-10) Contrary to defendants' contention that the claims of the '220 patent disclosing this fast titration are obvious in view of the '681 application, written by the inventors of the '220 patent, the '681 application recommends a slow titration schedule, and teaches away from using a fast

titration schedule. Defendants seek to overcome such deficiencies by using hindsight knowledge of the titration schedule later claimed in the '220 patent and then constructing a hypothetical titration schedule based on the teaching of the '681 application that are not specific to fibromyalgia. Defendants rely on this argument with the testimony of Dr. Fortunak, a chemist, who has no relevant experience in this area. Similarly, defendants point to references that use milnacipran to treat depression in Europe in the 1990s. As plaintiffs assert, obviousness must be assessed based on the prior art as a whole as of the effective filing date of the patent. Here, as of the 2005 effective filing date of the '220 patent, the successful Phase II clinical trials with milnacipran were published, and one skilled in the art would not have looked towards papers published a decade earlier that discussed depression, a different disease with a different patient population. (D.I. 281 at 987:2-988:6)

As explained by Dr. Mease, a person of ordinary skill in the art would have followed the slow titration schedule disclosed in the '681 application in using milnacipran to treat fibromyalgia patients. (D.I. 281 at 968:23-971:24, 973:5-10) Even Dr. Fortunak acknowledged that the titration schedule in Example 1 of the '681 application was safe and effective for the treatment of fibromyalgia, providing further evidence that there would have been no motivation to modify the disclosed schedule to arrive at a faster titration. (D.I. 277 at 501:16-19)

Defendants argue that the '681 application also discloses the following titration schedule:

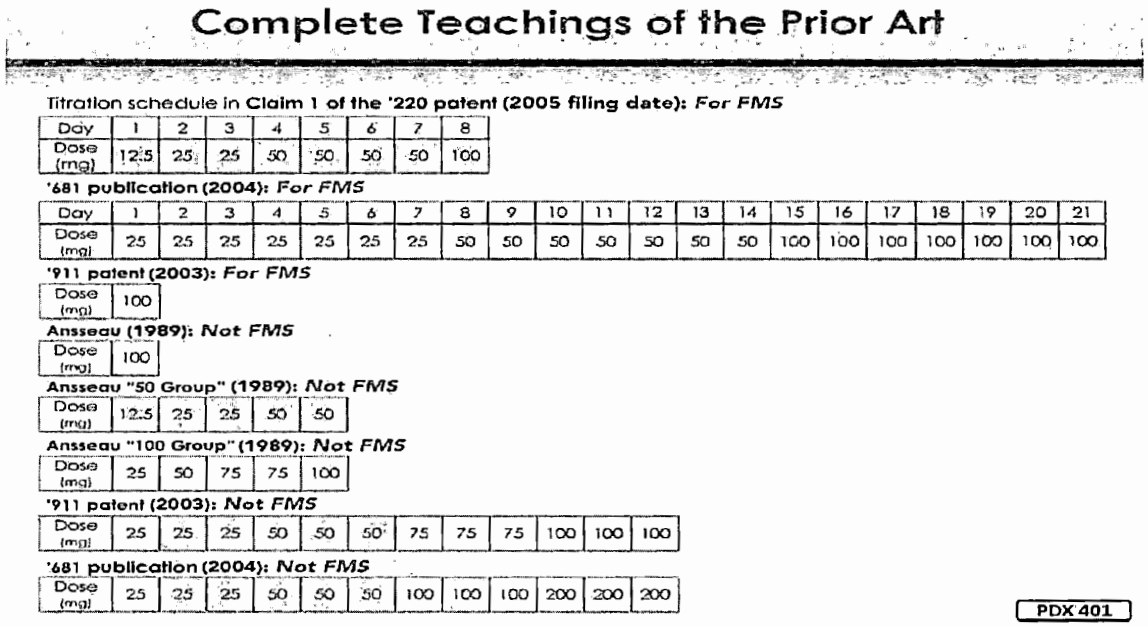
Day	1	2	3	4	5	6	7	8	9	10	11	12
Dose (mg)	25	25	25	50	50	50	100	100	100	200	200	200

This titration schedule, however, appears to be hypothetical, created by defendants for purposes of this litigation and based on defendants' hindsight-based survey of the broad teachings discussed in paragraphs 119-120 of the '681 application. (JTX 197 at ¶¶ [0119]-[0120]) Dr. Mease testified, and Dr. Fortunak conceded, that these paragraphs disclose twenty-one different active compounds including SNRIs, monoamine oxidase inhibitors, SSRIs, TCAs, and anticonvulsants, all of which have different side effect profiles. (JTX 197 at ¶¶ [0027]-[0032], [0056]-[0081]; D.I. 277 at 538:19-539:16; D.I. 278 at 545:23-546:1; D.I. 281 at 971:25-973:10) Further, the neurological conditions are not limited to fibromyalgia, but include numerous neurological disorders, including chronic fatigue syndrome, neuropathic pain, fibromyalgia, chronic pain, depression, and functional somatic disorders. (*Id.*) Given this broad disclosure, Dr. Mease testified that a person having ordinary skill in the art looking to use milnacipran to treat fibromyalgia would look to Example 1 of the '681 application, because it actually discloses using milnacipran to treat fibromyalgia in an actual clinical trial that took place. (D.I. 281 at 971:25-973:10)

Defendants also rely on references that disclose the use of milnacipran in indications other than fibromyalgia, including depression and painful diabetic neuropathy. (DTX 012 at 163-164; '911 patent at Example 4) As the population of patients suffering from fibromyalgia is more sensitive to side effects, the use of these other references would not have been relied on by those skilled in the art in determining how to treat fibromyalgia, particularly in light of the '681 application. (D.I. 277 at 519:19-23; D.I. 281 at 987:2-989:2, 965:25-966:24)

Defendants' reliance on the titration schedule in Ansseau is similarly misplaced, as Ansseau compares two doses of milnacipran (50 mg and 100 mg/day) against 150 mg/day of amitriptyline in depressed patients. (DTX 012) At trial, Dr. Fortunak used a demonstrative that sets forth an eight-day titration schedule (as per the '220 patent) for using milnacipran to treat depression, despite the fact that Ansseau's titration schedule lasted only 5 days. (D.I. 278 at 549:9-21) Such hindsight analysis is not persuasive. More importantly, Ansseau states that milnacipran does not need to be titrated at all in depressed patients, stating that "milnacipran could have been administered at the effective dose from the first day with a consequent shortening of the clinical latency." (DTX 090 at 166) The only reason milnacipran was titrated in that study was to match the titration schedule that was needed for patients assigned to the amitriptyline arm of the study. (*Id.*; D.I. 277 at 524:18-525:25; D.I. 281 at 989:4-990:4) Thus, a person of ordinary skill in the art would understand that Ansseau teaches that titration of milnacipran is not needed in the depressed patient population. (*Id.*) In contrast, it was well known that fibromyalgia patients are more susceptible to adverse events than other patient populations, primarily due to "generalized hyper-irritability." (D.I. 276 at 77:2-78:1; D.I. 277 at 519:19-23; D.I. 281 at 966:2-24, 987:2-989:2) The fact that depressed patients can reach an efficacious dose within a certain time frame says little about whether fibromyalgia patients will tolerate the same drug on the same schedule. (*Id.*) Accordingly, as Dr. Mease testified, persons of ordinary skill in the art would not find persuasive those references discussing how to dose depressed patients when information on how to dose fibromyalgia patients was available. (D.I. 281 at 987:2-989:2)

As to defendants' chart with overlapping ranges cited in the prior art, plaintiffs used the following chart at trial that presents a more complete description of the art:



Complete Teachings of the Prior Art

Titration schedule in Claim 1 of the '220 patent (2005 filing date): *For FMS*

Day	1	2	3	4	5	6	7	8
Dose (mg)	12.5	25	25	50	50	50	50	100

'681 publication (2004): *For FMS*

Day	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21
Dose (mg)	25	25	25	25	25	25	25	50	50	50	50	50	50	50	100	100	100	100	100	100	100

'911 patent (2003): *For FMS*

Dose (mg)	100

Ansseau (1989): *Not FMS*

Dose (mg)	100

Ansseau "50 Group" (1989): *Not FMS*

Dose (mg)	12.5	25	25	50	50

Ansseau "100 Group" (1989): *Not FMS*

Dose (mg)	25	50	75	75	100

'911 patent (2003): *Not FMS*

Dose (mg)	25	25	25	50	50	50	75	75	75	100	100	100

'681 publication (2004): *Not FMS*

Dose (mg)	25	25	25	50	50	50	100	100	100	200	200	200

PDX 401

(D.I. 278 at 550:20-554:7) As shown, none of the prior art disclosing titration schedules specific to the use of milnacipran for fibromyalgia patients teach the one-week titration schedule claimed in the '220 patent. Defendants admit that no single reference encompasses the titration schedule claimed in the '220 patent. (D.I. 262 at 55) This does not constitute "overlap." *In re Petersen*, 315 F.3d 1325, 1329 (Fed. Cir. 2003) (describing situation where a single prior art reference disclosed a range that a skilled artisan could select from to obtain the later claimed invention); *In re Harris*, 409 F.3d 1339, 1341-42 (Fed. Cir. 2005); *In re Geisler*, 116 F.3d 1465, 1467-68 (Fed. Cir. 1997). Further, as discussed above, the general teaching of the '681 application relied on by Dr. Fortunak is not specific to fibromyalgia and describes a vast number of permutations concerning different compounds, different diseases, and different lengths

of titration schedules.[44] The '681 application would not have motivated a person of ordinary skill in the art to develop the titration schedule claimed in the '220 patent for fibromyalgia; if anything, it would have taught away from such a schedule. As such, defendants have failed to present clear and convincing evidence of obviousness. Genetics Inst., LLC v. Novartis Vaccines & Diagnostics, Inc., 655 F.3d 1291, 1306-07 (Fed. Cir. 2011); *Allergan v. Sandoz Inc.*, 796 F.3d 1293, 1305 (Fed. Cir. 2015).

The court concludes that defendants' proffered arguments and evidence are not persuasive. Consequently, defendants have not demonstrated, by clear and convincing evidence, that the '220 patent is as obvious in light of the '681 application, the '911 patent, and Ansseau.

3. Secondary considerations

Plaintiffs assert that it would have been surprising and unexpected that the titration schedule in claim 1 of the '220 patent was safe and effective for the treatment of FMS. (D.I. 250, Ex. 2 at ¶¶ 471-82) In support of this assertion, Dr. Mease compared claim 1 to the 4-6 week titration schedule in the MD-03 study,[45] and concluded that it was unexpected that the patients in the 4-6 week study (MD-03) did not show greater tolerance than the patients in the two studies using the claimed

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[44] As noted, Dr. Fortunak is a medicinal chemist with no experience developing titration schedules, no experience treating fibromyalgia patients, and no experience as to how fibromyalgia patients actually respond to side effects. (D.I. 2yes 77 at 416:14-17, 517:16-519:23; D.I. 278 at 546:11-547:2, 510:5-512:10)

[45] MD-03 was a Phase III study with a 4-6 week titration schedule. (JTX 116 at FOR000131620) The 8-day titration schedule claimed in the '220 patent was used in the FMS-031 and MD-02 Pivotal Phase III studies. (D.I. 281 at 975:2-980:4, 995:16-997:1, 999:4-6, 1000:25-1001:2)

schedule. (D.I. 262 at 57 (citing FMS-031 and MD-02); D.I. 281 at 984:2-11, 985:22-987:1)

In response, defendants assert that, because Dr. Mease did not compare the claimed titration schedule to the closest prior art (the '681 application), his testimony is irrelevant and should be rejected. Moreover, defendants argue that the results of the claimed schedule are not unexpected in light of the teachings of the '681 application as described above.

Even if one accepts Dr. Mease's opinion, the court concludes that the alleged unexpected result, comparable tolerability under the claimed titration schedule, is a difference in degree rather than a difference in kind. Plaintiffs have not carried their burden to prove their proferred secondary consideration of obviousness.

III. CONCLUSION

For the foregoing reasons, the court finds that defendants infringe the asserted claims of the '911, 362, and '220 patents, and that the '911, 362, and '220 patents are valid. An appropriate order shall issue.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

FOREST LABORATORIES HOLDINGS LTD., and ROYALTY PHARMA COLLECTION TRUST,	)	
Plaintiffs,	)	
v.	)	Civ. No. 13-1602-SLR (Consolidated)
MYLAN INC., and MYLAN PHARMACEUTICALS INC.,	)	
Defendants.	)	

ORDER

At Wilmington this 11th day of July, 2016, consistent with the opinion issued this same date;

IT IS ORDERED that:

1. Defendants infringe the asserted claims of the '911, '342 and '220 patents.

2. The asserted claims of the '911, '342 and '220 patents are valid.

3. The clerk of court is directed to enter judgment in favor of plaintiffs and against defendants.

United States District Judge