IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVANIR PHARMACEUTICALS, INC., AVANIR HOLDING COMPANY, AND CENTER FOR NEUROLOGIC STUDY,	:	
Plaintiffs,	:	
v.	:	
ACTAVIS SOUTH ATLANTIC LLC, ACTAVIS, INC., PAR PHARMACEUTICAL, INC., PAR PHARMACEUTICAL COMPANIES, INC., IMPAX LABORATORIES, INC., WOCKHARDT, LTD., WOCKHARDT USA, LLC, WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., AND WATSON PHARMA, INC.,	:	C.A. No. 11-704-LPS (CONSOLIDATED)
Defendants.	:	

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MEMORANDUM OPINION

April 30, 2014
Wilmington, Delaware

STARK, U.S. District Judge:

Avanir Pharmaceuticals, Inc., Avanir Holding Company, and Center for Neurologic Study ("CNS") (collectively, "Avanir" or "Plaintiffs") allege that Par Pharmaceutical, Inc., Par Pharmaceutical Companies, Inc., and Impax Laboratories, Inc. (collectively, "Defendants") infringe United States Patent Nos. RE38,115 ("the '115 patent"), 7,659,282 ("the '282 patent"), and 8,227,484 ("the '484 patent") (collectively, the "patents-in-suit").[1] (C.A. No. 11-704-LPS D.I. 1; C.A. No. 11-705-LPS D.I. 1; C.A. No. 11-757-LPS D.I. 1; C.A. No. 12-1123-LPS D.I. 1; C.A. No. 12-1298-LPS D.I. 1) The '115 patent relates to formulations containing dextromethorphan ("DM") and quinidine ("Q") for the treatment of chronic or intractable pain. The '282 and '484 patents relate to the use of DM and Q for the treatment of a neurological disorder known as pseudobulbar affect ("PBA").[2] DM and Q are the active ingredients of Avanir's Nuedexta® product.

In December 2012, the Court construed the disputed terms of the patents-in-suit. (D.I. 256, 257)[3] The Court conducted a six-day bench trial in September and October of 2013. (*See* D.I. 463-70) (hereinafter, "Tr.") The parties completed post-trial briefing on November 15, 2013. (D.I. 429, 432, 444, 446, 449, 450) In connection with the briefing, the parties submitted proposed findings of fact and conclusions of law. (D.I. 430, 431, 443, 445, 447, 451)

Pursuant to Federal Rule of Civil Procedure 52(a), and after having considered the entire

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[1]These actions and several others were consolidated. (D.I. 21, 103, 173) Actions involving Actavis South Atlantic LLC, Actavis, Inc., Wockhardt, Ltd., Wockhardt USA, LLC, Watson Pharmaceuticals, Inc., Watson Laboratories, Inc., and Watson Pharma, Inc. have been dismissed by stipulation.

[2]Pursuant to the Court's claim construction order, PBA is "a neurological disorder characterized by intermittent spasmodic outbursts of emotion at inappropriate times or in the absence of any particular provocation." (D.I. 256 at 11-12)

[3]The Court refers to the "D.I." number in C.A. No. 11-704-LPS unless otherwise indicated.

record in this case and the applicable law, the Court concludes that: (1) Defendants have stipulated that their proposed products infringe claims 1-9 of the '282 patent; (2) Defendants have stipulated that their proposed products infringe claims 1-9, 12, 13, 15, and 17 of the '484 patent; (3) Plaintiffs have not proven by a preponderance of the evidence that Defendants infringe claims 18-21 of the '115 patent; (4) Defendants have failed to prove by clear and convincing evidence that claims 1-9 of the '282 patent are invalid; (5) Defendants have failed to prove by clear and convincing evidence that claims 1-9, 12, 13, 15, and 17 of the '484 patent are invalid; and (6) Defendants have failed to prove by clear and convincing evidence that claims 18-21 of the '115 patent are invalid. The Court's findings of fact and conclusions of law are set forth in detail below.

I. FINDINGS OF FACT

This section contains the Court's findings of fact for issues raised by the parties during trial. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. The Parties

1. Plaintiff Avanir Pharmaceuticals, Inc. is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 20 Enterprise, Suite 200, Aliso Viejo, California 92656. (D.I. 443 (Joint Findings of Fact ("JFF")) at ¶ 1)

2. Plaintiff Avanir Holding Company is a corporation organized and existing under the laws of the State of California, having a principal place of business at 20 Enterprise, Suite 200, Aliso Viejo, California 92656. (*Id.* at ¶ 2)

3. Avanir Holding Company is a wholly-owned subsidiary of Avanir

Pharmaceuticals. (*Id.* at ¶ 3)

4. Plaintiff CNS is a not-for-profit corporation organized and existing under the laws of the State of California, having a principal place of business at 7950 Fay Avenue, Suite 517, La Jolla, California 92037. (*Id.* at ¶ 4)

5. Defendant Par Pharmaceutical, Inc. is a Delaware corporation with a principal place of business at One Ram Ridge Road, Spring Valley, New York 10977. (*Id.* at ¶ 5)

6. Defendant Par Pharmaceutical Companies, Inc. is a Delaware corporation with a principal place of business at One Ram Ridge Road, Spring Valley, New York 10977. (*Id.* at ¶ 6)

7. Defendant Impax Laboratories, Inc. is a corporation organized and existing under the laws of Delaware and having a principal place of business at 30831 Huntwood Avenue, Hayward, California 94544. (*Id.* at ¶ 7)

B. U.S. Patent 7,659,282

8. The '282 patent, entitled "Pharmaceutical Compositions Comprising Dextromethorphan and Quinidine for the Treatment of Neurological Disorders," issued on February 9, 2010. (PTX-1; JFF at ¶ 8)

9. The '282 patent issued from U.S. Patent Application No. 11/035,213, filed on January 12, 2005, and claims priority to U.S. Provisional application No. 60/396,661, filed on July 17, 2002. (PTX-1)

10. Gerald Yakatan, James Berg, Laura E. Pope, and Richard A. Smith are the named inventors of the '282 Patent. (*Id.*; JFF at ¶ 9)

11. Plaintiffs assert that Defendants' proposed generic product and/or manufacturing

process infringe claims 1-9 of the '282 patent. (JFF at ¶ 10) Claim 1 is the only independent claim asserted. The asserted claims are reproduced below:

> 1. A method for treating pseudobulbar affect or emotional lability, the method comprising administering to a patient in need thereof dextromethorphan in combination with quinidine, wherein the amount of dextromethorphan administered comprises from about 20 mg/day to about 80 mg/day and wherein the amount of quinidine administered comprises from about 10 mg/day to less than about 30 mg/day with the proviso that the weight to weight ratio of dextromethorphan to quinidine is 1:0.5 or less.
>
> 2. The method of claim 1, wherein the pseudobulbar affect or emotional lability is caused by a neurodegenerative disease or condition or a brain injury.
>
> 3. The method of claim 1, wherein the dextromethorphan and the quinidine are administered as one combined dose per day.
>
> 4. The method of claim 1, wherein the dextromethorphan and the quinidine are administered as at least two combined doses per day.
>
> 5. The method of claim 1, wherein the amount of quinidine administered comprises from about 20 mg/day to about 30 mg/day.
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> 6. The method of claim 1, wherein the amount of dextromethorphan administered comprises from about 20 mg/day to about 60 mg/day.
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> 7. The method of claim 1, wherein at least one of the quinidine and the dextromethorphan is in a form of a pharmaceutically acceptable salt.
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> 8. The method of claim 1, wherein at least one of the quinidine and the dextromethorphan is in a form of a pharmaceutically acceptable salt selected from the group consisting of salts of free acids, inorganic salts, salts of sulfate, salts of hydrochloride, and salts of hydrobromide.
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> 9. The method of claim 1, wherein about 20 mg quinidine sulfate is administered per day.

C. U.S. Patent 8,227,484

12. The '484 patent, entitled "Pharmaceutical Compositions Comprising Dextromethorphan and Quinidine for the Treatment of Neurological Disorders," issued on July 24, 2012. (PTX-2; JFF at ¶ 20)

13. The '484 patent issued from U.S. Patent Application No. 13/415,067, filed on March 8, 2012, and claims priority to U.S. Provisional application No. 60/396,661, filed on July 17, 2002. (PTX-2)

14. Gerald Yakatan, James Berg, Laura Pope, and Richard Alan Smith are the named inventors of the '484 Patent. (*Id.*; JFF at ¶ 21)

15. Plaintiffs assert that Defendants' proposed generic product and/or manufacturing process infringe claims 1-9, 12, 13, 15, and 17 of the '484 patent. (JFF at ¶ 22) Claim 1 is the only independent claim asserted. The asserted claims are reproduced below:

> 1. A method for treating pseudobulbar affect or emotional lability, the method comprising administering to a patient in need thereof dextromethorphan in combination with quinidine, wherein the amount of dextromethorphan administered comprises from about 20 mg/day to about 60 mg/day and wherein the amount of quinidine administered comprises from about 10 mg/day to about 30 mg/day with the proviso that the weight-to-weight ratio of dextromethorphan to quinidine is 1:0.75 or less of quinidine.
>
> 2. The method of claim 1, wherein the pseudobulbar affect or emotional lability is caused by a neurodegenerative disease or condition or a brain injury.
>
> 3. The method of claim 1, wherein the dextromethorphan and the quinidine are administered as one combined dose per day.
>
> 4. The method of claim 1, wherein the dextromethorphan and the quinidine are administered as at least two combined doses per day.

5. The method of claim 1, wherein the amount of quinidine administered comprises from about 20 mg/day to 30 mg/day.

6. The method of claim 1, wherein the amount of dextromethorphan administered comprises from about 40 mg/day to 60 mg/day.

7. The method of claim 1, wherein at least one of the quinidine and the dextromethorphan is in a form of a pharmaceutically acceptable salt.

8. The method of claim 1, wherein at least one of the quinidine and the dextromethorphan is in a form of a pharmaceutically acceptable salt selected from the group consisting of salts of free acids, inorganic salts, salts of sulfate, salts of hydrochloride, and salts of hydrobromide.

9. The method of claim 1, wherein about 20 mg quinidine sulfate is administered per day.

* * *

12. The method of claim 1, wherein the weight-to-weight ratio of dextromethorphan to quinidine is 1:0.65 or less of quinidine.

13. The method of claim 1, wherein about 40 mg dextromethorphan hydrobromide is administered per day.

* * *

15. The method of claim 1, wherein about 40 mg of dextromethorphan and about 20 mg of quinidine is administered per day.

* * *

17. The method of claim 1, wherein about 40 mg of dextromethorphan hydrobromide and about 20 mg of quinidine sulfate is administered per day.

D. U.S. Patent RE38,115

16. The '115 patent, entitled "Dextromethorphan and an oxidase inhibitor for treating

intractable conditions," issued on May 6, 2003. (PTX-3; JFF at ¶ 36)

17. The '115 patent issued from U.S. Patent Application Serial No. 10/052,698, filed on January 18, 2002, which was an application for reissuance of U.S. Patent No. 5,863,927, which issued from U.S. Patent Application Serial No. 08/464,792, filed on September 19, 1996, which was the national stage application of PCT International Application No. PCT/US94/10771, filed on September 22, 1994, and claims priority back to U.S. Patent Application Serial No. 08/114,845 ("the '845 application"), filed on September 2, 1993. (*See* D.I. 441) (considering priority date)

18. Richard Alan Smith and Jonathan M. Licht are the named inventors of the '115 Patent. (PTX-3; JFF at ¶ 37)

19. Plaintiffs assert that Defendants' proposed generic product and/or manufacturing process infringe claims 18-21 of the '115 patent. (JFF at ¶ 38) Claim 18 is the only independent claim asserted. The asserted claims are reproduced below:

> 18. A unit dosage formulation for treatment of chronic or intractable pain, comprising:
>
> (a) dextromethorphan or a pharmaceutically acceptable salt thereof, and,
>
> (b) a debrisoquin hydroxylase inhibitor, in a combined form that is designed for oral ingestion by humans, wherein the dextromethorphan or salt thereof and the debrisoquin hydroxylase inhibitor are present at a combined dosage which renders the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects.
>
> 19. The unit dosage formulation of claim 18, comprising a digestible capsule which encloses the dextromethorphan or pharmaceutically acceptable salt thereof and the debrisoquin

hydroxylase inhibitor.

20. The unit dosage formulation of claim 18, wherein the debrisoquin hydroxylase inhibitor is selected from the group consisting of quinidine, quinine, and pharmaceutically acceptable salts thereof.

21. The unit dosage formulation of claim 20, wherein the dosage of quinidine is 300 milligrams/day or less.

E. Nuedexta®

20. Avanir Pharmaceuticals, Inc. holds approved New Drug Application ("NDA") No. 21-879 under Section 505(a) of the Federal Food Drug and Cosmetic Act ("FFDCA"), 21 U.S.C. § 355(a), for 20 mg dextromethorphan hydrobromide/10 mg quinidine sulfate capsules, which it sells under the trade name Nuedexta®. (D.I. 1 at ¶ 16; JFF at ¶ 44) The Nuedexta® capsule is taken once a day for the first week and twice a day thereafter for the treatment of PBA. (PTX-105 at AVAN-0207640; Tr. at 273-74)

21. Nuedexta® was approved by the FDA in October 2010 for the treatment of PBA. (DTX-40; JFF at ¶ 45)

22. Avanir Pharmaceuticals, Inc. has been marketing and selling Nuedexta® since February 2011. (PTX-150 at AVAN-0319386; JFF at ¶ 46)

23. Nuedexta® is the only drug product approved by the FDA for treatment of PBA. (JFF at ¶ 47)

F. Defendants' Generic Products

1. Par's Abbreviated New Drug Application ("ANDA")

24. Par filed ANDA No. 202-993 ("Par's ANDA"), pursuant to Section 505 of the FFDCA, seeking approval to engage in the commercial use, manufacture, sale, offer for sale,

or importation of 20 mg dextromethorphan hydrobromide/10 mg quinidine sulfate capsules ("Par's Generic Product") before the patents-in-suit expire. (*Id.* at ¶ 48)

25. In connection with the filing of its ANDA, Par provided written certifications to the FDA, pursuant to Section 505 of the FFDCA, alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Par's ANDA. (*Id.* at ¶ 49)

26. No earlier than June 29, 2011, Par sent written notice of its ANDA certification relating to the '282 and '115 patents to Avanir ("Par's First Notice Letter"), informing Avanir that Par seeks approval to market Par's Generic Product before the expiration of the '282 and '115 Patents. (*Id.* at ¶ 50)

27. No earlier than August 22, 2012, Par sent written notice of its ANDA certification relating to the '484 Patent to Avanir ("Par's Second Notice Letter"), informing Avanir that Par seeks approval to market Par's Generic Product before the expiration of the '484 patent. (*Id.* at ¶ 51)

2. Impax's ANDA

28. Impax filed ANDA No. 203-061 ("Impax's ANDA"), pursuant to Section 505 of the FFDCA, seeking approval to engage in the commercial use, manufacture, sale, offer for sale, or importation of 20 mg dextromethorphan hydrobromide/10 mg quinidine sulfate capsules ("Impax's Generic Product") before the patents-in-suit expire. (*Id.* at ¶ 52)

29. In connection with the filing of its ANDA, Impax provided written certifications to the FDA, pursuant to Section 505 of the FFDCA, alleging that the claims of the patents-in-suit are invalid, unenforceable, and/or will not be infringed by the activities described in Impax's

ANDA. (*Id.* at ¶ 53)

30. No earlier than July 19, 2011, Impax sent written notice of its ANDA certification relating to the '282 and '115 Patents to Avanir ("Impax's First Notice Letter"), informing Avanir that Impax seeks approval to market Impax's Generic Product before the expiration of the '282 and '115 Patents. (*Id.* at ¶ 54)

31. No earlier than September 20, 2012, Impax sent written notice of its ANDA certification relating to the '484 Patent to Avanir ("Impax's Second Notice Letter"), informing Avanir that Impax seeks approval to market Impax's Generic Product before the expiration of the '484 Patent. (*Id.* at ¶ 55)

G. The Expert Witnesses at Trial

32. Dr. Stanley H. Appel testified as an expert "in the field of neurology; in particular, ALS [Amyotrophic lateral sclerosis, also known as Lou Gehrig's disease] and the treatment of PBA and the prescribing of drugs in his specialty," on behalf of Plaintiffs. (Tr. at 264)

33. Dr. Mark C. Rainey testified as an expert "in the field of economics in the pharmaceutical industry and in particular in the field of industrial organization in the pharmaceutical industry," on behalf of Plaintiffs. (*Id.* at 775)

34. Dr. Edward M. Sellers testified as an expert "in clinical psychopharmacology and CNS [Central Nervous System] drug development," on behalf of Plaintiffs. (*Id.* at 856)

35. Dr. Daniel R. Wynn testified as an expert "in the field of neurology. In particular, MS [Multiple Sclerosis] and the treatment of PBA and chronic, intractable pain in the prescribing of drugs in this specialty," on behalf of Plaintiffs. (*Id.* at 1092)

36. Dr. Alan Boobis testified as an expert "in the area of clinical pharmacology," on

behalf of Defendants. (*Id.* at 343)

37. Dr. Henrik Poulsen testified as an expert "in clinical pharmacology," on behalf of Defendants. (*Id.* at 493)

38. Dr. Timothy R. Deer testified as an expert "in the treatment and evaluation of therapies for chronic or [in]tractable pain," on behalf of Defendants. (*Id.* at 679)

39. Dr. William T. Dauer testified as an expert "in diagnosis and treatment of neurological disease and associated symptoms," on behalf of Defendants. (*Id.* at 723-24)

40. Dr. Gordon Rausser testified as an expert "in the fields of economics, finance, and statistics," on behalf of Defendants. (*Id.* at 813)

41. Dr. John Kelly testified by deposition as an expert "in the diagnosis and treatment of neurologic conditions, including PBA and the treatment of neuropathic pain," on behalf of Defendants. (*Id.* at 1040)

H. Person Having Ordinary Skill in the Art

42. The Court has determined that a person having ordinary skill in the art relating to the inventions claimed by the '282 and '484 patents, at the time that the claimed inventions were made, would have at least an M.D. or Ph.D. in an area relevant to pharmacokinetics ("PK") and/or drug interactions, or a Bachelor's degree and at least five years of relevant industry or academic experience in the area of PK and/or drug interactions. (*Id.* at 496-97)

43. The Court has determined that a person having ordinary skill in the art relating to the inventions claimed by the '115 patent, at the time that the claimed invention was made, would have at least an M.D. with knowledge of or five years experience in treating pain or patients with neurologic conditions including pain. (*Id.* at 680)

I. Facts Relating to Infringement of the '282 and '484 Patents

44. Both Impax and Par have stipulated that their proposed ANDA products infringe each asserted claim of the '282 and '484 patents. (D.I. 238, 411)

J. Facts Relating to Infringement of the '115 Patent

45. The Court construed "chronic pain" to mean "long-term pain resulting from conditions such as stroke, cancer and trauma, as well as neuropathic pain due to deterioration of nerve tissue such as postherpetic neuralgia (PHN) resulting from herpes zoster infection, and diabetic neuropathy resulting from long-time diabetes. The conditions are not an exclusive list." (D.I. 257 at ¶ 3)

46. The Court construed "intractable pain" to mean "pain which failed to respond adequately to conventional treatments." (*Id.* at ¶ 4)

47. The Court determined "a combined dosage which renders the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects" did not require construction and is given its plain and ordinary meaning. (*Id.* at ¶ 5)

48. On November 20, 2012, Impax stipulated that, with the exception of the language of the preamble of Claim 18 of the '115 Patent ("A unit dosage formulation for the treatment of chronic or intractable pain"), as well as the claim term "are present at a combined dosage which renders the dextromethorphan therapeutically effective in substantially reducing chronic or intractable pain, without causing unacceptable side effects," Impax's Generic Product falls within the literal scope of claims 18-21 of the '115 patent. (D.I. 238 at ¶ 3; JFF at ¶ 58) Although Par filed no similar stipulation, the only limitation of the '115 patent Par disputed at

trial or in its post-trial briefing (*see* D.I. 450 at 19-22) is the same limitation challenged by Impax. Defendants do not challenge Plaintiffs' contention that, at least for purposes of infringement of the '115 patent, Par's and Impax's Generic Products are identical to Nuedexta®, such that if Nuedexta® is an embodiment of the '115 patent, then Par's and Impax's Generic Products infringe the '115 patent. (PTX-50; DTX-105; D.I. 446 at 41)

49. Avanir clinical studies AVR-106 ("Study 106") and AVR-107 ("Study 107") tested substantially higher dosages of DM and Q than what is contained in the Nuedexta® product. (Tr. at 1141-42)

50. Avanir's clinical study AVR-123 ("STAR Study") was not designed to look at pain. (*Id.* at 1142-43) The STAR Study concluded that there was no statistically significant difference in pain level between patients who received Nuedexta® and patients who received a placebo, when pain was measured as a secondary endpoint. (*Id.* at 1142-47)

51. On December 10, 2013, Avanir disclosed the results of its Phase II PRIME Study for the treatment of central neuropathic pain in patients with multiple sclerosis. Avanir reported that "there was no difference between the treatment arms [using AVP-923, which included '20mg DM/10mg Q'] and placebo," and further that "the treatment of central neuropathic pain in patients with multiple sclerosis did not meet the primary efficacy endpoint." (D.I. 458 Ex. 1) ("JTX-1")

52. Dr. Wynn testified that the patients to whom he has prescribed Nuedexta® are sometimes on more than a dozen medications, including, sometimes, other pain medications. He also testified that it is not uncommon for patients who are taking Nuedexta® for pain to take other pain medications regularly as well. (Tr. at 1156-58)

53. None of the examples in the '115 patent use the 20/10 mg/day dose of DM/Q found in Nuedexta®. (*Id.* at 689-91, 1166)

54. Neither the labels for Nuedexta® nor any of Defendants' products provide any indication that the 20/10 formulation of DM/Q can be used to treat pain. (*Id.* at 1171-73)

55. Pre- and post-treatment pain scores are important for making any judgment as to the efficacy of the drug. (*Id.* at 695) In prescribing medication to reduce pain, physicians rely on data reporting a measureable pain score reduction resulting from the drug, on a scale that has been validated. (*Id.* at 684)

56. There are no peer-reviewed publications or prospective studies reporting that Nuedexta® is therapeutically effective in treating chronic or intractable pain. (*Id.* at 685) Nuedexta® has not been the subject of any presentation at any of the major conferences related to pain. (*Id.* at 685-86) Nuedexta® is not mentioned in comprehensive pain treatment text books. (*Id.* at 686-87)

57. Nuedexta® has not been approved to treat chronic or intractable pain. Nuedexta® has only been approved by the FDA for the treatment of PBA. (DTX-40; Tr. at 687)

58. A person of ordinary skill in the art would consider unacceptable side effects to be those that cause limitations in the patient's daily function or those that cause other comorbidities or other disease states. (Tr. at 691)

59. Given the comorbidities that are often found in patients with chronic pain, it is difficult to understand the side effects of treating chronic or intractable pain with Nuedexta® without performing a study involving a sample of patients who all suffer from chronic or intractable pain. (*Id.* at 692-93)

60. Dr. Wynn's patient interviews do not provide measurements or information on the patients' pre- and post-treatment pain scores, do not control for any possible confounding variables, including placebo effect, do not control for patient activity – which is standard practice in pain research, due to the possibility of false-positives as a result of differences in patient activity level – and do not control for other medications that the patients may have been taking at the same time as their Nuedexta® treatment. (DTX-267; DTX-478; Tr. at 695, 697-99)

61. In his experience, Dr. Wynn has seen patients discontinue Nuedexta® due to side effects. (Tr. at 1168)

K. Facts Relating to Validity of the '282 and '484 Patents

62. Neither DM nor Q was a new chemical entity in July 2002. (*Id.* at 442, 883-84)

63. DM is rapidly metabolized by a liver enzyme known as cytochrome P450-2D6 enzyme (or "CYP2D6") into dextrorphan ("DX") and eliminated from the body. (DTX-10 at 2:30-37, 2:59-66)

64. In July 2002, Q was a known inhibitor of CYP2D6. (DTX-6 at 7:27-29)

65. Phenotypically, maximum inhibition of CYP2D6 can convert an "extensive metabolizer" ("EM") to a "poor metabolizer" ("PM"). (Tr. at 359) "Poor metabolizers" of drugs have a deficiency in CYP2D6 activity. (*Id.* at 353-54; DTX-124 at AVAN-0379192) All other individuals who do not exhibit reduced activity of the enzyme are called "extensive metabolizers." (Tr. at 354)

1. Scope and teachings of the prior art

a. '248 patent

66. U.S. Patent No. 5,206,248 (hereinafter, "the '248 patent") was admitted at trial

as DTX-6. The '248 patent issued on April 27, 1993. The '248 patent is entitled "Method for reducing emotional lability" and discloses the combination of 30-120 mg/day of DM and 150 mg/day of Q for treatment of PBA. (DTX-6 at 11:10-15, 11:39-41)

67. Example 2 of the '248 patent taught that a patient receiving 60 mg/day of DM and 150 mg/day of Q had blood concentrations of DM that "usually averaged" between 43-55 ng/mL, and the patient's PBA symptoms faded away. (*Id.* at 12:8-24)

68. Example 3 of the '248 patent taught that a patient who received 90 mg/day of DM and 150 mg/day of Q achieved DM blood levels of between 130-180 ng/mL and saw improvement in his PBA symptoms. (*Id.* at 12:27-56)

69. From the disclosures in Example 2, a person of ordinary skill would not have known when the reported blood samples were drawn, or how they were stored. (Tr. at 582-83, 867-68) A person of ordinary skill would also not have known how many blood samples were drawn, whether the patient had reached a steady state level of DM, and – even if he had – whether his blood levels were measured at C_{max} or trough levels. (*Id.* at 582-84) From the single patient of Example 2, a person of ordinary skill would not be able to conclude, with any statistical significance, that the 43-55 ng/mL DM blood levels treated PBA or determine any analytical errors. (*Id.* at 583-84) Example 2 gives no information about the patient's medical history or his pre-Q-dosing level of CYP2D6 activity, e.g., whether he was an EM or PM. (*Id.* at 867)

70. The patient in Example 3 was stopped and started on DM/Q several times, supporting causality between administration of the DM/Q and improvement in the patient's symptoms. (DTX-6 at 12:33-48; Tr. at 869) No causality was established for the patient in

Example 2. (Tr. at 584, 867, 910)

71. When no causality is established, a placebo effect, or a false positive – which is known to be very common in CNS drugs – cannot be ruled out as the reason for the apparent efficacy. (*Id.* at 698-99, 858)

b. Smith abstract

72. PTX-100 is an abstract by Smith, R.A., et al., entitled "The treatment of affective lability with dextromethorphan," published in *Neurology* in April 1995 (hereinafter, "the Smith Abstract"). The Smith Abstract reports a double-blind, placebo-controlled crossover trial reporting that 12 ALS patients' PBA episodes were safely and effectively treated with 60/150 mg/day DM/Q, resulting in DM blood concentrations of 100-200 ng/mL. (PTX-100; DTX-11; Tr. at 475-77, 519, 606-07)

c. Yakatan abstract

73. DTX-135 is an abstract published in the *Journal of Clinical Pharmacology* by Yakatan, G., et al., entitled "Low Dose Quinidine Inhibition of Dextromethorphan Metabolism by CYP 2D6" (hereinafter, "the Yakatan Abstract"). The Yakatan Abstract was published in September 1999. (DTX-135 at AVAN-0210414-415; DTX-499; Tr. at 120-22)

74. The Yakatan Abstract discloses a dose-response PK study, which explored the blood levels of DM obtained by giving subjects DM (60 mg/day) and Q (0, 5, 20, 50, 100, or 150 mg/day). (DTX-135 at AVAN-0210415; DTX-499; Tr. at 123-24, 380, 520)

d. Yakatan poster

75. DTX-144 is a poster Dr. Pope presented at the American College of Clinical Pharmacology ("ACCP") meeting in September 1999 (hereinafter, "the Yakatan Poster"). (DTX-

134; DTX-141; DTX-142; DTX-143; DTX-144; Tr. at 120, 205) The Yakatan Poster discloses similar teachings to those disclosed in the Yakatan Abstract. (DTX-135; DTX-144)

e. Other PK studies

76. DTX-21 is a paper by Nielsen, M, et al., entitled "A Dose-Effect Study of the *in vivo* Inhibitory Effect of Quinidine on Sparteine Oxidation in Man," published in the *British Journal of Clinical Pharmacology* in 1990 (hereinafter, "the Nielsen reference"). The Nielsen reference teaches that 5 mg Q has some effect on CYP2D6 inhibition. (DTX-21; Tr. at 376-78)

77. DTX-4 is a paper by Boobis, A, et al., entitled "The Contribution of Polymorphic Isozymes of Cytochrome P-450 to the Pharmacokinetics and Toxicity of Foreign Compounds in Man," published in *Microsomes and Drug Oxidations. Proceedings of the 7th International Symposium* (1987) (hereinafter, the "Boobis reference"). The Boobis reference teaches 5 mg Q can produce effects on CYP2D6 inhibition. (DTX-4 at Fig. 1)

78. DTX-8 is a paper by Desmeules, J, et al., entitled "Contribution of Cytochrome P-4502D6 Phenotype to the Neuromodulatory Effects of Dextromethorphan," published in the *Journal of Pharmacology and Experimental Therapeutics* in 1999 (hereinafter, "the Desmeules reference"). The Desmeules reference discloses that 50 mg Q converted five out of five extensive metabolizers of DM into poor metabolizers. (DTX-8 at Fig. 1; Tr. at 378, 903)

f. '053 application

79. DTX-32 is U.S. Patent Application No. 07/896,053 (hereinafter, "the '053 application"). The '053 application was filed in 1992. The '053 application teaches that the combination of DM and Q is effective in treating PBA. (DTX-32 at AVAN-0403504; Tr. at

517-18)

80. The '053 application discloses a large range of DM doses (20-400 mg/day). (DTX-32 at AVAN-0403512; Tr. at 517-18, 872)

81. The '053 application does not disclose the specific ranges of Q used in the asserted claims or any weight-to-weight ratios of DM to Q. (Tr. at 872-73) The '053 application does not disclose or suggest using doses of less than 150 mg/day Q for the treatment of PBA. (DTX-32 at AVAN-0403512-13)

g. '927 patent

82. DTX-20 is U.S. Patent No. 5,863,927 (hereinafter, "the '927 patent"). The '927 patent issued on January 26, 1999. The '927 patent was in front of the PTO during prosecution of the '282 and '484 patents. (PTX-1; PTX-2) The '927 patent is entitled "Dextromethorphan and an oxidase inhibitor for treating intractable conditions" and discloses a large range of DM doses (20-200 mg/day), in combination with Q at a range of 300 mg/day or less, with a preferred Q range of 50-150 mg/day, to treat intractable conditions. (DTX-20 at 3:67-4:1, 4:16-20; Tr. at 873)

83. The '927 patent's disclosures do not concern PBA. (Tr. at 911-12; *see also id.* at 351 (Boobis testifying: "[T]he dose of drug that's effective in one condition may be completely ineffective or much less effective in another condition."))

84. Claim 21 of the '927 patent states that the dose of Q is "300 mg/day or less" to treat chronic or intractable pain, not PBA. (DTX-20 at claim 21; Tr. at 911)

85. The '927 patent does not disclose any weight-to-weight ratios of DM to Q. (Tr. at 873)

h. Additional findings regarding prior art

86. As of July 2002, a person of ordinary skill would not have been able to predict efficacy of CNS drugs based on in vivo or in vitro pharmacokinetic studies when the dose-effect relationship was unknown. (*Id.* at 96, 458, 593-94, 857-62, 1055-57)

87. The prior art did not disclose any relationship between DM plasma levels and therapeutic efficacy for the treatment of specific disease states, such as PBA. Therefore, as of July 2002, persons of skill in the art were unaware of any dose-effect relationship for DM/Q in the treatment of PBA. (*Id.* at 99-100, 458, 593-94, 904-07, 1046)

88. Persons of ordinary skill seeking to develop a treatment for PBA would focus on dose, not concentration. (*Id.* at 906:1-12 (Sellers testifying: "I wouldn't be using serum drug concentrations for anything, especially in a situation where I was looking for something that was merely efficacious. I would always go with the dose that was reported to be effective."); *id.* at 99 (Yakatan testifying)) DM plasma levels do "not predict[] response, they are merely an observation in the context of observed efficacy." (*Id.* at 904-07)

89. As of July 2002, persons of skill in the art would not have attempted to develop PBA treatments based on DM concentrations alone. Instead, one of skill in the art developing a DM/Q treatment for PBA would have focused on the doses of DM ***and*** Q that proved effective in treating PBA. (*Id.* at 99-100, 904-07)

2. Motivation to combine or modify

a. Safety concerns

90. In the early 1990s, a neurologist named Dr. Richard Smith, relying on prior publications, speculated that DM might treat Lou Gehrig's Disease ("ALS"). (DTX-10 at

1:59-66; Tr. at 512-13)

91. Dr. Smith first ran a PK study which found that a dose of 150 mg/day of Q could maximally inhibit DM's metabolism by CYP2D6 and concluded that, at the 150 mg dose, Q was unlikely to cause any adverse side effects except in patients who are allergic to the drug. (DTX-60 at AVAN-0207765, 207768; Tr. at 164-66)

92. Dr. Smith subsequently ran a test in ALS patients which showed that DM/Q did not have any effect on ALS, but appeared to ameliorate symptoms of PBA in certain ALS patients. (DTX-10 at 2:25-27, 3:47-52; Tr. at 513-14)

93. Dr. Smith then ran a double-blind, placebo-controlled, crossover clinical trial in twelve patients, using a dose of 60 mg/day DM and 150 mg/day Q to treat PBA. On average, patients showed improvement in conditions; Smith did not identify safety concerns or a lack of efficacy. The patients had DM blood plasma levels of 100-200 ng/mL. (DTX-11; PTX-100; Tr. at 476, 519, 607, 869, 871) These results were reported in the Smith Abstract. (PTX-100)

94. Through a series of PK studies in healthy volunteers, Avanir determined that doses of Q below 150 mg/day could also maximally inhibit DM's metabolism by CYP2D6, and that the lowest dose that provided maximal inhibition was approximately 60 mg/day. (PTX-165 at AVAN-0214985; Tr. at 172-73, 176)

95. In 2001, Avanir conducted its first efficacy study, known as Study 102, with a 60/60 mg/day dosage of DM/Q in 140 ALS patients with PBA. (PTX-196A; PTX-322; Tr. at 180)

96. Study 102 concluded that the 60/60 dosage of DM/Q was efficacious in treating PBA, with a "p-value" of less than 0.001, meaning that the probability that the results of the

study were due to chance was less than 1 in 1000. (PTX-1 at 53:48-59; PTX-196A; PTX-322; Tr. at 100-01, 183-84)

97. At the time Study 102 was conducted using the 60/60 mg/day dosage of DM/Q, persons of skill in the art did not expect that doses of Q below the maximal inhibition level could be effective in a DM/Q product for the treatment of PBA. (Tr. at 195) Nothing in the prior art taught nor suggested using less than maximally-inhibiting doses of Q with DM to treat PBA. (PTX-3 at 4:30-32; Tr. at 579-80, 864-65, 871, 877-78, 882-83, 885-86, 1045-47)

98. On July 17, 2002, shortly after receiving the Study 102 results, the inventors filed the priority application for the '282 and '484 patents. (PTX-1; PTX-2; Tr. at 184)

99. In December 2002, Avanir began a second efficacy study, known as Study 106, with the same 60/60 dose, this time in 150 MS patients with PBA. (PTX-199A) The study concluded the 60/60 mg/day dosage of DM/Q was safe and effective. (*Id.*; PTX-323; Tr. at 104, 188-89)

100. In 2006, the FDA sent Avanir a letter informing Avanir that it had not approved the 60/60 dosage. (DTX-86; Tr. at 195) The FDA's concerns were based on newly-issued (in 2005) FDA guidance on cardiac QT prolongation and on a 2005 QT study conducted by Avanir. (Tr. at 195-96)

101. In response to the 2006 FDA letter, Avanir conducted a third efficacy study in PBA patients, between 2007 and 2009, known as Study 123, using DM/Q doses of 60/20 and 40/20. (PTX-104; PTX-213A, PTX-213B; Tr. at 196-97)

102. Study 123 surprisingly showed that both of the lower doses provided efficacy that was comparable to that of Study 102 and 106, and that both doses provided better safety than the

60/60 dosage. (PTX-285A at AVAN-0206633; Tr. at 197-99)

103. Based on Study 123, the FDA approved Nuedexta® at the 40/20 dose of DM/Q. (Tr. at 199)[4]

104. Prior to July 2002, persons of skill in the art would have considered 60 mg/day of DM combined with 150 mg/day of Q to be safe and effective in treating PBA. (DTX-6 at 12:8-24; DTX-11; PTX-100; Tr. at 363, 476-77, 515-16, 519, 579-80, 587, 871, 877, 879, 883-84)

105. Outside the context of PBA, there were many reported instances in the prior art of the safe administration of DM and 150 mg Q in human subjects. (*See, e.g.*, DTX-6 at 12:6-56; DTX-13; DTX-20; DTX-26; PTX-100; DTX-60 at AVAN-0207768 ("[T]he absence of any serious problems at this low quinidine dose [150 mg/day] led to its adoption for the subsequent studies."); Tr. at 883-84)

106. The only known side effects in the prior art certain to be related to Q were associated with the higher doses of Q (600-1600 mg/day) used to treat cardiac arrhythmias. (Tr. at 431-32, 435-36, 618-19, 879-80)

107. Before July 17, 2002, a person of skill in the art would not have had safety concerns at doses of 150 mg/day of Q, which were much lower than the already-approved antiarrhythmic doses of Q. (PTX-3 at 4:30-32; Tr. at 97, 423-27, 476-77, 515-16, 580, 596-97, 877, 879-80, 1047)

108. DTX-152 is a letter the FDA sent to Avanir in 2001. The 2001 FDA letter

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[4]The FDA approved a dosing regimen of DM 20 mg/Q 10 mg daily for seven days followed by the same dose taken twice daily thereafter. (PTX-285A)

stated "quinidine may alter the QTc [corrected QT] interval at the dose administered." (DTX-152 at Point 3) To the extent it cautioned about the potential effect of Q on the QTc interval, the FDA letter relied on what Avanir had already explained to the FDA about Q at the much higher antiarrhythmic level doses (600-1600 mg/day) only. (PTX-194 at AVAN-0025277; *see also* PTX-195A at AVAN-0025395; Tr. at 244-46)

109. DTX-123 is a National Institutes of Health application (hereinafter, "NIH application") filed by Dr. Yakatan on behalf of IriSys in 1996 regarding the proposed clinical trials to test the discovery that DM and Q could be used to treat PBA. (DTX 123 at CNS-0000131; Tr. at 127-28)

110. The NIH application noted that DM and Q posed some risk of adverse events or drug-to-drug interactions ("DDIs"); however, the application provided no reason to go below a maximally inhibiting dose. The application suggested using clinical trials to identify the lowest sub-therapeutic dose of Q that still accomplished maximal inhibition so that "the safety of the combination product would be maximized without compromising the therapeutic benefits of DM." (DTX-123 at CNS-0000133)

111. DTX-10 is U.S. Patent No. 5,366,980 (hereinafter, "the '980 patent"). The '980 patent issued on November 22, 1994. The '980 patent is entitled, "Use of dextromethorphan and an oxidase inhibitor to treat dermatitis" and discloses the combination of DM and Q to treat severe itching and pain associated with dermatitis, not to treat PBA. (DTX-10 at 7:5-18)

112. Dr. Smith reported in the '980 patent that, at the 150 mg/day Q dose, "the large majority of ALS patients (and all control subjects who were not afflicted with ALS) reported no adverse side effects." (*Id.* at 10:2-4)

113. The side effects reported in the '980 patent resulted in the discontinuation of medications, not a lowering of the dose of Q to the claimed dosage range. (*Id.* at 9:44-62)

114. As of July 2002, the prior art did not report any clinically meaningful adverse events at maximally-inhibiting doses of Q (50-150 mg/day). (*See, e.g.*, DTX-4; DTX-8; DTX-21; PTX-100; Tr. at 879-82)

b. Industry practice

115. The typical drug development process for new chemical entities starts with low doses and titrates up, beginning "experimentally in animal models" before "going into human subjects," i.e., pharmacokinetic studies in healthy volunteers. (Tr. at 348-49, 400, 865-66) This is not the typical process for testing chemical entities already known to be safe and effective for treating humans. (*Id.* at 866, 883-84)

116. A person of ordinary skill would have wanted to balance the risk-benefit ratio when determining what dose of Q to use in combination with DM for the treatment of PBA. (*Id.* at 174 (Pope testifying it is "typical to optimize the risk/benefit ratio"); *see also id.* at 136-37, 573-74)

117. In the context of developing a DM/Q product that had already been shown to be safe and effective at a dose of 60/150 mg/day DM/Q, optimization of the risk/benefit ratio would not have led one of ordinary skill to use less than a maximally inhibiting dose of Q. (*Id.* at 90, 95-99, 573-74, 863-65, 877-78, 882-84, 895)

3. Reasonable expectation of success

118. A person of ordinary skill in the art in 2002 would not have expected the 60/20 and 40/20 doses of DM/Q to be effective in treating PBA because the 20 mg/day dose of Q

would not maximally inhibit the metabolism of DM. (*Id.* at 195, 198-99, 864-65, 877-78, 882-83)

119. CNS drug development is challenging and inherently unpredictable, especially in relation to the treatment of PBA, as the mechanism by which PBA is treated remains unknown. (*Id.* at 593-94, 857-61)

120. The etiology of many CNS diseases, including PBA, are not known and, therefore, the development of a treatment cannot be driven by an understanding of the disease mechanism. Instead, studies must be conducted. (PTX-105 at AVAN-0207649; Tr. at 857)

121. CNS response measures are often subjective and variable, and placebo response can be very large for CNS diseases – making it impossible to draw firm conclusions from information about one patient or even a small number of patients. (Tr. at 857-58)

122. Development of a drug containing DM and Q is particularly unpredictable because of the complex kinetics of DM and Q, resulting in an inability to predict clinical efficacy of new dosage combinations based on PK data. (*Id.* at 858-59, 862)

L. Facts Relating to Validity of the '115 Patent

123. Because the asserted claims of the '115 patent include the "therapeutically effective" limitation, the parties' positions make it unnecessary for the Court to make additional findings of fact regarding the validity of the '115 patent.

M. Facts Relating to Secondary Considerations of Nonobviousness

1. Unexpected results

124. Before July 17, 2002, the only doses of DM and Q used for treating PBA were standard antitussive (cough suppressant) doses of DM together with maximally-inhibiting doses

of Q. (DTX-6; DTX-11; PTX-100; Tr. at 160, 519, 869, 871, 926) The maximally inhibiting dose of Q used with DM to treat PBA was 150 mg/day Q; nothing in the prior art taught or suggested using less than maximally-inhibiting doses of Q with DM to treat PBA. (PTX-3 at 4:30-32; Tr. at 160, 579-80, 864-65, 871, 877-78, 882-83, 885-86, 1045-47)

125. As of July 17, 2002, a person of ordinary skill in the art would have expected that DM blood levels greater than 100 ng/mL were necessary to effectively treat neurological disorders such as PBA. (PTX-100; PTX-138; DTX-13 at 4:29-37; Tr. at 478-79, 577-79, 607, 870-71, 885-86)

126. In Study 123, conducted between 2007 and 2009, the average DM blood plasma level for the 20/10 DM/Q treatment group (n=107) was 47.76 ng/mL. (PTX-213A; PTX-213B; PTX-104; Tr. at 196-98)

127. In terms of efficacy, as of July 17, 2002, it would have been surprising to a person of ordinary skill in the art that the claimed lower-dose DM/Q combination, 20 mg DM/10 mg Q, which provides DM plasma levels of around 50 ng/mL, exhibited therapeutic efficacy comparable to that of DM/Q combinations providing DM blood levels above 100 ng/mL. (DTX-13 at 4:29-37; PTX-100; Tr. at 161-64, 172, 174-75, 197-99, 478-79, 577-78, 607, 870-71, 885-86)

128. As of July 17, 2002, a person of ordinary skill in the art would have expected that using a partially inhibiting dose of 10-30 mg/day of Q with DM would result in decreased DM plasma levels compared to maximal inhibition. A person of ordinary skill would expect substantially decreased therapeutic efficacy and increased variability, due to the corresponding increased metabolism of DM. (Tr. at 864-65, 877-78, 882-83, 885-86)

129. In terms of safety, a person of ordinary skill in the art as of July 17, 2002 would have expected the claimed partially-inhibiting doses of Q to increase the potential for unacceptable side effects compared to maximally-inhibiting doses of Q because a reduction in the dose of Q would reduce the inhibition of DM's metabolism into DX, thereby increasing unwanted DX plasma levels. (*Id.* at 882-83, 885-86, 935-36, 1045-47)

130. As of July 17, 2002, it was well known that DX caused side effects, such as depression, and had a potential for abuse. (*Id.* at 883, 1045-46)

2. Long-felt need and failure of others

131. Before July 2002, numerous published sources in the peer-reviewed medical literature reported successes in treating PBA with tricyclic antidepressants ("TCAs"), selective serotonin reuptake inhibitors ("SSRIs"), and other medications (e.g., levodopa, reboxetine, venlafaxine, mirtazapine, lamotrigine, methylphenidate, dexamfetamine, and amantadine). (DTX-50; DTX-53; DTX-185; DTX-191; DTX-192; DTX-194; DTX-195; PTX-1; PTX-2; Tr. at 729-44, 1177-79)

132. As early as 1985, amitriptyline was shown, through a double-blind, placebo-controlled, crossover study reported in *The New England Journal of Medicine*, to treat PBA within days with only mild side effects. (DTX 194; Tr. at 731-33)

133. However, off-label use of drugs such as dopaminergic drugs (e.g., levodopa), TCAs, and SSRIs, among others, were not always considered effective treatments for PBA as of July 2002. (DTX-49; DTX-129; DTX-185; DTX-191; DTX-192; DTX-193; DTX-194; Tr. at 269, 287-88, 293-301)

134. There was no long-felt need or failure of others to develop a safe and effective

treatment for PBA. (Tr. at 743-44, 746)

3. Commercial success

135. Avanir has marketed and sold Nuedexta® since February 2011. (PTX-150)

136. Nuedexta® had net sales of $93.6 million from its launch in February 2011 through June 2013 and its net sales have increased in every quarter, including 265% growth from year one to year two. (PTX-305; Tr. at 672, 796-97)

137. Nuedexta®'s prescription totals were over 240,000 through early August 2013 and Nuedexta® has exhibited prescription growth every quarter since launch, including 257% from year one to year two. (PTX-326; Tr. at 778-79)

138. Nuedexta®'s profits were over $88 million through June 2013, with a consistent 94% gross profit margin, and Nuedexta®'s revenues have been growing faster than its expenses. (PTX-305; Tr. at 673-77)

139. [redacted]

140. Five pharmaceutical companies have filed ANDAs seeking to market generic versions of Nuedexta®. (PTX-81; PTX-168; Tr. at 787-88, 1037-39)

141. Each of the asserted claims of the '282 and '484 patents covers the use of Nuedexta® according to its package insert to treat PBA. (PTX-1; PTX-2; PTX-105; Tr. at 271-85, 788)

142. There exists a nexus between Nuedexta®'s commercial success and the claimed

inventions. (Tr. at 788-94)

143. Nuedexta® is promoted only as a treatment for PBA, and the record suggests that Nuedexta® is primarily used to treat PBA. (PTX-150; PTX-167; Tr. at 787, 789, 791-92)

II. INFRINGEMENT

A. Legal Standards

A patent is infringed when a person "without authority makes, uses, offers to sell, or sells any patented invention, within the United States . . . during the term of the patent." 35 U.S.C. § 271(a). Courts employ a two-step analysis in making an infringement determination. *See Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 976 (Fed. Cir. 1995). First, a court must construe the asserted claims. *See id.* Next, the trier of fact must compare the properly construed claims with the accused infringing product. *See id.* If an accused product does not infringe an independent claim, it also does not infringe any claim depending from that independent claim. *See Wahpeton Canvas Co. v. Frontier, Inc.*, 870 F.2d 1546, 1553 (Fed. Cir. 1989). However, "[o]ne may infringe an independent claim and not infringe a claim dependent on that claim." *Id.* at 1552 n.9.

In order to establish literal infringement, "every limitation set forth in a claim must be found in an accused product, exactly." *Southwall Techs., Inc. v. Cardinal IG Co.*, 54 F.3d 1570, 1575 (Fed. Cir. 1995). The patent owner has the burden of proving infringement by a preponderance of the evidence. *See SmithKline Diagnostics, Inc. v. Helena Lab. Corp.*, 859 F.2d 878, 889 (Fed. Cir. 1988).

B. Infringement of the '282 and '484 Patents

Plaintiffs assert that Defendants' proposed generic products and/or manufacturing

processes infringe claims 1-9 of the '282 patent and claims 1-9, 12, 13, 15, and 17 of the '484 patent. Both Impax and Par have stipulated that their proposed ANDA products literally infringe each asserted claim of the '282 and '484 patents. (D.I. 238, 411)

Therefore, the Court concludes that Defendants infringe claims 1-9 of the '282 patent and claims 1-9, 12, 13, 15, and 17 of the '484 patent.

C. Infringement of the '115 Patent

1. Defendants' ANDA products do not meet the "therapeutically effective" limitation

Plaintiffs assert that Defendants' ANDA products infringe claims 18-21 of the '115 patent because they are identical to Nuedexta®. At trial, the parties' dispute focused on whether Nuedexta® contains a combined unit dosage of DM and Q that is "therapeutically effective in substantially reducing chronic or intractable pain, without unacceptable side effects." Plaintiffs contend the daily dose of DM/Q in Nuedexta® meets the "therapeutically effective" limitation because the drug is capable of treating chronic pain without unacceptable side effects. Defendants assert that Nuedexta® fails to meet the disputed limitation because (i) there is no evidence Nuedexta® is therapeutically effective in substantially reducing chronic or intractable pain, and (ii) there is no evidence Nuedexta® can do so without "unacceptable side effects." The Court agrees with Defendants.

a. "Therapeutically effective in substantially reducing chronic or intractable pain"

Claim 18 of the '115 patent requires a unit dosage formulation of either DM or a pharmaceutically acceptable salt thereof and a debrisoquin hydroxylase inhibitor, such as Q, in a combined dosage that renders the DM "therapeutically effective in substantially reducing chronic

or intractable pain, without causing unacceptable side effects."[5] During claim construction, the Court held that this "therapeutically effective" limitation is given its plain and ordinary meaning. (D.I. 257 at ¶ 5) Plain and ordinary meaning is the meaning a term would have to a person of ordinary skill in the art at the time of the invention. *See Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005). A person of ordinary skill at the time of the effective filing date of the claimed invention would have had at least an M.D. degree as well as knowledge of or 5 years experience in treating pain or patients with neurological conditions including pain. The Court also construed "chronic pain" to mean "long-term pain resulting from conditions such as stroke, cancer and trauma, as well as neuropathic pain due to deterioration of nerve tissue such as postherpetic neuralgia (PHN) resulting from herpes zoster infection, and diabetic neuropathy resulting from long-time diabetes. The conditions are not an exclusive list." (D.I. 257 at ¶ 3) Finally, the Court construed "intractable pain" to mean "pain which failed to respond adequately to conventional treatments." (*Id.* at ¶ 4)

It is undisputed that Nuedexta® has been approved by the FDA only to treat PBA. (DTX-40; JFF at ¶ 45) Plaintiffs' expert, Dr. Wynn, explained that Nuedexta®'s package insert provides no statement that Nuedexta® can treat pain – let alone that it is "therapeutically effective" in treating long-term pain from other conditions, neuropathic pain from nerve tissue deterioration, or pain not responding to conventional treatments. (Tr. at 1172; *see also id.* (Wynn testifying: "There is nothing about pain in the labels in Par or Impax's package insert.")) It is also undisputed that there are no peer-reviewed publications, no presentations at major annual

[5]Claim 18 is the only independent claim asserted. Claims 19 and 20 depend from claim 18; claim 21 depends from claim 20.

conferences, and no pain treatment textbooks that discuss the 20/10 mg/day dosage of DM/Q for the treatment of chronic pain. (*Id.* at 685-87)

To support its position that Nuedexta® is therapeutically effective for these forms of pain, Plaintiffs primarily rely on a recently completed clinical study by Avanir testing the dosage used in Nuedexta®, prior clinical trials testing doses of DM and Q higher than those used in Nuedexta®, and testimony from Dr. Wynn regarding those studies and his own observations. Avanir's evidence is unpersuasive.

Plaintiffs' cited clinical studies do not establish that Nuedexta® is "therapeutically effective" in substantially reducing chronic pain. During the pendency of this action, the 20/10 mg/day DM/Q formulation was being tested in a Phase II double-blind, randomized, placebo-controlled study, called the PRIME Study, to evaluate the safety and efficacy of the drug in the treatment of central neuropathic pain in patients with MS. (*Id.* at 192-93, 1088, 1091)[6] The final study report itself has not been offered into evidence. Plaintiffs, however, rely on a recent Avanir press release reporting the results, which stated that "the treatment of central neuropathic pain in patients with multiple sclerosis did not meet the primary efficacy endpoint." (D.I. 458 Ex. A) The press release further stated that while some pain reduction from baseline levels was observed, "there was no difference between the treatment arms [(one of which used 20/10 mg/day DM/Q)] and placebo." (*Id.*) The record does not show what the baseline is, nor the margin the patients' pain scores were reduced from that baseline. Most significantly,

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[6]As of the time of trial and the completion of the principal post-trial briefs, this PRIME Study had not concluded and no results were available. On December 17, 2013, the parties jointly moved for leave to supplement the trial record under Fed. R. Civ. P. 52(b) to (i) include a December 10, 2013 press release by Avanir regarding the results of the PRIME Study and (ii) provide related proposed findings of fact, a motion which the Court granted. (D.I. 458, 459)

whatever that reduction, there was no difference between Nuedexta® and placebo. A person of ordinary skill in the art would require some difference between Nuedexta® and placebo to conclude that the 20/10 mg/day dose renders the DM "therapeutically effective" in ***substantially reducing*** chronic or intractable pain, as required by Claim 18.

The remaining earlier publications and clinical studies on which Plaintiffs rely are also unavailing. Dr. Wynn[7] admitted that Studies 106 and 107 concerned dosages of DM and Q at higher levels than Nuedexta®. (Tr. at 1141-42; PTX-199A (Study 106 testing 30/30 mg/day of DM/Q))[8] Beyond the fact that those studies did not use the Nuedexta® dose (20/10 mg/day of DM/Q), Defendants' expert Dr. Deer testified that a publication discussing the results of Study 106 showed efficacy was actually ***dropping*** at the dose closest to Nuedexta®. (Tr. at 711) ("[P]atients didn't do as well on 30/30 as they did on 45/30. Therefore, there appeared to be a linear regression downward as you lowered the dose.") Study 123, the STAR Study, did use the

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[7]Defendants move to exclude Dr. Wynn's testimony regarding these clinical trials, as well as his testimony on specific patients he treated, other doctors prescribing Nuedexta® for pain, and all other testimony cited in Plaintiffs' Findings of Fact ("PFF") at ¶¶ 226-28, as well as assertions in Plaintiffs' answering brief (D.I. 446 at 40-41). Defendants contend all of this testimony was outside the scope of Dr. Wynn's expert reports. (D.I. 450 at 22-24) (citing Fed. R. Civ. P. 37(c)) Determining whether an expert has impermissibly testified beyond the scope of a report is a matter within the Court's discretion, informed by the following factors: "(1) the prejudice or surprise in fact to the opposing party, (2) the ability of the party to cure the prejudice, (3) the extent of disruption of the orderly and efficient trial of the case, and (4) the bad faith or willfulness of the non-compliance." *Hurley v. Atl. City Police Dep't*, 174 F.3d 95, 113 (3d Cir. 1999), *abrogated on other grounds by Potente v. Cnty. of Hudson*, 187 N.J. 103, 114, 900 A.2d 787, 794 (2006) (applying state law). Having reviewed the disclosures in Dr. Wynn's expert report, the Court overrules Defendants' objections.

[8]The witnesses devoted little attention to Studies 105 and 109, and the parties followed suit in their briefing. These studies concerned dosages significantly above those used in Nuedexta®. (*See* PTX 198A (Study 105 testing 30/30 mg/day up to 120/120 mg/day of DM/Q); PTX-204A (Study 109 testing 90 mg DM/60 mg Q, 60 mg DM/60 mg Q, or placebo))

same 20/10 mg/day dose of DM/Q as in Nuedexta® but examined only the drug's efficacy in treating PBA, not its efficacy in treating pain – as Dr. Wynn admitted. (*Id.* at 1143) ("The trial was not designed to look at pain.") Dr. Wynn also admitted that the STAR Study concluded the 20/10 mg/day DM/Q dose did not have a statistically significant p-value versus the placebo when pain treatment was measured as a secondary endpoint. (*Id.* at 1146)

Plaintiffs also elicited testimony from Dr. Wynn[9] recounting his own clinical experience using Nuedexta®, testimony he based on patient interviews, which he opined are reliable as "the most important aspect of treating pain" from the perspective of a clinical physician. (*Id.* at 1165) ("[W]e don't have a so-called pain-o-meter where I can stick an individual['s] finger in and find out if they have pain.")

In the circumstances presented here, these patient interviews, which are undocumented and lack objective measures of efficacy, provide little evidence that Nuedexta® is therapeutically effective in substantially reducing chronic or intractable pain. Dr. Wynn's observations did not establish that administering Nuedexta® to a patient was the cause of any observed reduction in pain, especially given that Dr. Wynn did not record the patient's medical history or other medications being taken, which is of particular concern since Dr. Wynn admitted it "wouldn't be uncommon" for patients being treated with Nuedexta® in his practice also to be taking other pain medications. (*Id.* at 1157) Relatedly, Dr. Wynn provided no explanation as to how the patient interviews controlled for placebo effect. (*See id.* at 1168-69) Dr. Wynn's observations also lacked any measurement of patient parameters, pre- and post-treatment pain scores, and statistical

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[9]Defendants have renewed their motion to preclude Dr. Wynn's testimony under *Daubert*, a motion which the Court previously denied. (D.I. 366; D.I. 450 at 27) For the same reasons as stated before, the Court again denies the motion. (*See* Pretrial Conference ("PT") Tr. at 63-64)

analysis, all of which are important factors for determining efficacy. (*See id.* at 695) Dr. Deer persuasively testified that "the definition of being therapeutically effective means we can measure improvement by pain score reduction on a scale that's been validated and proven functional." (*Id.* at 684)[10] Thus, the Court concludes that, to a person of ordinary skill in the treatment of chronic or intractable pain, Dr. Wynn's patient interviews, and his testimony about them, fail to provide reliable indicia that Nuedexta® is therapeutically effective in treating such pain.

Dr. Wynn's remaining testimony concerned other neurologists in his practice, as well as physicians he knows around the country, many of whom "have also noted marked improvement with the treatment of chronic or intractable pain with Nuedexta[®]." (*Id.* at 1107) However, Dr. Wynn displayed little to no familiarity with the experiences of these other physicians; the only physician Dr. Wynn identified by name was Dr. Licht, an Avanir employee to whom he had never spoken nor ever met. (*Id.* at 1169) Dr. Wynn admitted he did not know whether Dr. Licht was prescribing Nuedexta® to patients with just PBA or patients with PBA and pain, what type of pain (if any) Dr. Licht's patients were experiencing, the patients' pain scores, and whether or not these patients were taking other pain medications simultaneously. (*Id.* at 1170) Therefore, the Court finds that Dr. Wynn's testimony regarding other physicians' experience provides little evidence that Nuedexta® is "therapeutically effective" in treating chronic or intractable pain.

b. "Without causing unacceptable side effects"

To satisfy the claim limitation, therapeutic efficacy must be achieved "without

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[10]Dr. Deer further testified that he has treated patients for pain issues who were already taking Nuedexta® to treat other symptoms. (Tr. at 684-85)

unacceptable side effects." Dr. Wynn opined that "unacceptable side effects" are determined by each clinician, based on his or her experience treating patients with pain disorders, and are present when it appears the patient is "unable to continue taking medication and the patient stopped the medication" because he or she exhibited a "sign or symptom" of a possible side effect. (*Id.* at 1106, 1167-68) Dr. Wynn admitted to taking patients off of Nuedexta® due to such adverse reactions. (*Id.* at 1168) ("I have had some patients discontinue medication [i.e., Nuedexta®] because of side effects.") The record does not establish whether Dr. Wynn's colleagues using Nuedexta® to treat pain have also found it necessary to take patients off of it.

Furthermore, the studies upon which Avanir relies offer little evidence that Nuedexta® can treat chronic pain without unacceptable side effects because those studies, with the exception of the PRIME Study, do not examine Nuedexta® in a chronic pain population. Dr. Deer, who has been a pain specialist for over 20 years and annually sees approximately 1,000 patients who suffer from chronic or intractable pain, appropriately described "unacceptable side effects" as those side effects that "cause[] limitations in [a patient's] daily function or . . . cause [the patient] to have other comorbidities or other disease states." (*Id.* at 676-79, 691) For several reasons, Dr. Deer explained, chronic pain patients are especially at risk for experiencing unacceptable side effects from a new drug. First, unlike healthy patients, patients afflicted with chronic pain often suffer from other conditions or comorbidities simultaneously, such as immobility, which lead to obesity, trouble with blood sugars, and hypertension. (*Id.* at 692) Second, in order to address these other disease states, chronic pain patients take other drugs, which means they are particularly at risk for adverse interactions among medications. (*Id.* at 691-92) For example, other medications could lead to cardiac arrhythmia disturbances when combined with

Nuedexta®. (*Id.*) Therefore, studies measuring the response to Nuedexta® among normal subjects experiencing pain – such as the bulk of the studies identified by Plaintiffs – are only minimally relevant to whether Nuedexta® can effectively treat patients with chronic or intractable pain without causing unacceptable side effects.

2. Defendants' ANDA products do not infringe the asserted claims of the '115 patent

For the reasons explained, the Court concludes that Avanir has failed to prove by a preponderance of the evidence that Nuedexta® satisfies the "therapeutically effective" limitation of independent Claim 18 of the '115 patent. Consequently, Avanir has also failed to prove that Defendants' ANDA products – which the parties treat as identical to Nuedexta® – infringe independent claim 18 or dependent claims 19, 20, or 21 of the '115 patent.[11]

III. VALIDITY

Defendants contend that both the '282 and '484 patents are invalid due to obviousness and lack of written description. Defendants also assert that if the Court finds the asserted claims of the '115 patent do not contain the "therapeutically effective" limitation, then the '115 patent is invalid as obvious. The Court addresses each asserted basis for invalidity below.

A. Legal Standards

An issued patent is presumed to be valid. *See* 35 U.S.C. § 282. Therefore, to invalidate a patent, a party must carry its burden of proof by "clear and convincing evidence." *See Procter &*

[11]Defendants ask the Court to order that the '115 patent be "delisted" from the "Orange Book" entry for Nuedexta®, pursuant to 21 U.S.C. § 355(b)(1)(G). (D.I. 429 at 21) The parties devote very little briefing to this issue. In light of the Court's finding that Nuedexta® does not meet the "therapeutically effective" limitation of the '115 patent, the Court will solicit the parties' further input on the delisting issue.

Gamble Co. v. Teva Pharm. USA, Inc., 566 F.3d 989, 994 (Fed. Cir. 2009) (obviousness); *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1354 (Fed. Cir. 2010) (written description). Clear and convincing evidence is evidence that "proves in the mind of the trier of fact an abiding conviction that the truth of [the] factual contentions [is] highly probable." *Intel Corp. v. ITC*, 946 F.2d 821, 830 (Fed. Cir. 1991) (internal quotation marks omitted).

1. Obviousness

A patent may not issue "if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains." 35 U.S.C. § 103(a). Obviousness is a question of law based on underlying factual findings concerning: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective considerations of nonobviousness. *See Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966).

To prove that a patent is obvious, a party must demonstrate "that a skilled artisan would have had reason to combine the teaching of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success from doing so." *In re Cyclobenzaprine*, 676 F.3d 1063, 1069 (Fed. Cir. 2012), *cert. denied*, 133 S. Ct. 933 (U.S. 2013) (citing *Procter & Gamble*, 566 F.3d at 994); *see also Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009) ("An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art."). While an analysis of any teaching, suggestion, or

motivation to combine known elements is useful to an obviousness analysis, the overall obviousness inquiry must be expansive and flexible. *See KSR Int'l Co. v. Teleflex, Inc.*, 550 U.S. 398, 415, 419 (2007). In addition, the use of hindsight is not permitted when determining whether a claim would have been obvious to one of ordinary skill in the art. *See id.* at 421 (cautioning against "the distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning").

"[D]ependent claims are nonobvious if the independent claims from which they depend are nonobvious." *In re Fritch*, 972 F.2d 1260, 1266 (Fed. Cir. 1992); *see also Ortho-McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1365 (Fed. Cir. 2008).

2. Written description

The written description requirement is set forth in 35 U.S.C. § 112, ¶ 1. A patent's written description must "clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed." *Ariad*, 598 F.3d at 1351. Accordingly, "the test for sufficiency is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date." *Id.*

B. Obviousness: '282 and '484 Patents[12]

Defendants contend that the asserted claims of the '282 and '484 patents are invalid as obvious over the prior art because: (1) it would have been obvious to a person of ordinary skill to

[12]Defendants move to strike references to Plaintiffs' demonstrative exhibits included in Plaintiffs' PFF because the demonstrative exhibits are not in evidence and should not be considered. (D.I. 444 at 2 n.2) (citing D.I. 431 at ¶¶ 23, 34, 39, 44, 46, 49-52, 54, 56-59, 61, 62, 64-70, 74-77, 79, 80, and 84) Having reviewed the references, the Court agrees and grants Defendants' motion.

lower the dose of Q to the claimed ranges, (2) there was motivation to do so because of safety concerns and industry practice, and (3) there would have been a reasonable expectation of success that low doses of Q combined with DM would be effective in treating PBA. Avanir responds that the evidence shows: (1) the prior art did not teach the claimed sub-maximally inhibiting dose of Q in combination with DM to treat PBA, (2) Defendants' "motivation" and "obvious to try" theories are improperly based entirely on hindsight using the '282 and '484 patents as a blueprint, and (3) a person having ordinary skill in the art would not have reasonably expected doses of Q below maximal inhibition could be combined with DM to safely and effectively treat PBA. Avanir also argues that secondary considerations of nonobviousness support a finding of validity. (*See* D.I. 432, 449)

For the reasons explained below, the Court agrees with Avanir that Defendants have failed to establish, by clear and convincing evidence, that the claimed inventions would have been obvious to a person of ordinary skill at the time the '282 and '484 patents were filed.

1. The scope of the prior art and the differences between the claimed subject matter and the prior art

According to Defendants, "[t]he only difference between the prior art and the asserted claims of the '282 and '484 patents is the dose ranges of Q." (D.I. 429 at 5; D.I. 444 at 10 n.11; D.I. 450 at 15) Plaintiffs respond that focusing on Q alone "improperly urges the Court to ignore the subject matter of the claims as a whole, including the claimed amounts of DM and the claimed weight to weight ratios of DM to Q." (D.I. 449 at 13 n.12)

The Court finds that the differences between the asserted claims and the prior art are the lower doses of Q, at the 10-30 mg/day range, ***in combination with DM*** at the claimed dosage amounts and weight ratios, ***to treat PBA***. Claim 1 of each patent claims a dose range of Q "from

about 10 mg/day to less than about 30 mg/day with the proviso that the weight to weight ratio of dextromethorphan to quinidine is 1:0.5 or less." It is undisputed that the prior art generally taught a combination of DM and Q; however, the Court must consider the claimed subject matter as a whole and, in doing so, it would be improper to focus only on the dosage of Q in isolation. *See* 35 U.S.C. § 103; *see also KSR*, 550 U.S. at 406 (holding that a party asserting obviousness must show "the subject matter [of the asserted claims] ***as a whole*** would have been obvious") (emphasis added).

2. Defendants' references neither teach nor suggest lowering the dose of Q to the claimed ranges in combination with DM

Defendants advance several theories as to why the prior art teachings allegedly made it obvious to lower the dose of Q from the 150 mg/day used with DM in the prior art to the claimed range of 10-30 mg/day of Q to treat PBA. Specifically, Defendants contend that the asserted claims of the '282 and '484 patents are obvious over the following prior art references: (1) the '248 patent; (2) the Yakatan Abstract, Yakatan Poster, and other PK studies; (3) the '053 application; and (4) the '927 patent. The Court addresses this prior art below.

a. The '248 patent, Yakatan Abstract, Yakatan Poster, and other PK studies

It is undisputed that the '248 patent does not disclose a 10-30 mg/day Q dose and does not suggest employing a Q dose lower than the maximally inhibiting 150 mg/day dose. However, Defendants contend that "a skilled artisan would have been motivated to achieve the effective 43-55 ng/mL DM blood levels from Example 2 of the '248 patent with as low a dose of Q as possible, utilizing the Q dose/DM blood level correlations from the Yakatan Poster or

Abstract," rendering the claimed dose ranges obvious. (D.I. 429 at 14)[13] Plaintiffs counter that Defendants' argument fails because a person of ordinary skill would have had no reason to use the Yakatan references to recalculate a new dose of Q from the blood concentrations in the '248 patent given that the '248 patent already disclosed using a Q dose – at a much higher level – to achieve those very blood concentrations. As an independent reason for rejecting Defendants' argument, Plaintiffs contend that the single 43-55 ng/mL DM blood plasma concentration is unreliable and inconsistent with the weight of the prior art, since the existing PK data as a whole taught a range of DM concentrations of between 100 and 200 ng/mL for effective treatment of PBA. The Court agrees with Plaintiffs.

Example 2 teaches that for a single patient, PBA symptoms faded away when he was given 60 mg/day of DM and a ***maximally inhibiting*** dose of ***Q at 150 mg/day***, which resulted in blood concentration of 43-55 ng/mL DM. (DTX-6 at 11:39-43, 12:15-24) Defendants argue that a person of ordinary skill would have viewed Example 2 as teaching a blood concentration alone that is effective in treating PBA while ignoring the maximally inhibiting dose of Q used to achieve it; however, the Court is persuaded by Plaintiffs' experts' opinions that a person of ordinary skill developing a treatment for PBA would focus on dose, not blood concentration. (Tr. at 99-100, 904-07 (Sellers testifying: DM plasma levels do "not predict[] response, they are

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[13]Plaintiffs contend that the Yakatan Poster is not prior art as it fails to qualify as a "printed publication" under 35 U.S.C. § 102(b) because it was not "publically accessible." (D.I. 446 at 10 n.5) In *In re Klopfenstein,* in which a poster was "never distributed to the public and was never indexed," the Federal Circuit balanced several factors to determine whether the disclosure was "publically accessible" under § 102(b). 380 F.3d 1345, 1350 (Fed. Cir. 2004) (balancing "the length of time the display was exhibited, the expertise of the target audience, the existence (or lack thereof) of reasonable expectations that the material displayed would not be copied, and the simplicity or ease with which the material displayed could have been copied"). Having considered the relevant factors, the Court determines the Yakatan Poster was publicly accessible.

merely an observation in the context of observed efficacy"))

Even if a person of ordinary skill were to focus on blood concentrations, Defendants failed to prove that reliable efficacy conclusions could be drawn from the limited information disclosed in Example 2. Defendants also failed to prove that one of ordinary skill would select the 43-55 ng/mL blood concentration disclosed in a single patient over more reliable disclosures in the prior art as of July 2002, including Example 3 in the same patent and the results reported in the Smith Abstract. Example 3 of the '248 patent disclosed the safe and effective treatment of a patient's PBA at DM blood levels of 130-180 ng/mL, using a 90/150 mg/day combination of DM/Q. (DTX-6 at 11:39-43, 12:33-50) As Dr. Sellers testified, a person of ordinary skill would have considered the data reported in Example 3 to be more reliable than the data set forth in Example 2 because the patient in Example 3 was stopped and started on DM/Q several times, establishing causality (*id.* at 12:26-48; Tr. at 869), allowing one to rule out placebo effect, which is very common in CNS drugs (Tr. at 698-99, 858). Similarly, the Smith Abstract disclosed a double-blind, placebo-controlled, crossover trial reporting that 12 patients' PBA episodes were safely and effectively treated using 60/150 mg/day DM/Q, resulting in DM blood concentrations of 100-200 ng/mL. (PTX-100; DTX-11; Tr. at 475-77, 519, 606-07)

By contrast, Example 2, which involved only a single patient, is insufficiently reliable. Example 2 contains no report on how many blood samples were drawn, whether the patient had reached a steady state of DM, and whether his blood concentrations were measured at C_{max} or trough levels. (Tr. at 582-84) It also does not document the single patient's prior medical history, or whether the patient was an EM or PM of DM based on pre-dosing CYP2D6 activity. (*Id.* at 867)

When the prior art evidence discussed at trial is viewed as a whole, Example 3, the Smith Abstract, the Yakatan Abstract, and the Zhang reference disclosed a total of 29 individuals treated for PBA, all of whom had blood concentrations of between 100 and 200 ng/mL, in contrast to the one patient reported in Example 2. (PTX-100; DTX-6 at 12:26-48; DTX-60 ("Zhang reference") at AVAN-0207767 (Fig. 3 reporting DM concentrations for "patients receiving 150 mg quinidine per day"); DTX-499 at Abstract 61; Tr. at 624-25, 868-70) The Court is unpersuaded that a person of ordinary skill, lacking the guidance provided by the patents-in-suit, would have taken Example 2, discarded the 150 mg/day dose of Q it used, focused instead on the DM blood concentration in isolation and despite the weight of the prior art, and then looked to the PK data from the Yakatan Abstract/Poster to recalculate the dose of Q to reach the claimed invention.

Finally, the PK data Defendants rely on provides no teaching on effective treatment of PBA. The Yakatan references, along with the Boobis, Desmeules, and Nielsen references, all teach PK data alone. (DTX-135; DTX-4; DTX-8; DTX-21) The cited PK data only show that low doses of Q could cause partial inhibition of CYP2D6; not one of these PK studies addresses whether a partially inhibiting dose of Q can treat PBA when combined with DM.[14] Defendants' theory that these PK references teach sub-maximally inhibiting doses of Q to treat PBA rests entirely on the premise that a person of ordinary skill would find that Example 2 teaches effective blood concentrations – which the Court has determined it does not. Accordingly, Defendants'

[14]Indeed, only two of these references even mention DM, and they both use doses of 50 mg/day DM.

arguments are unavailing.[15]

b. '053 application

Defendants next contend that the claimed invention would have been obvious to a person of ordinary skill in the art in July 2002 in light of the '053 application, which teaches the claimed dose range of DM, and suggests that dosages below 150 mg/day of Q would be effective in treating PBA. Defendants once more conflate the difference between PK data and dose-efficacy results for treating PBA. Both sides' experts agreed the disclosed DM dose ranges (20-400 mg/day) in the '053 application were not directed to the treatment of PBA. (DTX-32 at AVAN-0403512-13, AVAN-0403517-18; Tr. at 517-18, 872)

Additionally, the disclosed range of Q in the '053 application falls outside the claimed range. Only 150 mg/day of Q – or a speculated low-end Q dose "such as 50 mg/day Q" – is disclosed. (DTX-32 at AVAN-0403512-13) Moreover, regardless of whether the '053 application could be read to disclose even lower doses of Q, these Q ranges do not concern the treatment of PBA. The portion of the '053 application on which Defendants rely states that "dosages of only 150 mg/day are ***effective in increasing DM concentrations***, and it is believed by the Applicant that even lower dosages (such as 50 mg/day) will be effective in at least some patients." (*Id.* at AVAN-0403512-13) (emphasis added) The '053 application makes no disclosure of whether the DM and Q dose ranges are ***effective in treating PBA.***

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[15]Though Defendants' ultimate burden does not change, in evaluating the weight of this evidence the Court observes that the '248 patent, Yakatan Abstract, and Yakatan Poster were all in front of the PTO during prosecution of the '282 and '484 patents. *See Sciele Pharma Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1260 (Fed. Cir. 2012) ("[I]t may be harder to meet the clear and convincing burden when the invalidity contention is based upon the same argument on the same reference that the PTO already considered.").

In sum, a person of ordinary skill would not have found it obvious to arrive at the claimed invention based on the PK data disclosed in the '053 application.

c. '927 patent

Defendants contend that the claims are obvious over the '927 patent because the claimed doses are merely a modification of the '927 patent's 20-200 mg/day dose of DM and 300 mg/day or less dose of Q. As with the '053 application, Defendants' cited disclosures only concern effectiveness in changing DM blood concentration, not effectiveness in treating PBA. The '927 patent's disclosure of "50 mg/day to 150 mg/day" of Q did not relate to PBA treatment. (DTX-20 at 4:14-17) ("The dosage of quinidine which was found to provide a major ***increase in DM concentration*** in the blood of most patients was equal to or less than 150 mg/day, depending on the individual.") (emphasis added) Likewise, the cited dose of 30/25 mg/day of DM/Q was for the treatment of a patient with dermatitis, not PBA. (*Id.* at 13:36-42) The record does not establish that DM/Q doses effective for treating dermatitis are also effective for treating PBA. Accordingly, the Court finds a person of ordinary skill would not find the claimed low dosage of Q, combined with the claimed doses of DM, obvious for the effective treatment of PBA in light of the '927 patent.

3. Motivation to modify the dose of Q[16]

Defendants presented several theories as to why one of ordinary skill in the art would have been motivated to lower the maximally inhibiting doses of Q taught by the prior art to the sub-maximally inhibiting 10-30 mg/day claimed doses, and then combine that lower amount of Q with certain doses of DM, all for the treatment of PBA. Defendants' arguments relate to (i) safety concerns and (ii) industry practice.[17]

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[16]Defendants contend that Plaintiffs' motivation analysis is legally flawed because it forecloses consideration of "common sense," which the Supreme Court specifically authorized as an obviousness consideration when it rejected the "teaching, suggestion, or motivation" ("TSM") test in *KSR*. (D.I. 444 at 3) *KSR* rejected a ***rigid*** application of the TSM test, 550 U.S. at 419, and subsequently the Federal Circuit has articulated an "expansive and flexible approach" to the obviousness analysis, one that "not only permits, but requires, consideration of common knowledge and common sense." *Randall Mfg. v. Rea*, 733 F.3d 1355, 1362 (Fed. Cir. 2013) (reversing finding of non-obviousness where court "narrowly focus[ed] on the four prior-art references" and ignored record evidence of "the knowledge and perspective of one of ordinary skill in the art" to explain motivation to combine or modify references). The Court agrees it must consider "common sense" in its analysis, though the use of hindsight remains impermissible and Defendants continue to bear the burden of showing motivation. *See St. Jude Med., Inc. v. Access Closure, Inc.*, 729 F.3d 1369, 1381 (Fed. Cir. 2013) ("Even under our 'expansive and flexible' obviousness analysis, we must guard against 'hindsight bias' and '*ex post* reasoning.'") (citations omitted).

[17]Defendants suggest that the Federal Circuit's recent ruling in *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013) ("*Galderma II*"), undermines Plaintiffs' nonobviousness analysis, which in part relied upon the earlier District Court decision ("*Galderma I*"). (*See* D.I. 479) The Court disagrees. First, the legal standards upon which Plaintiffs rely – in particular, well-established precedent on *prima facie* non-obviousness (motivation) and secondary considerations (teaching away, unexpected results, commercial success) – were not changed by *Galderma*. Rather, as Defendants later concede, in *Galderma II* the Federal Circuit reversed the District Court based on the facts of that case. The facts here are distinguishable. In *Galderma II*, the sole dispute was whether a 0.3% dose of the active ingredient, adapalene, in a composition for the treatment of acne was obvious. The Federal Circuit found that because the prior art taught a preferred range of adapalene (0.01-1.0%) for the treatment of acne – thus encompassing the claimed dose – the dispute did not center on "motivation to combine" but rather "motivation to select the claimed 0.3% adapalene composition in the disclosed range." *Id.* at 737-38. Under the circumstances, the patentee's failure to come forward with evidence of pertinent secondary considerations was insufficient to prevent a finding of obviousness. *See id.* at 738 ("[W]here

a. Safety concerns associated with DM and Q

Defendants contend that Q was known to have harmful side effects, such as cardiotoxicity associated with an excessive prolongation of the QTc interval, as well as dizziness and other conditions. Defendants additionally argue that drug-to-drug interactions ("DDIs") and DM accumulation would have served as independent bases motivating a person of ordinary skill to lower the dose of Q. Plaintiffs respond that Defendants' evidence for cardiotoxicity pertained only to the far higher antiarrhythmic dose levels of Q and the other side effects were associated with DM rather than Q. Plaintiffs further contend that any remaining safety concerns about Q taught a person of ordinary skill either to obtain only the lowest dose that still maximally inhibited the CYP2D6 enzyme or to discontinue use of Q altogether. The Court agrees with Plaintiffs.

At the time of the invention, maximal inhibition of the CYP2D6 enzyme was known to occur at a 50-150 mg/day dose of Q; and a 150 mg/day dose of Q was specifically known to effectively treat PBA when combined with a 60 mg/day dose of DM. (DTX-8; DTX-6) Plaintiffs introduced substantial evidence that, prior to July 17, 2002, there were few safety concerns associated with the 150 mg/day dose of Q. (PTX-3 at 4:30-32; Tr. at 97, 423-27, 476-77, 515-16, 580, 596-97, 877, 879-80, 1047)[18]

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there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee"). Here, by contrast, the motivation analysis is different. The prior art here does not disclose (i) ranges encompassing the claimed doses of ***combination*** of DM/Q at the claimed doses or weight ratios (ii) ***for the treatment of PBA***. Here, also, Defendants' arguments about "teaching away" and "unexpected results" are unpersuasive given the distinct facts of the present case.

[18]Defendants argue the Nielsen reference would provide a motivation to lower the dose of Q to sub-maximally inhibiting levels because it "teaches that as little as 5 mg Q has significant effects

Defendants contend there were safety concerns with Q regarding cardiotoxicity due to prolongation of the QTc interval. However, cardiotoxicity was not present at the 150 mg/day dose level of Q known in the prior art; such concerns related only to the much higher ***antiarrhythmic doses*** of Q in the range of 600-1600 mg/day. (PTX-163 (Physicians' Desk Reference ("PDR") entry for Q dosed at 600-1600 mg/day); Tr. at 138, 142-43 (Yakatan citing PDR); Tr. at 536 (Poulsen: "The side effects, particularly relating to quinidine, would be known at the very high doses used to treat cardiac arrhythmia.")) While the 2001 FDA letter to Avanir that Defendants cite did observe "quinidine ***may*** alter the QTc interval" at the 60 mg/day Q dose administered, it did not imply that the altered QTc interval would lead to cardiotoxicity, or any serious physical harm. (DTX-152) (emphasis added)[19] Defendants presented no persuasive evidence that a person of ordinary skill, aware that such cardiac-related risks arose at significantly higher dose levels of Q – that is, 600 mg/day and above – would nonetheless be concerned about similar side effects arising at Q doses well below antiarrhythmic doses, particularly at the low dose level of 150 mg/day known in the prior art to effectively treat PBA

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on CYP2D6 inhibition" and "further teaches that a dose of 5 or 10 mg Q would avoid converting people from extensive to poor metabolizers, but still achieve inhibition of CYP2D6." (D.I. 429 at 12; Tr. at 376-78) However, the Nielsen reference, like the Boobis and Yakatan references Defendants also cite, merely observes that partial inhibition can occur at these low levels; these references make no mention of side effects, DDIs, or any other reason to use this insight to modify the dose of Q to a level below maximal inhibition. In fact, Nielsen states "[a] standard dose of at least 200 mg quinidine sulfate would be required to change the phenotype in all subjects," noting that "this would still be a pharmacodynamically inert dose in most subjects." (DTX-21 at ParPharma DEX 0014312)

[19]To the extent the 2001 FDA letter motivated the inventor of the patents-in-suit to conduct Study 123 at lower doses of Q, this evidence does not help Defendants' motivation argument. *See Life Techs., Inc. v. Clontech Labs.*, 224 F.3d 1320, 1325 (Fed. Cir. 2000) ("[T]he inventors' reliance on [certain prior art] and the motivations that they derived from it have no bearing on the issue of patentability.").

when combined with DM.

Defendants' evidence related to side effects of sub-antiarrhythmic doses of Q also does not support a motivation to pursue a sub-maximally inhibiting dose of Q. In relation to "cumulative side effects" observed from the co-administration of DM and Q in patients discussed in the '980 patent cited by Defendants, the physicians were motivated to stop administering the medication entirely, not merely to lower the Q dose. (DTX-10 at 9:30-62)

As for side effects involving dizziness, disorientation, a "drugged" feeling, and nausea, the evidence overwhelmingly pointed to the fact a person of ordinary skill would have known such side effects are attributable to DM, not to Q. (DTX-60 at AVAN-0207767; PTX-131 at AVAN-0287082; PTX-134 at AVAN-0043732-733; PTX-138 at AVAN-0289350; PTX-145 at AVAN-0291082-083; PTX-158 at AVAN-0296881; DTX-20 at 13:54-55 ('927 patent reduced dose from 75 to 25 mg/day of Q, but "patient reported continued headache side effects even when on a reduced dosage"); Tr. at 372-73, 1205) Accordingly, the motivation would not have been to lower the Q dose, but rather to reduce the DM dose, as Dr. Smith was prompted to do in response to "severe phencyclidine-like reactions" at 60/150 mg/day of DM/Q, which led him to drop the DM dose to 30 mg/day while keeping the Q dose constant. (DTX-60 at AVAN-0207763-764; DTX-10 at 9:55-62) Patients on such adjusted DM dosages did not experience similar side effects. (DTX-60 at AVAN-0207766) The dangers of DM are further evidenced by another confidential study conducted by Dr. Smith involving a high dose of DM (120 mg/day), along with 150 mg/day Q, in which "[s]evere side effects were experienced in 3/17 patients" and "[t]he majority of these side effects were due to reactions to dextromethorphan." (DTX-121 at CNS-0002366) As Defendants' expert, Dr. Poulsen, admitted, "[i]f you were

absolutely certain that the side effects relate[] to dextromethorphan, it would be very natural to decrease that dose." (Tr. at 621)

Finally, Defendants point to an NIH application in which Drs. Smith and Yakatan discussed the side effects from the combination of DM and Q. However, their response was ***not to seek sub-maximally inhibiting doses*** of Q, but rather to "determine the lowest sub-therapeutic dose of Q which would convert 100% of extensive metabolizers (EM) of DM to poor metabolizers (PM)" – i.e. achieve ***maximal inhibition*** – such that "the safety of the combination product would be maximized without compromising the therapeutic benefits of DM." (DTX-123 at CNS-0000133)[20] Hence, to the extent side effects were observed in relation to Q and safety was a concern, Defendants' evidence supports the conclusion that a person of ordinary skill was motivated to react by lowering the dose of Q only so far as to result in a dose that would still cause maximal inhibition, which the prior art taught was necessary for effective treatment of PBA.

Defendants also argue that DDIs would have provided an independent motivation to lower the dose of Q with DM, but other than the unsupported testimony of Dr. Boobis (Tr. at

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[20]Defendants cite a letter from the FDA to Avanir in 2006 – ***four years after*** the '248 and '484 patents were filed – in which the FDA suggested to Avanir that a 10 mg/day Q dose might be used with DM to more safely and effectively treat PBA. (D.I. 429 at 5) (citing Defendants' Proposed Findings of Fact ("DFF") at ¶ 30) Additionally, Defendants cite FDA meeting minutes from March 14, 2007, in which the FDA first raised concerns about DDIs, which Avanir agreed to investigate in subsequent testing. (*Id.* at 10) (citing DFF at ¶ 64) While Defendants may rely on disclosures other than prior art to show motivation, *see Nat'l Steel Car, Ltd. v. Canadian Pac. Ry., Ltd.*, 357 F.3d 1319, 1337 (Fed. Cir. 2004), the Court finds these particular documents possess little probative value. Defendants have failed to provide any persuasive evidence that these proposals from 2006 and 2007 reflect safety concerns a person of ordinary skill in the art would have had four years earlier, at the time of the invention, about Q administered at a maximally inhibiting dose.

427-28),[21] Defendants provided no evidence that DDIs raised such concerns as of July 2002. (*See also* DTX-123 at CNS-0000146) ("The risk to subjects should be minimal . . . [because] DM/Q is well tolerated by most patients, including the elderly.")

Based on the evidence as a whole, therefore, the Court finds that the prior art taught away from dropping the dose of Q down to levels that would compromise maximal inhibition of the CYP2D6 enzyme when formulating a combined dosage of DM and Q for treating PBA.

b. Industry practice

Defendants argue that routine industry practice would have motivated a person of ordinary skill to start at the lowest dose of both DM and Q possible and "titrate up" until efficacy was achieved, thus leading to sub-maximally inhibiting doses of Q. However, Defendants' only expert to opine on the standard course of drug development, Dr. Boobis, admitted the "start low and go slow" approach is directed toward ***new*** chemical entities, at the point at which the drug is first being administered to a human after animal testing. (Tr. at 349-50) This was hardly the situation applicable to DM/Q dosing as of July 2002, as DM and Q were not new chemical entities but instead had progressed to a much later stage of development, both individually and in combination, and had long been safely administered to humans.

Thus, the Court concludes that a person of ordinary skill in July 2002 would not have been motivated to go backwards and repeat the drug development process for DM and Q to arrive at sub-maximally inhibiting doses of Q combined with DM to treat PBA. To find otherwise

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[21]Plaintiffs objected to Dr. Boobis's testimony that the risk of a DDI with Q is just as great at a 50 mg dose as it is at a 1600 mg dose, as being outside the scope of his expert report. (D.I. 446 at 21; PFF at ¶ 163 (citing Tr. at 360)) Having reviewed the expert reports, the Court denies Plaintiffs' motion.

would impermissibly rely on hindsight.

4. A person of ordinary skill would not have had a reasonable expectation of success when lowering the dose of Q

Defendants contend "a person of ordinary skill in the art could determine an effective DM/Q combination based on the empirical data concerning the amount of Q that produced a given DM blood level in a 'straightforward' manner," leading to a reasonable expectation of success. (D.I. 444 at 9) (citing Tr. at 594) Plaintiffs respond that there is no evidence a person of ordinary skill would have reasonably expected the cited DM blood concentrations to be achieved by dropping the dose of Q; in turn, even if such DM blood concentrations could be achieved, there is no evidence therapeutic efficacy could be maintained for the treatment of PBA. The Court agrees with Plaintiffs.

As a general matter, CNS drug development is challenging and unpredictable, especially in relation to treatment of PBA, a disease for which the mechanism for treatment remains unknown. (Tr. at 593-94, 857-61) Since the etiology of PBA is not known, the development of a treatment cannot be driven by an understanding of the disease mechanism; rather, as Dr. Sellers testified, actual studies must be conducted. (*Id.* at 857; PTX-105 at AVAN-0207649)

Defendants contend that effective blood levels for the treatment of PBA were shown in the prior art, and would have led to a reasonable expectation of success. Defendants do not dispute, however, that the primary evidence they cite for the dose-efficacy information available to a person of ordinary skill as of July 17, 2002 – the single example of a patient with a 43-55 ng/mL DM blood concentration correlated with effective treatment of PBA – was achieved ***using a dose of 150 mg/day Q***. That is, a maximally inhibiting dose was used to achieve the effective DM blood levels. As Plaintiffs correctly observe, Defendants failed to adduce any evidence that

a person of ordinary skill would have expected this patient's DM blood levels to remain at 43-55 ng/mL "if the dose of Q administered was reduced by approximately 80-93% to arrive at the claimed 10-30 mg/day doses of Q." (D.I. 446 at 33)

Even if it was believed that these DM blood levels could be achieved at sub-maximally inhibiting levels of Q, there is no indication in the record that, prior to July 2002, a person of ordinary skill would have reasonably believed that the 43-55 ng/mL DM blood levels effective in the single patient in Example 2 would prove effective in other patients with PBA. It is undisputed that the relationship between DM blood concentration and therapeutic efficacy in treating PBA in the majority of patients was not known. (PTX-108; Tr. at 479, 578-79) Other than the single patient in Example 2, the evidence Defendants cite concerns ***PK studies*** in healthy volunteers, which is relevant to the effect Q has on inhibiting DM in the body, but does not demonstrate efficacy of DM/Q in treating patients afflicted with PBA.

Therefore, the Court finds that a person of ordinary skill in July 2002 would not have had a "reasonable expectation of success" that PBA could be effectively treated by DM combined with Q at a sub-maximally inhibiting dosage.

5. Lowering the dose of Q with DM was not "obvious to try"

Repackaging its earlier arguments, Defendants contend: (1) the knowledge that "the co-administration of DM and Q successfully treated PBA with DM blood concentrations of 43-55 ng/mL" in the single patient from Example 2, and (2) "the correlation between Q dose and DM blood levels" from PK data would have made the claimed invention "obvious to try" under *KSR*. (D.I. 444 at 4)

Under *KSR*, when there is "a design need" or "market pressure" to solve a problem and

"there are a finite number of identified, predictable solutions," a person of ordinary skill has "good reason to pursue the known options" and, if this leads to the anticipated success, "the fact that a combination was obvious to try might show that it was obvious under § 103." 550 U.S. at 421. Beyond mere conclusory statements in its post-trial briefing, Defendants present no evidence that the "design need" they identify – the need to "use a lower dose of Q because of its powerful ability to inhibit the enzymatic activity of CYP2D6" (D.I. 444 at 4) – was indeed a problem in the prior art, especially given that a maximally inhibiting dose of 150 mg/day of Q combined with DM was known to safely and effectively treat PBA.

Defendants assert that a "finite number of identified, predicable solutions" for solving this problem existed. But Plaintiffs presented evidence that several alternative CYP2D6 inhibitors were available to solve the Q-related problem by avoiding the use of Q altogether, leading to a vast number of possible solutions. (DTX-10 at 10:16-26) ("A number of drugs have been identified as being effective in inhibiting debrisoquin hydroxylase . . . nortriptyline, cblorpromazine, domperidone, haloperidol, pipamperone, labetalol, metaprolol, oxprenolol, propranolol, timolol, mexlletine, quinine, diphenhydramine, ajmaline, lobeline, papaverine, and yohimbine all have significant in vitro activity in inhibiting debrisoquin hydroxylase.") Even assuming Q remained the selected inhibitor, Defendants' own expert, Dr. Boobis, testified that varying the dose of a DM/Q combined product would result in a "very large number of combinations." (Tr. at 465-66) Dr. Poulsen opined that one would proceed in "5, 10, 15 [mg/day]" increments, which he considered "a limited number of combinations," but he failed to address whether both DM and Q would be varied, and he made no comment on the predictability or expected effectiveness of each permutation as the levels of DM and Q were incrementally

changed and their dosage relationship was altered. (*See id.* at 595)

Defendants also fail to show a reasonable expectation of success for the reasons already articulated above. Therefore, based on the evidence, Defendants have not prevailed on their "obvious to try" theory. *See Leo Pharm. Products, Ltd. v. Rea*, 726 F.3d 1346, 1356-57 (Fed. Cir. 2013) ("The problem was not known, the possible approaches to solving the problem were not known or finite, and the solution was not predictable. Therefore, the claimed invention would not have been obvious to try to one of ordinary skill in the art.").

6. Secondary considerations

In evaluating obviousness, courts must consider objective evidence of nonobviousness in the form of secondary considerations, as that "may often be the most probative and cogent evidence in the record" related to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983). Here, Plaintiffs point to unexpected results, satisfaction of a long-felt but unmet need, failure of others, and commercial success as objective evidence of nonobviousness. (D.I. 432 at 11-16)

a. Unexpected results

Plaintiffs contend that prior to July 17, 2002, "a person of ordinary skill in the art would not have expected that the claimed uses of low-dose DM/Q could provide comparable efficacy in treating PBA and a better safety profile compared to the use of higher DM/Q." (*Id.* at 12) While Defendants insist that the issue is really limited to unexpected results from a lower dosage of Q, Defendants do not challenge the evidence that nothing in the prior art taught using less than a maximally inhibiting dose of 150 mg/day Q with DM to treat PBA. (PTX-3 at 4:30-32; Tr. at 579-80, 864-65, 871, 877-78, 880, 882-83, 885-86, 935-36, 1045-47)

Plaintiffs presented evidence that, as of the date of invention, partially-inhibiting doses of Q were expected to increase the potential for unacceptable side effects compared to maximally-inhibiting doses of Q because a reduction in the dose of Q would reduce the inhibition of DM's metabolism to DX, consequently increasing unwanted DX plasma levels. (Tr. at 882-83, 885-86, 935-36, 1045-47) It is undisputed that when a dose of DM is introduced to a patient, DM is rapidly metabolized by CYP2D6 into DX; in turn, DX was known to cause side effects, such as depression. (*Id.* at 883, 1045-46) In contrast, maximally inhibiting doses of Q (such as 150 mg/day) ameliorated DX build-up, yet presented no serious safety concerns, as they were much lower than antiarrhythmic doses of Q, as discussed above.

In addition to unexpected safety benefits, sub-maximally inhibiting doses of Q also presented unexpected efficacy in the treatment of PBA. As Defendants' own cited reference, Example 2 of the '248 patent, makes clear, as of July 2002 the maximally inhibiting dose of Q at 150 mg/day was known to effectively treat PBA when combined with DM. Defendants' experts, Drs. Boobis and Poulsen, were silent on why a person of ordinary skill would expect the level of efficacy in treating PBA to be maintained despite dropping the dose of Q by well over 80% from this prior art dosage.

The Court finds a person of ordinary skill would not have expected that significantly decreasing Q could maintain the efficacy profile of a combined DM/Q dosage for treating PBA while improving the safety profile compared to the prior art.

b. Long-felt need and failure of others

Plaintiffs contend that as of July 2002, "there was a long-felt, but unmet need for a safe and effective treatment for PBA because none of the off-label drugs that had been previously

used to treat PBA showed significant efficacy and the off-label drugs had substantial side-effects." (D.I. 432 at 16) Defendants respond that "the claimed invention did not meet a long-felt but unmet need for a safe and effective PBA treatment because, prior to the '282 and '484 patents, several drugs were considered by the medical community to be safe and effective in treating PBA." (D.I. 444 at 13) The Court agrees with Defendants.

Plaintiffs argue that off-label use of drugs prior to the '282 and '484 patents, such as dopaminergic drugs (e.g., levodopa), tricyclic antidepressants ("TCAs"), and selective serotonin reuptake inhibitors ("SSRIs"), among others, were not considered effective treatments for PBA. (DTX-49; DTX-129; DTX-185; DTX-191; DTX-192; DTX-193; DTX-194; Tr. at 269, 287, 293-301) However, Defendants offered several published sources in the peer-reviewed medical literature that reported successes with TCAs, SSRIs, and medications such as levodopa, reboxetine, venlafaxine, mirtazapine, lamotrigine, methylphenidate, dexamfetamine, and amantadine in treating PBA. (DTX-50; DTX 53; DTX 185; DTX 191; DTX 192; DTX 194; DTX 195; DTX 419; PTX 1; PTX 2; Tr. at 729-44) As early as 1985, amitriptyline was shown, through a double-blind, placebo controlled, crossover study reported in *The New England Journal of Medicine*, to treat PBA within days with only mild side effects. (DTX 194; Tr. at 731-33) The available off-label treatments demonstrated noticeable efficacy, though some exhibited side effects.

To the extent there was a long-felt, unmet need for a treatment for PBA with fewer such side effects, Plaintiffs have failed to prove how the claimed inventions satisfy such a need by treating PBA without those particular side effects. The Court also finds that Plaintiffs have not proven a failure of others.

c. Commercial success

Commercial success is an indication of nonobviousness "because the law presumes an idea would successfully have been brought to market sooner, in response to market forces, had the idea been obvious to persons skilled in the art." *Merck & Co., Inc. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Plaintiffs contend Nuedexta® is commercially successful, as demonstrated by the sales totals, sales growth, profits, profit margins, sales forecasts, prescription totals, prescription growth, and the number of generic ANDA filers. (D.I. 432 at 14-15)

Based on the evidence as a whole, the Court finds Plaintiffs have proven "commercial success." Plaintiffs began marketing and selling Nuedexta® in February 2011 and, through June 2013, Nuedexta® had reached net sales of $93.6 million; its net sales have increased in every quarter, including 265% growth from year one to year two. (PTX-305; Tr. at 672, 777) Nuedexta®'s prescription totals were over 240,000 through early August 2013 and the drug has exhibited prescription growth every quarter since launch, including 257% growth from year one to year two. (PTX-326; Tr. at 778-79) Profits from Nuedexta® were over $88 million through June 2013, with a consistent 94% gross profit margin. (PTX-305; Tr. at 673-77) Plaintiffs' expert, Dr. Rainey, opined that, based on actual financial and prescription data for Nuedexta®, [redacted] Five generic pharmaceutical companies have filed ANDAs seeking to market generic versions of Nuedexta®. (PTX-81; PTX-168; Tr. at 787-88, 1037-39)

Defendants contend Plaintiffs have failed to prove a nexus between Nuedexta®'s commercial success and the claimed invention. It is undisputed that each of the asserted claims of the '282 and '484 patents covers the use of Nuedexta® according to its package insert to treat PBA. (PTX-1; PTX-2; PTX-105; Tr. at 271-85, 788) Defendants' expert, Dr. Rausser, opined "the evidence from NDTI data suggests that Nuedexta is actually being prescribed off-label" and such sales have no nexus to the patents-in-suit because the patent claims only go to treatment of PBA. (Tr. at 821-23) However, Nuedexta® is promoted only as a treatment for PBA and Dr. Rainey opined, persuasively, that Nuedexta® is primarily used to treat PBA. (*Id.* at 787, 789, 791-92; *see also* PTX-167; PTX-150)

Thus, the Court concludes based on the evidence as a whole that a nexus exists between Nuedexta®'s commercial success and the claimed inventions, providing further objective evidence of nonobviousness.

C. Written Description: '282 and '484 Patents[22]

Defendants contend that the '282 and '484 patents lack sufficient written description under 35 U.S.C. § 112, ¶ 1 because the application from which the '282 and '484 patents issued was missing the "10-30 mg/day dose range of Q," demonstrating the patentees did not have possession of the invention. (D.I. 429 at 19) Plaintiffs respond that Defendants' argument must be rejected because it improperly requires working examples to satisfy written description; more

[22]Plaintiffs assert Defendants have waived the written description argument set forth in Defendants' opening brief because it is not exactly the same as the argument Defendants set forth in their invalidity contentions or in the Final Pretrial Order. (D.I. 404 Ex. 3 at ¶ 179; D.I. 429 at 19-20) The Court is not persuaded that this adjustment resulted in surprise to Plaintiffs sufficient to justify a finding of waiver. *See Praxair, Inc. v. ATMI, Inc.*, 543 F.3d 1306, 1315 (Fed. Cir. 2008). Accordingly, the Court concludes that Defendants' argument is not waived.

precisely, the underlying premise of Defendants' argument is "the ***clinical studies*** disclosed in the '282 and '484 patents discuss administering 60/60 mg/day DM/Q, instead of DM in combination with the claimed 10-30 mg/day Q doses." (D.I. 446 at 37-38) (emphasis added) The Court agrees with Plaintiffs.

"The written description requirement does not demand either examples or an actual reduction to practice; a constructive reduction to practice that in a definite way identifies the claimed invention can satisfy the written description requirement." *Ariad*, 598 F.3d at 1352. Here, the specifications of both the '282 and '484 patents expressly disclose the claimed 10-30 mg/day Q dosage range, along with the 20-30 mg/day and 20 mg/day Q dosages as "particularly preferred" for treating PBA. (DTX-1 at 16:26-7; DTX-2 at 16:26-7; *see also Ariad*, 598 F.3d at 1352 ("[I]t is the specification itself that must demonstrate possession.")) Accordingly, Defendants' argument fails.

D. Conclusion on Validity of the '282 and '484 Patents

The Court finds that Defendants have not shown, by clear and convincing evidence, that any claim of the '282 or '484 patents is obvious over the prior art references. Further, secondary considerations of unexpected results and commercial success support a conclusion of nonobviousness. For these reasons, the Court concludes that the '282 and '484 patents are valid.

E. Obviousness: '115 Patent

Defendants assert that if the Court determines the asserted claims of the '115 patent do not include a "therapeutically effective in substantially reducing chronic or intractable pain" limitation, then the patent is invalid as obvious over the '888 patent in combination with the Zhang Abstract or '207 patent. (D.I. 429 at 20) The parties and the Court agree, however, that

the asserted claims of the '115 patent do contain such a limitation. (D.I. 446 at 39, 39 n.24; D.I. 257 at ¶ 5) (term given its plain and ordinary meaning)[23]

Since Defendants have failed to proffer any evidence that a person of ordinary skill would have found the claimed invention of the '115 patent obvious in light of the "therapeutically effective" limitation, the Court concludes that Defendants have not shown, by clear and convincing evidence, that claims 18, 19, 20, and 21 of the '115 patent are obvious over the prior art references.

IV. CONCLUSION

Plaintiffs have proven by a preponderance of the evidence that asserted claims 1-9 of the '282 patent and claims 1-9, 12, 13, 15, and 17 of the '484 patent are infringed. Defendants have failed to prove by clear and convincing evidence that claims 1-9 of the '282 patent and claims 1-9, 12, 13, 15, and 17 of the '484 patent are invalid. With respect to the '115 patent, Plaintiffs have failed to prove by a preponderance of the evidence that asserted claims 18-21 are infringed while Defendants have failed to prove by clear and convincing evidence that these same claims are invalid.

An appropriate Order will be entered.

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[23]Additionally, to the extent Defendants now argue that this claim element should be read out of Claim 18 (which is contradictory, as this element forms the basis of Defendants' non-infringement position), the Court finds this new argument waived, as Defendants failed to advance any such argument during claim construction or through a motion for reconsideration.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

AVANIR PHARMACEUTICALS, INC., AVANIR HOLDING COMPANY, AND CENTER FOR NEUROLOGIC STUDY,	:	
Plaintiffs,	:	
v.	:	
ACTAVIS SOUTH ATLANTIC LLC, ACTAVIS, INC., PAR PHARMACEUTICAL, INC., PAR PHARMACEUTICAL COMPANIES, INC., IMPAX LABORATORIES, INC., WOCKHARDT, LTD., WOCKHARDT USA, LLC, WATSON PHARMACEUTICALS, INC., WATSON LABORATORIES, INC., AND WATSON PHARMA, INC.,	:	C.A. No. 11-704-LPS (CONSOLIDATED)
Defendants.	:	

ORDER

At Wilmington this **30th** day of **April, 2014**:

For the reasons set forth in the Memorandum Opinion issued this date,

IT IS HEREBY ORDERED that:

1. The parties shall meet and confer and submit, no later than **May 5, 2014**, a proposed order consistent with the Memorandum Opinion, to enter final judgment: (i) FOR Plaintiffs and AGAINST Defendants for infringement of the '282 and '484 patents, including any appropriate remedy, (ii) AGANST Plaintiffs and FOR Defendants for infringement of the '115 patent, and (iii) FOR Plaintiffs and AGAINST Defendants for validity of the '282, '484, and '115 patents.

2. Plaintiffs' objection to portions of Dr. Boobis's testimony (D.I. 446 at 21) is

OVERRULED.

3. Defendants' motion to exclude portions of Dr. Wynn's testimony (D.I. 450 at 22-24) is DENIED.

4. Defendants' renewed motion to strike the testimony of Dr. Wynn (D.I. 450 at 27) is DENIED.

5. Defendants' motion to strike references to Plaintiffs' demonstrative exhibits included in Plaintiffs' Proposed Findings of Fact (D.I. 444 at 2 n.2) is GRANTED.

6. The parties shall submit briefs, not to exceed five (5) pages, addressing whether, in light of the Court's finding that Nuedexta® does not meet the "therapeutically effective" limitation of the '115 patent, the Court should grant Defendants' request to "delist" the '115 patent from the "Orange Book" entry for Nuedexta®, pursuant to 21 U.S.C. § 355(b)(1)(G), no later than **May 5, 2014.** The parties shall file responsive briefs not to exceed three (3) pages no later than **May 8, 2014**.

7. The parties shall submit a proposed redacted version of the Memorandum Opinion no later than **May 1, 2014.**

UNITED STATES DISTRICT JUDGE