IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

ACORDA THERAPEUTICS, INC., *et al.*	:	
	:	
Plaintiffs,	:	
	:	
v.	:	Civil Action No. 14-882-LPS
	:	(CONSOLIDATED)
ROXANE LABORATORIES, INC., *et al.*	:	
	:	
Defendants.	:	

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MEMORANDUM OPINION

March 31, 2017
Wilmington, Delaware

STARK, U.S. District Judge:

Acorda Therapeutics, Inc. and Alkermes Pharma Ireland Limited ("Plaintiffs") allege that Apotex Corp., Apotex Inc., Mylan Pharmaceuticals Inc., Roxane Laboratories, Inc., and Teva Pharmaceuticals, USA, Inc. ("Defendants") infringe several United States Patents. Patent No. 5,540,938 (the "'938 patent" or the "Elan Patent") relates to the use of a sustained-release formulation of 4-AP, administered once or twice daily, to treat neurological diseases including multiple sclerosis ("MS"). Patent Nos. 8,007,826 (the "'826 patent"), 8,663,685 (the "'685 patent"), 8,354,437 (the "'437 patent"), and 8,440,703 (the "'703 patent") (collectively, the "Acorda Patents") relate to the use of 10 mg sustained-release formulations of 4-AP to treat walking impairments in individuals with MS.

The Court adopted stipulated constructions for certain claim terms in the patents-in-suit. (D.I. 187, 193) With respect to disputed claim terms, the Court held a claim construction hearing on March 7, 2016 and issued an opinion and order on March 16, 2016. (D.I. 195, 196) In September 2016, the Court held a four-day bench trial. (*See* D.I. 266-69) ("Tr.") The parties have submitted a Statement of Uncontested Facts ("SUF") (D.I. 252-1 Ex. 1) and their competing versions of proposed findings of fact (D.I. 262, 263). They have also submitted extensive post-trial briefing, which concluded with supplemental letter briefs filed on March 6, 2017. (D.I. 265, 272, 273, 274, 278, 279)[1]

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

[1]The parties have also advised the Court of the recent conclusion of an inter partes review ("IPR"), in which the Patent Trial and Appeal Board ("PTAB") found that the Acorda Patents had not been shown to be unpatentable. (*See* D.I. 280) As Defendants point out, two of the three references the PTAB was considering are not part of the trial record here. (*See* D.I. 281)

record in this case and the applicable law, the Court concludes that: (1) Defendants have stipulated that their proposed products infringe the asserted claims of the patents-in-suit; (2) Defendants have failed to prove by clear and convincing evidence that the asserted claims of the Elan Patent are invalid for obviousness; and (3) Defendants have proven by clear and convincing evidence that the asserted claims of the Acorda Patents are invalid for obviousness. The Court's findings of fact and conclusions of law are set forth in detail below.

FINDINGS OF FACT

This section contains the Court's findings of fact ("FF") on disputes raised by the parties during trial, as well as facts to which the parties have stipulated. Certain findings of fact are also provided in connection with the Court's conclusions of law.

A. The Parties

i. Plaintiffs

1. Plaintiff Acorda Therapeutics, Inc. ("Acorda") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 420 Saw Mill River Road, Ardsley, New York 10502. (SUF ¶ 1)

2. Plaintiff Alkermes Pharma Ireland Limited ("Alkermes") is an Irish corporation having a principal place of business at Connaught House, 1 Burlington Road, Dublin 4, Ireland. (SUF ¶ 2)

3. Plaintiffs have standing with respect to each of Plaintiffs' claims asserted against Defendants. (D.I. 254 ¶ 9)

ii. Defendants

4. Defendant Apotex Corp. (together with Apotex, Inc., "Apotex") is a corporation

organized and existing under the laws of the State of Delaware, having a principal place of business at 2400 North Commerce Parkway, Suite 400, Weston, Florida 33326. (SUF ¶ 3)

5. Defendant Apotex Inc. is a corporation organized and existing under the laws of Canada, having its principal place of business at 150 Signet Drive, Toronto, Ontario M9L 1T9, Canada. (SUF ¶ 4)[2]

6. Defendant Mylan Pharmaceuticals Inc. ("Mylan") is a corporation organized and existing under the laws of the State of West Virginia, having a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505. (SUF ¶ 5)

7. Defendant Roxane Laboratories, Inc. ("Roxane") is a corporation organized and existing under the laws of the State of Nevada, having a principal place of business at 1809 Wilson Road, Columbus, Ohio 43228. (SUF ¶ 6)

8. Defendant Teva Pharmaceuticals USA, Inc. ("Teva") is a corporation organized and existing under the laws of the State of Delaware, having a principal place of business at 1090 Horsham Road, North Wales, Pennsylvania 19454. (SUF ¶ 7)

B. Multiple Sclerosis

9. Multiple Sclerosis ("MS") is a chronic disease of the neuroimmunological system. (Peroutka Tr. at 52-53)[3] MS causes a loss of myelin, the fatty material that insulates many of the nerves in the central nervous system. (Peroutka Tr. at 53-54; *see also* Lublin Tr. at 392) This

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[2]On March 28, 2017, the Court so ordered a stipulation of dismissal that was filed the day before by Plaintiffs, Apotex Corp., and Apotex Inc. (*See* D.I. 283) As Apotex participated in the trial and the post-trial briefing, the Court has included findings of fact that may be pertinent to the now-resolved disputes between Plaintiffs and Apotex.

[3]Citations to trial testimony are in the form: "([Witness name] Tr. at pp.-pp)".

loss of myelin is called demyelination. (Peroutka Tr. at 52-53; Lublin Tr. at 392)

10. Demyelination slows or blocks the movement of nerve impulses along the nerve, resulting in diminished coordination of nervous system signals. (Lublin Tr. at 392; Goodman Tr. at 432-33) This disruption results in a wide variety of symptoms affecting a range of body parts and systems. (Lublin Tr. at 392) The symptoms of MS may include walking impairment, visual difficulty, fatigue, bladder dysfunction, tingling or pain, sexual dysfunctions, balance problems, and cognitive changes. (*Id.*; Peroutka Tr. at 55; Goodman Tr. at 433)

11. Weakness in the legs and/or alterations in walking are among the most common symptoms of MS. (Peroutka Tr. at 55; Goodman Tr. at 432) Roughly 50-75% of MS patients experience difficulty walking. (Peroutka Tr. at 55)

12. MS may also cause brain scarring, which can lead to permanent symptoms and make MS patients susceptible to seizures or convulsions. (Goodman Tr. at 430-31, 442)

13. There is substantial variability in how MS manifests itself both among different patients and within a single patient over time. (Goodman Tr. at 431-32, 434-36; Peroutka Tr. at 121) Any particular patient's symptoms may vary on a day-to-day, or even hour-to-hour, basis. (Goodman Tr. at 435-36; Peroutka Tr. at 121-22)

C. Treating MS

14. There is presently no known cure for MS. (Peroutka Tr. at 53-54)

15. Current treatments for MS fall into two categories: (1) the use of disease-modifying agents, which alter the course of the disease and lessen the chance that a patient's condition deteriorates; and (2) therapies that attempt to alleviate the individual symptoms of MS, to improve a patient's quality of life. (Lublin Tr. at 393-94)

16. Designing and interpreting the results of clinical trials for MS therapies is complex because the wide variety of MS symptoms makes it difficult to select clinical endpoints (*i.e.*, measures of efficacy) and leads to mixed results. (Goodman Tr. at 436-37) In particular, it can be difficult to determine whether changes in symptoms result from the treatment being tested, from independent changes in the course of the disease, or from day-to-day variability in symptoms. (*Id.* at 436-38)

17. Placebo effect is also a problem in analyzing results of MS trials. (Lublin Tr. at 401-05) Placebo effect is an improvement in symptoms among test subjects who do not receive a drug. (*See id.* at 412; Goodman Tr. at 468-69)

18. There are a number of methods for assessing the disease state of a patient with MS. Some measures consist of numerical scales designed to interpret patients' subjective assessment of particular symptoms – such as fatigue or walking – or their condition in general. (Goodman Tr. at 455, 481, 518-19) Other measures, such as timed walking tests, provide objective, quantitative indications of results. (Lublin Tr. at 394)

19. In addition to tests that measure clinically manifested symptoms, other tests directly assess nerve impulse transmission. For example, researchers and clinicians can measure subclinical visually evoked potentials ("VEP") to detect the speed of nerve impulse transmissions. (JTX-0065;[4] Lublin Tr. at 394-96) Research established in the 1970s that VEP could serve as a valuable test in the early diagnosis of MS. (JTX-0065; Lublin Tr. at 395-97) By the 1980s and 1990s, VEP was also being used in conjunction with clinical metrics as a measure

[4]Citations to exhibits admitted at trial are in the form: "([JTX or PTX or DTX]-####)," referring to Joint Trial Exhibits, Plaintiffs' Trial Exhibits, or Defendants' Trial Exhibits, respectively.

of therapeutic efficacy in clinical trials. (JTX-0025) VEP is an especially useful tool because it is not susceptible to placebo effect. (Lublin Tr. at 401-05)

D. Ampyra®

20. Acorda holds an FDA-approved New Drug Application ("NDA"), No. 022250, for the use of 10 mg dalfampridine extended release tablets to improve walking in patients with MS. (D.I. 1 ¶ 30; SUF ¶ 8) Acorda markets the approved drug product under the registered name Ampyra®. (D.I. 1 ¶ 30; SUF ¶ 8)

21. Dalfampridine, also known as fampridine, 4-Aminopyridine, or "4-AP," is the active ingredient in Ampyra®. Ampyra® was the first FDA-approved use of 4-AP. (SUF ¶ 9, 68)

22. The FDA approved Ampyra® on January 22, 2010. (SUF ¶ 67) Acorda has been marketing and selling Ampyra® in the United States since March 2010. (*Id.* ¶ 69)

i. Active Ingredient (4-Aminopyridine)

23. The 4-AP molecule improves nerve conduction by blocking potassium channels and is sometimes referred to as a "potassium channel blocker." (Peroutka Tr. at 122)

24. Adverse effects such as seizures have been related to 4-AP's potassium channel blocking mechanism of action. (Goodman Tr. at 438-39, 482; Peroutka Tr. at 122) The concern about seizures is heightened in MS patients because brain scarring associated with the disease can increase seizure risk. (Goodman Tr. at 441-42)

ii. Ampyra® Label

25. The "INDICATIONS AND USAGE" portion of Ampyra®'s label states that "AMPYRA (dalfampridine) is indicated as a treatment to improve walking in patients with

multiple sclerosis (MS). This was demonstrated by an increase in walking speed . . . ." (JTX-0076 at AMPDEL0170808; SUF ¶ 73) Improvement of walking in MS patients is Ampyra®'s only approved use. (SUF ¶ 9)

26. The "DOSAGE AND ADMINISTRATION" portion of Ampyra®'s label states:

> The maximum recommended dose of AMPYRA is one 10 mg tablet twice daily, taken with or without food, and should not be exceeded. Doses should be taken 12 hours apart. Tablets should only be taken whole; do not divide, crush, chew, or dissolve. Patients should not take double or extra doses if a dose is missed . . . . No additional benefit was demonstrated at doses greater than 10 mg twice daily and adverse reactions and discontinuations because of adverse reactions were more frequent at higher doses.

(JTX-0076 at AMPDEL0170808; SUF ¶ 74)

27. The "DESCRIPTION" portion of Ampyra®'s label states that "AMPYRA (dalfampridine) is a potassium channel blocker, available in a 10 mg tablet strength. Each tablet contains 10 mg dalfampridine, formulated as an extended release tablet for twice-daily oral administration." (JTX-0076 at AMPDEL0170811; SUF ¶ 75)

E. The Elan Patent

28. The FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" ("Orange Book") lists the Elan Patent with respect to Ampyra®. (SUF ¶ 12)

i. Development

29. In the 1980s, Dusan Stefoski and Floyd A. Davis of the Rush Medical School began to develop immediate release formulations of 4-AP to treat MS. (JTX-0112; JTX-0043)

30. By 1990, Elan Corporation PLC ("Elan") entered into an agreement with Rush to allow Elan to use Rush's research on 4-AP to develop pharmaceutical formulations of the drug.

(Fogarty Tr. at 158-59) At the time, Elan was at the forefront of the development of sustained-release formulations. (*Id.* at 159-60; Myers Tr. at 151; Fassihi Tr. at 325)

31. Sustained-release formulations release a drug continuously over a long period of time, such that, compared to an immediate release formulation, the body absorbs drug more slowly, the drug's concentration in the body peaks later, and the drug dissipates from the body more slowly. (Kibbe Tr. at 186) As a result, a sustained-release formulation of a drug is effective for longer than an immediate release formulation of the same drug. (*Id.*)

32. The inventors of the Elan Patent required about three or four weeks to design three or four sustained-release 4-AP formulations "on paper," and about a day thereafter to actually prepare a sustained-release formulation of 4-AP. (Myers Tr. at 154-55) In preparing formulations, one of the inventors, Dr. Michael Myers, used sustained-release platforms with which he already had experience, then substituted 4-AP for the active ingredients he had previously used, and "adjusted the platforms with routine testing" until he obtained the desired dissolution pattern. (*Id.* at 211)

ii. Patent and Claims

33. The United States Patent and Trademark Office ("USPTO") issued the Elan Patent, entitled "Formulations and Their Use in the Treatment of Neurological Diseases," on July 30, 1996. (JTX-0001; SUF ¶ 10) The inventors listed on the face of the Elan Patent are Joseph G. Masterson and Michael Myers. (JTX-0001; SUF ¶ 13)

34. The Elan Patent is a divisional of U.S. Application No. 73,651 ("Application No. 73,651"), filed June 7, 1993, which issued as U.S. Patent No. 5,370,879 on December 6, 1994. (JTX-0001) Application No. 73,651 was a continuation of U.S. Application No. 786,400, filed

November 1, 1991, which was subsequently abandoned by the applicant. (*Id.*; SUF ¶ 11)[5] The Elan Patent also claims priority to an Irish patent application filed November 2, 1990. (SUF ¶ 11) The Elan Patent expires on July 30, 2018. (*Id.*)

35. Elan is named on the face of the Elan Patent as the assignee on the patent. (JTX-0001) Acorda has an exclusive license to the Elan Patent. (SUF ¶ 15) Alkermes, which acquired Elan, is the successor-in-interest to the Elan Patent. (Goodman Tr. at 535)

36. Plaintiffs assert that Defendants infringe claims 3 and 8 of the Elan Patent. (SUF ¶ 16)

37. Claims 3 and 8 both depend from claim 1. Claim 1 recites:

> A method for the treatment of a neurological disease where the disease is characterised by a slowing of nerve impulse transmission, which comprises administering to a patient in need thereof a medicament containing a mono- or di-aminopyridine active agent, said medicament being effective to permit sustained release of said mono- or di-aminopyridine active agent at a rate allowing controlled absorption thereof which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis.

(JTX-0001 at 22:16-25)

38. Claim 3 also depends from claim 2. Claim 2 recites: "[a] method according to claim 1, wherein the neurological disease is characterised by demyelination of the central nervous system." (JTX-0001 at 22:26-28) Claim 3 recites: "[a] method according to claim 1 or 2, wherein the neurological disease is multiple sclerosis." (*Id.* at 22:29-30)

39. Claim 8 recites: "[a] method according to claim 1, wherein the active agent is 4-

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[5]It is undisputed that the priority date for the Elan Patent is November 1, 1991. (*See* D.I. 272 at 2 n.4)

aminopyridine." (JTX-0001 at 22:50-51)

iii. 4-AP: Scope and Content of the Prior Art

40. A German paper first identified 4-AP in 1902. (Peroutka Tr. at 73) The drug was subsequently used as a bird toxin and as an agent to induce seizures in animals. (Fassihi Tr. at 361)

41. 4-AP was first used in humans in studies conducted in the 1970s, when a Swedish group tested the drug in connection with neurological diseases that resulted in muscle weakness associated with an impasse in nerve transmission. (Peroutka Tr. at 73)

42. A 1980 British study examined the effect of 4-AP on rats with demyelinated nerves and suggested that the drug could be used to improve their condition. (Peroutka Tr. at 73-74)

43. In 1981, Drs. Nicholas M.F. Murray and John Newsom-Davis disclosed the use of 4-AP in pharmaceutical preparations, to evaluate the safety and efficacy of the drug. (Peroutka Tr. at 74; JTX-0089)

a. Stefoski

44. In 1987, Stefoski and Davis, researchers at Rush Medical School, conducted a study and published a paper entitled "4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis," *Annal. Neurol.*, 21:71-77 (1987) ("Stefoski"). (JTX-0112) Stefoski is a printed publication in the United States and available to persons of ordinary skill in the art in 1987. (SUF ¶ 62)

45. Stefoski studied the effect of 4-AP on VEP, ocular motor function, and motor function (defined by the researchers as power, coordination, and gait). (JTX-0112 at 71) The

researchers monitored 12 MS patients and five men without MS before, during, and after IV injection of seven to 35 mg of 4-AP. (*Id.*) Stefoski found that ten of the 12 MS patients showed mild to marked improvement, with vision improving in seven patients, ocular motor function improving in five patients, and motor function improving in five patients. (*Id.*) Some of the improvements developed within minutes and at doses as low as two mg. (*Id.*) Stefoski concluded that 4-AP might be useful in treating MS patients, adding that studies were "currently in progress to determine the clinical usefulness of 4-AP as a symptomatic treatment." (*Id.* at 75)

46. A later article by Christopher T. Bever *et al.*, "The Effects of 4-Aminopyridine in Multiple Sclerosis Patients," *Neurology*, 44:1054-59 (1994), stated that the conclusions to be drawn from the results reported in Stefoski were "limited by questions about blinding, failure to randomize treatment, and failure to either use prospectively-defined neurologic deficits or adjust significance levels to compensate for multiple comparisons." (JTX-0028 at 1058) A later article by Bever also noted several limitations with Stefoski, including that it was small in size, did not use a randomized treatment design, was not double-blind, involved only short-term use of 4-AP, and relied on outcome measures that were not widely accepted. (JTX-0027 at S119)

b. Davis

47. In February 1990, Stefoski and Davis published a paper entitled "Orally Administered 4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis," *Annal. Neurol.*, 27:186-92 (1990) ("Davis"). (JTX-0043) Davis is a printed publication published in the United States and available to persons of ordinary skill in the art in 1990. (SUF ¶ 47)

48. Davis examined the effect of 4-AP at doses of 10-25 mg versus a placebo. (JTX-0043 at 186) Fifteen patients received immediate-release capsules of 4-AP and five received

placebo. (*Id.*) Davis found that all patients experienced mild to marked improvements, with motor function (defined by the researchers as power, coordination, and gait) improving in nine of 13 subjects. (*Id.*) Davis further found that improvements were observed with use of doses as low as 10 mg. (*Id.*) No serious adverse events, such as seizures, occurred in patients taking 10-25 mg doses of the drug. (*Id.* at 191) Although the study became unblinded, several patients demonstrated reversible improvements in VEP that could not be explained by placebo effect. (*Id.*) Davis concluded that orally-administered 4-AP produces clinically important improvements in multiple chronic deficits resulting from MS. (*Id.*)

49. A later article by Christopher T. Bever *et al.*, "The Effects of 4-Aminopyridine in Multiple Sclerosis Patients," *Neurology*, 44:1054-59 (1994), described the conclusions that could be drawn from the results reported in Davis were "limited by questions about blinding, failure to randomize treatment, and failure to either use prospectively-defined neurologic deficits or adjust significance levels to compensate for multiple comparisons." (JTX-0028 at 1059) A still later article by Bever also noted that Davis had several limitations, including that it was small in size, did not use a randomized treatment design, was not double-blind, involved only short-term use of 4-AP, and relied on outcome measures that were not widely accepted. (JTX-0027 at S119)

c. Murray

50. In 1981, Nicholas M.F. Murray *et al.* published a paper entitled "Treatment with Oral 4-Aminopyridine in Disorders of Neuromuscular Transmission," *Neurology*, 31:265-81 (1981) ("Murray"). Murray is a printed publication published in the United States and available to persons of ordinary skill in the art in 1991. (JTX-0089)

51. Murray reports on a study evaluating 4-AP as an immediate release oral

preparation in nine patients: four with Eaton-Lambert syndrome, four with congenital myasthenia, and one with myasthenia gravis.[6] (JTX-0089 at 265) The patients in Murray received a starting dose of 10 mg/twice daily, which was gradually increased, depending on response, to up to 200 mg daily. (*Id.* at 266)

52. Of the nine patients in the study, one had an "acute confusional episode" and three others experienced seizures. (JTX-0089 at 270) Murray concluded that "[t]he central effects of 4-AP, especially seizures, limit its use." (*Id.*)

iv. Sustained-Release Technology: Scope and Content of the Prior Art

53. Every active pharmaceutical ingredient (*e.g.*, 4-AP) is unique, with its own physical-chemical properties and pharmacokinetics. (*See* Fassihi Tr. at 340) There was (and is) no sustained-release formulation that works for all drugs. (*Id.*)

54. In 1990-91, the FDA had not developed guidelines to aid pharmaceutical companies in developing sustained-release formulations. (JTX-0108)

55. Once a product has been widely-consumed in immediate release form, information about the safety, efficacy, and pharmacokinetics of the drug becomes available. (Fassihi Tr. at 336-38) In 1990-91, all of the drugs that were commercially available in sustained-release dosage forms had previously been approved by the FDA in immediate release forms. (*Id.* at 335-36, 366)

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[6]Dr. Goodman testified that the diseases studied in Murray differ from MS because they are diseases relating to different parts of the nervous system: whereas MS is a disease of the central nervous system, the diseases studied in Murray are diseases of the peripheral nervous system and neuromuscular junction. (Goodman Tr. at 440, 442-43)

a. Remington's (1985 and 1990)

56. "Sustained-Release Drug Delivery Systems," *Remington's Pharmaceutical Sciences*, Alfonso R. Gennaro ed., 18th ed., pp. 1676-93 (1990) ("Remington's") is a printed publication published in the United States and available to persons of ordinary skill in the art in 1990. (JTX-0081; SUF ¶ 59) Remington's is an authoritative treatise on the subject of pharmaceutical formulations. (*See* Peroutka Tr. at 81 (describing Remington's as "the Bible of pharmaceuticals sciences"))

57. The 1985 edition of Remington's highlights that, prior to 1990, there were numerous sustained-release drugs on the market. (JTX-0082 at 1644) ("1985 Remington's") The 1990 edition of Remington's lists five types of sustained-release formulation "platforms" (*e.g.*, encapsulated dissolution) and 39 FDA-approved, commercially-available sustained-release products. (JTX-0081 at 1683-86) The 1990 edition of Remington's also explains how to make a sustained-release drug using each of the disclosed platforms, listing excipients appropriate for each. (*Id.*)

58. The 1985 edition of Remington's includes a table setting forth various known advantages of sustained-release formulations. (JTX-0082 at 1646) One recognized advantage of sustained release is improved patient compliance, as the less frequently a patient has to take a dose the more likely a patient will be to take the required doses. (*Id.*)

59. The 1985 edition of Remington's also lists several characteristics of a drug that are compatible with a sustained-release formulation. First, a drug with a relatively short-half-life is a good candidate for sustained release because sustained release eliminates the need for

frequent dosing.[7] (JTX-0082 at 1647-50) Second, a drug with efficient absorption is a good candidate for sustained release. (*Id.*) Third, a drug requiring a relatively small dose is a good candidate for sustained-release dosing because the resulting sustained-release product will not be too large to swallow. (*Id.*) Finally, because sustained-release dosage forms are often used to treat chronic conditions that require consistent concentration of drug in the blood stream for a long period, drugs used to treat chronic conditions are good candidates for sustained-release formulations. (*Id.*)

b. Robinson & Lee

60. Robinson & Lee, whose full title is *Methods to Achieve Sustained Drug Delivery* and is authored by Joseph R. Robinson and Vincent Hon-Leung Lee, is a printed publication in the United States and available to persons of ordinary skill in the art in 1978. (JTX-0079) Robinson & Lee is an authoritative treatise on the subject of pharmaceutical formulations. (*See* Kibbe Tr. at 236-37 (describing Robinson as "a real authority on sustained release"))

61. The 1990 edition of the Robinson & Lee treatise stated that the design of a sustained-release product was "normally a very difficult task." (PTX-0095 at 201) It further explained that the "[s]uccessful fabrication of sustained-release products . . . involves consideration of the physical-chemical properties of the drug, pharmacokinetic behavior of the drug, route of administration, disease state to be treated and, most importantly, placement of the drug in a dosage form that will provide the desired temporal and spatial delivery pattern for the

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[7]Dr. Peroutka testified that a person of ordinary skill in the art ("POSA") would understand that a drug in an immediate release formulation must be administered approximately once every half-life in order to maintain a consistent level of drug in a patient's blood. Thus, if a drug has a half-life of 3-4 hours, a patient must take the drug once every 3-4 hours to maintain a consistent concentration of it in the body. (Peroutka Tr. at 61)

drug." (*Id.* at 199; *see also* Fassihi Tr. at 326-27, 329-30)

c. Uges

62. In 1982, Donald R.A. Uges *et. al.* published a paper entitled "4-Aminopyridine Kinetics," *Clin. Pharmacol. Ther.* 31(5):587-593 (1982) ("Uges"). Uges is a printed publication published in the United States and available to persons of ordinary skill in the art in 1990. (JTX-0137)

63. Uges examined the pharmacokinetics of 4-AP in nine healthy subjects. (JTX-0137) The subjects received three different administrations of 20 mg of 4-AP: intravenous administration ("IV"), administration via an uncoated (immediate release) tablet, and administration via an enteric (delayed release) dose. (*Id.*) Uges reported that the half-life of 4-AP is about four hours. (*Id.*) Uges also reported that the bioavailability (percent absorption) of enteric-coated tablets was 95% ± 29%, suggesting that the drug was highly bioavailable even when release was delayed. (*Id.*) Finally, Uges taught that almost 100% of the drug was excreted unchanged in the urine, regardless of how the drug was administered. (*Id.*)

F. The Acorda Patents

i. Development

64. Dr. Ron Cohen founded Acorda in 1993. (Cohen Tr. at 277) Dr. Cohen learned of 4-AP through Dr. Andrew Blight, one of Acorda's first employees, who had previously done some exploratory work with 4-AP and spinal cord injury. (*Id.* at 278-79) Acorda initially focused on developing immediate-release formulations of 4-AP. (*Id.* at 280)

65. In 1997, Elan licensed the Elan Patent to Acorda, allowing Acorda to use Elan's sustained-release 4-AP formulations for clinical trials in spinal cord injury patients. (Cohen Tr.

at 280-81; JTX-0020) In 1998, Elan and Acorda expanded the license to give Acorda exclusive rights over the use of the 4-AP formulations, including for use in the treatment of MS. (Cohen Tr. at 303-04; JTX-0021) Acorda did not do any independent development or formulation work on any sustained-release formulation of 4-AP but, instead, used Elan's formulation in its trials. (Cohen Tr. at 304; Blight Tr. at 163)

66. Prior to licensing its sustained-release formulations to Acorda, Elan conducted a double-blind, randomized, placebo-controlled, 161-patient study of the safety and efficacy of twice-daily sustained-release formulations of 4-AP in MS patients. (PTX-0360) (the "Elan Study") Patients in the 4-AP group initially received 12.5 mg doses/twice daily, a dose that was increased by 5 mg every two weeks until the patients either experienced intolerable side effects or reached the maximum dose of 22.5 mg/twice daily. (*Id.* at 8-9) The primary endpoint of the study was the Expanded Disability Status Scale (EDSS), a composite measure of functioning that was widely accepted in the MS community. (*Id.* at 1; JTX-0104 at 817; Goodman Tr. at 284, 467) The only outcome measure with a statistically significant difference compared to placebo was the secondary outcome measure of lower extremity muscle strength; all other secondary outcome measures, including ambulation, showed no statistically-significant difference from placebo. (PTX-0360 at 101-02)

67. In 2000 and 2001, Acorda conducted a 36-patient study on the use of sustained-release formulations of 4-AP to treat MS (the "MS-F201 Study"). (*See* PTX-0466A; Cohen Tr. at 287-88) The 25 patients in the 4-AP group received initial doses of 10 mg/twice daily for the first week of the study, with dosages increasing by 5 mg per week to a maximum of 40 mg/twice daily. (Cohen Tr. at 288) The outcome measures of the study included fatigue, a lower

extremity manual muscle test, the multiple sclerosis functional composite (including a timed 25-foot walk), and subjective measures. (*Id.* at 289) The study failed as to all of the prospectively-defined outcome measures other than the lower-extremity manual muscle test. (*Id.* at 289-90) The results of the timed 25-foot walking test were not statistically significant, as members of the placebo group showed greater improvement than the 4-AP group in multiple weeks. (PTX-0466A; Cohen Tr. at 290-92) In three of the seven weeks, the placebo group demonstrated greater improvement than the members of the 4-AP group had exhibited during the 10 mg/twice-daily week. (PTX-0466A at 63) However, a post-hoc analysis of the data analyzing walking speed (rather than time) indicated a statistically-significant difference between the 4-AP and placebo groups when the 4-AP results were aggregated across all of the various doses combined together. (Cohen Tr. at 292; Goodman Tr. at 478-79)

68. In 2003, Acorda conducted a 206-patient, "Phase II" study regarding the use of sustained-release 4-AP to improve walking speed in patients with MS. (PTX-0168A ("the MS-F202 Study")) The study explored sustained-release doses of 10 mg, 15 mg, and 20 mg 4-AP administered twice daily. (Cohen Tr. at 293) The study included a two-week up-titration period to limit side effects, followed by a twelve-week period of stable dosing. (*Id.* at 295) None of the 4-AP groups demonstrated a statistically significant difference in walking speed compared to placebo. (*Id.* at 296-98) However, a post-hoc, unblinded "responder" analysis indicated that the responders were, overwhelmingly, members of the 4-AP group ($p < 0.0001$). (*Id.*) The responder analysis also indicated that there was no meaningful difference in efficacy among the 10 mg, 15 mg, and 20 mg 4-AP groups. (*Id.* at 298-99)

69. Following the Phase II study, Acorda conducted two Phase III studies of 4-AP,

using 10 mg/twice-daily dosing and the walking improvement responder analysis as a prospectively-defined primary outcome measure. (Cohen Tr. at 299-300) Both studies were successful ($p < 0.0001$). (*Id.*)

ii. Patents and Claims

70. The inventors listed on the face of the Acorda Patents are Andrew R. Blight and Ron Cohen. (*See* JTX-0002; JTX-0003; JTX-0004; JTX-0005; SUF ¶¶ 21, 27, 33, 39)

71. Acorda is listed as the assignee of each of the Acorda Patents. (*See* JTX-0002; JTX-0003; JTX-0004; JTX-0005; SUF ¶¶ 22, 28, 34, 40)[8]

a. The '826 Patent

72. The USPTO issued the '826 patent, entitled "Sustained Release Aminopyridine Composition," on August 30, 2011. (SUF ¶ 18)

73. The '826 patent issued from U.S. Patent Application No. 11/010,828, which was filed on December 13, 2004, and claims priority to U.S. Provisional Application No. 60/560,894, filed on April 9, 2004. (*See* JTX-0002; SUF ¶ 19) The patent expires on May 26, 2027. (SUF ¶ 19)

74. Plaintiffs assert that Defendants infringe claims 1, 7, 38, and 39. (SUF ¶ 23)

75. Claim 1 recites:

> A method for maintaining a therapeutically effective concentration of 4-aminopyridine in order to improve walking in a human with multiple sclerosis in need thereof, said method comprising:
>
> orally administering to the human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day; and

[8]It is undisputed that the priority date for each of the Acorda Patents is April 9, 2004. (*See* D.I. 272 at 2 n.4)

thereafter, maintaining administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, whereby an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.

(JTX-0002 at 27:17-30)

76. Claim 7 depends from claim 6. Claim 6 recites:

> A dosing regimen method for providing a 4-aminopyridine at a therapeutically effective concentration in order to improve walking in a human with multiple sclerosis in need thereof, said method comprising:
>
> initiating administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day without a prior period of 4-aminopyridine titration, and then, maintaining administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily;
>
> without a subsequent period of 4-aminopyridine titration, whereby an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human.

(JTX-0002 at 27:41-57) Claim 7 recites: "[t]he method of claim 6, whereby an increase in walking speed is obtained in said human." (*Id.* at 27:58-59)

77. Claims 38 and 39 depend from claim 37. Claim 37 recites:

> A method of increasing walking speed in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of greater than two weeks, wherein said sustained release composition provides a mean T_{max} in a range of about 2 to about 5.2 hours after administration of the sustained release composition to the patient.

(JTX-0002 at 30:14-21)

78. Claim 38 recites: "[t]he method of claim 37 wherein the sustained release composition elicits a C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 when administered b.i.d. [*i.e.*, twice daily] or administered at 12-hour intervals to a human." (JTX-0002 at 30:22-25)

79. Claim 39 recites: "[t]he method of claim 37 wherein said time period is twelve weeks." (JTX-0002 at 30:26-27)

80. The parties have stipulated that if the two-week limitations (of, for example, claim 37) is obvious, then the 12-week limitations (of, for example, claim 39) are also obvious. (D.I. 254 ¶ 5) This stipulation applies to all of the Acorda Patents. (*Id.* ¶¶ 6-8)

b. The '685 Patent

81. The USPTO issued the '685 patent, entitled "Sustained Release Aminopyridine Composition," on March 4, 2014. (SUF ¶ 36)

82. The '685 patent issued from U.S. Patent Application No. 13/187,158. (*See* JTX-0005; SUF ¶ 37) The application was a continuation of U.S. Patent Application No. 11/010,828, which was filed on December 13, 2004, and claims priority to U.S. provisional application No. 60/560,894, filed on April 9, 2004. (SUF ¶ 37) The patent expires on January 18, 2025. (*Id.*)

83. Plaintiffs assert that Defendants infringe claims 3 and 5 of the '685 patent. (SUF ¶ 41)

84. Claim 3 depends from claim 2, which depends from claim 1. Claim 1 recites:

> A method of improving walking in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, wherein the sustained release composition further comprises one or more pharmaceutically-acceptable excipients.

(JTX-0005 at 27:22-28) Claim 2 recites: "[t]he method of claim 1 wherein said sustained release

composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient." (*Id.* at 28:1-4) Claim 3 recites: "[t]he method of claim 2 wherein the sustained release composition is capable of providing, upon administration to the patient, a release profile of 4-aminopyridine extending over at least 6 hours." (*Id.* at 28:5-8)

85. Claim 5 depends from claim 1 and recites: "[t]he method of claim 1 wherein the sustained release composition provides an average plasma concentration at steady state in humans in the range of about 15 ng/ml to about 35 ng/ml." (JTX-0005 at 28:14-17)

c. The '437 Patent

86. The USPTO issued the '437 patent, entitled "Method of Using Sustained Release Aminopyridine Compositions," on January 15, 2013. (SUF ¶ 24)

87. The '437 patent issued from U.S. Patent Application No. 11/102,559, which was filed on April 8, 2005, and claims priority to U.S. Provisional Application No. 60/560,894, filed on April 9, 2004. (*See* JTX-0003; SUF ¶ 25) The patent expires on December 22, 2016. (SUF ¶ 25)

88. Plaintiffs assert that Defendants infringe claims 1, 2, 5, 22, 32, 36, and 37 of the '437 patent. (SUF ¶ 29)

89. Claim 1 recites:

> A method of increasing walking speed in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, wherein said 10 milligrams of 4-aminopyridine twice daily are the only doses of 4-aminopyridine administered to said patient during said time period.

(JTX-0003 at 27:55-61)

90. Claim 2 recites:

> A method of improving walking in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, wherein said 10 milligrams of 4-aminopyridine twice daily are the only doses of 4-aminopyridine administered to said patient during said time period.

(JTX-0003 at 27:62-67)

91. Claim 5 depends from claim 1 and recites: "[t]he method of claim 1 wherein said time period comprises twelve weeks." (JTX-0003 at 28:16-17)

92. Claim 22 depends from claim 18, which depends from claim 1. Claim 18 recites: "[t]he method of claim 1 wherein said sustained release composition is a tablet." (JTX-0003 at 28:48-49) Claim 22 recites: "[t]he method of claim 18 wherein said tablet exhibits a release profile to obtain a C_{avSS} of about 15 ng/ml to about 35 ng/ml." (*Id.* at 28:55-57)

93. Claim 32 recites:

> A method of increasing walking speed in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release tablet of 10 milligrams of 4-aminopyridine at about every 12 hours for a time period of at least two weeks, wherein said 10 milligrams of 4-aminopyridine at about every 12 hours are the only doses of 4-aminopyridine administered to said patient during said time period.

(JTX-0003 at 29:10-17)

94. Claim 36 depends from claim 32 and recites: "[t]he method of claim 32 wherein said time period comprises twelve weeks." (JTX-0003 at 30:11-12)

95. Claim 37 depends from claim 33. Claim 33 recites:

> A method of improving walking in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release tablet of 10 milligrams of 4-aminopyridine at about every 12 hours for a time period of at least two weeks, wherein said 10 milligrams of 4-aminopyridine at about every 12 hours are the only doses of 4-aminopyridine administered to said patient during said time period.

(JTX-0003 at 29:17-24) Claim 37 recites: "[t]he method of claim 33 wherein said time period comprises twelve weeks." (*Id.* at 30:13-14)

d. The '703 Patent

96. The USPTO issued the '703 patent, entitled "Method of Using Sustained Release Aminopyridine Compositions," on May 14, 2013. (SUF ¶ 30)

97. The '703 patent issued from U.S. Patent Application No. 13/299,969. (*See* JTX-0004; SUF ¶ 31) The application was a continuation of U.S. Patent Application No.11/102,559, which was filed on April 8, 2005, and claims priority to U.S. Provisional Application No. 60/560,894, filed on April 9, 2004. (SUF ¶ 31) The patent expires on April 8, 2025. (*Id.*)

98. Plaintiffs assert that Defendants infringe claims 36, 38, and 45 of the '703 patent. (SUF ¶ 35)

99. All of the asserted claims depend from claim 2. Claim 2 recites:

> A method of improving lower extremity function in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks.

(JTX-0004 at 29:63-67)

100. Claim 36 recites: "[t]he method of claim 2, wherein the lower extremity function is walking, and wherein said sustained release composition provides a release profile to obtain a

C_{avSS} of about 15 ng/ml to about 35 ng/ml." (JTX-0004 at 31:28-31)

101. Claim 38 recites: "[t]he method of claim 2, wherein the lower extremity function is walking, and wherein said sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient." (JTX-0004 at 31:36-40)

102. Claim 45 recites: "[t]he method of claim 2, wherein the lower extremity function is walking, and wherein said time period is more than two weeks." (JTX-0004 at 32:20-22)

iii. Scope and Teachings of the Prior Art[9]

103. It was well-known and accepted prior to the priority dates of the patents-in-suit that impaired walking is a common symptom of MS. (Peroutka Tr. at 56)

104. It was known and accepted prior to the priority dates of the patents-in-suit that MS is a chronic disease that requires ongoing treatment. (Peroutka Tr. at 52)

a. Van Diemen

105. Harriët A.M. Van Diemen *et al.*, "4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety," *Clin. Neuropharmacol.*, 16(3):195-204 (1993) ("Van Diemen"), is a printed publication published in the United States and available to persons of ordinary skill in the art in 1993. (PTX-0330)

106. Van Diemen evaluated the "relationship between dosage, serum level, efficacy, and safety" of 4-AP in 70 patients with MS. (PTX-0330 at 196) The study examined both intravenous and oral administration of 4-AP for up to 12 weeks. (*Id.*) For oral doses, the

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[9]All references that constitute prior art to the Elan Patent are also prior art to the Acorda Patents. The Elan Patent itself, which was published in 1996, is also prior art to the Acorda Patents. (*See* JTX-0001)

researchers used an individualized titration scheme based on tolerability up to a maximum amount calculated based on patient weight. (*Id.* at 196-97) The study assessed efficacy by "registering horizontal smooth pursuit eye movements." (*Id.* at 197) Van Diemen concluded that "higher dosages and serum levels are likely to produce greater improvement in those MS patients who are capable of favorably responding to 4-AP." (*Id.* at 203)

b. Polman

107. Chris H. Polman *et al.*, "4-Aminopyridine in the Treatment of Patients with Multiple Sclerosis," *Arch. Neurol.*, 51:292-296 (March 1994) ("Polman"), is a printed publication published in the United States and available to persons of ordinary skill in the art in 2003. (JTX-0095)

108. Polman disclosed an open-label, unblinded study of the treatment of 23 MS patients with 4-AP and placebo. (JTX-0095 at 295) The study employed an upward titration dosing scheme based on tolerability up to a maximum (determined based on weight) over the course of four to eight weeks. (*Id.* at 293) Polman measured efficacy based on subjective information collected from patients during clinic visits. (*Id.*)

109. Polman reported that "[i]mprovements in fatigue and ambulation were mentioned quite often by the patients as being responsible" for positive effects. (JTX-0095 at 295) Two patients in the Polman study had to discontinue their use of 4-AP due to seizures. (*Id.* at 292)

c. Schwid

110. Steven R. Schwid *et al.*, "Quantitative Assessment of Sustained Release 4-Aminopyridine for Symptomatic Treatment of Multiple Sclerosis," *Neurology*, 48:817-21 (April 1997) ("Schwid"), is a printed publication published in the United States and available to persons

of ordinary skill in the art in 1997. (JTX-0104)

111. Schwid summarizes the Elan Study. (*See supra* ¶ 66) Schwid reports that the Elan Study consisted of administering a sustained-release formulation of 4-AP to 161 MS patients for six weeks. (JTX-0104 at 817) Schwid further explains that the Elan study used a sustained-release formulation of 4-AP because high serum concentrations of 4-AP were associated with seizures and toxicity. (*Id.*) Schwid also states that the Elan Study did not "establish clinical efficacy" because there was no improvement in EDSS relative to placebo – 22% of patients in both groups showed improvement. (*Id.*)

112. Schwid also reports the results of an original study involving the use of sustained-release 4-AP in MS patients. (JTX-0104 at 817) The Schwid study was a randomized, placebo-controlled, crossover design in ten MS patients. (*Id.* at 817-18) All ten patients were randomly assigned to receive either a placebo or 17.5 mg sustained-release 4-AP twice daily for seven days. (*Id.*) After an intervening washout period of seven days, the patients that had received placebo treatment were given 4-AP, and vice versa, for an additional seven days. (*Id.*)

113. The Schwid study did not disclose any prospectively-defined efficacy outcome measure. (JTX-0104 at 817) Instead, the Schwid study was designed to assess a variety of quantitative measurements, including maximum voluntary isometric contraction, manual muscle testing, grip strength, time to ambulate eight meters, time to climb four stairs, EDSS score, and global impression score. (*Id.*)

114. Schwid reported that nine out of ten MS patients experienced improvements in timed gait relative to the placebo group. (JTX-0104 at 820) This was the only outcome measure for which the Schwid study demonstrated a statistically significant improvement relative to

placebo (p = 0.02). (*Id.*) However, the statistically significant result was not adjusted for the fact that multiple outcome measures were included in the study.[10] (*See id.*)

115. Schwid reported that the mean serum level of 4-AP during treatment was "65±25 ng/ml (range, 34-99)" and that the treatment "appeared particularly efficacious in subjects who achieved serum 4AP levels above 60 ng/ml." (JTX-0104 at 819-20) Schwid also stated that "[n]one of the patients with a serum level less than 60 ng/ml felt better (according to their global impressions) on 4AP SR than placebo." (*Id.* at 819) Conversely, all patients with serum levels above 60 ng/ml demonstrated improvement in timed gait, grip strength, and subjective impression. (*Id.* at 820)

116. The Schwid authors (among them, Dr. Andrew Goodman, Plaintiffs' expert witness at trial) suggested further studies of 4-AP, stating, "[i]n addition to establishing efficacy in larger trials, future studies of 4AP SR will need to examine long-term efficacy and tolerability as well as further refine dosing regimens to optimize delivery despite a relatively narrow therapeutic window." (JTX-0104 at 820)

d. Goodman I

117. Dr. Andrew Goodman *et al.*, "Placebo-Controlled Double-Blinded Dose Ranging Study of Fampridine-SR in Multiple Sclerosis," *Multiple Sclerosis*, 8:S116-S117 (P308) (July 2002) ("Goodman I"), is a printed publication (abstract) published in the United States and available to persons of ordinary skill in the art in 2002. (*See* JTX-0062) The lead author of

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[10]Dr. Goodman testified that studies that evaluate multiple efficacy endpoints can result in false-positive findings. (*See* Goodman Tr. at 471-72, 562-64; *see also* PTX-0416 at 5 (Solari)) Dr. Goodman opined that, adjusted for the number of measures assessed in Schwid, the timed gait p-value would be 0.14, indicating a 14% likelihood that the measured result was due to chance. (Goodman Tr. at 562-63)

Goodman I, Dr. Andrew Goodman, appeared at trial as one of Plaintiffs' expert witnesses. (Goodman Tr. at 474)

118. Goodman I disclosed the results of Acorda's MS-F201 study – a randomized-double-blind, placebo-controlled, dose-ranging study of 4-AP in MS patients. (JTX-0062 at S116) Goodman I explained that the MS-F201 study's "primary aim" was to "determine the safety and tolerability of escalating doses of a sustained-release ('SR') formulation given orally to patients with MS." (*Id.*) Goodman I also stated that the MS-F201 study aimed "to explore efficacy over a broad dose range using measures of fatigue and motor function." (*Id.*)

119. Goodman I reported that the MS-F201 study involved 36 patients who were randomized to treatment (25 patients) and placebo (11 patients) groups. (JTX-0062 at S116-17) The treatment group received placebo for the first week, 20 mg of 4-AP per day during the second week, and then an additional 10 mg per day each subsequent week to a maximum of 80 mg/day during the eighth week of the study. (*Id.* at S117) Five subjects withdrew due to adverse side effects: two due to seizures, one due to tremors, one due to dizziness and nausea, and one due to leg pain. (*Id.*)

120. Goodman I stated that analysis of the MS-F201 study data "showed statistically significant improvement from baseline compared to placebo in functional measures of mobility (timed 25 walking speed; p=0.04) and lower extremity strength (manual muscle testing; p=0.01).[11] (JTX-0062 at S117) None of the other measures showed "significant treatment effects." (*Id.*)

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[11]Dr. Goodman testified that the p-values reported in Goodman I reflected the aggregated value for the treatment group ***as a whole***, including all dosages, and did not reflect the results associated with any single dosage. (Goodman Tr. at 482-84)

121. Goodman I also observed that "[d]ose response curves showed increasing benefit in both measures in the 20 to 50 mg/day range." (JTX-0062 at S117)

e. Goodman Poster

122. The Goodman Poster is a poster presented at the September 2002 annual meeting of the America's Committee for Treatment and Research in Multiple Sclerosis, held in Baltimore, Maryland. (*See* JTX-0080; JTX-0080A) The Goodman Poster was a public presentation in the United States and available to a person of ordinary skill in the art in September 2002. (*See* Goodman Tr. at 523-24)

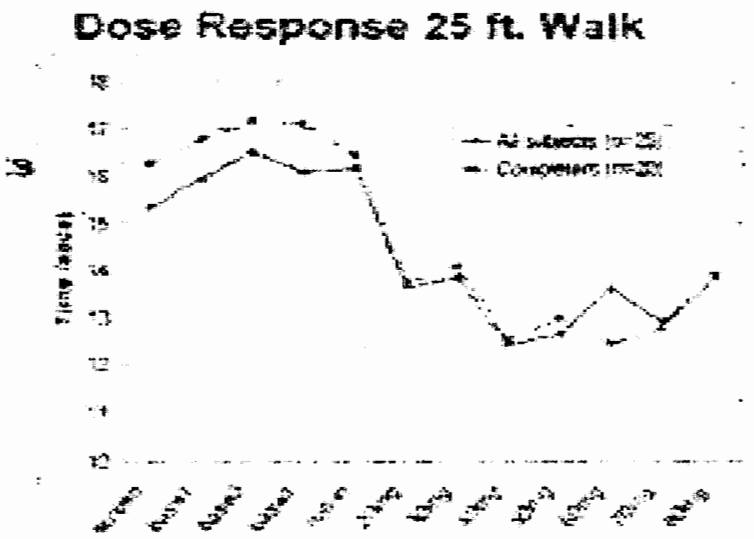
123. Like Goodman I, the Goodman Poster reports results from the MS-F201 study. (Goodman Tr. at 479-80)

124. The Goodman Poster reports that the MS-F201 study was designed to "[d]etermine [the] safety of multiple doses of [sustained-release 4-AP] (one week each of 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70 mg/day and 80 mg/day)" and to "[o]btain evidence of efficacy and dose-response using several outcome measures." (JTX-0080A) The poster identifies multiple efficacy endpoints, including the timed 25-foot walk, manual muscle testing, and patient self-reports using subjective fatigue scales. (*Id.*)

125. The Goodman Poster disclosed that the MS-F201 study data reflected statistically significant improvements in the timed 25-foot walk and manual muscle test relative to placebo. (JTX-0080A (stating that MS-F201 study showed "[s]ignificant benefit on timed walking")) The poster also reported a greater improvement in fatigue in the placebo-treated group as compared to the 4-AP treated group. (*Id.*)

126. The Goodman Poster includes a graph (reproduced below) entitled "Dose

Response 25 Ft. Walk" which shows the measured improvement in walking among members of the treatment group at each dose. (JTX-0080A) The graph does not include data for the placebo group. (*Id.*)



127. The Goodman Poster disclosed adverse events in the treatment group "consistent with the findings of previous studies." (JTX-0080A) It also noted that further study was required to determine whether there was a seizure risk in the disclosed dose range. (*Id.*)

f. Goodman II

128. Dr. Andrew Goodman *et al.*, "Placebo-Controlled Double-Blinded Dose Ranging Study of Fampridine-SR in Multiple Sclerosis," *Neurology*, vol. 60 (Supp. 1):A167 (March 2003) ("Goodman II"), is a printed publication published in the United States and available to persons of ordinary skill in the art in March 2003. (*See* JTX-0061) The lead author is again Dr. Andrew Goodman. (Goodman Tr. at 479)

129. Goodman II disclosed the results of the MS-F201 study. (Goodman Tr. at 479)

g. Hayes

130. Keith C. Hayes *et al.*, "Pharmacokinetic Studies of Single and Multiple Oral Doses of Fampridine-SR (Sustained-Release 4-Aminopyridine) in Patients with Chronic Spinal Cord Injury," *Clin. Neuropharmacol.*, 26(4):185-92 (2003) ("Hayes III"), is a printed publication published in the United States and available to persons of ordinary skill in the art in 2003. (JTX-0069)

131. Hayes reported the pharmacokinetic ("PK") data from early Acorda clinical trials using 4-AP with patients having spinal cord injuries. (Peroutka Tr. at 87-88; JTX-0069 at 191; JTX-0002 at 25:1-28) The first study evaluated single doses of sustained-release 4-AP (10 mg, 15 mg, 20 mg, and 25 mg) administered once a week for 4 weeks in 14 patients with spinal cord injuries. (JTX-0069 at 186) The second study examined the effect of multiple oral doses of sustained-release 4-AP (10 mg, 15 mg, 20 mg, and 25 mg, each given twice daily for six days and once on the seventh day) in six patients with spinal cord injury. (*Id.*)

132. Hayes reported that the plasma half-life of 4-AP was 5.6 to 7.6 hours; that the peak plasma concentration of 4-AP shortly after doses was 2.6 to 3.7 hours; and that 4-AP concentrations reached steady state after four days of twice-daily administration. (JTX-0069 at 185)[12]

h. Solari

133. Alessandra Solari *et al.*, "Aminopyridines for Symptomatic Treatment in Multiple

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[12]The T_{max}, C_{avg} at steady state, and ratio of C_{max} to C_{min} at steady state are all within the claimed pharmacokinetic ranges of the Acorda Patents. (*Compare* JTX-0069 *with* JTX-0002) The '826 patent refers to the data in Hayes, and one of this patent's tables is identical to a table disclosed in Hayes. (Kibbe Tr. 223:25-224:15)

Sclerosis," Cochrane Review, *The Cochrane Library*, Issue 2 (2003) ("Solari"), is a printed publication published in the United States and available to persons of ordinary skill in the art in 2003. (*See* PTX-0416)

134. Solari is a systematic review of the literature related to 4-AP, including a meta-analysis of the few randomized clinical trials of 4-AP that had been conducted in MS patients. (PTX-0416 at 1) Solari excluded from its analysis several prior art studies, including Hayes and the MS-F201 study disclosed in the Goodman references. (*Id.*)

135. Among the studies considered, Solari found that 54% of patients taking 4-AP experienced improved motor functions, compared with only 7% of patients taking placebo. (PTX-0416 at 1) However, Solari noted that "publication bias remain[ed] a pervasive problem," as well as the "distinct possibility of false positive findings" in trials where " the primary endpoint was not specified." (*Id.* at 1, 5) Solari concluded that, while "[p]otassium blocking drugs [including 4-AP] may be able to improve nerve function in nerves without enough myelin," there was at that time "not enough evidence about the safety of these drugs or whether [symptomatic] benefits are certain." (*Id.* at 15)

G. Secondary Considerations

i. Commercial Success

136. Annual net sales of Ampyra® in the United States were $133.1 million in 2010, the year of its launch, and increased to $436.9 million in 2015. (PTX-0795 at 1) Total sales were $1.7 billion by the end of 2015. (*See id.*) Net income from those sales was $998.7 million. (*See id.*)

137. The volume of Ampyra® tablets sold increased from 8 million in 2010 to

16.6 million in 2015, despite an increase in price per tablet from $17 to $26. (Bell Tr. at 578, 592) From 2011 (the first full year of sales) through 2015, domestic unit sales (tablets) of Ampyra® grew at an average rate of 8% per year, and net sales (dollars) increased at an average rate of 20% per year. (PTX-0794; PTX-0795; PTX-0796) Over this same period, Acorda's annual marketing expenditures decreased. (Bell Tr. at 590)

138. Acorda receives additional revenue from milestone and royalty payments associated with licenses it granted to Biogen to sell dalfampridine outside the U.S. (PTX-0733 at 25-27) Payments from Biogen have totaled approximately $135 million to date. (*Id.*)

139. Surveys have found that 87% of Ampyra® prescribers and 83-87% of Ampyra® patients were moderately to highly satisfied with the drug. (PTX-0556 at 7; PTX-0547 at 4; PTX-0549 at 4) Sales to patients continuing with Ampyra® therapy accounted for 76-78% of Ampyra®'s revenue in 2012-13. (PTX-0579 at 2; PTX-0604 at 3) Patients' ability to renew prescriptions was in some cases contingent upon whether the patients could demonstrate to their insurance companies that they had experienced improvements in walking. (PTX-0543 at 2; PTX-0603 at 1; PTX-0664 at 5)

140. Ampyra® is promoted to physicians and patients only as a treatment to improve walking in patients with MS. (PTX-0111 at 20; PTX-0115; PTX-0116; PTX-0119; PTX-0121; PTX-0556 at 8, 10; PTX-0586 at 25) Acorda's key Ampyra® messages to physicians and patients are based on clinically meaningful improvement in walking speed. (*Id.*)

141. The commercial opportunity for Ampyra® is constrained by its limited indication (improving walking in patients with MS) and the relatively small proportion of MS patients (25-30%) who are eligible to take the drug. (McDuff Tr. at 630; JTX-0076; DTX-0419; DTX-0057)

Ampyra® sales revenue is equal to approximately 2-3% of the total sales of the top ten MS drugs. (McDuff Tr. at 633-34)

142. Plaintiffs' expert, Dr. Bell, opined that the preclinical costs associated with developing Ampyra® were lower than for the typical drug, because 4-AP was a pre-existing drug. (Bell Tr. at 595-96)

143. The expected success rate for Ampyra® was higher than average, for reasons including that it is an orphan drug. (Bell Tr. at 596)

ii. Long-Felt Need

144. Difficulty walking is one of the most common difficulties faced by MS patients. (Goodman Tr. at 432, 511) The symptoms of MS that affect mobility have a significant impact on independence, quality of life, safety, and financial and emotional health. (*Id.* at 432, 512) MS patients often cite walking impairments as among the most devastating symptoms of their disease. (*Id.* at 432)

145. The FDA granted priority review to Acorda's Ampyra® New Drug Application. (Cohen Tr. at 300) The FDA's decision to grant priority review indicated that the FDA considered Ampyra® a potentially important therapy for an important condition. (Goodman Tr. at 512)

146. Ampyra® is the first and only FDA-approved drug indicated for improving walking in patients with MS. (Goodman Tr. at 512-13) However, only 15-20% of the patients who suffer from walking difficulties are prescribed Ampyra®. (*Id.* at 539-40)

iii. Failure of Others

147. Elan attempted to demonstrate the effectiveness of 4-AP in treating MS but failed

to show therapeutic efficacy (using the EDSS test). (Goodman Tr. at 513)

148. Sanofi-Aventis attempted to create a therapy, Nerispirdine, to improve walking in MS patients. (*See* PTX-0569 (Nerispirdine Report); Lublin Tr. at 411-12) The active ingredient in Nerispirdine was (like 4-AP) a potassium channel blocker. (Lublin Tr. at 412) Like Acorda's Ampyra® trial, the Sanofi-Aventis Nerispirdine trial used a timed 25-foot walk as a measure of efficacy and used a responder analysis to analyze whether the data reflected efficacy. (PTX-0569; Lublin Tr. at 412) Sanofi-Aventis found "no evidence" of efficacy. (Lublin Tr. at 412)

H. Defendants' ANDAs

149. Each Defendant filed an ANDA, pursuant to the Food, Drug, and Cosmetic Act, 21 U.S.C. § 301 *et. seq.* ("FDCA"), seeking approval to engage in the commercial manufacture, sale, or use of dalfampridine (10 mg) oral extended release tablets before the patents-in-suit expire. (SUF ¶¶ 78, 98, 111, 131)

150. In connection with the filing of its respective ANDA, each Defendant submitted a Paragraph IV certification under 21 U.S.C. § 355(j)(2)(A)(vii)(IV), alleging that each of the patents-in-suit is invalid, unenforceable, or will not be infringed by the commercial manufacture, use, or sale of that defendant's generic dalfampridine tablet. (SUF at ¶¶ 79, 99, 112, 132)

I. Infringement

151. Each Defendant has stipulated that the filing of its ANDA with the FDA, seeking approval to market its generic dalfampridine tablets prior to the expiration of the patents-in-suit, infringed the asserted claims of the patents-in-suit under 35 U.S.C. § 271(e)(2)(A), to the extent those claims are found to be valid and enforceable. (D.I. 254 ¶ 1)

152. Each Defendant has stipulated that the asserted claims of the patents-in-suit would

be infringed by use of the proposed generic products that are the subject of its ANDA, to the extent those claims are valid and enforceable. (D.I. 254 ¶ 2)

J. Fact Witnesses

153. Dr. Ron Cohen was called by Plaintiffs to testify live at trial as a fact witness. Dr. Cohen is a medical doctor and a named inventor on the Acorda Patents. (Cohen Tr. at 274) He is the President and CEO of Acorda, which he founded in 1993. (*Id.* at 274, 277)

154. Michael Myers testified by deposition. Mr. Myers is a named inventor of the Elan Patent and was designated as Alkermes' Rule 30(b)(6) witness on numerous topics. (Tr. at 148)

155. Mairead Fogarty testified by deposition. Ms. Fogarty was designated as Alkermes' Rule 30(b)(6) witness on numerous topics. (Tr. at 158)

156. Andrew Blight testified by deposition. Mr. Blight is a named inventor of the Acorda Patents and was designated as Acorda's Rule 30(b)(6) witness on numerous topics. (Tr. at 161)

157. The Court found all of the fact witnesses who testified to be credible.

K. Expert Witnesses

i. Plaintiffs' Experts

158. Dr. Reza Fassihi testified on behalf of Plaintiffs as an expert witness in pharmaceutics and, in particular, sustained-release formulations. (Fassihi Tr. at 320-21) Dr. Fassihi is a professor of pharmacy at Temple University School of Pharmacy. (*Id.* at 315) He holds a Ph.D. in pharmaceutics from Brighton University (U.K.). (*Id.* at 316; JTX-0040 at 3) A majority of Dr. Fassihi's publications relate to the development of sustained-release pharmaceutical formulations. (Fassihi Tr. at 320; *see also* JTX-0040 at 6-22)

159. Dr. Andrew Goodman testified on behalf of Plaintiffs as an expert in neurology and, in particular, MS, the treatment of MS, and clinical trials in MS. (Goodman Tr. at 428) Dr. Goodman is a Professor of Neurology at the University of Rochester, where he directs the Immunology and Multiple Sclerosis Division within the Department of Immunology. (*Id.* at 424) He has for decades specialized in treating MS patients and conducting MS clinical trials, treating thousands of MS patients, publishing widely regarding MS, and training other doctors regarding the care of MS patients. (*Id.* at 423-27) Dr. Goodman has also advised and consulted with Elan for many years, beginning in 1994. (*Id.* at 536) He has served as a paid consultant for Acorda since the late 1990s, and in the course of his consulting relationship he worked with the inventors of the Acorda Patents on the development of Ampyra®. (*Id.*) He continues to receive compensation from Acorda when he attends meetings of its MS advisory committee. (*Id.* at 537)

160. Dr. Fred Lublin testified on behalf of Plaintiffs as an expert in neurology, with specific expertise in research on MS and care of patients with MS. (Lublin Tr. at 392) Dr. Lublin is a board-certified neurologist and Professor of Neurology at the Icahn School of Medicine at Mount Sinai in New York. (*Id.* at 386) He has for decades specialized in treating MS patients and conducting MS clinical trials, treating thousands of MS patients, publishing widely regarding MS, and training other doctors regarding the care of MS patients. (*Id.* at 388-90)

161. Dr. Gregory Bell testified on behalf of Plaintiffs as an expert in the economics of the pharmaceutical industry. (Bell Tr. at 576) Dr. Bell is a Group Vice President at Charles River Associates, a global economics and management consulting firm, where he is the global head of the life sciences practice and works on, among other things, new drug strategy, product

launches, pricing, and market strategy. (*Id.* at 573-74) He earned a Ph.D. in business economics and an M.B.A. (*Id.* at 573)

ii. Defendants' Experts

162. Dr. Stephen Peroutka testified on behalf of Defendants as an expert in neurology, pharmacology, and drug development. (Peroutka Tr. at 49) Dr. Peroutka is currently Vice President of Neuroscience and Global Therapeutic Head of inVentiv Health, a company that focuses on neurosciences. (*Id.* at 47) Previously, Dr. Peroutka worked as an Assistant Professor of Neurology at Stanford University and in the neuroscience sector of the pharmaceutical industry. (*Id.* at 45-47) He also treated roughly 100 MS patients during the 1980s. (*Id.* at 45) Dr. Peroutka holds an M.D. and a Ph.D. in pharmacology and experimental therapeutics. (*Id.*)

163. Dr. Arthur Kibbe testified on behalf of Defendants as an expert in pharmacokinetics and the development and evaluation of pharmaceutical dosage form formulations, including immediate and sustained-release formulations. (Kibbe Tr. at 179-80) Dr. Kibbe is an Emeritus Professor of Pharmacy at Wilkes University. (*Id.* at 177) Since 1989, Dr. Kibbe has also served on the Steering Committee, as Editor-in-Chief, and as an author of 20-25 monographs included in the *Handbook of Pharmaceutical Excipients*, an internationally-recognized reference text disclosing information on excipients, including those used to achieve sustained release. (*Id.* at 176-78) He has almost 50 years of experience in the development and formulation of pharmaceutical dosage forms, including the development of dosage forms to be used for the first time in patients, as well as the development and review of pharmacokinetic studies (although he has not researched or published on sustained-release pharmaceutical

formulations). (*Id.* at 175, 229-31) Among his other degrees, Dr. Kibbe holds a Master's Degree in pharmaceutics, focusing on formulation development and pharmacokinetics. (*Id.* at 174)

164. Dr. DeForest McDuff testified on behalf of Defendants as an expert on economics and commercial success as it relates to patentability. (McDuff Tr. at 627) Dr. McDuff is a Vice President at Intensity Corporation, a consulting firm with expertise in economics, finance, law, computer sciences, and data science. (*Id.* at 626) He has substantial experience in the pharmaceutical industry, including working on approximately 20 cases considering commercial success. (*Id.* at 627) He holds a Ph.D. in economics. (*Id.* at 626)

165. The Court found each of the expert witnesses who testified for each side to be credible.

L. Person Having Ordinary Skill in the Art

166. The parties have offered different definitions of a person of ordinary skill in the art ("POSA"). Plaintiffs define POSA as having "the knowledge of someone with an M.D. with experience treating MS patients and a Ph.D. in pharmaceutics, or pharmacology, and at least five years of experience in clinical research and drug development, including researching, designing, and testing drug formulations, particularly for the treatment of multiple sclerosis." (D.I. 262 ¶ 68) Defendants' definition differs from Plaintiffs' only in that Defendants do not believe that a POSA must have experience treating MS patients. (*See* D.I. 252-1 Ex. 3 ¶¶ 22-24) All of the testifying experts agreed, however, that their opinions regarding obviousness would be the same regardless of which definition the Court adopts. (Peroutka Tr. at 72; Kibbe Tr. at 184; Fassihi

Tr. at 323; Lublin Tr. at 406; Goodman Tr. at 430) Therefore, the Court need not make an express finding as to which party's definition of a POSA it will use.[13]

167. A POSA at the priority date would have understood that all scientific studies are subject to limitations, including investigator bias, number of subjects, and limitations on the inferences that may be drawn from various statistical analyses. (Peroutka Tr. at 143) It is common for authors of journal articles to comment on limitations of studies reviewed in their papers. (*Id.*) Persons of ordinary skill in the art consider these limitations in the context of the reported study results and the teachings of the prior art. (*Id.*)

168. A POSA at the priority date of the Acorda Patents would have understood that MS studies are particularly unpredictable in view of the great variability in MS patients' responses to treatment and the high risk of placebo effect. (*See* Lublin Tr. at 401-04; Goodman Tr. at 436-38)

LEGAL STANDARDS

I. Presumption of Validity

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 & Gamble Co. v. Teva Pharm. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009). 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; first alteration in original).

[13] *See generally Supernus Pharms. Inc. v. Actavis Inc.*, 2016 WL 527838, at *5 (D.N.J. Feb. 5, 2016) (making no express finding of POSA when there was no material difference between plaintiff's and defendant's definitions and court's analysis was same under either definition).

A defendant's burden to prove obviousness is "especially difficult when the prior art [on which the party relies] was before the PTO examiner during prosecution of the application." *Hewlett-Packard Co. v. Bausch & Lamb Inc.*, 909 F.2d 1464, 1467 (Fed. Cir. 1990).

II. 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 Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1069 (Fed. Cir. 2012) (internal quotation marks and citation omitted); *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).

The use of hindsight is not permitted when determining whether a claim would have been obvious to one having ordinary skill in the art. *See id.* at 421 (cautioning against "distortion caused by hindsight bias" and obviousness "arguments reliant upon *ex post* reasoning"). To protect against the improper use of hindsight when assessing obviousness, the Court is required to consider objective (or "secondary") considerations of non-obviousness, such as commercial success, failure of others, unexpected results, and long-felt but unmet need. *See, e.g., Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013). Secondary considerations "may often be the most probative and cogent evidence in the record" relating to obviousness. *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538 (Fed. Cir. 1983).

DISCUSSION

I. The Elan Patent

The asserted claims of the Elan Patent – claims 3 and 8 – require that the claimed sustained-release formulation of 4-AP is directed to a "method of treatment of a neurological disease" by administering a sustained-release mono- or di-aminopyridine "which achieves therapeutically effective blood levels over a 12-24 hour period when administered on a once- or twice-daily basis."[14] (JTX-0001 at 22:16-25) The Court previously construed the term "therapeutically effective blood levels" as meaning "blood levels sufficient to produce a therapeutic effect." (D.I. 195 at 6)

[14]Claim 3 specifies that the neurological disease is MS. (JTX-0001 at 22:29-30) Claim 8 specifies that the aminopyridine is 4-AP. (*Id.* at 22:50-51)

Defendants argue that claims 3 and 8 of the Elan Patent are obvious because the prior art taught the use of sustained-release drug formulations as well as the use of 4-AP to treat MS, and a POSA would have been motivated to combine these prior art teachings and to have a reasonable expectation of success in doing so. (*See* D.I. 265 at 17) Plaintiffs do not dispute that, as of the priority date of the Elan Patent,[15] 4-AP was a known drug (*see* D.I. 272 at 14) and sustained release was a known formulation type (*see id.* at 20). Plaintiffs do dispute, however, whether a POSA would have had a reasonable expectation of success in developing a sustained-release formulation of 4-AP.[16] In particular, Plaintiffs contend that a POSA would not have had a reasonable expectation of success in using ***any*** 4-AP formulation to treat MS – and emphasize that such a person would not have reasonably expected success with a ***sustained-release*** formulation. (*See id.* at 25)

Defendants have the burden to prove invalidity by clear and convincing evidence. *See Otsuka*, 678 F.3d at 1289-90; *Procter & Gamble Co.*, 566 F.3d at 994. As explained below, the Court concludes that Defendants have failed to meet their burden to establish that the Elan Patent is invalid for obviousness. Although Defendants have shown that a POSA would have had a

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[15]Plaintiffs "rely[]" on a November 1991 priority date. (D.I. 265 at 11 n.1) "Defendants' arguments do not turn on whether the date for determining prior art is November 1990 or November 1991." (*Id.*)

[16]Plaintiffs frame their discussion regarding the teachings of the prior art as posing a question of whether a POSA would have been "motivated to develop" a sustained-release formulation of 4-AP, given how little was known about the drug's safety and efficacy. (D.I. 272 at 14-20) (internal punctuation omitted) In substance, however, Plaintiffs' arguments relate more so to whether the prior art would have given a POSA a reasonable expectation of success in developing ***any*** formulation of 4-AP to treat MS. (*See id.* at 25) Specifically, Plaintiffs argue that "proof of safety and efficacy beyond what could be gleaned from [the prior art] would be needed to motivate a POSA to undertake the development of a sustained-release formulation of 4-AP." (*Id.* at 19)

reasonable expectation of success in using 4-AP to treat MS, Defendants have not shown that a POSA would have had a reasonable expectation of success in developing an effective ***sustained-release*** formulation of the drug.

A. Use of 4-AP to Treat MS

The parties dispute whether a POSA would have had a reasonable expectation of success in using ***any*** formulation of 4-AP to treat MS. Defendants argue that the prior art establishes that 4-AP could be used to treat MS. In support of their contention, Defendants cite principally to two categories of prior art: (1) Stefoski and Davis (collectively, the "Rush Studies"), which describe the use of 4-AP to improve symptoms in MS patients, and (2) early human studies and animal models that explore 4-AP's safety and benefits in improving neurotransmission. (*See* D.I. 265 at 12-15) Plaintiffs contend that this prior art amounts to "at best, fragmentary hints" that 4-AP could be a clinically useful treatment for MS – particularly given the questions about the safety of 4-AP. (D.I. 272 at 16)

The Court is persuaded that the Rush Studies establish that a POSA would have had a reasonable expectation of success of administering 4-AP to achieve a therapeutic effect in MS patients. In the first study, reported in Stefoski, 12 patients with MS and five men without MS received intravenous doses of between seven and 35 mg of 4-AP. (Findings of Fact ("FF") ¶ 45) As Plaintiffs acknowledge, most of the MS patients demonstrated some improvement in symptoms, including vision, ocular motor function, and motor function (defined as power, coordination, and gait). (*Id.*) Stefoski concluded that "4-AP lessens multiple neurological deficits in multiple sclerosis" and "suggests a clinical usefulness for [4-AP]." (JTX-0112 at 71, 76) Similarly, the second study, reported in Davis, found that orally administered 4-AP produces

clinically important improvements in multiple, chronic deficits resulting from MS. (JTX-0043 at 186) Davis was a placebo-controlled study of the effect of 10-25 mg immediate-release doses of 4-AP in 20 MS patients (15 patients received 4-AP and five patients received placebo). (FF ¶ 48) Davis reported mild to marked improvement in all patients, including improvements in motor coordination in nine out of 13 subjects tested. (*Id.*)

In addition to suggesting that 4-AP could improve symptoms of MS, the Rush Studies' findings about 4-AP's safety suggested that there would be a viable therapeutic window for the drug (*i.e.*, a range of doses at which the drug was both non-toxic and had therapeutic effects). Davis, for example, reported no serious adverse events in patients taking 10-25 mg oral doses. Davis concluded that, even in light of prior research indicating that 4-AP could cause seizures, the results of the reported study suggested that 10-25 mg per day could be a "safe and effective therapeutic window for orally administered 4-AP for visual and motor deficits in . . . MS patients."[17] (JTX-0043 at 191)

Plaintiffs argue that the Rush Studies provide a limited basis for drawing conclusions about the possible therapeutic effects of 4-AP. As the 1994 Bever article points out, and as Dr. Fassihi testified at trial, the Rush Studies were conducted in small numbers of patients, "did not use randomized treatment design, were not double-blinded, and relied on outcome measures that

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[17]Defendants argue that Murray, along with two studies conducted in the 1970s, also established the safety of long-term use of 4-AP in humans. (*See* D.I. 265 at 12-13) Although these studies tend to suggest that 4-AP is not toxic in all patients, a POSA would have found the data in these studies to have limited probative value in assessing the safety of 4-AP in MS patients, particularly concerning the seizure risk associated with the use of 4-AP in MS patients. This is because each of the three earlier studies were conducted in patients who suffered from medical conditions that, unlike MS, do not affect the central nervous system. (*See* D.I. 272 at 14) Dr. Goodman testified that a POSA would have understood that MS patients had a greater risk of suffering seizures than did the patients in the Murray study. (*See* Goodman Tr. at 441-42)

were not widely accepted." (Fassihi Tr. at 355) Indeed, Stefoski and Davis themselves draw qualified conclusions from the Rush Studies.[18] Stefoski describes the need to conduct further studies to assess the "possibility" that 4-AP would have "clinical usefulness." (JTX-0112 at 76) Similarly, Davis notes that the "possible use of oral 4-AP as a clinical treatment in MS requires further study to assess long-term efficacy, safety, and patient selection criteria." (JTX-0043 at 190)

The Court agrees with Plaintiffs that a POSA would have found in the results of the Rush Studies only limited information regarding the safety and efficacy of 4-AP for treating MS. A POSA would have understood that additional clinical research would be needed to establish, among other things, 4-AP's therapeutic effects and the dosages necessary to achieve them. (*See* JTX-0043 at 190) Further, a POSA would have understood that additional testing would be required to establish that the drug could meet the FDA's standards of safety and efficacy. (*See id.*)

Still, as even Plaintiffs acknowledge, the prior art need not contain "[c]onclusive proof of efficacy" in order to support a finding that a POSA would have been motivated to develop, and would have had a reasonable expectation of success in developing, a medical treatment. *See Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014). Rather, a POSA need only have a "reasonable expectation of success in developing [the claimed invention]." *Allergan, Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1292 (Fed. Cir. 2013).

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[18]As Defendants note, however, the studies' titles both state that 4-AP "improves clinical signs in multiple sclerosis." (*See* D.I. 273 at 7) (internal quotation marks omitted)

Here, the patentee broadly claimed the use of 4-AP to achieve blood levels having ***any*** "therapeutic effect." (D.I. 195 at 6) The prior art would have given a POSA a reasonable expectation of success in using 4-AP to achieve a therapeutic effect in MS patients. Although the Rush Studies each involved a limited number of patients and did not include statistical analysis (*see* D.I. 272 at 15), a vast majority of patients involved in these studies reported some improvement in symptoms. Further, the trials reported that many patients experienced improvements in VEP, a test that is indisputably immune to placebo effect. (*See* D.I. 265 at 15; D.I. 272 at 17; JTX-0043 at 190; FF ¶ 48) This result would have allayed a POSA's concerns that the Rush Studies' results were attributable to the placebo effects often observed in MS trials. (*See* D.I. 265 at 15) Similarly, the results were consistent with a small animal study that showed that 4-AP could "reverse and improve" the disruption in nerve flow caused by demyelination. (D.I. 263 ¶ 55) Consistent with these results, the authors of the Rush Studies concluded that 4-AP produced improvements in the condition of MS patients (despite noting that the studies did not conclusively establish 4-AP's "clinical" usefulness). Similarly, Stefoski concluded that "the magnitude of the improvements . . . observed without serious side effects suggests a clinical usefulness for [4-AP], administered orally in selected patients" (JTX-0112 at 76), and Davis concluded that "orally administered 4-AP produces clinically important improvements in multiple, chronic deficits in MS" (JTX-0043 at 186).

Taken as a whole,[19] the evidence would have strongly suggested to a POSA at the pertinent time that 4-AP could be used to improve symptoms of MS. Thus, the Court concludes that a POSA would have had a reasonable expectation that 4-AP would be "therapeutically effective" in treating MS.[20] (JTX-0001 at 22:23)

B. Developing a Sustained-Release Dosage Form

Having found that a POSA would have had a reasonable expectation of success in using 4-AP to treat MS, the Court must next determine whether a POSA would also have had a reasonable expectation of success in developing a ***sustained-release*** formulation of 4-AP to treat MS. It is undisputed that the asserted claims of the Elan Patent are directed to sustained-release formulations of 4-AP. (Kibbe Tr. at 219; Fassihi Tr. at 374) Thus, the parties' dispute centers

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[19]The parties' post-trial briefs addressed two other sources of evidence regarding whether the prior art taught the use of 4-AP to treat MS. Defendants argue that the Elan Patent itself characterizes the prior art as establishing that 4-AP could be used to treat MS patients. (*See* D.I. 265 at 15) Citing a Davis and Stefoski study, the Elan Patent explains that 4-AP had previously been found to "alleviat[e] symptoms in MS patients." (JTX-0001 at 1:53-54) Plaintiffs contend that these statements do not refer to the published prior art discussed above, pointing out that the conditions of the study described are inconsistent with those outlined by the Rush Studies. (*See* D.I. 272 at 17-18) In Plaintiffs' view, the cited statements reflect only "the inventors' personal knowledge about the continuing work by Davis and Stefoski" and cannot support a finding as to a POSA's expectations based on publicly-available prior art. (*Id.*) The parties also dispute whether a later published study – Stefoski and Davis, "4-Aminopyridine In Multiple Sclerosis: Prolonged Administration," *Neurology*, 41:1344-48 (Sept. 1991) ("Stefoski II") – should be treated as prior art. Defendants contend that this study precedes the priority date of the Elan Patent (*see* D.I. 265 at 16 n.2); Plaintiffs counter that Defendants waived any right to discuss the study because they identified the paper as prior art only with respect to the Acorda Patents. (*See* D.I. 272 at 18-19) Because the Court has found that the Rush Studies, even by themselves, establish that a POSA would have had a reasonable expectation of success in using 4-AP to treat MS, the Court does not need to make any findings as to the disputes described in this footnote. Resolution of these disputes would not alter the Court's pertinent conclusions.

[20]As the Court noted in its claim construction opinion, decreasing or preventing symptoms is one type of therapeutic effectiveness. (*See* D.I. 195 at 6-7)

on whether development of a sustained-release dosage form would have been obvious to a POSA.

Defendants argue that a POSA would have had a reasonable expectation of success in developing such a formulation because a POSA would have recognized the advantages of such a dosage form for 4-AP and would have found the development process to be routine. (*See* D.I. 265 at 30-31) Plaintiffs respond that there was insufficient information in the prior art to provide a POSA with a reasonable expectation of success in developing such a formulation. (*See* D.I. 272 at 20-25)

The parties do not genuinely dispute that a POSA would have understood the hypothetical advantages of a sustained-release formulation of 4-AP as compared to an immediate release formulation. (*See* Fassihi Tr. at 325; Kibbe Tr. at 207-08) Dr. Peroutka testified that a POSA would have concluded that 4-AP's short half-life (reported in Stefoski and Uges) and narrow therapeutic window (reported in Davis) would make a sustained-release formulation of the drug particularly advantageous, because a sustained-release formulation could overcome the need for dosing at inconvenient three- or four-hour intervals. (Peroutka Tr. at 77-78, 81) Indeed, Dr. Blight, one of the two named inventors on the Acorda Patents, testified that it was "not unusual" or "particularly mysterious" to pursue development of a sustained-release formulation for a drug with a short half-life. (Blight Tr. at 164)

Based on this testimony, it is evident that the prior art would have provided a clear motivation for a POSA to prepare a sustained-release formulation of 4-AP. The Elan Patent itself, in discussing the prior art, expressly states that "it can be appreciated . . . that there is a need for an improved dosage form" of 4-AP, as a POSA would have known based on the prior

art that "it is desirable that the drug be formulated so that it is suitable for once- or twice-daily administration to aid patient compliance." (JTX-0001 at 2:8-12) Thus, the key factual dispute for the Court to resolve is whether a POSA would have had a "reasonable expectation of success" in developing a sustained-release formulation that could realize those hypothetical and strongly-desired, benefits.

Defendants argue that the prior art supports such a finding. (*See* D.I. 265 at 30-33) Defendants' expert, Dr. Kibbe, testified that development of a sustained-release formulation would have been "straightforward" for a POSA in light of the information included in Remington's, an indisputably authoritative treatise on pharmaceutical formulations. (Kibbe Tr. at 208-11) Remington's discloses five sustained-release platforms, explains how to prepare them, and lists appropriate excipients for each. (*See id.* at 208-09) Dr. Kibbe testified that a POSA would have known how to choose a platform from among those listed; from there, could perform compatibility tests to identify, within approximately four months, appropriate excipients; could then make several prototypes over the course of a day or two; and thereafter could perform dissolution testing to confirm that, when administered, the drug would have the desired release profile. (*See id.* at 210-11)

Plaintiffs argue that Remington's demonstrates only that certain platforms had been used to produce sustained-release formulations of other drugs but would not have provided a POSA with sufficient information as to whether it was possible to develop a sustained-release formulation of 4-AP that could achieve therapeutic blood levels. (*See* Fassihi Tr. at 328-29, 343-45, 348-52) Plaintiffs' expert, Dr. Fassihi, highlighted several attributes of 4-AP that would have made the development of a sustained-release formulation of it particularly challenging. He

explained that a POSA would have understood, based on the incidence of seizures in past trials of immediate-release 4-AP, that there was only a limited range of concentrations over which 4-AP was both effective and non-toxic. (*See id.* at 328, 350) This combination of potency and potential toxicity would have complicated the design of a sustained-release formulation because of concerns related to dose-dumping and the need to achieve a uniform distribution of 4-AP throughout the formulation. (*See id.* at 325-26, 328, 341-43) Further, 4-AP is highly soluble, making it difficult to slow its release. (*See id.* at 342-43; *see also* Myers Tr. at 153-54; JTX-0081 at 1679)

In addition to the uncertainty regarding whether it would be possible to overcome the challenges posed by 4-AP's high solubility and narrow therapeutic window, Dr. Fassihi testified that a POSA would have had insufficient information about 4-AP's pharmacokinetics. Unlike all other sustained-release drugs that were on the market at the pertinent time, 4-AP had never been approved by the FDA in an immediate-release form. (*See* Fassihi Tr. at 335-36, 366) Consequently, there was a dearth of information about 4-AP's pharmacokinetics relative to what would normally have been available to a POSA attempting to develop a sustained-release formulation. (*See id.* at 336-38) In particular, a POSA would have known little about how 4-AP is distributed, metabolized, and eliminated by the body when released at various points throughout the gastrointestinal tract. (*See id.* at 337-38; *see also id.* at 326-27 (explaining that sustained-release formulations differ from immediate release formulations because they travel through gastrointestinal tract, which subjects sustained-release formulations to wider varieties of environments)) The data presented in Uges, the only prior art publication containing any

pharmacokinetic information regarding 4-AP, reflected the results of only a small number of patients and demonstrated a high degree of variability. (*See id.* at 348-52)

In Defendants' view, a POSA could have overcome the challenges Dr. Fassihi highlighted by engaging in "routine experimentation[]." (D.I. 273 at 18) Dr. Kibbe testified that resolving concerns unique to sustained-release formulations, such as avoiding "dose dumping," was a common consideration for formulators and part of the routine optimization process to formulate a sustained-release drug. (Kibbe Tr. at 194-98) Similarly, Dr. Kibbe pointed out that at least one polymer suitable for developing sustained-release formulations of soluble products already existed in the prior art. (*See id.* at 209-10) Additionally, Dr. Kibbe disagreed with Dr. Fassihi's views about the impact of a lack of pharmacokinetic information, noting that all of the available information about 4-AP's pharmacokinetics tended to suggest that the drug would be a good candidate for sustained release. Dr. Kibbe noted that Uges reported that 4-AP had a short (four-hour) half-life, high bioavailability, low risk of biotransformation, and a low risk of first pass effect – all characteristics that made 4-AP a favorable candidate for the development of a sustained-release formulation. (*See id.* at 201-02)[21] In Dr. Kibbe's view, this information would have given a POSA a reasonable expectation of success in developing a sustained-release 4-AP formulation to treat MS. Based on this testimony, Defendants argue that, despite some uncertainty about exactly which formulations would work, a POSA would have had a reasonable expectation of success in developing a sustained-release formulation of 4-AP.

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[21]Dr. Peroutka further noted that, although the Uges study size was small, a POSA would be encouraged by the consistency between the reported half-life and bioavailability data and between the consistency of the half-life reported in Uges and the half-life reported in Stefoski. (*See* Peroutka Tr. at 77-78)

The need to engage in routine testing or optimization efforts – even if expensive and technically challenging – does not render an invention non-obvious, if a POSA would reasonably expect the testing or optimization efforts to succeed. *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367-68 (Fed. Cir. 2007). Thus, a POSA may have a reasonable expectation of success despite "a showing of some degree of unpredictability in the art." *Id.* at 1364; *see also Allergan*, 726 F.3d at 1292.

The Federal Circuit's decision in *Cyclobenzaprine* is instructive. There, the Federal Circuit considered a claim directed to a "method of relieving muscle spasms" which "provides [a] therapeutically effective plasma concentration over a period of 24 hours . . . ."[22] 676 F.3d at 1066 (brackets in original). Similar to here, the term "therapeutically effective plasma concentration" was construed to mean "the amount of a drug required to produce the therapeutic result." *Id.* at 1067 (internal quotation marks omitted). The Federal Circuit held that a POSA would not have had a reasonable expectation of successfully developing a formulation to satisfy the "therapeutically effective" limitation unless a POSA would have both (i) known what blood levels would produce a therapeutic result ***and*** (ii) would have had a reasonable expectation of success in developing a sustained-release formulation that could achieve those blood levels. *See id.* at 1070 ("Because . . . skilled artisans did not know the [relationship between the pharmacokinetics and therapeutic effect] . . . for the immediate-release formulation, there was no way to match the dosage for the extended-release formulation to achieve a known therapeutic effect.") (emphasis omitted) Absent specific knowledge of the relationship between the

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[22]Additional asserted claims specified particular pharmacokinetic values, including the concentration of drug. *See Cyclobenzaprine*, 676 F.3d at 1066.

pharmacokinetics and therapeutic effectiveness, the Federal Circuit noted, the claims could not be obvious without a "finding that the prior art would have taught or suggested a [specific] therapeutically effective formulation to one of ordinary skill in the art." *Id.*

Of relevance to this case, the Federal Circuit's analysis in *Cyclobenzaprine* illustrates that knowledge of a ***correlation*** between a particular set of pharmacokinetic values and the therapeutic effectiveness of an immediate release formulation is ***not necessarily sufficient*** to raise a reasonable expectation that a sustained-release formulation achieving the same pharmacokinetic values would be therapeutically effective. *See id.* at 1071. The drug at issue in *Cyclobenzaprine* had already been released in an immediate-release form, and its pharmacokinetic parameters were available in the prior art. *See id.* Nevertheless, the Federal Circuit rejected the argument that a POSA would have considered it obvious to "target extended-release [pharmacokinetic] values 'mirroring' – in other words, bioequivalent to – those of the immediate release . . . formulation." *Id.* at 1069. The Federal Circuit explained that, without a known relationship between pharmacokinetics and effectiveness, "immediate-release [pharmacokinetic] values are of little use in calculating extended-release values, [absent] proof that a skilled artisan would expect the extended-release values to produce a therapeutic effect solely because they are drawn from immediate-release values." *Id.* at 1071. Rather, a POSA would need evidence that "in the specific context" of the drug at issue, a skilled artisan would expect the particular "[pharmacokinetic] values drawn from the prior art to yield a therapeutically effective formulation." *Id.* at 1072. Thus, without information about which particular parameters (*i.e.* T_{max}, C_{max}, etc.) were crucial to therapeutic effectiveness, "[t]he fact that a skilled artisan could have predicted [that a sustained-release formulation could achieve] a particular

blood plasma concentration . . . does not mean that such knowledge would have provided a skilled artisan a reasonable expectation of success." *Id.* at 1071.

As with the active ingredient at issue in *Cyclobenzaprine*, there was no well-characterized relationship between 4-AP's pharmacokinetics and its therapeutic effects at the time of the priority date of the Elan Patent. (*See* Kibbe Tr. at 241) Uges, the only pharmacokinetic study of 4-AP available at that date, did not link pharmacokinetic data to therapeutic effects. The record does not support a finding that Uges, combined with other prior art references, would have allowed a POSA to infer the relationship between the pharmacokinetics and therapeutic effects. As a result, a POSA would not have known what *in vitro* dissolution profile a sustained-release formulation would have needed to achieve in order to maintain safe and effective therapeutic blood levels of 4-AP over time. Thus, a POSA would not have had the information necessary to assess whether a sustained-release formulation could be developed to achieve those blood levels. *See Cyclobenzaprine*, 676 F.3d at 1071.

Absent prior art showing the 4-AP blood levels that would be therapeutically effective, a POSA might nevertheless have formed a reasonable expectation of success in developing a sustained-release formulation had the prior art "taught or suggested" that a particular formulation could be effective. *Id.* at 1070. Here, however, the record lacks such evidence as well. Although Dr. Kibbe testified that a POSA would be able to identify prior art sustained-release platforms and excipients that would be particularly likely to complement 4-AP, given the drug's characteristics (*see, e.g.*, Kibbe Tr. at 208-10) (explaining that POSA would understand that encapsulated dissolution, and particular known polymers, would be appropriate for 4-AP), he did not testify as to why a "skilled artisan would have had a reasonable expectation [that these

platforms and excipients] would succeed in being ***therapeutically effective***." *Cyclobenzaprine*, 676 F.3d at 1070 (emphasis added). Thus, while the record indicates that it may have been obvious to experiment with certain approaches to developing a sustained-release formulation, nothing in the record demonstrates that a POSA would have had a "reasonable expectation" that at least one of those approaches would have resulted in a therapeutically effective sustained-release formulation of 4-AP. *Id.*

Defendants urge the Court overlook these evidentiary shortcomings, arguing that there is no "credible evidence" to support a finding that a POSA would ***not*** have had "a reasonable expectation of successfully formulating 4-AP into ***any*** of multiple available sustained-release dosage forms." (D.I. 273 at 18) (emphasis in original) But the burden in this case does not reside with Plaintiffs. Rather, it is Defendants' burden to present clear and convincing evidence that a POSA would have had a reasonable expectation that one of the multiple available sustained-release dosage forms could be combined with 4-AP to create a therapeutically effective formulation when administered as claimed. Defendants have shown that the prior art included many sustained-release platforms, that many drugs had been formulated using these sustained-release platforms, and that no affirmative evidence existed that would have ***dissuaded*** a POSA from ***pursuing*** a sustained-release dosage form of 4-AP. Defendants have ***not*** shown, however, that a POSA would have inferred from this evidence that success would reasonably be expected from an attempt to develop a therapeutically-effective, sustained-release formulation for ***any*** drug, and most particularly for 4-AP.

The Court is mindful that the evidence regarding the inventors' actual experience in developing the invention of the Elan Patent is not inconsistent with Dr. Kibbe's testimony. Dr.

Myers, one of the inventors, stated that it took him only three or four weeks to put three or four formulations of 4-AP on paper and then about a day actually to prepare a sustained-release formulation of 4-AP. (*See* Myers Tr. at 154-55) Dr. Myers further explained that this process essentially involved substituting 4-AP for the active ingredients he had previously used in sustained-release platforms, and "adjust[ing] the platform[s] with routine testing" until he obtained the desired dissolution pattern. (Kibbe Tr. at 211) Among the disclosed sustained-release formulations in the Elan Patent is one platform that had been disclosed in the 1990 edition of Remington's. (*See* JTX-0001 at 4:41-46; Kibbe Tr. at 219-20)

While this evidence does nothing to discredit Dr. Kibbe's testimony that developing a sustained-release formulation of 4-AP was straightforward, it also does not help Defendants to meet their burden of showing that a POSA would reasonably have ***expected it to be so***. "[I]n addressing the question of obviousness a judge must not pick and choose isolated elements from the prior art and combine them so as to yield the invention in question if such a combination would not have been obvious at the time of the invention." *Abbott Labs. v. Sandoz*, 544 F.3d 1341, 1348 (Fed Cir. 2008) (internal quotation marks omitted). Without the benefit of hindsight, the record here does not support a finding that the approach taken by the Elan Patent represented an "identified, predictable solution[]" that produced an "anticipated success." *KSR*, 550 U.S. at 421. As such, the Court finds that Defendants have not met their burden to establish, by clear and convincing evidence, that the Elan Patent is invalid as obvious.

C. Secondary Indicia of Non-Obviousness

As detailed below in the discussion of the Acorda Patents, the Court finds that Ampyra® is a commercially successful product. This success has a nexus with the Elan Patent because, as

is undisputed, Ampyra®'s sustained-release formulation allowed for infrequent dosing that improves patient compliance. (JTX-0001 at 2:22-32) As such, Court finds that the invention of the Elan Patent likely contributes to this commercial success. This finding is further evidence supporting the Court's conclusion that Defendants have failed to prove that the invention of the Elan Patent is non-obvious.

D. Section 112 Defenses

Defendants contend in the alternative that, if the Elan Patent is not found to be obvious, then it should be found to be invalid for lack of adequate written description and/or lack of enablement. *See* 35 U.S.C. § 112.[23] Defendants' Section 112 defenses could likely be found to have been waived, given the lack of evidence presented at trial. (*See* D.I. 272 at 57 n.38 (Plaintiffs arguing for waiver); D.I. 274 at 1 n.1 (same); *but see* D.I. 273 at 22 n.3 (Defendants responding that they noted defenses in pretrial order, as well as in opening statement and closing arguments at trial)) Indeed, these defenses barely even got mention at trial.[24] Notably, none of the experts testified at trial about the Section 112 defenses and, accordingly, none opined that the Elan Patent is invalid due to lack of enablement or written description. (*See* Tr. at 272)

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[23]*See Teva Pharms. USA, Inc. v. Sandoz, Inc.*, 723 F.3d 1363, 1370 (Fed. Cir. 2013) (explaining that test for enablement requires specification to teach one of skill in art "how to make and use the full scope of the claimed invention without undue experimentation") (internal quotation marks omitted); *Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1566 (Fed. Cir. 1997) (explaining that test for written description requires specification to describe invention in sufficient detail that one of skill in art can conclude "the inventor invented the claimed invention") (internal quotation marks omitted).

[24]According to the index to the trial transcript, the terms "written description," "enablement," and "112" were mentioned only five times over the four days of trial. (*See* Tr. at 800)

Even assuming these defenses were not waived, they are unavailing on the merits. To the extent Defendants have articulated their Section 112 invalidity theory, it is a theory based on contingencies which, given the Court's findings, have not been satisfied.

In the less than two pages (out of 66) Defendants devote in their opening brief to these defenses, they explain that the defenses are predicated on the Court accepting certain arguments or evidence relied on by Plaintiffs. (*See* D.I. 265 at 65-66; *see also* D.I. 273 at 2, 19-22) Defendants argue: "In rebutting Defendants' evidence of obviousness for the Elan [P]atent, Plaintiffs have repeatedly made arguments, or elicited testimony, that – ***if accepted by the Court*** – would render the Elan [P]atent invalid for lacking enablement or written description." (D.I. 265 at 65) (emphasis added) But (as best as the Court can tell) the Court has not "accepted" these arguments or evidence relied on by Plaintiffs. Contrary to Plaintiffs' position, the Court has found that a POSA would have been, at the priority date, motivated to use 4-AP to improve walking in MS patients, and would have had a reasonable expectation of success in doing so, for all the reasons Defendants contend.

So, for example, Defendants argue that "either Davis and Stefoski teach using 4-AP to treat clinical symptoms of MS (including gait) or the Elan [P]atent is invalid for lacking enablement and written description." (*Id.* at 66) The Court has found that Davis and Stefoski ***do*** teach using 4-AP to treat clinical symptoms of MS (including gait). Hence, on Defendants' own reasoning, it follows that the Elan Patent does not lack enablement or written description.

Defendants expand their arguments in their reply brief, stating:

> [Plaintiffs] further refer to the prior art as providing "meager data" with only "fragmentary hints" that 4-AP might have some clinical usefulness in MS patients. ***If true***, these are significant admissions

> under 35 U.S.C. § 112, given that the Elan [P]atent claims methods of "treatment" for MS, and the patent disclosure does not identify any 4-AP testing conducted independently by the inventors.

(D.I. 273 at 19) (emphasis added; internal citation omitted) But, again, the Court has not been persuaded that the statements Defendants here call out are "true." The Court has found for Plaintiffs on the parties' dispute as to the invalidity of the Elan Patent based on other grounds. It follows, again, that Defendants have failed to prove their Section 112 defenses.

In sum, assuming the defenses have not been waived, Defendants have failed to meet their burden to prove, by clear and convincing evidence, that the Elan Patent is invalid due to lack of enablement or written description.

II. The Acorda Patents

The asserted claims of the Acorda Patents are directed to a method of improving walking in a human with multiple sclerosis by administering a 10 milligram dose of 4-AP twice per day, for either two weeks or twelve weeks.[25] Certain claims also require that this dosage regimen produce particular pharmacokinetic results.[26] (*See, e.g.*, JTX-0002 at 27:55-57; JTX-0003 at 28:55-57; JTX-0004 at 31:28-31) Certain claims further mandate that there be no titration before or after administration of the 10 mg/twice-daily dose. (JTX-0002 at 27:48-49) Defendants argue that all of these claims are obvious because the prior art would have given a POSA a reasonable expectation of success in combining these limitations. (*See* D.I. 265 at 38-43) Plaintiffs disagree

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[25]As noted earlier, the parties have stipulated that if the claims requiring stable dosing for two weeks are obvious, then the twelve-week limitations are obvious as well. (D.I. 254 ¶¶ 5-8)

[26]The claims including pharmacokinetic or release profile limitations are: claims 1, 7, 38, and 39 of the '826 patent; claims 3 and 5 of the '685 patent; claim 22 of the '437 patent; and claims 36 and 38 of the '703 patent.

and further argue that secondary indicia of non-obviousness preclude a finding that the invention of the Acorda Patents was obvious. (*See* D.I. 272 at 31)

As explained below, the Court concludes that Defendants have shown that the prior art taught the four disputed limitations: the use of 4-AP to improve walking; the use of a 10 mg/twice-daily dosage; the use of stable dosing; and the inherent pharmacokinetic limitations. The Court finds that a POSA would have been motivated to combine these limitations with a reasonable expectation of success. The Court also agrees with Defendants that the secondary indicia do not support a finding of non-obviousness with respect to any claim. As such, the asserted claims of the Acorda Patents are invalid.[27]

A. Use of 4-AP to Improve Walking

All of the asserted claims of the Acorda Patents are directed to methods of administering sustained-release 4-AP to "improving walking." (JTX-0003 at 27:62-67) It is undisputed that the claims do not require that the patents be effective to treat MS in all patients. (*See* D.I. 265 at 50; D.I. 272 at 38) Thus, the parties' dispute with respect to this limitation centers on whether the claimed studies would provide a POSA with a reasonable expectation that 4-AP could be

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[27]Defendants contend that the Acorda Patents "are ***presumed obvious*** as a matter of law, because they simply claim an optimized dose selected from a discrete, narrow range of doses disclosed in the prior art," including the Elan Patent. (D.I. 265 at 5) (emphasis in original) (citing *Tyco Healthcare Grp., LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1372-73 (Fed. Cir. 2011); *Galderma Labs., L.P. v. Tolmar*, 737 F.3d 731, 738 (Fed. Cir. 2013)) Plaintiffs disagree, arguing that "unlike in *Galderma* and *Tyco*, there was no prior art teaching that ***any*** dose of 4-AP – any single dose or any range of doses – was safe and effective to improve walking or increase walking speed in MS patients. The Acorda inventors were not seeking to improve upon what was already a known process, and their invention was not the mere optimization of a known dose range." (D.I. 272 at 54) (emphasis in original) Given the Court's conclusion that Defendants have proven, by clear and convincing evidence, that the asserted claims of the Acorda Patents are obvious, it is unnecessary for the Court to also determine whether these claims should be presumed obvious.

successfully used as claimed to treat (*i.e.*, achieve therapeutically-effective blood levels in) even a single patient. (*See* D.I. 272 at 38)

Defendants argue that the prior art made it obvious to a POSA that 4-AP could be used to treat impaired walking in some MS patients. For this contention, Defendants rely on three prior art references: Schwid, Goodman I, and the Goodman Poster. (*See* D.I. 265 at 38-41)

Schwid begins by disclosing the failure of the Elan Study, a rigorous clinical trial into the effect of sustained-release 4-AP on EDSS in MS patients.[28] (*See* JTX-0104 at 817) Schwid theorized that EDSS – which is a composite of several measures of effectiveness, including improvements in walking – "may have been an inadequate outcome variable" for measuring the effectiveness of 4-AP. (*Id.*) Schwid thus tested seven outcome measures that the authors thought might be "more sensitive." (*Id.*) Doing so, Schwid found a statistically significant improvement in only one measure: timed gait, which was found to be improved in nine out of 10 patients, in comparison to the placebo group. (*See id.*)

The Goodman references disclose the results of the MS-F201 study, which, like the Schwid study, examined multiple outcome measures. The Goodman references disclose that the MS-F201 study was randomized, double-blinded, and placebo-controlled. Goodman I explains that one of the goals of the MS-F201 study was "to explore efficacy over a broad dose range using measures of fatigue and motor function," and it concludes that the study data "showed statistically significant improvement from baseline compared to placebo in functional measures

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[28]The trial was multi-center, double-blind, and placebo-controlled, and it used parallel-groups involving 161 patients who took 4-AP for six weeks. (*See* JTX-0104 at 817) Plaintiffs' expert, Dr. Goodman, testified that Schwid disclosed "all of the key characteristics one looks for" to obtain "a rigorous assessment of efficacy." (Goodman Tr. at 468)

of mobility (timed 25 walking speed; p=0.04) and lower extremity strength (manual muscle testing; p=0.01)." (JTX-0062 at S116-17) Likewise, the Goodman poster reports a "[s]ignificant benefit on timed walking" and a "[s]ignificant benefit on lower extremity strength." (JTX-0080A)

Defendants argue that these prior art references – viewed in light of earlier studies, such as Stefoski (which showed that 4-AP improved MS symptoms), Davis (which showed that 4-AP improved motor function), and Polman (which showed that 4-AP could improve ambulation) – represent the culmination of a "consistent march by those skilled in the art towards using 4-AP to improve walking in MS patients." (D.I. 273 at 31)

Defendants' characterization of the prior art is not entirely persuasive. It understates the complexity and uncertainty of the prior art, given what a POSA would know about both the broader content of the prior art related to 4-AP and the challenges of interpreting MS studies more generally. In particular, Defendants ignore the fact that the Schwid and MS-F201 studies arose in the midst of significant uncertainty in the field of 4-AP research. Each study came in the wake of the larger and more "rigorously designed" Elan study, which failed to show that 4-AP had an effect on EDSS (which includes a walking component). (Goodman Tr. at 469) Although researchers believed that alternative outcome variables could be more appropriate, it was not yet clear that ***any*** variable would meet the requirements for clinical approval. The 2003 Solari review, which analyzed the results of the Schwid and Van Diemen studies, concluded that the information then available allowed "no unbiased statement about safety or efficacy of aminopyridines for treating MS symptoms." (PTX-0416 at 1)

As Plaintiffs point out, both the Schwid and MS-F201 studies were exploratory studies, designed to identify possible alternatives to EDSS as measures of efficacy, rather than studies aimed at establishing effectiveness of the tested drug. Neither study includes a single, pre-defined measure of efficacy; instead, each consider multiple possible measures. (*See* D.I. 272 at 33) A POSA would understand that the risk of a false positive result is higher for such studies than it is for studies with a single, pre-defined endpoint. (*See* Goodman Tr. at 472; PTX-0416 at 5 (recognizing "[a] distinct possibility of false positive findings" in studies involving multiple measures of effectiveness))[29] As Plaintiffs' expert Dr. Goodman explained, a POSA would have recognized that the statistical significance of the Schwid and MS-F201 results did not account for the increased probability of obtaining a false positive in the study as a whole.[30] (Goodman Tr. at 472)

Further, a POSA at the pertinent date would have known that "complexity, variability, and [the] high placebo effect that characterize MS . . . complicate the design and interpretation of MS trials." (D.I. 272 at 38) Also, as Solari noted, "publication bias remain[ed] a pervasive problem" in MS studies, meaning a POSA would have been concerned that the prior art may have misleadingly excluded studies showing no effect.[31] (PTX-0416 at 1)

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[29]As evidence of this concept, Plaintiffs point out that "leads that had appeared promising on the basis of [earlier] reports of small, multiple-endpoint studies were not" reproduced in later studies. (D.I. 272 at 35) (comparing Polman's report of improvement in fatigue with Goodman's finding of no such improvement)

[30]Plaintiffs argue that, were a POSA to adjust the results of the Schwid and MS-F201 studies, the study results would not be statistically significant. (*See* D.I. 272 at 61 (arguing that adjusted p-value for Schwid would be 0.14); *id.* at 66 (arguing that adjusted p-value for MS-F201 would be 0.16))

[31]Plaintiffs note that Acorda itself opted in some cases not to publish data related to failed trials. (*See* D.I. 272 at 50-51)

Taking all of this into account, the Court concludes that a POSA would have examined and interpreted the prior art holistically and cautiously. Despite all of Plaintiffs' valid concerns, the Court finds that Defendants have proven, by clear and convincing evidence, that a POSA would have formed a reasonable expectation of success based on Schwid and Goodman, in light of the totality of the prior art. That neither Schwid nor the Goodman references report on the results of a randomized, placebo-controlled study that was "properly designed to assess efficacy" would be taken into account by a POSA, but would not have led a POSA to conclude that there was not a reasonable expectation of success in using 4-AP to improve walking speed. (D.I. 272 at 38)

Several aspects of the record support the Court's conclusion on this issue. First, both the Schwid and MS-F201 studies have two of the three characteristics Plaintiffs deem essential to a persuasive efficacy study: each is randomized and placebo-controlled. (*See id.*) The studies' key shortcomings are their relatively small size and multi-endpoint, exploratory design. (*See id.*) While these features increase the probability of obtaining a false positive result (*see* Goodman Tr. at 472; PTX-0416 at 5), the combined message a POSA would have discerned from Schwid together with the Goodman references was a reasonable expectation of success in treating walking with 4-AP. Just as conducting a study with multiple endpoints increases the overall likelihood of uncovering at least one false-positive, obtaining the same result in a second study decreases the likelihood that the first result was a fluke. (*See* D.I. 273 at 31-33)

Considering the prior art as a whole would not have tempered a POSA's expectations. The results Schwid and Goodman present are consistent with the results of earlier studies such as Polman, in which patients subjectively reported improvements in ambulation (*see* JTX-0095 at

295), and Davis, in which patients demonstrated improvements in motor function (*see* JTX-0043 at 186). These results are also consistent with Solari, which reported that a meta-analysis of past studies of aminopyridines (including 4-AP) suggested that such drugs improved ambulation in MS patients ($p < 0.001$). (*See* PTX-0416 at 1) Considering these results in light of the VEP results reported in the Rush Studies, which demonstrated that 4-AP had real physiological effects in MS patients at doses falling within a viable therapeutic window,[32] the prior art would not have undermined the conclusion that a POSA would have drawn from the combination of Stefoski and Goodman: that 4-AP could reasonably be expected to be successful in improving walking in patients with multiple sclerosis.[33]

Plaintiffs argue that this view of the prior art fails to take account of contemporaneous uncertainty about the usefulness of 4-AP that only Acorda's later studies have made it possible to disregard. (*See* D.I. 272 at 52) (arguing that Defendants' view of prior art "us[es] the path actually followed by the inventors as a map" to "argue that it would have been obvious to follow

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[32]As discussed above with respect to the Elan Patent, the pre-Elan Patent prior art would have given a POSA a reasonable expectation of success in finding a viable therapeutic window for 4-AP, despite incidents of seizures and other side effects in some patients. None of the subsequent studies presents results that would have negated this conclusion. Indeed, Goodman stated that 4-AP's safety profile was "consistent with previous experience." (JTX-0080A)

[33]Plaintiffs suggest that a POSA would consider the results of the Schwid and MS-F201 studies to be inconsistent with the results of the Elan Study, as reported in Schwid. (*See* D.I. 272 at 46-47) The Court disagrees. The Elan Study failed to show a statistically significant improvement in MS symptoms as measured by EDSS, a composite measure of functioning. (*See id.* at 37) Walking is just one component of the EDSS scale. Thus, a finding of no statistically significant improvement in EDSS as a whole is not inconsistent with improvements in walking. In fact, the Schwid study showed a statistically significant improvement in walking, but not in EDSS. (*See* JTX-0104 at 817, 820) Therefore, the Court finds that a POSA would not assign great weight to the results of the Elan Study in assessing whether it was reasonable to expect that 4-AP could be used to treat walking, specifically.

that path with a reasonable expectation of success") In the Court's view, Plaintiffs' position unreasonably suggests that proof of obviousness in this case must include at least one prior art study demonstrating, to a statistically significant certainty, that the use of 4-AP is effective to treat walking in MS patients. The law does not set the bar that high. In the context of obviousness, an "expectation of success need only be reasonable, not absolute." *Pfizer*, 480 F.3d at 1364 (stating patentee cannot avoid finding of obviousness "simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success"); *Hoffmann-LaRoche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014) ("Conclusive proof of efficacy is not necessary to show obviousness."); *In re Merck & Co.*, 800 F.2d 1091, 1097 (Fed. Cir. 1986) ("Obviousness does not require absolute predictability.").

For these reasons, Defendants have shown by clear and convincing evidence that a POSA would reasonably expect that 4-AP could be used to improve walking in at least some MS patients. Given this evidence, the Court finds that the use of 4-AP to treat walking in MS patients would have been obvious to a POSA.

B. Use of 10-mg, Twice-Daily Dosing

The asserted claims of the Acorda Patents are directed to the use of 10 mg, twice-daily doses of sustained-release 4-AP to improve walking in a patient with MS. The parties dispute whether the claims' 10 mg/twice-daily dosing pattern would have been obvious to a POSA.

Defendants argue that the claimed dosing pattern is unpatentably obvious under an "obvious-to-try" standard. An invention may be obvious to try "[w]hen there is a design need or market pressure to solve a problem" and the invention is one of "a finite number of identified, predictable solutions" to that problem. *KSR*, 550 U.S. at 421. In Defendants' view, the 10

mg/twice-daily dose of the claims was one of a finite number of doses that a POSA would have reasonably expected to be effective based on the prior art. Defendants point out that both Schwid and Goodman disclosed studies that showed statistically significant benefits in walking among MS patients who took 10-20 mg of 4-AP in sustained-release form twice daily. (*See* JTX-0104 at 817) The Goodman Poster, which described the MS-F201 study as being designed to "[d]etermine [the] safety of" sustained release, concluded that the study showed "[e]vidence of dose-response in [the] 20-40 mg/day range" and "[l]ittle added benefit, and increased [adverse events] at doses above 50 mg/day." (JTX-0080A) In Defendants' view, a POSA who had reviewed these references would have reasonably expected that the 10-20 mg/twice-daily dosages of 4-AP disclosed in the prior art would be effective to treat walking in patients with MS. (*See* D.I. 265 at 44)

Plaintiffs' response includes the observation that some of the prior art suggested that 4-AP was more effective in higher doses – including doses higher than 20 mg, twice per day. Van Diemen, a prior art study designed to assess the relationship among dosage, serum level, safety, and efficacy, concluded that "higher doses and serum levels are likely to produce greater improvement in those MS patients who are capable of favorably responding to 4-AP." (PTX-0330 at 203) Likewise, Schwid concluded that "[t]reatment appeared particularly efficacious in subjects who achieved serum . . . levels above 60 ng/ml." (JTX-0104 at 820) Lastly, as Defendants' expert Dr. Peroutka admits, the pharmacokinetic information available to a POSA indicated that a dose higher than 25 mg/twice daily would be required to sustain that serum level. (*See* Peroutka Tr. at 130-31; *see also* Goodman Tr. at 508)

Although the prior art might have given a POSA reasons to consider a broader range of doses than 10-20 mg/twice daily, the prior art as a whole nevertheless suggests a "finite" set of plausible solutions. A set of solutions is "finite" within the meaning of *KSR* when the prior art provides direction about "which parameters were critical" or "which of many possible choices is likely to be successful," and thereby reduces the options to a set that is "small and easily traversed." *Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (internal quotation marks omitted). While the prior art may have generally suggested that 4-AP would be more effective in higher doses, the art also reduced the set of plausible doses because it suggested that higher doses of 4-AP were more likely to cause adverse events. The Goodman Poster, for example, explains that, "consistent with prior experience," adverse events were more likely at doses beyond 25 mg/twice daily. (JTX-0080A) Thus, while it is unclear what the highest dosage is that a POSA would have reasonably explored based on the prior art, the prior art reduced the range of doses falling within 4-AP's perceived therapeutic window to a fairly narrow band. (*See* Peroutka Tr. 104) (explaining that POSA would be motivated to find lowest effective dose of 4-AP based on prior art showing that serious adverse events are more likely to occur at higher dosages) As such, the prior art showed that the "field of endeavor" was limited to a "finite" number of solutions. *KSR*, 550 U.S. at 420.

Plaintiffs further argue that, even if the prior art suggested a "finite" set of doses, the claimed dosing scheme would not have been among them. They note that the Goodman references, which disclose the only study that specifically explored dosages as low as 10 mg/twice daily, supply no dosage-specific information regarding the performance of 4-AP versus placebo. Instead, the references report that the MS-F201 study demonstrated statistically-

significant improvements in the timed walk and manual muscle test for the treatment group as a whole (*i.e.*, based on combining the data for each patient at each dosage level). (Goodman Tr. at 482-84; Peroutka Tr. at 137-38) Thus, the study did not disclose a statistically-significant treatment effect at a dose of 10 mg/twice daily, or at any other single, specific dose. (Peroutka Tr. at 137-38) In Plaintiffs' view, the limited information regarding this dose would preclude a POSA from having a reasonable expectation that the dose would be successful. (*See* D.I. 272 at 66-70)

Plaintiffs' contention, however, proves too much. On their reasoning, a POSA could not have had a reasonable expectation of success in treating walking with ***any*** of the 4-AP doses disclosed in the Goodman references – despite the fact that the results of treatment with those dosages, taken as a whole, showed a statistically-significant effect on walking in MS patients – simply because the significance of each individual result was unknown. This reasoning is unpersuasive. Furthermore, the Goodman references are not silent as to the results of individual doses. Instead, Goodman states that the results showed "evidence of a dose response in the 20 to 40 milligram per day range," indicating that patients taking these dosages of 4-AP demonstrated a greater response to treatment than did patients receiving placebo. (Tr. at 801; *see also* Goodman Tr. at 477-78 ("[A] dose response curve is looking at a series of increasing or decreasing doses, and assessing the effects seen at the different dose levels . . . to see whether or not there is a pattern of correlation between . . . increasing a dose and increasing a response.")) A POSA would have inferred from this finding that patients' walking responded to 4-AP dosed

at a 10 mg level.[34] Consequently, a POSA would consider 10 mg/twice daily to be among the finite group of doses of sustained-release 4-AP that could reasonably be expected to improve walking in MS patients.[35] As the lowest of the range of encouraging doses, 10mg/twice daily would have been an attractive starting point for a POSA.

Given this evidence, the Court finds that the use of a 10 mg sustained-release dose of 4-AP twice per day to treat walking in MS patients would have been obvious to a POSA at the priority date of the Acorda Patents.

C. Use of Stable Dosing/No Titration

Each of the asserted claims of the Acorda Patents is directed to administration of a "stable" dosing regimen of 10 mg sustained-release 4-AP.[36]

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[34]Plaintiffs argue that a POSA would not draw this inference because the Goodman references do not state that the dose response was statistically significant or highlight how the doses in this range compared to placebo. (*See* D.I. 272 at 66-71) While the Court agrees with Plaintiffs that a POSA would not infer anything about the statistical significance of any individual dose based on the Goodman references' claims about a dose response, the Court also finds that a POSA would have understood the Goodman authors to have considered the results of the placebo group before representing that there was "evidence of a dose response" in the listed range. (Tr. at 733) Put differently, a POSA would assume that a printed publication presented at an academic conference did not omit context that a POSA would have found material to interpreting the study results. (*See generally* Goodman Tr. at 525)

[35]Dr. Goodman indicated at trial that this is the message that the Goodman Poster was intended to convey. (*See* Goodman Tr. at 529-30) Dr. Goodman also conceded that a POSA would have been motivated based on the results of the MS-F201 study to design a study "along the lines of what became the [subsequent Acorda MS-F]202 study," which explored sustained-release doses of 10 mg, 15 mg, and 20 mg/twice daily to treat walking in patients with MS. (*Id.* at 559; *see also* PTX-0168A)

[36]Some of the claims require that the claimed 10 mg/twice-daily dose be administered for a specified period (*i.e.*, two weeks or twelve weeks) and that the claimed dose be the only dose of 4-AP administered during that period. Other asserted claims specify that there be no titration before or after administration of the 10 mg/twice-daily dose – precluding any adjustment of the dosage at any time. These differences are not material to the Court's analysis. Nor do the parties argue that they are. (*See generally* D.I. 272 at 30)

The parties disagree about whether a POSA would have had a reasonable expectation of success in improving walking in a patient with MS by administering a stable dose of 10 mg/twice-daily 4-AP over several weeks. Defendants argue that a POSA would have expected success with stable dosing because the prior art suggests that it can be safe and effective. References including Van Diemen and Polman included reports of safe and effective long-term use of stable dosing of immediate-release 4-AP. (*See* PTX-0330 at 196; JTX-0095 at 294) Further, the MS-F201 study reported in Goodman indicates that 4-AP can be used safely over the long-term; although participants received escalating rather than stable doses, the study did not report unexpected adverse effects with use over several weeks. (*See* JTX-0080A) (stating that observed safety profile was "consistent with the findings of previous studies") Dr. Peroutka testified that a POSA would have had a reasonable expectation of success with stable dosing because nothing in the prior art suggested that 4-AP could not be used chronically. (*See* Peroutka Tr. at 104)

Plaintiffs argue that a POSA would not have had a reasonable expectation that stable dosing would be safe and effective because "[n]o prior art reference cited by [D]efendants shows the administration of any stable dose of 4-AP . . . for more than a single week." (D.I. 272 at 78) Plaintiffs add that prior art studies, including Murray and Polman, demonstrated that 4-AP could cause adverse effects, including seizures. (*See id.* at 79)

As discussed above, however, any concerns a POSA would have had in light of these studies would not have been sufficient to preclude a reasonable expectation that 4-AP could be used to treat MS. Plaintiffs offer no evidence indicating why stable, long-term dosing would change or magnify these concerns. Thus, the Court is not persuaded that safety concerns would

have undermined a POSA's otherwise reasonable expectation of success in implementing stable dosing of 10 mg of sustained-release 4-AP twice daily. *See generally Allergan*, 726 F.3d at 1293 (stating that finding of nonobviousness cannot be predicated solely on "no reasonable expectation of success in view of the general unpredictability of the formulation arts").

Plaintiffs also argue that stable dosing without titration would not have been obvious to a POSA because the prior art taught that titration or dose escalation could be used to "gain maximum efficacy while seeking to avoid adverse events." (D.I. 272 at 82) Plaintiffs argue that this art would "not have provided a POSA with a reasonable expectation of success" in any dosing regimen other than titration. (*Id.* at 42) But while it may be true that the prior art's consistent use of titration did not specifically support stable dosing, it also did not undermine the other evidence in the prior art that supports a finding that a POSA would have had a reasonable expectation of success with stable dosing.

Plaintiffs' post-trial brief suggests that their argument regarding the titration schemes of the prior art may be better understood in connection with the "motivation to combine" prong of the obviousness inquiry. (*See, e.g.*, *id.* at 40) ("The prior art taught upward titration as a means of addressing 4-AP's narrow therapeutic index.") Plaintiffs point to Dr. Goodman's testimony that there were "all kinds of" alternative dosing schemes that might be attractive to a POSA. (Goodman Tr. at 551-52) They further argue that titration could be preferable to stable dosing, as it could allow a POSA to optimize the dosage on a patient-by-patient basis. (*See* D.I. 272 at 82)

Even crediting these arguments, however, the Court finds that a POSA would have been motivated to seek a stable dose of 4-AP. Dr. Peroutka stated this very opinion, explaining that

stable dosing was particularly desirable for treating MS, a chronic disease requiring long-term treatment. (*See* Peroutka Tr. at 99) Similarly, Dr. Goodman conceded that, in at least some circumstances, "it would be desirable that one would have some . . . dose that . . . the patient would be prescribed to take on a regular basis."[37] (Goodman Tr. at 553)

Because the evidence in the record reflects that a POSA would have been motivated to pursue stable dosing and would have had a reasonable expectation of success in doing so, the Court finds that stable dosing of a 10 mg sustained-release dose of 4-AP twice per day to treat walking in MS patients would have been obvious to a POSA.

D. Pharmacokinetic Limitations

Several of the asserted claims of the Acorda Patents specify particular pharmacokinetic parameters or a particular release profile to be achieved by administering the specified dosing regimen to improve walking or increase walking speed.

The pharmacokinetic ranges listed in the asserted claims of the Acorda Patents fall within the ranges previously disclosed in Hayes. (*See* Peroutka Tr. at 96-97; JTX-0069 at 185-86) Hayes is a prior art study that disclosed the pharmacokinetics of a 10 mg sustained-release formulation when administered twice a day for six consecutive days, and once daily on the seventh day. (*See* JTX-0069 at 186) It is undisputed that the Hayes researchers used the Ampyra® formulation in their study. (*See* D.I. 272 at 71) There is also no disagreement that the

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[37]Dr. Goodman also testified that a POSA "could look at the entirety of the art and still believe that there was a desire to increase, escalate, titrate doses towards higher levels." (Goodman Tr. at 552) Even accepting this opinion as true, however, does not overcome the Court's finding that there was a motivation to identify a stable dose as well. The goal of a stable dose (for at least some MS patients) and the goal of a dose that could be titrated upwards (perhaps for other patients) are not incompatible.

pharmacokinetic parameters reported in Hayes are inherent properties of that formulation. (*See* D.I. 265 at 42-43)

To Defendants, it follows that inclusion of the pharmacokinetic parameters in the claims cannot render the claims non-obvious. (*See id.* at 48) This position assumes that a POSA would have been aware that a sustained-release dosage form achieving the pharmacokinetic parameters disclosed in Hayes would have resulted in an improvement in walking, as required by the asserted claims. (*See* D.I. 279 at 4; *Cyclobenzaprine*, 676 F.3d at 1071) While the record on this issue is not as clear as the Court would have hoped, the Court ultimately finds that Defendants have met their burden of proof with respect to the PK limitations of the Acorda Patents.

Plaintiffs insist that Defendants failed to prove that the PK parameters of the asserted claims of the Acorda Patents "are inherent properties of the administration of every sustained-release formulation of 4-AP administered at 10 mg BID."[38] (D.I. 272 at 83; *see also id.* at 84 (arguing that "most significantly" "there is nothing in the prior art identifying the pharmacokinetic values recited in the claims as being effective to improve walking or increase

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[38]In their supplemental letter brief, Plaintiffs argue that the Court previously "reject[ed] an argument that 'conflate[d] the difference between PK data and dose-efficacy results'" in *Avanir Pharmaceuticals, Inc. v. Actavis South Atlantic LLC*, 36 F. Supp. 3d 475 (D. Del. 2014). (D.I. 279 at 4) (quoting *Avanir*, 36 F. Supp. 3d at 501) In Plaintiffs' view, *Avanir* supports Plaintiffs' contention that it was not obvious that the PK values disclosed in Hayes would lead to improved walking in patients with MS. (*See id.*) The Court disagrees. The instant case is distinguishable from *Avanir* because, here, several experts testified as to the relationship between the PK values disclosed in the prior art and improved walking in patients with MS. (*See, e.g.*, Goodman Tr. at 510 (stating that PK profiles reported in Hayes "may certainly show the pharmacokinetic profile that[] [is] analogous to what would be found in MS patients"); Kibbe Tr. at 224 (stating that POSA would expect no difference in PK results from dosing patients with MS or patients with spinal cord injuries)) By contrast, in *Avanir*, "[b]oth sides' experts agreed [that] the disclosed . . . dose ranges . . . in the [prior art] were not directed to the treatment of PBA." *Avanir*, 36 F. Supp. 3d at 501.

walking speed in MS patients")) The Court disagrees. Instead, the Court agrees with Defendants that the pharmacokinetic responses that are incorporated as limitations into certain asserted claims of the Acorda Patents are "inherent in the claimed dosing and [are] taken directly from the prior art." (D.I. 265 at 5 (citing JTX-0002 at 23:1-23; JTX-0069 at AMP-DEF-000498, Table 2)[39]; *see also* Goodman Tr. at 510 (stating that PK profiles reported in Hayes "may certainly show the pharmacokinetic profile that[] [is] analogous to what would be found in MS patients"); *Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) ("[A]n obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations."))

Further, the parties recently submitted supplemental letter briefs to respond to questions from the Court. (*See* D.I. 278, 279) Having considered the letter briefs, and having considered the evidence of record, the Court agrees with Defendants that they have proven that, at the priority date of the Acorda Patents, a POSA would have been aware that a sustained-release dosage form achieving the pharmacokinetic parameters disclosed in Hayes III would have been associated with an improvement in walking in MS patients. (*See* D.I. 278 at 4) (citing evidence)

E. Secondary Indicia of Non-Obviousness

Plaintiffs argue that four secondary considerations support the non-obviousness of the Acorda Patents: commercial success, unexpected results, failure of others, and long-felt but unmet need. Defendants respond that none of these factors is probative of non-obviousness. As

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[39]At trial, in response to the Court's questioning, Plaintiffs' counsel conceded that the claimed PK data were obvious. (*See* Tr. at 793-94) ("It was known in the art that a sustained-release formulation of 10 megs BID could achieve that PK, [but] not that that PK would yield any efficacy for walking.")

discussed below, the Court finds that secondary considerations do not support a finding of non-obviousness in this case.

1. Commercial Success

Commercial success can be 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. v. Teva Pharm. USA, Inc.*, 395 F.3d 1364, 1376 (Fed. Cir. 2005). Evidence of commercial success is only relevant, however, when it "results from the claimed combination of elements that constitutes the invention," rather than being attributable to what was "already known in the prior art" or to the benefits of "unclaimed features." *ArcelorMittal France v. AK Steel Corp.*, 700 F.3d 1314, 1326 (Fed. Cir. 2012). Thus, a party proffering evidence of commercial success must demonstrate that there is a "causal relation or 'nexus' between an invention and commercial success of a product embodying that invention." *Merck*, 395 F.3d at 1376.

The parties here dispute both whether Ampyra® is a commercial success and whether any commercial success it has achieved has a nexus with the invention claimed in the Acorda Patents. For the reasons discussed below, the Court finds that Ampyra® is a commercial success and that there is a nexus between that success and the features claimed in the Acorda Patents. However, the Court also finds that this success does not support a finding that the Acorda Patents are non-obvious because the existence of a "blocking" patent provides an independent, alternative reason why a POSA would not have attempted to develop the invention claimed in the Acorda Patents.

a. Ampyra® is a commercial success

Ampyra® has demonstrated considerable success. Between its launch in 2010 and the end of 2015, domestic sales of Ampyra® reached $1.7 billion and profits reached nearly $1 billion. (D.I. 262 ¶ 157) Over that time-frame, sales of Ampyra® tablets more than doubled, even as the price per tablet increased from $17 to $26. (*Id.*) Acorda was also able to license Ampyra® to another drug company, Biogen, to sell the drug outside the United States – a partnership that has led to an additional $135 million in royalties to date. (*Id.*)

Defendants argue that these sales data do not support a finding of commercial success because the projected sales of Ampyra® are insufficient to cover the costs of its development. Defendants' expert, Dr. McDuff, made several estimates of the cost of developing Ampyra®, accounting for factors such as (1) direct expenditures on research and development; (2) success rates; (3) development time; and (4) costs of capital. (*See* D.I. 265 at 63) After tailoring his estimates to reflect several factors specific to Ampyra®, he found that the present value of Ampyra®'s profits, even projected until the Acorda Patents' 2027 expiration date, does not exceed the estimated costs of Ampyra®'s development. (*See id.*)

In Defendants' view, the entire cost of developing Ampyra® is relevant to the analysis because no "rational decision[]maker" would proceed to develop a drug unless he or she expected its eventual revenues to cover its development costs. (*Id.*) Thus, the decision to proceed with incurring the costs of development gives some indication as to what, at a minimum, a rational decisionmaker expected the commercial opportunity for the drug to be. (McDuff Tr. at 629) If a drug does not realize ***at least*** that commercial opportunity, Defendants argue, then the drug is commercially ***unsuccessful*** from the perspective of one who has invested in the process

of bringing it to market. (*See id.*) In Defendants' view, if a drug is unsuccessful according to this analysis, then it is unclear whether the invention had not been previously brought to market because (i) it was non-obvious or, instead, because (ii) it was obvious but a rational decisionmaker would have known that its commercial potential was too limited to justify the costs of its development.

Examination of Ampyra®'s development history demonstrates that a comparison of actual sales to total development costs constitutes an inappropriate portrayal of how a rational decisionmaker would have analyzed Ampyra®'s commercial potential. As Defendants themselves note, the Acorda inventors licensed the Elan Patent in 1997, with the intention of developing a drug for treatment of spinal cord injuries and MS. (*See* D.I. 265 at 61-62) It was only after expending considerable time and money on licensing a formulation and conducting clinical trials that the Acorda patentees recognized the likelihood that the drug would be suited to treat only walking in MS patients. (*See* McDuff Tr. at 630) Further, it was not until after the priority date of the Acorda Patents that published clinical trials revealed that Ampyra® was effective in just a subset of patients who suffered from walking disabilities. (*See id.*) At each stage of this process, a rational decisionmaker could have had a different estimation as to the likely future sales of Ampyra®, as well as the costs of future development. But at any given time, the pertinent comparison could have supported a rational decision to proceed with development.[40]

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[40]Defendants argue that a POSA considering whether to proceed with developing Ampyra® in 2004 would compare likely revenues to the entire cost of bringing Ampyra® to market. (*See* D.I. 265 at 63) At trial, Dr. McDuff further stated that a POSA would consider sunk costs in deciding whether to proceed with drug development, because such costs would capture a drug's "full development cost." (McDuff Tr. at 688) However, Plaintiffs did not incur all of those sunk

In arguing that Ampyra®'s purported economic unprofitability may have been the reason no one attempted to develop it sooner, Defendants urge the Court to find that a rational decisionmaker performing this analysis in 2004 would have been able to project Ampyra®'s sales and to determine that the drug would be unprofitable. (*See* D.I. 265 at 63) But the record does not support such a finding. Crucially, the record does not make clear how a rational decisionmaker in 2004 would have projected the eventual size of the market for Ampyra® to be, particularly given that later clinical trials demonstrated that the drug had a more limited patient population than previously expected. Nor is it clear what remaining development costs a rational decisionmaker would expect to incur, because Dr. McDuff did not adjust estimates of direct expenditure, development time, or anticipated success rate to reflect the work that had been done. Hence, even assuming that economic profitability calculations could in some cases undermine the persuasive force of apparently strong sales, the Court finds that Defendants have not made a sufficient showing to support such a finding in this case.

Given the strength of Ampyra®'s sales, and the absence of any evidence that its sales are disappointing given its limited indication and patient population,[41] the Court finds that Ampyra® is a commercial success.

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costs; they obtained a license to the Elan Patent. It is not necessarily the case that the cost of the license met or exceeded the amount of Elan's sunk costs in developing the Elan Patent.

[41]Defendants argue that Ampyra®'s sales figures are weak in comparison to the sales of top MS treatments. (*See* D.I. 265 at 63) This comparison is not particularly probative of commercial success in this case because, unlike Ampyra®, none of the drugs to which Defendants are comparing it is approved exclusively for the narrow indication of improving walking. (*See* Goodman Tr. at 512)

b. Nexus with the invention of the Acorda Patents

The Court further finds that there is a nexus between Ampyra's® commercial success and the inventions claimed in the Acorda Patents. There is considerable evidence that the drug's success is at least partially attributable to its unique indication: treating walking in MS patients. In addition to being indicated exclusively for walking, Ampyra®'s marketing messaging to physicians and patients specifically highlights the drug's ability to improve walking-related symptoms of MS.[42] (*See* D.I. 272 at 10) A large proportion of Ampyra®'s prescriptions are renewals, indicating that the drug is successful in treating MS. (*See id.* at 87) Indeed, some insurance companies require patients to demonstrate improved walking in order to be able to renew their prescription. (*See id.*) These data, like consumer and physician surveys showing that over 80% of doctors and patients are satisfied with Ampyra®, suggest that the drug's ability to treat walking drives its commercial success. (*See id.*)

As Defendants point out, the record does not support a finding that Ampyra®'s success is ***exclusively*** attributable to the Acorda Patents. For example, Ampyra®'s commercial success is also attributable in part to the drug's sustained-release formulation (claimed in the Elan Patent) and the 4-AP active ingredient (disclosed in the prior art). Plaintiffs did not attempt to apportion Ampyra®'s success among its various features. Nevertheless, the proffered evidence regarding the importance of the drug's efficacy (in treating walking in MS patients) to its sales is sufficient for establishing a nexus between the Acorda Patents and Ampyra®'s success. *See Apple Inc. v. Samsung Elecs. Co.*, 839 F.3d 1034, 1068, 1073 (Fed. Cir. 2016) (indicating that nexus is

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[42]Notably, the record suggests that Ampyra® sales are not due to aggressive marketing: both Ampyra® revenues and tablet sales have increased even as marketing expenditures for the drug have declined. (Bell Tr. at 590-91)

established when patentee shows consumers are more likely to buy product if it includes patented features).

c. Commercial success and a blocking patent

Although the Court finds that Ampyra® is a commercial success and that its commercial success has a nexus with the patents-in-suit, this evidence is of little probative value to the obviousness inquiry with respect to the Acorda Patents because the earlier Elan Patent "blocked" competitors from practicing the Acorda Patents. *See Merck*, 395 F.3d at 1377. Because the Acorda Patents practice the Elan Patent,[43] no one other than the Elan patentees and their licensees could have practiced the invention of the Acorda Patents without facing liability for patent infringement. The risk of such liability would have provided an independent incentive for a patentee not to develop the invention of the Acorda Patents, even if those inventions were obvious. *See Warner Chilcott Co, LLC v. Teva Pharm. USA, Inc.*, 37 F. Supp. 3d 731, 739 (D. Del. 2014), *aff'd*, 594 F. App'x 630 (Fed. Cir. Nov. 18, 2014).

For this reason, the Court finds that Plaintiffs' evidence that Ampyra®'s commercial success had a nexus to the Acorda Patents does not support a finding that the claims of the Acorda Patents are non-obvious.

2. Unexpected Results

Evidence that a "claimed invention exhibits some superior property or advantage that a person of ordinary skill in the relevant art would have found surprising or unexpected" may suggest that the invention is non-obvious. *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995). Plaintiffs argue that the efficacy of a 10 mg/twice-daily dose of 4-AP would have been surprising

[43]It is undisputed that the Acorda Patents practice the Elan Patent. (*See* D.I. 265 at 37)

to a POSA, as would have been the fact that a 10 mg dose was as effective in treating walking as higher doses. In Plaintiffs' view, these results are unexpected because "[n]one of the [prior] art, viewed alone or in combination, supported an expectation that the 10 mg[/twice-daily] dosing regimen of the Acorda [P]atent claims would improve walking or increase walking speed." (D.I. 274 at 6) Specifically, Plaintiffs argue that the limited and varied data in the prior art would have prevented a POSA from developing such an expectation. (*See id.* at 6-9)

A showing that a drug was slightly more or less effective than the prior art would suggest does not constitute an "unexpected result" for purposes of assessing obviousness. *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731, 739 (Fed. Cir. 2013); *In re Merck*, 800 F.2d at 1098-99. As discussed above with respect to the obviousness of the 10 mg dose, the prior art, while perhaps insufficient to ***prove*** the effectiveness of that dosage, did not render its effectiveness ***unexpected***. Further, although the prior art in this case suggested that larger doses of 4-AP might be more effective than smaller doses, there was not sufficient evidence of dose-response to render a 10 mg/twice-daily dose non-obvious under an obvious-to-try-standard.

For these reasons, the Court finds that Plaintiffs have not presented evidence of unexpected results that militates in favor of finding that the claims of the Acorda Patents are non-obvious.

3. Failure of Others

The "failure of others to find a solution to the problem which the patent[s] . . . purport[] to solve" may be probative of non-obviousness because it suggests "the presence of a significant defect [in the prior art], while serving as a simulated laboratory test of the obviousness of the solution to a skilled artisan." *Symbol Techs., Inc. v. Opticon, Inc.*, 935 F.2d 1569, 1578-79 (Fed.

Cir. 1991) (internal quotation marks omitted; brackets in original). Plaintiffs argue that the non-obviousness of the Acorda Patents is evident from the failure of others to develop a "safe and effective therapy to improve walking in MS patients." (D.I. 274 at 24)

The record includes only minimal evidence that anyone other than the Acorda patentees attempted to develop a "safe and effective therapy to improve walking in MS patients." (*Id.*) Drs. Lublin and Goodman testified that another pharmaceutical company, Sanofi-Aventis, tried and failed to develop a therapy to improve walking in MS patients, using as an active ingredient a potassium channel blocker other than 4-AP. (*See* Lublin Tr. at 411-13; Goodman Tr. at 513-15) But this failed effort is not particularly probative of a "gap" in the prior art that would render non-obvious the invention of the Acorda Patents. Sanofi-Aventis likely did not use 4-AP because it was blocked from doing so by the Elan Patent. (*See* D.I. 272 at 92) Hence, Sanofi-Aventis' failure does not provide much evidence that the formulation of the Acorda Patents was non-obvious.

The record also reflects that Elan failed in its attempts to develop MS therapies for indications other than walking. (PTX-0360 at 101-02) Since Elan's failed efforts preceded the Schwid and MS-F201 studies that demonstrated 4-AP's effects in walking – indeed, as Dr. Goodman testified, the study documenting Elan's failure prompted those later studies (*see* Goodman Tr. at 469) – Elan's failure is not particularly probative of what would have been obvious to a POSA on the priority date of the Acorda Patents. Moreover, the Acorda Patents themselves have also not been successful as a therapy for indications other than walking – and Ampyra® is not FDA-approved for treatment of any other symptom of MS. (*See* McDuff Tr. at 630)

For these reasons, the Court finds that Plaintiffs have not presented evidence of "failure of others" that militates in favor of finding that the claims of the Acorda Patents are non-obvious.

4. Long-Felt but Unmet Need

"Evidence of a long-felt but unresolved need can weigh in favor of . . . non-obviousness of an invention because it is reasonable to infer [that] the need would not have persisted had the solution been obvious." *Apple*, 839 F.3d at 1056. The record reflects that Ampyra® satisfied a long-felt, unmet need for a method of treating walking in MS patients. It is undisputed that walking impairments have long been recognized as a devastating symptom of MS. The FDA's decision to grant priority review status to Acorda's NDA for Ampyra® suggests that the industry considered that need to be at least partially unmet. *See Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1401, 1407 (Fed. Cir. 2014) (holding that FDA's decision to "fast-track" approval supported finding of long-felt and unmet need).

Nevertheless, this evidence of long-felt and unmet need is of limited probative value with respect to the obviousness of the invention claimed by the Acorda Patents. As of the Acorda Patents' priority date, a POSA would not have been able to practice the invention of the Acorda Patents without infringing the Elan Patent. Thus, it is possible that the need for a therapy to improve walking in MS patients remained unmet ***despite*** the ***obviousness*** of the solution claimed in the Acorda Patents. For these reasons, the Court finds that, although Plaintiffs have presented convincing evidence that there existed a long-felt, unmet need for a method of improving walking in MS patients, this evidence does not militate in favor of finding that the claims of the Acorda Patents are non-obvious.

F. Conclusion as to Acorda Patents

While Defendants face a high burden in proving that the Acorda Patents are invalid as obvious, the Court finds, after weighing all of the credible evidence, that they have met this burden. As explained above, Defendants have adduced clear and convincing evidence that a POSA at the priority date would have been motivated and would have had a reasonable expectation of success to practice and combine each of the limitations of the asserted claims of the Acorda Patents. The evidence of secondary considerations is not sufficient to overcome these findings.

This is not to say that there is no significant evidence of nonobviousness. The Court has explained above that there is merit in many of Plaintiffs' contentions. Of particular note, the Court found credible the testimony of co-inventor (Acorda CEO) Dr. Cohen. At trial, Dr. Cohen vividly recounted the sometimes harrowing financial risks he and his nascent company took, and the several occasions on which it looked as if his "bet-the-company" approach had suffered a fatal blow. (*See, e.g.*, Cohen Tr. at 282) It may well be that Dr. Cohen's subjective experience of the "invention story" was that the purported invention of the Acorda Patents was anything but obvious. The Court has considered this evidence – but the law directs a different analysis. For the reasons explained above, the evidence as a whole establishes, clearly and convincingly, and objectively, that the asserted claims of the Acorda Patents would have been obvious to a person of ordinary skill in the art at the priority date, notwithstanding the actual inventors' subjective experience.

Also, the Court agrees with Plaintiffs that, at the priority date of the Acorda Patents, the risk of seizures "loomed over the work of exploring the use of 4-AP in MS." (D.I. 272 at 5) A

POSA would have known in 2004 that 4-AP was known to have the capacity to induce seizures, and would further have known that seizures could be particularly dangerous for individuals suffering from MS. (*See id.*) However, as Defendants correctly argue, a POSA can have a motivation and reasonable expectation of success notwithstanding recognition of a substantial risk. As Defendants further point out, even today seizure risk remains a significant concern associated with the use of 4-AP (especially at doses greater than those of Ampyra®), but that known and significant risk has not deterred POSAs or pharmaceutical companies – including Plaintiffs and Defendants – from developing drugs with 4-AP as their active ingredient. (*See* Tr. at 746)

In the end, there is evidence on both sides of the parties' dispute, and this was an eminently "triable case." But the Court's assessment of the evidence as a whole is that Defendants have proven clearly and convincingly that the Acorda Patents are invalid due to obviousness.

CONCLUSION

Defendants have failed to prove by clear and convincing evidence that claims 3 and 8 of the Elan Patent are invalid due to obviousness. Defendants have proven by clear and convincing evidence that claims 1, 7, 38, and 39 of the '826 patent; claims 3 and 5 of the '685 patent; claims 1, 2, 5, 22, 32, 36, and 37 of the '437 patent; and claims 36, 38, and 45 of the '703 patent are invalid due to obviousness.

An appropriate Order follows.