APPENDIX

APPENDIX A

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ACORDA THERAPEUTICS, INC.,
Plaintiff-Appellant

ALKERMES PHARMA IRELAND LIMITED,
Plaintiff-Appellee

v.

ROXANE LABORATORIES, INC., MYLAN PHARMACEUTICALS INC., TEVA PHARMACEUTICALS USA, INC.,
Defendants-Cross-Appellants

2017-2078, 2017-2134

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-00882-LPS, 1:14-cv-00922-LPS, 1:14-cv-00935-LPS, 1:14-cv-00941-LPS, Chief Judge Leonard P. Stark.

Decided: September 10, 2018

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Before NEWMAN, DYK, and TARANTO, *Circuit Judges*.

Opinion for the court filed by *Circuit Judge* TARANTO.

Opinion dissenting filed by *Circuit Judge* NEWMAN.

TARANTO, *Circuit Judge.*

Before us are patents that claim the administration of a medication containing the active ingredient 4-aminopyridine (4-AP) to improve walking in individuals with multiple sclerosis. Acorda Therapeutics, Inc., holds New Drug Application No. 022250, approved by the U.S. Food and Drug Administration (FDA). Pursuant to that approval, Acorda markets, under the name "Ampyra®," 10 milligram 4-AP sustained-release tablets for twice-daily oral administration. In the FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations*, or Orange Book, Acorda has listed, as claiming methods of using Ampyra, four patents that Acorda owns: U.S. Patent No. 8,007,826; No. 8,663,685; No. 8,354,437; and No. 8,440,703. Those patents ("the Acorda patents") are the main patents at issue on appeal.

One additional patent is before us. Acorda holds an exclusive license to an earlier, broader patent, U.S. Patent No. 5,540,938, referred to as "the Elan patent" because it was originally assigned to Elan Corporation, plc (whose successor in interest is Alkermes Pharma Ireland Ltd.). The Elan patent, listed in the Orange Book for Ampyra along with the Acorda patents, claims methods of treating patients having certain conditions, including multiple sclerosis, by administering a drug containing a sustained-release formulation of any of certain agents, one of them 4-AP. The later Acorda patents claim species of the Elan patent's genus claims by adding further, more specific requirements to the Elan patent's claimed methods.

While the Elan patent's claims broadly cover administering a sustained-release formulation of 4-AP to individuals with multiple sclerosis, the Acorda patents' claims further specify that such a drug must be administered (1) in a 10 mg dose twice a day (2) at that stable dose for the entire treatment period of at least two weeks (3) to achieve 4-AP serum levels of 15–35 ng/ml and (4) to improve walking.

Roxane Laboratories, Inc.; Mylan Pharmaceuticals, Inc.; and Teva Pharmaceuticals USA, Inc., have submitted Abbreviated New Drug Applications seeking FDA approval to market generic versions of Ampyra. In July 2014, Acorda and Alkermes sued those entities ("defendants") in the District of Delaware, alleging infringement of several claims in each of the Elan and Acorda patents. The defendants stipulated to infringement but challenged the validity of the asserted claims. The district court held that the asserted claims in the Acorda patents are invalid for obviousness. But the court upheld the asserted claims of the Elan patent against invalidity challenges and enjoined the defendants from activity infringing that patent until it expired on July 30, 2018.

Acorda appealed the invalidity ruling regarding the Acorda patents. The defendants cross-appealed the validity ruling regarding the Elan patent and the resulting injunction. We now affirm the judgment that the asserted Acorda patent claims are invalid. We dismiss the cross-appeal as moot.

I

A

In view of our decision that the issues concerning the Elan patent are moot, we focus on the background

of the Acorda patents. Essential to understanding the obviousness issue is an understanding of the prior art.

4-AP, also called "dalfampridine" and "fampridine," was first identified in 1902. *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 1:14-cv-00882-LPS, 2017 WL 1199767, at *3, *5 (Mar. 31, 2017) (*Dist. Ct. Op.*). Belonging to a class of compounds that function as potassium-channel blockers, 4-AP "has been found to slow the potassium flow in nerve impulse transmission" and, by doing so, help "restor[e] conduction in blocked and demyelinated nerves," '826 patent, col. 2, lines 5–11, *i.e.*, nerves whose myelin insulation has been damaged. 4-AP was first used in human studies in the 1970s to investigate its effect on neurological diseases resulting in muscle weakness. *Dist. Ct. Op.* at *5. For several decades, 4-AP has been the focus of research regarding the treatment of multiple sclerosis in particular. *See*, *e.g.*, *id.* at *5–7 (reciting studies); J.A. 6697 (paper published in 1987 describing study of the effect of 4-AP on subjects with multiple sclerosis). Multiple sclerosis causes the demyelination, or loss of myelin, of nerves in the central nervous system and results in a wide variety of symptoms, including walking impairment, tingling or pain, brain scarring, cognitive changes, visual impairments, and fatigue. *See* '826 patent, col. 1, lines 36–42; *Dist. Ct. Op.* at *2. Eventually, 4-AP research led to the development, patenting, and FDA approval of Ampyra.

1

In the 1980s, researchers at the Rush Medical School conducted a study on 12 patients with multiple sclerosis, and 5 without, to determine whether intravenous administration of 7 to 35 mg of 4-AP had any therapeutic effect on multiple sclerosis. J.A. 6697

(Dusan Stefoski et al., *4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis*, 21 Annals of Neurology 71 (1987)). According to the published paper reporting that study (Stefoski), 10 of the 12 patients with multiple sclerosis "showed mild to marked improvement"; "[v]ision improved in 7 patients, oculomotor function in 5, and motor function (power, coordination, gait) in 5." J.A. 6697. Improvements were seen at doses as low as 2 mg: In one patient, gait improvement occurred within 25 minutes of administration of a total dose of 2 mg. J.A. 6699. Stefoski also reported:

> [W]e observed no serious or bothersome side effects at total doses below 30 to 35 mg injected not less than 20 minutes apart for aliquots up to 3 mg. Moreover, the clinical improvements in many of our patients were of sufficient magnitude to represent a functionally noteworthy therapeutic benefit. Studies are currently in progress to determine the clinical usefulness of oral 4-AP as a symptomatic treatment.

J.A. 6701; *accord* J.A. 6697.

In 1990, an overlapping group of researchers published a paper (Davis) reporting another study on 4-AP's effect on symptoms of multiple sclerosis. J.A. 6327 (Floyd A. Davis et al., *Orally Administered 4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis*, 27 Annals of Neurology 186 (1990)). In that study, 20 patients with multiple sclerosis were given either a single oral dose of 4 AP (15 patients) or a placebo (5 patients). J.A. 6327. Of those in the active treatment group, 4 patients were given a 10 mg dose of 4-AP, 2 were given 12.5 mg, 4 were given 15 mg, 4 were given 20 mg, and 1 was given 25 mg. Davis at

187 tbl.1. Davis states that "[m]ild to marked improvements occurred in all of the 15 [multiple sclerosis] patients given 4-AP." J.A. 6329; *accord* J.A. 6327. "Improvements developed gradually with doses as low as 10 mg 4-AP, usually beginning within 60 minutes after drug administration." J.A. 6329. Motor function improved in 9 of 13 patients in the active treatment group (motor function was not measured in 2). Davis at 187 tbl.1; J.A. 6329. The improvements were "most striking[] with respect to power and coordination" and "were apparent with both simple function tests and the performance of complex motor tasks such as gait and repetitive movements." J.A. 6329. Finally, Davis notes, no "serious or bothersome side effects," including seizures, were observed at single oral doses up to 25 mg. J.A. 6332.

A few years later, researchers at a university hospital in the Netherlands published a paper (Van Diemen) reporting a randomized, double-blind, placebo-controlled crossover study that "demonstrated efficacy of [4-AP] in improving disability of patients with multiple sclerosis." J.A. 7037 (Harriët A. M. Van Diemen et al., *4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety*, 16 Clinical Neuropharmacology 195 (1993)). In the second phase of the study lasting 12 weeks, 69 patients were orally administered 10–20 mg 4-AP per day, split into two or three doses. J.A. 7038, 7042. The doses were escalated during the second week, and again during the sixth week, by 5–15 mg. J.A. 7038–39. The paper reports improvements in certain measures of eye functioning. J.A. 7042. And it reports that "side effects were mild" for those patients given oral doses of 4-AP (versus intravenous 4-AP). J.A. 7045; *see also* Van Diemen at 200–01 (no seizures).

Soon thereafter, some of the same researchers published a second paper (Polman) about the long-term efficacy and safety of 4-AP given to patients with multiple sclerosis. J.A. 6654 (Chris H. Polman et al., *4-Aminopyridine in the Treatment of Patients with Multiple Sclerosis*, 51 Archives of Neurology 292 (1994)). Polman reports a study of 31 patients with multiple sclerosis, 19 of whom took a stable dose of 4-AP between 10–50 mg per day (the exact dose for each patient is unknown), and 12 of whom initially took 10–15 mg per day and then took increasing doses in 4 to 8 weeks. J.A. 6655; *see* J.A. 7042. In the first group, 18 of the 19 patients "had a favorable response to the medication" and "reported a subjective improvement in the ability to perform the activities of normal daily life, which was mainly owing to improved ambulation and reduction in severity of fatigue." J.A. 6655. In 3 patients, the subjective improvement was significant on the Expanded Disability Status Scale (EDSS), *id.*—a composite measure of function in multiple sclerosis patients, including a walking component, that is "widely accepted in the [multiple sclerosis] community," *Dist. Ct. Op.* at *8; *see id.* at *30; J.A. 6681. In the second group, 6 patients reported a "favorable response" to 4-AP treatment, "as defined by the ability to perform activities of normal daily life." J.A. 6655–56. One patient demonstrated a significant improvement in EDSS score. J.A. 6656.

Overall, 23 patients (17 in the first group; 6 in the second group) continued active treatment for 6 to 32 months, with daily doses ranging from 15–40 mg. J.A. 6655–56. Those patients "indicated the drug to be beneficial because, by improving several neurologic functions, it increased their capability to perform the activities of normal daily life," including—for 13 of the 23 patients—a reported improvement in ambulation

and fatigue. J.A. 6656 & tbl.1; *see* J.A. 6654.[1] The paper states:

> Although a placebo effect cannot be excluded, the dynamics of the response in relation to the intake of the medication and the deterioration and subsequent improvement in functioning during a drug-free interval and subsequent restarting of the therapy are, in our view, highly suggestive of a real effect being induced by the 4-[AP]. Improvements in fatigue and ambulation were mentioned quite often by the patients as being responsible for the favorable overall effect . . . .

J.A. 6657. The paper thus reports improvements in specific measures, while few patients experienced a significant change in EDSS, the overall composite measure. *Id*. As for adverse effects, two patients experienced a seizure—one on the second day of treatment and the other after 18 months of treatment. J.A. 6656–57.[2] Otherwise, the subjective side effects reported by the patients "never were reported to be very troublesome." J.A. 6657.

Polman states several conclusions and suggestions for further research. First, the study "demonstrates that 4 [AP] therapy, in the majority of patients who favorably respond to it, results in responses that can continue for periods of up to 32 months or more without interfering with the course of the disease."

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[1] By comparison, only 5 reported an improvement in visual function; 4 in cognitive function/concentration; and 1 in diplopia (double vision), speech, spasticity, and urinary and fecal incontinence. J.A. 6656 tbl.1; *see* J.A. 6654.

[2] A third patient was presumptively diagnosed with a case of 4-AP-induced hepatitis. J.A. 6657.

Polman at 296. Second, the fact that "three major, though not life-threatening, side effects" occurred (including 2 seizures) "indicates that careful medical supervision is warranted during 4-[AP] therapy." *Id.* Third, based on the study data, the authors "suggest that approximately 30% of patients with [multiple sclerosis] will report a significant clinical response when they begin treatment with 4-[AP] and that 80% to 90% of these responders will benefit from long-term administration. More studies are needed for further elaboration of the exact value of 4-[AP] in the long-term treatment of patients with [multiple sclerosis]." *Id.*

Around the same time, researchers at the University of Maryland, the Baltimore VA Medical Center, and Elan published a paper (Bever I) reporting the results of a randomized, placebo-controlled, double-blind, concentration-controlled, crossover trial in 8 patients with multiple sclerosis. Christopher T. Bever, Jr., et al., *The effects of 4-aminopyridine in multiple sclerosis patients: Results of a randomized*, *placebo-controlled*, *double-blind*, *concentration-controlled*, *crossover trial*, 44 Neurology 1054 (1994); *see* J.A. 6180 (excerpt of Bever I). Noting that 4-AP has a "narrow toxic-to-therapeutic range[]," the study aimed to evaluate the toxicity and efficacy of 4-AP when the resulting peak concentration in blood was low (30–59 ng/ml) versus when it was high (60–100 ng/ml). Bever I at 1055. Regarding toxicity, the report states that "[a]ll patients experienced side effects" when serum concentration was high, with two serious adverse events: a seizure when serum 4-AP peaked at 104 ng/ml, and an episode of encephalopathy when serum 4-AP peaked at 114 ng/ml. *Id.* at 1054, 1056. Regarding efficacy, "[i]mprovements were seen in lower extremity strength," including significant improvement

in mean videotape scores of lower extremity strength (scoring muscle strength, reflexes, and ambulation) in both the low- and high-serum concentration ranges, although no significant changes were seen in EDSS scores or ambulation index (AI) scores.[3] *Id.* at 1056–57 & tbl.4; *but see id.* at 1058 (commenting that the increased side effects from the short treatment duration "may have contributed to the lack of improvement in overall function (EDSS and AI scores)").

Bever I concludes that the therapeutic response was not concentration-related as between the two ranges tested and, therefore, that "[t]he lower serum concentration range of 30 to 59 ng/ml may . . . be adequate for inducing improvement of some neurologic deficits." Bever I at 1058; *see id.* ("Because the high-serum-concentration arm produced much greater toxicity than the low without any obvious therapeutic advantage, it seems likely that clinically useful serum concentrations would be in the 30 to 59 ng/ml range."). Bever I also states that the "rates of treatment-related improvements in visual and lower extremity motor function . . . were similar to those reported in similar short-term trials of [4-AP]," including Stefoski and Davis. Bever I at 1057–58. The article notes the limitations of the earlier trials' designs, including "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." *Id.* at 1058. Bever I then observes that another study "addressed some of

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[3] *See* Stephen L. Hauser et al., *Intensive immunosuppression in progressive multiple sclerosis*, 308 New Eng. J. Med. 173, 174, 180 (1983) (ambulation index is a rating scale to assess mobility by measuring the time and degree of assistance needed to walk 25 feet).

the design weaknesses in earlier studies and suggested that not only can AP treatment improve specific residual deficits, but it can also improve overall function." *Id.*

The same year as Bever I appeared, Dr. Bever, with the University of Maryland and the Baltimore VA Medical Center, published a review article on studies of the effect of 4-AP on multiple sclerosis (Bever II). Christopher T. Bever, Jr., *The Current Status of Studies of Aminopyridines in Patients with Multiple Sclerosis*, 36 Annals of Neurology S118 (1994); *see* J.A. 6172 (excerpt of Bever II). The article states: "Recently completed randomized, double-blind, placebo-controlled trials show that treatment with the potassium channel blockers 4-aminopyridine (AP) or 3,4-diaminopyridine (DAP) can improve residual neurological deficits in some multiple sclerosis (MS) patients." Bever II at S118; *accord id.* at S120. As to efficacy, "[t]hese studies suggest that amino-pyridines may provide a new approach to the symptomatic treatment of [multiple sclerosis]." *Id.* at S118.[4] As to toxicity, "seizures are common at higher doses," but 4-AP "rarely cause[s] seizures at the doses used in [multiple sclerosis] trials." *Id.* at S120; *see also id.* at S118

[4] Although criticizing a few 4-AP studies as involving a small sample size or lacking a double-blinded or randomized design, Bever II also looked at "[l]arger randomized, double-blind, placebo-controlled crossover trials of" 4-AP with treatment periods as long as three months. J.A. 6172; *accord* Bever II at S118 (in the article abstract, stating that "[p]reliminary studies of [4-]AP demonstrated benefit in many temperature-sensitive patients with [multiple sclerosis], and improvement of function was found in a large randomized double-blind, placebo-controlled crossover trial of 3 months of oral treatment in 68 patients with [multiple sclerosis]").

("Both agents [4-AP and DAP] have rarely caused seizures."). The paper notes that one 4-AP study "showed that side effects correlated with peak serum concentrations, while efficacy correlated with total drug exposure, suggesting that controlled release formulations may be useful in minimizing toxicity." *Id.* at S120.

2

The foregoing studies involved immediate-release, rather than sustained-release, formulations of 4-AP. *See Dist. Ct. Op.* at *4; J.A. 761, 763, 767, 769, 774 (testimony of Acorda's expert, Dr. Andrew Goodman). By 1990, Elan, which was known for its work on sustained-release formulations, entered into an agreement with the researchers at Rush Medical School to obtain their work on 4-AP pharmaceutical formulations. *Dist. Ct. Op.* at *4. According to Dr. Michael Myers, who worked at Elan at that time and is a named inventor on the Elan patent, Elan was interested in developing a sustained-release formulation of 4-AP to "potentially reduce or eliminate some of th[e] side effects" associated with the immediate-release formulation. Sept. 19, 2016 Trial Tr. at 149, 155–56, *Acorda Therapeutics*, *Inc. v. Alkem Labs. Ltd.*, No. 1:14-cv-00882 LPS (D. Del. Oct. 21, 2016), ECF No. 266.

Elan developed a 4-AP sustained-release formulation in approximately a month's time. *Dist. Ct. Op.* at *4. The inventors then filed for what became the Elan patent, which claims, among other things, administration of a sustained-release formulation of 4-AP once or twice daily for the treatment of neurological diseases, including multiple sclerosis. Elan patent, col. 22, lines 16–25, 29–30, 50–51 (independent claim 1 and dependent claims 3 and 8). The Elan patent has

a priority date of November 1, 1991; issuance date of July 30, 1996; and expiration date of July 30, 2018.

In 1994, Elan conducted a double-blind, randomized, placebo-controlled clinical trial involving 161 patients with multiple sclerosis to study the safety and efficacy of the sustained-release 4-AP formulation. *Dist. Ct. Op.* at *8. Patients were administered 12.5 mg 4-AP twice a day, which was later increased to 17.5 mg twice a day and finally to 22.5 mg twice a day. *Id.* One of the primary endpoints measured was the EDSS composite measure of function. *See id.* For the primary endpoints and most of the secondary endpoints, including ambulation, the trial revealed no statistically significant improvements for 4-AP versus placebo. *Id.* But it did show a statistically significant improvement in the secondary outcome of lower extremity motor score, a measure of muscle strength in the legs. *Id.* The 1994 Elan study was not published.

Elan also sponsored a smaller, double-blind, placebo-controlled, crossover study in ten patients with multiple sclerosis. That study was reported in a paper published in 1997 (Schwid), on which Dr. Goodman, Acorda's expert at trial, was the senior author. J.A. 6681–84 (Steven R. Schwid et al., *Quantitative assessment of sustained-release 4-aminopyridine for symptomatic treatment of multiple sclerosis*, 48 Neurology 817 (1997)). In the background section, Schwid reports that an earlier, 161-patient study had been conducted to test improvement in EDSS for multiple sclerosis patients (the unpublished 1994 Elan study), but that it did not detect a significant improvement in that measure. J.A. 6681. Schwid notes, however, that the EDSS "may have been an inadequate outcome variable for [the 1994 Elan] trial." *Id.* The paper explains:

> [The EDSS] is imprecise due to substantial intra-rater and inter-rater variability, and relatively insensitive to change due to its ordinal nature. For example, a patient who needed a cane to walk 100 meters would need to improve enough to walk without the cane before the EDSS score would change. Lesser improvements in gait would not be reflected by the EDSS, and notable changes in strength or other deficits could also be overlooked. We planned the present pilot study to assess the effect of 4AP [sustained release] on more sensitive, quantitative measures of function in [multiple sclerosis].

Id. (internal references omitted).

In the Schwid study, ten patients were each given 17.5 mg sustained-release 4-AP twice a day for a week and placebo for a week. *Id.* The study measured (1) time to walk 8 meters (timed gait), (2) time to climb four stairs, (3) maximum voluntary isometric contraction measured quantitatively, (4) manual muscle testing, (5) grip strength, (6) EDSS, and (7) the patient's global impression. *Id.* Schwid reports that the administered drug demonstrated a statistically significant improvement over placebo for timed gait in 9 of 10 patients, with $p = 0.02$. *Id.*[5] In addition to that result, Schwid observes that "most of the other outcomes showed trends favoring 4AP [sustained-release]." J.A. 6684. Schwid concludes that, in the reported study, "4AP [sustained-release] improved motor function in

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[5] Dr. Goodman testified at trial (for Acorda) that the p-value would be 0.14 (greater than the customary 0.05 ceiling for "statistical significance") if adjusted for the fact that there were multiple outcome measures (7 total). J.A. 878; *see Dist. Ct. Op.* at *13 n.10.

[multiple sclerosis] patients." J.A. 6681. The article notes that the results of the Schwid study are consistent with "[p]revious double-blind, placebo-controlled studies" using an immediate-release formulation of 4-AP, including another study reported by Stefoski (13 of 17 patients "showed 'clinically important' improvements"), Bever I (reporting that 4-AP "improved lower-extremity strength" and "a composite score of leg strength, spasticity, and ambulation"), and another study reported by Van Diemen (improvement in neurologic deficits, as measured by the EDSS). J.A. 6684.

Schwid also states: "The quantitative outcomes used in this study permit more sensitive evaluation of the therapeutic effect and promise to be useful in future trials of symptomatic treatments for [multiple sclerosis]." J.A. 6681. It notes particularly that timed gait showed improvement where the EDSS did not. *Id.*; J.A. 6684. Schwid advises that future studies evaluate the more sensitive outcome measures, "establish[] efficacy in larger trials," and "examine long-term efficacy and tolerability as well as further refine dosing regimens to optimize delivery despite a relatively narrow therapeutic window." J.A. 6684.

3

While Elan was conducting those studies, Acorda was exploring the use of 4-AP in patients with spinal cord injuries. *Dist. Ct. Op.* at *8. In 1997, Elan granted Acorda an exclusive license to the Elan patent for the use of Elan's sustained-release formulation of 4-AP in patients with spinal cord injuries. *Id.* Acorda conducted two studies to evaluate the pharmacokinetic and safety profile of the sustained-release formulation, and the results of both studies are reported in a paper published in 2003 (Hayes). J.A. 6433–40

(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*, 26 Clinical Neuropharmacology 185 (2003)). In the second study, Acorda tested doses of 10 mg, 15 mg, 20 mg, and 25 mg of the sustained-release formulation of 4-AP administered twice daily in patients with spinal cord injuries. J.A. 6434. The average serum concentration level (at steady state) for the 10 mg twice-daily dose was 20.8 ± 5.7 ng/ml. J.A. 6439; *accord.*'826 patent, col. 25, lines 1–28 (Table 7); '685 patent, col. 25, lines 5–32 (Table 7). Acorda also conducted clinical trials to evaluate the efficacy of that sustained-release formulation of 4-AP in patients with spinal cord injuries, but those studies failed.

Soon after, Acorda learned that Elan was "no longer interested in pursuing or supporting" research into use of Elan's sustained-release formulation of 4-AP for treatment of multiple sclerosis. J.A. 596 (testimony of Dr. Ron Cohen, Acorda founder). Acorda told Elan that it wished to take over that research. *Id.* In 1998, Elan agreed to expand the earlier license to Acorda; it granted Acorda exclusive rights over the 4-AP sustained-release formulation for use in the treatment of multiple sclerosis. *Dist. Ct. Op.* at *8.

Acorda reviewed Elan's research, including Elan's pharmacokinetic data and clinical study reports of the 1994 Elan study. Acorda then conducted its own clinical trials. *Id.* at *9.

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In 2000 and 2001, Acorda ran a study—the MS-F201 study—which involved 36 patients with multiple sclerosis and whose results were published only in

part. *Id.*[6] After one week of a placebo lead-in, a group of 25 patients received 10 mg 4-AP twice daily for a week, then higher dosages, which increased weekly in 5 mg increments up to 40 mg twice daily at week 7. *Id.* The rest of the patients consistently received a placebo. *See id.* The outcome measures included fatigue, a lower extremity muscle test, a multiple sclerosis functional composite (timed 25-foot walk; nine-hole peg test; cognitive test), and subjective measures. *Id.* Only the lower extremity muscle test showed a statistically significant difference—"when comparing the seven week range [4-AP] group against placebo." J.A. 604–05. The results were not statistically significant for the timed 25-foot walk for any particular dose of 4-AP; and in 3 of the 7 weeks, the placebo group did better in the timed walk than the 4-AP group taking 10 mg twice daily. *Dist. Ct. Op.* at *9.[7] After the study was completed, Acorda conducted a post-hoc analysis

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[6] This was a Phase II study within the meaning of the FDA's classification of certain studies as Phase I, II, or III. *See* J.A. 870; U.S. Dep't of Health & Human Servs., U.S. Food & Drug Admin., *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective* (2017), https://www.fda.gov/drugs/resourcesforyou/consumers/ucm143534.htm.

[7] During oral argument, counsel for Acorda repeatedly noted the result that the placebo group actually outperformed the 10 mg twice-daily group in 3 of the 7 weeks. *E.g.*, Oral Arg. at 8:57–9:20; *id.* at 10:05–20. But Acorda has not shown where that result was published in the prior art. *See* Sept. 23, 2016 Trial Tr. at 785, *Acorda Therapeutics, Inc. v. Alkem Labs. Ltd.*, No. 1:14 cv-00882-LPS (D. Del. Oct. 21, 2016), ECF No. 269 (counsel for Acorda stating at trial that the MS-F201 data was not publicly available prior art, other than the data reported in the Goodman references). On this record, that result could not have informed the legally relevant person of skill in the art about whether to expect (or, as Acorda argues, not to expect) the 10 mg twice-daily dose to succeed in improving walking.

of the data on walking speed—which, unlike timed 25-foot walk, was not an endpoint the study was designed to test—and identified a statistically significant difference between the placebo and 4-AP groups considering all doses in the aggregate. *Id.*

Most but not all of the just-described results of the MS-F201 study were published. Dr. Goodman published two nearly identical abstracts in early 2003 (Goodman I, J.A. 6371–72, and Goodman II, J.A. 6370) and presented a poster in connection with those abstracts in late 2002 (Goodman Poster, J.A. 6497–504). Goodman I explains that "[t]he primary aim" of the randomized, placebo-controlled, double-blinded Phase II dose-ranging study was to "determine the safety and tolerability of escalating doses of a sustained release (SR) formulation [of 4-AP], given orally to patients with [multiple sclerosis]," and that "[t]he secondary aim was to explore efficacy over a broad dose range using measures of fatigue and motor function." J.A. 6371; *see Dist. Ct. Op.* at *14. The abstract discloses that the study involved 36 patients, 25 in the active-treatment and 11 in the placebo group, and that the active-treatment group received 20 mg/day 4-AP, with doses escalating 10 mg/day to reach a maximum of 80 mg/day during week 8 of the study. J.A. 6371–72; *see Dist. Ct. Op.* at *14. In the "Results" section, Goodman I reports that five subjects withdrew as a result of adverse effects, including two seizures, and that adverse effects were "more severe at doses of 50 mg/day and higher," including the two seizures that occurred at doses of 60 and 70 mg/day. J.A. 6372; *see Dist. Ct. Op.* at *14. Another reported result is that the 4-AP sustained-release treatment "group 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). Dose-response curves showed increasing benefit in both measures in the 20 to 50 mg/day range." J.A. 6372; *see Dist. Ct. Op.* at *14. The abstract clarifies that "[n]o other measures showed significant treatment effects." J.A. 6372; *see Dist. Ct. Op.* at *14. The "Conclusions" section reads:

> The safety profile of [4-AP sustained-release] was consistent with previous experience. Doses above 50 mg [per day] added little benefit and increased adverse effects. There was significant improvement in measures of mobility and muscle strength.

J.A. 6372.

The Goodman Poster is similar. It reproduces almost all of the material in Goodman I in the "Abstract" section at the upper-left-hand corner of the poster. J.A. 6502 (capitalization altered). The Poster contains more detail in the "Background" section, which notes that "[r]ecent clinical studies have indicated that [4-AP] promotes improvement in motor strength, walking, fatigue, and endurance in people with [multiple sclerosis]"; that observed adverse events, including seizures, were associated with higher peak plasma concentrations and rapid plasma concentration changes caused by immediate-release 4-AP; and that sustained-released formulations were developed to address those problems. *Id.* (capitalization altered). The study objectives were defined as: (1) "[d]etermine 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 80mg/day)"; and (2) "[o]btain evidence of efficacy and dose-response using several outcome measures." *Id.*; *accord id.* (Methods section). The Goodman Poster notes

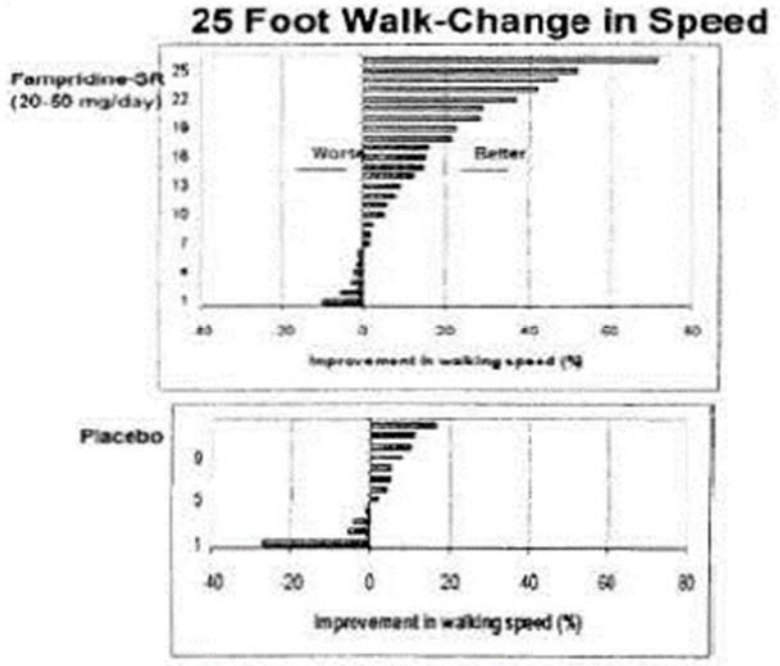
that, because individuals taking 4-AP "frequently report" improvements in activity and fatigue levels, the study focused on outcomes associated with such effects—namely, timed ambulation, manual muscle testing, and patients' self-reports of fatigue—rather than the EDSS, because "it was not clear whether" the EDSS "would adequately reflect this type of improvement." *Id.* (Methods section).

As to the study's results concerning safety, the Goodman Poster provides, in the "Results Summary," that "more severe adverse events," including seizures, occurred "[a]t doses above 40 mg/day." J.A. 6504 (capitalization altered). The Poster states that "the risk of seizure requires further study and characterization[,] particularly in the anticipated dose range." *Id.*

As to the results concerning efficacy, the Goodman Poster includes a graph of a dose-response curve for the 25-foot walk:

J.A. 6503. The graph shows that the total time for the walk decreased significantly between the placebo dose (run-in) and the 20 mg/day dose. *Id.* The total time seems to have plateaued at higher doses. *Id.* (total time remained between approximately 12.5 and 14 seconds as doses increased from 20 mg/day to 80 mg/day); *see also* Sept. 19, 2016 Trial Tr. at 102–03, 137 (testimony of defendants' expert Dr. Peroutka, observing a walk time between 12 and 14 seconds for a "stable clinical effect at 20 to 40" mg/day in the "flat part of the dose response curve").

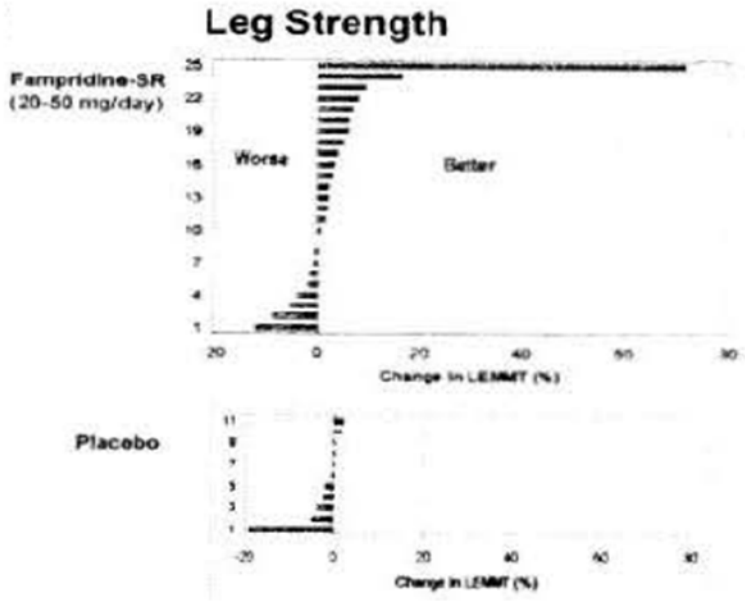
The results section also provides bar graphs showing changes in individual patients' speed on the 25-foot walk.



J.A. 6503. The upper bar graph shows, on average, improvements in speed for patients in the active-

treatment group, aggregated for doses ranging from 20–50 mg/day. *Id.*; *see* J.A. 416. It appears that a few of those patients' speed decreased by approximately 0–10%, while more than a dozen patients' speed increased by more than 10%—nine by more than 20%, four by more than 40%, and one by more than 60%. J.A. 6503. The lower bar graph shows, on average, zero or slight improvement in speed for patients in the placebo group, with no patient's speed having improved by more than 20% and one patient's speed having decreased by more than 20%. *Id.*

The results for improvements in leg strength between the active-treatment group (aggregating the doses of 20–50 mg/day) and placebo group showed a similar trend:



Id.

In the "Results Summary," the Goodman Poster states that "[s]ignificant improvement in walking speed was observed in the [4-AP sustained-release] treated group (p=0.04*)," where the p-value reflects a "*repeated measure ANOVA (weeks 1–7)"—*i.e.*, the walking speed for the active-treatment group, aggregating the dose levels. J.A. 6504; *see Dist. Ct. Op.* at *14 n.11 (noting that Dr. Goodman explained that the p-value reflects "the aggregated value for the treatment group as a whole, including all dosages, and did not reflect the results associated with any single dosage" (emphasis omitted)). More specifically, the Goodman Poster reports that (1) "[t]he average improvement in walking speed [in the 25-foot walk] during the low dose period (20–50 mg/day) included > 20% increase for 9 of the 25 subjects" and (2) "[c]hanges in the placebo-treated group were equally distributed between increases and decreases in walking speed and none of the 11 subjects showed increases > 18% during the low dose period." J.A. 6504. The Poster also reports, for the lower extremity manual muscle test (LEMMT), a "[s]tatistically significant improvement in the [4-AP sustained-release] treated group (p=0.01*)." *Id.*

The Conclusions section contains six bullet points. The first states that the "[s]afety profile [is] consistent with previous experience." J.A. 6503. The next few bullet points report a "[s]ignificant benefit on timed walking," "[s]ignificant benefit on lower extremity strength," "[n]o evidence of benefit on overall fatigue—susceptibility of fatigue to placebo effect," and "[e]vidence of dose-response in 20–40 mg/day range." *Id.* Finally, there was "[l]ittle added benefit, and increased [adverse events,] at doses above 50 mg/day." *Id.*

This Goodman prior art—which post-dates Elan's transfer of the research project to Acorda and which added significantly to the teachings of the earlier prior art—became the most important prior art in the obviousness analysis in this case.

b

In 2003, after completion of the MS-F201 study, Acorda conducted another placebo-controlled Phase II study (MS-F202 study) to test 4-AP's effect on walking speed. *Dist. Ct. Op.* at *9. After a two-week up-titration period beginning with a 10 mg dose, patients were administered a stable dose of 10 mg, 15 mg, or 20 mg sustained-release 4-AP twice daily for twelve weeks. *Id.* Although none of the 4-AP groups demonstrated a statistically significant improvement in walking speed relative to placebo, another post-hoc analysis showed that responders were in the 4-AP group ($p < 0.0001$) and that there was no meaningful difference in efficacy among the tested 4-AP doses. *Id.*; *see also* J.A. 612–14 (Acorda founder Dr. Cohen explaining that isolating responders in the study—those patients with improved walking—showed that responders were overwhelmingly in the active treatment groups and that there was no meaningful difference in efficacy among the responders in those treatment groups taking 10 mg, 15 mg, or 20 mg twice daily).

Acorda then conducted two Phase III studies to evaluate the effect of 10 mg sustained-release 4-AP twice daily, with walking improvement responder analysis as the primary outcome measure. *Id.* Both studies were successful, with $p < 0.0001$. *Id.*

Neither the results of the MS-F202 study nor the results of the Phase III studies constitute publicly available prior art to the Acorda patents in this case.

On April 9, 2004, Acorda employees filed a provisional patent application; that date is undisputedly the priority date of the Acorda patents. *Id.* at *9 n.8. The Acorda patents issued between August 2011 and March 2014.

The parties treat the Acorda patents' claims, for purposes of the invalidity issue on appeal, as involving methods of administering to a patient with multiple sclerosis a sustained-release 4-AP formulation (1) in a 10 mg dose twice daily, (2) at that stable dose for the entire treatment period of at least two weeks, (3) maintaining 4-AP serum levels of 15–35 ng/ml, (4) with walking improved. The parties treat claim 7 of the 826 patent and claim 22 of the '437 patent as representative. Claim 7 of the '826 patent depends on claim 6, which reads:

> 6. 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 C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human.

'826 patent, col. 27, lines 41–57. Claim 7 covers "[t]he method of claim 6, whereby an increase in walking speed is obtained in said human." *Id*., col. 27, lines 58–59.

Claim 22 of the '437 patent depends on claim 18, which depends on claim 1. Claim 1 of the '437 patent reads:

> 1. 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.

'437 patent, col. 27, lines 55–61. Claim 18 requires that the sustained release composition in claim 1 be "a tablet," *id.*, col. 28, lines 47–48; and claim 22 requires that the tablet of claim 18 "exhibit[] a release profile to obtain a C_{avSS} of about 15 ng/ml to about 35 ng/ml," *id.*, col. 28, lines 55–57. The parties have not distinguished the claims for purposes of the invalidity issue before us.[8]

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[8] Although the '826 patent's claim 7 does not require a regimen of at least two weeks, asserted claim 39 does (claim 39 requires 12 weeks), as do the '437 patent's asserted claims 1, 2, 5, 22, 32, 36, and 37; the '685 patent's asserted claims 3 and 5; and the '703 patent's asserted claims 36, 38, and 45.

Acorda submitted New Drug Application No. 022250 to the FDA for the use of 10 mg 4-AP extended-release tablets (Ampyra). The FDA granted priority review to that application and approved it on January 22, 2010.

According to the approved FDA label, Ampyra "'is indicated as a treatment to improve walking in patients with multiple sclerosis (MS). This was demonstrated by an increase in walking speed.'" *Dist. Ct. Op.* at *4 (citation omitted). "Improvement in walking in MS patients is [the] only approved use" of Ampyra. *Id.* The "Description" section of the label states that "'Ampyra (dalfampridine) is a potassium channel blocker, available in a 10 mg tablet strength . . . , formulated as an extended release tablet for twice-daily oral administration.'" *Id.* (capitalization altered). The "Dosage and Administration" section explains that "'[t]he maximum recommended dose of Ampyra is one 10 mg tablet twice daily, taken with or without food, and should not be exceeded. . . . 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.'" *Id.* (capitalization altered).

Between the time of FDA approval in 2010 and the end of 2015, total sales of Ampyra were $1.7 billion and net income was $998.7 million. *Id.* at *16. Net sales of Ampyra, in dollars, increased at an average rate of 20% per year, and the volume of tablets sold increased at an average rate of 8% per year, despite an increasing price per tablet over that period (2010 to 2015). *Id.* Acorda also receives royalty payments from licenses to sell Ampyra outside the United

States; it has collected at least $135 million from those licenses. *Id.*

Commercial opportunity, however, is constrained because Ampyra is indicated only for improvement of walking. *Id.* at *16–17. Ampyra sales revenue is approximately 2–3% of the total sales revenue from the top ten multiple sclerosis drugs. *Id.* at *17. Not all multiple sclerosis patients respond to Ampyra. Among multiple sclerosis patients who experience walking difficulties, 15–20% of those patients are prescribed Ampyra. *Id.*

On the other hand, Ampyra is the first and only drug approved for improving walking in multiple sclerosis patients. *Id.* When Sanofi-Aventis in 2008 conducted a Phase III study to test whether a different potassium-channel blocker, nerispirdine, would improve walking in patients with multiple sclerosis, it did not find evidence of a "specific significant difference between the responders [and] non-responders that received nerispirdine or placebo" in a timed 25-foot walk. J.A. 726–28 (testimony of Acorda's expert Dr. Fred Lublin); *see Dist. Ct. Op.* at *17.

B

In 2014, the defendants notified Acorda and Alkermes of the defendants' submission of Abbreviated New Drug Applications seeking FDA approval to market generic versions of Ampyra. In mid-July 2014, Acorda and Alkermes filed suits against Roxane, Mylan, and Teva, among others, in the District of Delaware for the alleged infringement of several claims in each of the Elan and Acorda patents under 35 U.S.C. § 271(e). The cases were consolidated in 2015.

The defendants stipulated to infringement of the asserted claims—claims 3 and 8 of the Elan patent;

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. *Dist. Ct. Op.* at *9–12, *18. The defendants, however, challenged the validity of the asserted claims of all five patents for obviousness under 35 U.S.C. § 103.[9] The defendants also challenged the validity of the asserted claims of the Elan patent for insufficient written description and enablement under 35 U.S.C. § 112, ¶ 1.

After a bench trial held in September 2016, the district court determined that the defendants had not proven invalidity of the Elan patent. *Dist. Ct. Op.* at *20–29. But the court held that the defendants had proven that the asserted claims of the Acorda patents are invalid for obviousness. *Id.* at *29–41. As to the Acorda patents: Based on the publications discussed above, as well as expert testimony, the court found that, as of 2004 (the priority date), a relevant skilled artisan would have been motivated to administer a stable dose of 10 mg of 4-AP twice daily and had a reasonable expectation of success in the objective of improving the walking ability of multiple sclerosis patients. *Id.* at *30–35. The court also found that the Acorda patents' claim limitations regarding serum levels (the pharmacokinetic limitations) were inherent in the dosing claimed. *Id.* at *35–36. Finally, the court, while finding certain facts in Acorda's favor regarding objective indicia of obviousness, ultimately discounted such indicia, relying on the fact that the Elan patent was a "blocking patent" for the claimed

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[9] Because the effective filing date of the claims of the Acorda patents are before March 16, 2013, the version of § 103 preceding the enactment of the Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011), governs this case.

methods of the Acorda patents: any marketer of a drug for uses practicing those methods would need a license to the Elan patent—to which Acorda, for years preceding the 2004 priority date, had an exclusive license from Elan. *Id.* at *36–40.[10]

On April 25, 2017, the court entered final judgment in favor of the defendants as to the Acorda patents and in favor of Acorda as to the Elan patent. The court set the effective date of any final FDA approval of the defendants' Abbreviated New Drug Applications no earlier than the expiration date of the Elan patent—July 30, 2018—and enjoined the defendants from any infringing activity before that date.

Acorda and the defendants timely appealed and cross-appealed, respectively. We have jurisdiction under 28 U.S.C. § 1295(a)(1).

II

Acorda makes essentially three arguments on appeal regarding the district court's ruling that the Acorda patent claims are invalid for obviousness. First, Acorda contends, on a number of grounds, that the district erred in finding that a person of skill would have had a motivation to combine the prior art to arrive at the Acorda invention and a reasonable ex-

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[10] In inter partes reviews initiated by a petitioner not included among the defendants here, the Patent Trial and Appeal Board considered challenges to the Acorda patents that did not involve Schwid or the Goodman references but, instead, depended on whether a particular filing with the Securities and Exchange Commission was prior art to the patents. The Board concluded that it was not. *Coalition for Affordable Drugs* (*ADROCA*) *LLC v. Acorda Therapeutics, Inc.*, Nos. IPR2015-01850, -01853, -01857, -01858, 2017 WL 950736, at *9–20 (P.T.A.B. Mar. 9, 2017). That ruling does not change the analysis in this case.

pectation of success in doing so. Second, Acorda challenges the court's determination that the claim limitations relating to pharmacokinetics—*i.e.*, achieving 4-AP serum levels of 15–35 ng/ml—are inherent in the claimed invention and therefore obvious. Third, Acorda argues that the court improperly applied a categorical rule that a blocking patent (the Elan patent) negates any findings in favor of Acorda on the objective indicia of commercial success, failure of others, and long felt but unmet need.[11]

Under 35 U.S.C. § 103(a), obviousness is a question of law based on underlying questions of fact, including the level of ordinary skill in the art, the scope and content of the prior art, the differences between the claims and the prior art, motivation to modify or combine with a reasonable expectation of success, and objective indicia of non-obviousness. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *In re Stepan*, 868 F.3d 1342, 1345–46 (Fed. Cir. 2017); *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1193–94, 1196–97 (Fed. Cir. 2014). We review the district court's determination of obviousness de novo and its underlying factual findings for clear error. *In re Cy-*

[11] Acorda also argues that the district court failed to analyze the claimed inventions as a whole. We see no methodological error. The court did nothing other than follow the parties' own breakdown of what aspects of the claimed inventions, alone or together, a skilled artisan at the priority date would have been motivated to adopt with a reasonable expectation of success and, more generally, would have found obvious. The court did not overlook any meaningful argument by Acorda that certain aggregations of claim elements, including the whole, required analysis beyond the analysis of the walking-benefit, dosage, stability, and serum-level aspects of the claims.

clobenzaprine Hydrochloride Extended-Release Capsule Patent Litig., 676 F.3d 1063, 1069 (Fed. Cir. 2012).

A

Acorda challenges the district court's findings about the relevant skilled artisan's motivations and expectations regarding the administration of a stable 10 mg 4-AP dose twice daily to improve walking. It presents two relatively focused arguments: that Schwid teaches away from the claimed invention; and that the prior art teaches the administration of sustained-release 4-AP in a titrated dosing regimen rather than a stable-dosing regimen. More broadly, Acorda argues that neither the Goodman Poster nor the prior art collectively teaches the efficacy of a stable 10 mg twice-daily dose or indicates that such a dose is among the small number of options that a skilled artisan would have been motivated to test with a reasonable expectation of success to improve walking. We reject these challenges.

1

Acorda contends that Schwid "affirmatively teaches away from Acorda's invention." Acorda Br. 36. The district court considered Schwid, as Acorda urged, among the teachings of the overall art available at the 2004 priority date, and it made findings as to the motivation and expectations of a relevant skilled artisan at that date regarding a stable 10 mg dosage of 4-AP to improve walking. *Dist. Ct. Op.* at *30–31. Acorda has not shown that Schwid renders the court's findings on those issues clearly erroneous.

Schwid supports a motivation to test, with a reasonable expectation of success, a 10 mg twice-daily dose of sustained-release 4-AP to improve walking in

multiple sclerosis patients. Schwid itself used a 17.5 mg twice-daily dose, but it found *success* with that dosage: as stated in Schwid, "[t]he results of this double-blind crossover study provide evidence that 4AP [sustained release] had a therapeutic effect on neurologic deficits from [multiple sclerosis]." J.A. 6684. In particular, there was a statistically significant improvement for the 17.5 mg 4-AP versus placebo in timed gait (*i.e.*, in walking ability); and the improvements in other outcomes, while not statistically significant, "showed trends favoring 4AP [sustained release]." J.A. 6681, 6684. Schwid expressly concludes that the study shows "4AP [sustained release] improved motor function in [multiple sclerosis] patients." J.A. 6681. And, stressing toxicity concerns with high doses, Schwid provides affirmative reason to investigate low doses. *See* J.A. 6681 ("4AP can provoke seizures and acute encephalopathy"—episodes that "tend to occur when serum 4AP levels peak, suggesting that lower peak levels may increase safety."); J.A. 6684 ("[F]uture studies of 4AP [sustained release] 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.").

Schwid makes certain observations that its study showed favorable results in some outcome measures at high serum levels of 4-AP (60 ng/ml)—levels that, according to evidence emphasized by Acorda, may require the administration of 4-AP doses higher than 10 mg twice a day. *See* J.A. 445–48 (defendant's expert's testimony that 17.5 mg twice-daily or 25 mg twice-daily could result in serum levels at or above 60 ng/ml); J.A. 823 (Acorda's expert's testimony: simi-

lar). But Acorda overstates the significance of this serum-level observation to the issue of a reasonable expectation of success for *walking improvement*.

Schwid found no statistically significant difference between the 4-AP and placebo groups as to patients' subjective global impression of their condition, one of seven outcome measures in the Schwid study. J.A. 6683. As to that outcome measure, Schwid states that "[n]one of the patients with a serum level less than 60 ng/mL felt better (according to their global impressions) on 4AP [sustained release] than placebo." *Id.* But efficacy in patients' global impression is not the issue—efficacy in timed gait is. Schwid made no such finding as to timed gait. Schwid also observes, as a general matter, that "[t]reatment [with 4AP sustained release] appeared particularly efficacious in subjects who achieved serum 4AP levels above 60 ng/mL, with everyone improving in timed-gait testing and grip strength, and five of six improving by MVICT [maximum voluntary isometric contraction, measured quantitatively] and their own subjective assessment [global impression]." J.A. 6684. But Schwid's measured improvement in timed gait was not limited to patients with high serum levels. *See* J.A. 6683 (9 of 10 patients improved in timed gait, and only 6 patients achieved serum levels greater than 60 ng/ml).

In short, high serum levels were not required, and a dose of 17.5 mg sustained-release 4-AP twice-daily was sufficient, for improvement in timed gait in Schwid. Meanwhile, Acorda has pointed to nothing in Schwid declaring that doses lower than 17.5 mg twice-daily would *not* be effective in improving walking. Schwid therefore supports a finding that a person of skill would have had a reasonable expectation of success regarding the administration of 17.5 mg of 4-AP

twice-daily—or perhaps even a lower dose since 17.5 mg was sufficient—to improve walking in multiple sclerosis patients. And in light of Schwid's warning that seizures may occur at higher doses, the district court did not clearly err in finding that a person of skill would look to lower doses rather than higher ones. *See Dist. Ct. Op.* at *32 ("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.").

2

Acorda's second argument is that the prior art teaches administering sustained-release 4-AP only in a titrated-dosing regimen to avoid the risk of seizure, and therefore that the district court could not properly find that a person of skill would have been motivated to pursue, or had a reasonable expectation of success concerning, a stable-dosing regimen. We reject this argument.

The prior art is not limited to titrated dosing (where doses start low and move higher) but rather contains evidence of stable dosing (where the dose starts and stays at the claimed level). As the district court noted, Polman is evidence of safe and effective long-term oral administration of a stable dose of immediate-release 4-AP. *Dist. Ct. Op.* at *34; *see* J.A. 6655. Schwid also provides evidence of a stable-dosing regimen of 4-AP, if only for a week. As for the studies that used escalating doses, some of those studies began with 10 mg as the lowest dose before titrating upwards to doses that may increase the risk of seizure. *E.g.*, Davis at 187 tbl.1; *see also Dist. Ct. Op.* at *8 (1994 Elan study began with 12.5 mg 4-AP twice

daily); *id.* at *9 (10 mg twice daily was the lowest dose used in the Acorda MS-F202 study); *cf.* J.A. 6647 (trial in patients with other conditions began with dose of 10 mg 4-AP twice daily and titrated up to 200 mg daily); J.A. 6434 (Acorda's trial in patients with spinal cord injury began with 10 mg twice daily as the lowest dose). Significantly, the most important prior art, the Goodman references, report a start dose of 10 mg twice daily. J.A. 6370, 6372, 6502.

Even if many earlier studies used a titrated-dosing scheme to avoid adverse effects caused by starting at higher doses, those studies do not, as the district court found, undermine the other evidence in the prior art that a person of skill would have a reasonable expectation of success for a stable-dosing scheme at low doses. *Dist. Ct. Op.* at *34. The Bever II prior-art review article reports that while "seizures are common at higher doses," 4-AP "rarely cause[s] seizures at the doses used in [multiple sclerosis] trials." Bever II at S120. Other published studies say the same: seizures were seen at higher doses, but not lower ones like 10 mg. *E.g.*, J.A. 6651 (trial in patients with Eaton-Lambert syndrome, congenital myasthenia, and myasthenia gravis starting at dose of 10 mg 4-AP twice daily and escalating to 200 mg daily found that all of the patients who experienced seizures during the study "were receiving 80 mg or more of 4-AP daily"); J.A. 6504 (Goodman Poster "Results Summary": "At doses above 40 mg/day, more severe adverse events were reported, including two cases of seizure (at 60 and 70 mg/day)"). And in Schwid, the authors advise that future studies pursue lower doses for long-term tolerability. *See* J.A. 6681 ("4AP can provoke seizures and acute encephalopathy," but those episodes "tend to occur when serum 4AP levels peak, suggesting that lower peak levels may increase safety."); J.A. 6684

("[F]uture studies of 4AP [sustained release] 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.").

Expert testimony supports the district court's finding that a person of ordinary skill in the art would have been motivated to pursue, and had a reasonable expectation of success in pursuing, a stable-dosing regimen of 10 mg 4-AP twice daily. According to Dr. Peroutka, "the general goal of drug development [is] to provide a stable dosing regimen." J.A. 414. He testified that stable dosing was particularly desirable for treating multiple sclerosis because, as a chronic disease that requires long-term treatment, a stable oral dose is much easier to administer. *See* Sept. 19, 2016 Trial Tr. 110 ("Obviously, it's a lot easier simply to take one pill, the same pill twice a day than to have to figure out, well, this morning I need this much, that much. But with pills, it is almost impossible to titrate easily."). Even Dr. Goodman conceded that "it would be desirable" to have a stable-dosing regimen where "the patient would be prescribed [some dose] to take on a regular basis." J.A. 868. And titration was not required given such a low starting dose: Acorda founder Dr. Cohen testified that, upon recognizing the efficacy of the 10 mg twice-daily dose, "we realized we didn't have to titrate anymore." J.A. 614. Finally, Dr. Peroutka explained that nothing in the prior art suggested that 4-AP could not be used for long-term treatment for a chronic condition. Sept. 19, 2016 Trial Tr. 104.

3

Acorda's most general argument is that the district court improperly found that a relevant skilled artisan "would have formed a reasonable expectation of

success based on Schwid and Goodman [in particular, the Goodman Poster], in light of the totality of the prior art," regarding a 10 mg twice-daily dose of 4-AP to improve walking. *Dist. Ct. Op.* at *31. We reject Acorda's argument.

As described above, Schwid reports a statistically significant improvement in timed gait for patients given 17.5 mg 4-AP twice-daily versus placebo. Also as described above, the Goodman Poster reports a statistically significant improvement in walking speed and in lower extremity strength for patients given 10–40 mg 4-AP twice daily versus placebo; an average improvement in walking speed during the low-dose period (10–25 mg 4-AP twice daily) of more than 20% for 9 of 25 subjects; and "more severe adverse events," including seizures, at doses above 20 mg 4-AP twice daily. J.A. 6504. The Goodman Poster also reports a dose response in the timed walk at doses in the range of 10–20 mg 4-AP twice daily. *See Dist. Ct. Op.* at *33 ("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.").

The district court did not clearly err in finding that a person of skill would have looked to both of those references, considered their limits, and had a reasonable expectation of success as to the efficacy of 10–20 mg 4-AP twice daily to improve walking. Despite certain identified "shortcomings" in the principal references, "the combined message a [person of skill in the art] would have discerned from Schwid together with the Goodman references was a reasonable expectation of success in treating walking with 4-AP." *Id.*

at *31. Other prior art was consistent with that message. *Id.* As to dosages, the disclosures of Schwid and the Goodman Poster regarding relevant benefits at doses including or near to the Acorda-claimed range (recounted above), together with the reported concerns about high doses, support the further finding that a relevant skilled artisan would have "consider[ed] 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." *Id.* at *33 (footnote attached citing further partial support from testimony of Acorda's Dr. Goodman). In a finding reflecting both motivation and reasonable expectation of success, the district court stated: "As the lowest of the range of encouraging doses, 10mg/twice daily would have been an attractive starting point for a [person of skill in the art]." *Id.* These findings not only have adequate evidentiary support but comport with the guidance of *KSR* to "take account of the inferences and creative steps that a person of ordinary skill in the art would employ." 550 U.S. at 418.[12]

Expert testimony further supports the district court's findings. The defendants' expert Dr. Peroutka explained that Schwid showed that the claimed formulation was effective at a 17.5 mg twice-daily dose and that the result was statistically significant. J.A. 406–07, 410. Dr. Peroutka also stated that the Goodman abstracts "said that dose response curves showed

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[12] In its formulation describing the narrow set of choices facing the relevant artisan in 2004 in this case, the district court quoted *KSR*'s discussion of obviousness where the claimed invention was "obvious to try." *Dist. Ct. Op.* at *32 (quoting 550 U.S. at 421). But the court fully applied the familiar standards focused on the relevant artisan's motivation to make the claim-required combinations with a reasonable expectation of success.

an increasing benefit in both measures in the 20 to 50 milligram a day range [10– 25 mg twice-daily range], meaning timed walking or lower extremity strength." J.A. 414. According to Dr. Peroutka, the study presented in the Goodman abstracts was a dose-ranging study where "the goal" is "to find the most efficacious dose without adverse events." *Id.*; *accord* J.A. 869 (Acorda's expert Dr. Goodman: "[W]hat we really want to find is the most effective dose that can be given safely."). The additional information provided in the bar graph in the Goodman Poster showed that people taking 10–25 mg twice daily did better in walking speed than placebo, and the dose-response curve showed improvement in walking speed at the 10 mg twice-daily dose—a level of improvement that was maintained at higher doses. *See* J.A. 416; Sept. 19, 2016 Trial Tr. 102 ("They got the 10 milligrams to work at this level and that level of efficacy was maintained through the dose ranges."); *id.* at 103 ("[I]t's certain stable clinical effect at 20 to 40" milligrams per day (doses of 10 mg. 15 mg, and 20 mg twice-daily).). Dr. Peroutka testified that he would have included the 10 mg dose in a Phase III study because there are "very serious" side effects at higher doses so "you would take the lowest effective dose that was safe." *Id.* at 104. He also testified that a person of skill might even want to try a lower dose, but "based on the [Goodman] data, 10 is the lowest effective dose." *Id*. Acorda's expert Dr. Goodman himself stated that the Goodman Poster "suggest[s]" "that the range for further testing would be the 20 to 40 milligrams per day [10 to 20 mg twice-daily] range." J.A. 844–45; *see also* J.A. 874 (Dr. Goodman stating during his deposition that "a person of ordinary skill in the art in December 2003 would have been motivated based on the 201 study to design a study along the

lines of what became the 202 study," which tested the 10 mg twice-daily dose). Ultimately, the court found, based on the prior art and expert testimony, that a person of skill before the 2004 priority date would have looked (1) to the 10–20 mg twice-daily dose range for effective doses that would be reasonably expected to improve walking in multiple sclerosis patients and (2) to the low end of that range to avoid adverse effects. *Dist. Ct. Op.* at *32–33.

Acorda's core argument appears not to be that the evidence fails to support the finding of a motivation to combine. Rather, it appears to be that the evidence cannot support a finding of a reasonable expectation of success (in 2004) in the absence of publications showing a statistically significant difference in walking tests between the specific dose of 10 mg 4-AP taken twice daily versus placebo. *See* Acorda Br. 41–42; Acorda Reply Br. 20–21; Oral Arg. at 6:10–30. We reject this contention.

To the extent that Acorda's contention is a legal one, asserting a law-required minimum for what can support a "reasonable" expectation of success, Acorda has offered no support for the contention. This court has long rejected a requirement of "[c]onclusive proof of efficacy" for obviousness. *See*, *e.g.*, *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331 (Fed. Cir. 2014); *PharmaStem Therapeutics*, *Inc. v. ViaCell*, *Inc.*, 491 F.3d 1342, 1364 (Fed. Cir. 2007); *Pfizer*, *Inc. v. Apotex*, *Inc.*, 480 F.3d 1348, 1364, 1367–68 (Fed. Cir. 2007) (reasoning that "the expectation of success need only be reasonable, not absolute"). And Acorda has cited no authority from the Supreme Court or this court requiring as a matter of law, for reasonableness of an expectation of success, testing of specific doses versus placebo that shows the relevant result with

statistical significance. Acorda has furnished no basis for treating the question in this case as anything but one of context-specific fact based on evidence.

In some cases, of course, the evidentiary basis for an inference of reasonable expectation of success may be inadequate. *See*, *e.g.*, *In re Cyclobenzaprine*, 676 F.3d at 1070–71. Here, though, as we have discussed, expert and othe evidence indicates that a person of skill in the present context *can* draw reasonable inferences about the likelihood of success even without a perfectly designed clinical trial showing a statistically significant difference in efficacy between a specific dose and a placebo. *See also* J.A. 6657 (Polman: "Although a placebo effect cannot be excluded, the dynamics of the response in relation to the intake of the medication and the deterioration and subsequent improvement in functioning during a drug-free interval and subsequent restarting of the therapy are, in our view, highly suggestive of a real effect being induced by the 4-[AP]. Improvements in fatigue and ambulation were mentioned quite often by the patients as being responsible for the favorable overall effect."). We see no clear error in the district court's finding to that effect.

We are not persuaded by Acorda's reasons for a contrary finding. To begin with, "Elan's failure in the only large-scale and properly statistically powered trial of sustained-release 4-AP that deflated expectations for the drug," Acorda Reply Br. 28, is not particularly relevant to the expectations of success for the Acorda invention. The record shows that the Elan trial was unpublished and is only cursorily discussed in the introduction in Schwid, limiting any "deflat[ing]" effect on expectations in the field. Sept. 19, 2016 Trial Tr. 143–44 (Dr. Peroutka noting that, even

in the short discussion of the 1994 Elan study in Schwid, there is very little detail and no mention of the dose of 4-AP that was used). Moreover, the abbreviated discussion of that trial in Schwid distinguishes the aggregate outcome measure (EDSS) and results in the Elan study from the Schwid study's measure of particular functionalities (*e.g.*, timed gait). J.A. 6681 (noting the failure of the Elan study but stating that "[t]he EDSS . . . may have been an inadequate outcome variable for this trial," as EDSS measures several outcomes and could "overlook" significant but lesser improvements in walking). And the 1994 Elan study preceded the successes reported later in Schwid and the Goodman references, which were a sound basis for altering earlier expectations.

Similarly, the "inconclusiveness of the exploratory studies of 4-AP, a 102-year old drug," Acorda Reply Br. 28, does not speak to the more recent research relied on by the district court—namely, Schwid and the Goodman references. And "the rigorous 2003 Solari review of the field dispelling any confidence in using am[ino]pyridines to treat [multiple sclerosis]," *id.* at 29, does not dispel confidence in a walking improvement; rather, Solari, a prior-art literature review, reports a statistically significant improvement in walking, J.A. 7208 (reviewing three studies that "assessed the efficacy of aminopyridines on ambulation" and reporting that patients who received 4-AP showed a statistically significant improvement in ambulation compared to placebo ($p<0.0001$)).[13] When Acorda asserts that the "prior art's [Schwid's] teaching that 4-AP had a narrow therapeutic window where high doses and

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[13] Alessandra Solari et al., *Aminopyridines for symptomatic treatment in multiple sclerosis* (*Review*), Cochrane Database of Systematic Reviews, Issue 4 (2002).

high blood serum levels were necessary for any meaningful therapeutic effect," Acorda Reply Br. 29, Acorda is incorrect, as discussed previously: Schwid reports that a relatively *low* (17.5 mg twice a day) dose showed a statistically significant improvement in walking and that high serum levels were not required for improvements in timed gait. Schwid, which reports success and no seizure events with a stable dose of 17.5 mg twice daily, also undermines Acorda's argument that "the prior art's consistent use of titration to achieve a therapeutic dose because of seizure risk" conclusively precludes a reasonable expectation of success even for a low dose like 10 mg twice daily that avoids high peak serum levels. *Id.* In the end, Schwid, Goodman as a whole, and expert testimony supply a sufficient basis for the district court's finding of a reasonable expectation of success in this case.

In light of the record evidence, the district court did not clearly err in finding that a person of skill at the time of the invention would have had a motivation to combine, and a reasonable expectation of success in combining, the teachings of the prior art to arrive at the Acorda invention of a stable regimen of 10 mg twice-daily sustained-release 4-AP to improve walking in multiple sclerosis patients.

B

Acorda nevertheless contends that a skilled artisan would not have a reasonable expectation of success regarding the invention of the Acorda patents because the prior art did not teach or suggest a final limitation of the asserted claims—the pharmacokinetic limitation, which requires 4-AP serum levels in the 15–35 ng/ml range. *E.g.*, '826 patent, col. 27, line 29. We disagree.

The district court found that the prior art taught that a dose of 10 mg sustained-release 4-AP twice daily would result in serum levels within the range claimed in the Acorda patents. *Dist. Ct. Op.* at *35. Hayes discloses that when a sustained-release formulation of 4-AP is administered in a 10 mg dose twice daily, and steady-state conditions are reached, the result is a 4-AP average serum level of 20.8 ± 5.7 ng/ml (15.1–26.5 ng/ml, which is within, and in fact covers most of, the Acorda patents' claimed range). J.A. 6436, 6439 tbl.3. The Hayes study is summarized—and Hayes's table listing the pharmacokinetic results is replicated—in the specifications of two of the Acorda patents. '826 patent, col. 24, line 25 through col. 25, line 50 (Example 7 and Table 7); '685 patent, col. 24, line 30 through col. 25, line 54 (Example 7 and Table 7). The district court noted that the parties did not dispute either of two propositions: the Hayes researchers used the Elan formulation that is claimed in the Acorda patents and is now marketed as Ampyra; and the pharmacokinetic results reported in Hayes are inherent properties of that formulation. *Dist. Ct. Op.* at *35. As discussed in the previous subsections, the district court also found that a person of skill would have been motivated, with a reasonable expectation of success, to administer a dose of 10 mg sustained-release 4-AP twice daily to improve walking in multiple sclerosis patients. *Id.* at *35–36. Based on those findings, the court invoked the principle that "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations," *Santarus*, *Inc. v. Par Pharm.*, *Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012), and concluded that the pharmacokinetic limitation could not alter the obviousness analysis.

On appeal, Acorda does not directly object to the district court's inherency finding about Hayes, but Acorda suggests that a person of skill would expect that the inherent pharmacokinetic profiles would differ between patients with spinal cord injury (as in Hayes) and patients with multiple sclerosis (as in the Acorda patents). But Acorda cites no support for that assumption, and Acorda appears to have made the opposite assumption by including the Hayes pharmacokinetic data in its own patents on using 4-AP to treat multiple sclerosis. Acorda's expert also admitted at trial that Hayes "may certainly show the pharmacokinetic profile that's analogous to what would be found in MS [multiple sclerosis] patients. I don't have any dispute with that." J.A. 825. The defendants' expert agreed, testifying that a person of skill would expect the same pharmacokinetic profile in patients with either condition. J.A. 539–40. And while Acorda argues that a person of skill in the art "would have no basis to connect Hayes with [multiple sclerosis] prior art," Acorda Br. 54, Hayes's introduction explicitly makes that connection, stating that "[4-AP] is the first compound shown to restore some neurologic function in patients with chronic [spinal cord injury] or other demyelinating conditions such as multiple sclerosis." J.A. 6433 (internal references omitted).[14]

Even if the pharmacokinetic profile is inherent in the 10 mg twice-daily administration of sustained-release 4-AP in Hayes, Acorda complains that a person

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[14] Hayes also discloses that the reported study on the pharmacokinetics of sustained-release 4-AP was sponsored by Acorda. J.A. 6433. That disclosure links Hayes to the Goodman references, which also disclose an association with Acorda in a sustained-release 4-AP study. J.A. 6370, 6372, 6498.

of skill may not have known the details of the formulation used in Hayes (Ampyra) and therefore would not have known whether the formulation claimed in the Acorda patents would produce the same pharmacokinetic profile. *Cf. In re Cyclobenzaprine*, 676 F.3d at 1069–71 (obviousness analysis of patent claims to a "therapeutically effective plasma concentration" and to particular pharmacokinetic parameters required a factual finding regarding what a skilled artisan would know about the serum levels needed to produce a therapeutic effect). But Acorda, in response to the district court's question as to whether the pharmacokinetic limitation would have been obvious, conceded at trial that a skilled artisan in 2003 would know the pharmacokinetic data for a 10 mg twice-daily dose of sustained-release 4-AP. J.A. 1108–09 (counsel for Acorda: "It was known in the art that a sustained-release formulation of 10 [mg] [twice daily] could achieve that PK [pharmacokinetic result], not that that PK would yield any efficacy for walking."). Acorda itself therefore assumed that a person of skill would know that a regimen of 10 mg twice-daily dosing of sustained-release 4-AP—regardless of the specifics of the rest of the formulation—would achieve that pharmacokinetic profile. And, again, Acorda has not pointed to any evidence to contradict that assumption, such as evidence showing that a person of skill would expect another sustained-release formulation containing the same dose of 4-AP to produce a different pharmacokinetic profile, how that formulation would differ, or how the associated profile would differ.

C

Acorda's remaining argument on appeal concerns the proper analysis of objective indicia of nonobviousness in this case. Acorda focuses on the district court's

reliance on the Elan patent as a blocking patent for the Acorda patents' claimed inventions, in determining that commercial success, failure of others, and long-felt but unmet need did not "support" or "militate in favor of" nonobviousness. *Dist. Ct. Op.* at *39, *40. Acorda characterizes the district court as having applied a categorical rule that a blocking patent defeats the significance of such objective indicia to the obviousness determination. We think, however, that the district court's opinion is best read not as invoking a categorical rule, but as drawing conclusions on the limited factual record created in this case bearing on the effect of a blocking patent. In any event, the court did not err in concluding that the defendants proved obviousness, considering the evidence on objective indicia.

1

A patent has been called a "blocking patent" where practice of a later invention would infringe the earlier patent. The existence of such a blocking patent may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, "blocked" invention, because of the risk of infringement liability and associated monetary or injunctive remedies. If the later invention is eventually patented by an owner or licensee of the blocking patent, that potential deterrent effect is relevant to understanding why others had not made, developed, or marketed that "blocked" invention and, hence, to evaluating objective indicia of the obviousness of the later patent. *See* Note, *Subtests of "Nonobviousness": A Nontechnical Approach to Patent Validity*, 112 U. Pa. L. Rev. 1169, 1177 (1964) (Regarding commercial success, "a court must be assured that the patentee's market domination is not attributable to monopoly

power or other economic coercion, or to other factors unrelated to patent validity.") (cited in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1, 18, 36 (1966)).

We briefly discussed blocking patents in *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005) (*Merck I*). The Merck patent at issue, applied for in 1998, was for the weekly administration of alendronate monosodium trihydrate (Fosamax). *Id.* at 1366–67. That patent was preceded by Merck's earlier patent (issued in 1986) covering a method of administering an effective amount of Fosamax to treat osteoporosis, as well as Merck's statutory right, since obtaining FDA approval in 1995, to the exclusive marketing of any dosage strength of Fosamax for the next five years. 395 F.3d at 1367, 1377; Br. for Def.-Appellant Teva Pharm. USA, Inc., *Merck I*, No. 04-1005, 2003 WL 24307848, at *62–63 (Fed. Cir. Dec. 17, 2003). We ruled that the district court had erred in its analysis of commercial success because the earlier patent and FDA regulatory approval depressed incentives for others to invent the weekly-dosing scheme. 395 F.3d at 1377 ("Because market entry by others was precluded on those bases, the inference of non-obviousness of weekly-dosing, from evidence of commercial success, is weak."). In that context, we said, the evidence of commercial success was "not enough to show the claims at bar are patentably distinct from the weekly-dosing ideas in the [invalidating prior art]." *Id.*

In *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013), we considered the district court's finding, in support of commercial success, that the FDA-approved product "quickly gained and

maintained market share." *Id.* at 740. Because earlier patents owned by Galderma may have "blocked" competition to market the FDA-approved product by any entity other than Galderma, we reasoned that the commercial success of the product was "of 'minimal probative value'" and not sufficient to justify a conclusion of nonobviousness in light of the other evidence supporting obviousness. *Id.* at 741 (quoting *Merck I*, 395 F.3d at 1376).

Recently, in *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724 (Fed. Cir. 2017) (*Merck II*), we concluded that Merck's exclusive license to a blocking patent did not, all by itself, justify discounting evidence of commercial success. *Id.* at 730–31. We explained that commercial success is "a fact-specific inquiry" that may involve considering the operation of specific blocking patents on possible competition. *Id.* at 731. But the mere existence or sheer number of blocking patents does not, without more, "necessarily detract from evidence of commercial success of a product or process." *Id.* Nevertheless, "even giving the evidence of commercial success its full and proper weight," we affirmed the judgment invalidating the claims at issue for obviousness in light of "the evidence that the claimed process was substantially described in the prior art" and that "merely ordinary experimentation was required to arrive at the [patent at issue]." *Id.*

Merck II's reasoning reflects a common-sense recognition that, as a theoretical matter, a blocking patent may or may not deter innovation in the blocked space by commercially motivated potential innovators

other than the owners or licensees of the blocking patent.[15] Where the owner of the blocking patent or exclusive licensee is different from the owner of the patent in suit, the granting of a license may be a realistic possibility. Even where, as here, the owner of the patent in suit and the exclusive licensee of the blocking patent are the same, such a potential innovator might or might not think it could successfully challenge the blocking patent. And such a potential innovator might or might not be willing to research in the blocked space without a license to a blocking patent—even if the research itself is within the safe harbor provided by 35 U.S.C. § 271(e)(1)—and wait until it has already developed and patented its aimed-at improvement to negotiate for a cross-license with the blocking patent's owner to share the profits from the improvement. Besides the assessment of whether the blocking patent can be successfully challenged, a number of variables appear generally relevant to the calculus, including: the costliness of the project; the risk of research failure; the nature of improvements that might arise from the project, and whether such improvements will be entirely covered by the blocking patent; the size of the market opportunities anticipated for such improvements; the costs of arriving at the improvements and getting them to market; the risk of losing the invention race to a blocking-patent owner or licensee; the risk that the blocking-patent owner (making its own economic calculations, perhaps

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[15] We use the term "blocked space" to refer to what would infringe given the "boundaries," *Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co.*, 535 U.S. 722, 730 (2002), or "metes and bounds," *Brenner v. Manson*, 383 U.S. 519, 534 (1966), set by the blocking patent's claims. *See Andrew Corp. v. Gabriel Electronics, Inc.*, 847 F.2d 819, 823 (Fed. Cir. 1988).

in light of its own other products or research activities) will altogether refuse to grant a license to the improvement or will demand so large a share of profits that the whole project is not worthwhile for the potential innovator—all evaluated in light of other investment opportunities.

For such reasons, it is clear that, if all other variables are held constant, a blocking patent diminishes possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing, therefore reducing incentives for innovations in the blocked space by non-owners and non-licensees of the blocking patent. Such a blocking patent therefore can be evidence that can discount the significance of evidence that nobody but the blocking patent's owners or licensees arrived at, developed, and marketed the invention covered by the later patent at issue in litigation. But the magnitude of the diminution in incentive in any context—in particular, whether it was great enough to have actually deterred activity that otherwise would have occurred—is "a fact-specific inquiry." *Merck II*, 874 F.3d at 731. That inquiry, conducted within the framework under which the challengers always retain the burden of persuasion on obviousness, may be a difficult one as a practical matter. In a particular case, a court may ultimately be left, for its evaluation, with the solid premise of diminished incentives, plus some evidence (possibly weak or ambiguous) about the significance of the deterrence, together with a background sense of the general realities in the area at issue that can affect the weight to be given to the evidence in the specific case.

Against this background, we review the district court's consideration of objective indicia of nonobviousness in light of the Elan patent. Acorda licensed the Elan patent in the late 1990s, before the period of commercial success alleged by Acorda and found by the district court. Here, Acorda bore the burden of producing evidence of objective indicia, but the "ultimate burden of proving obviousness" at all times remained with the defendants. *Galderma*, 737 F.3d at 736–38. We conclude that the district court did not err in viewing the Elan patent, among other evidence, as evidence that discounted the weight of Acorda's evidence of commercial success, failure of others, and long-felt but unmet need so that "the evidence as a whole" in the case "prove[d] clearly and convincingly that the Acorda Patents are invalid due to obviousness." *Dist. Ct. Op.* at *41.

The parties presented evidence on the objective indicia of commercial success, failure of others, and long-felt but unmet need.[16] In particular, the defendants presented evidence of blocking by the Elan patent. *See Dist. Ct. Op.* at *38 & n.43 (undisputed that invention of Acorda patents practice the Elan patent).

As to commercial success, the district court found that "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

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[16] Acorda also presented evidence of unexpected results, but the district court found the evidence unpersuasive. *See Dist. Ct. Op.* at *39. Acorda does not appeal that finding.

those inventions were obvious." *Id.* at *38. The district court therefore found that the evidence of commercial success did not support the conclusion that the Acorda patent claims were non-obvious. *Id.* at *39.

We will interpret the district court's statements together as referring to domestic marketing of a product. As discussed below, the Elan patent would not preclude practice of the Elan invention outside the United States or under the safe harbor provision of 35 U.S.C. § 271(e)(1) for specified FDA-related activities. The district court's key finding, therefore, is that "[t]he risk of [infringement] liability" for marketing in the United States "would have provided an independent incentive for a patentee not to develop the invention of the Acorda patents, even if those inventions were obvious." *Dist. Ct. Op.* at *38.

That finding is supported by the record. The defendants offered unrebutted testimony from an expert in economics and pharmaceuticals that the Elan patent acted as a blocking patent for entities other than Acorda (the exclusive licensee to the Elan patent) that wanted to pursue commercial opportunities like Ampyra. J.A. 965–66 ("[O]ther entities that might want to pursue commercial opportunity like Ampyra . . . would not have access to [the sustained-release 4-AP formulation claimed in the Elan patent] because Acorda has that exclusive license."). The Elan patent issued in 1996 and was licensed exclusively to Acorda in 1997 for spinal cord injury and in 1998 for multiple sclerosis treatment. J.A. 965. After that, the exclusive license blocked others from domestic marketing without risk of infringement.

Other evidence supports a finding that the Elan patent would have deterred entities other than Elan

(holder of the Elan patent) and Acorda (exclusive licensee) from investing in research whose reward depended on marketing a drug like Ampyra. After more than a decade of research by different groups and then issuance of the Elan patent in 1996, clinical trial research into sustained-release 4-AP treatment for multiple sclerosis appears, based on the prior art introduced at trial, to have been limited to Elan and Acorda. When seeking to use 4-AP for multiple sclerosis, Acorda itself sought and obtained a license to the Elan patent. There is no evidence that Elan sought to license the Elan patent to any entity other than Acorda, or that Acorda sought to sublicense the Elan patent, either of which would dilute the power of the blocking patent. J.A. 966. And what Elan granted Acorda was an *exclusive* license, suggesting the significance of the Elan patent's blocking power.

Acorda notes that U.S. patents do not block sales outside the United States. That observation is relevant, but it is not shown to be weighty in this case by any concrete evidence about the particular inventions at issue. Indeed, the two international studies that Acorda highlights were both conducted *before* issuance of the Elan patent in 1996. *See* J.A. 6654 (1994 Polman study); J.A. 7037 (1993 Van Diemen study).

Acorda also notes that potential innovators would not have been blocked from practicing the Elan patent in the ways covered by the safe harbor provision of 35 U.S.C. § 271(e)(1), which declares specified activities to be non-infringing if undertaken "solely for uses reasonably related to the development and submission of information" to the FDA. *See Merck KGaA v. Integra Lifesciences I, Ltd.*, 545 U.S. 193, 205–08 (2005). That safe harbor is certainly relevant, but it does not eliminate infringement liability for the eventual reward-

collecting activity of generally marketing the product. We have no basis for finding clear error in the district court's finding about the explanatory significance of the risk of such liability. Acorda did not supply evidence to make unreasonable the implicit finding that securing freedom from blocking patents in advance is likely important to pharmaceutical research investments.[17] And amici appearing in this court on appeal have not supplied such evidence either.[18]

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[17] Without contrary evidence, we see nothing inherently unreasonable about the implicit finding to that effect. *See* Stoyan A. Radkov, *Freedom to Operate* (*FTO*) *from a large company's perspective* 3, 5, Royal Society of Chemistry (Oct. 11, 2010), http://www.rsc.org/images/StoyanRadkov_tcm18-192425.pdf (in a presentation by an attorney for Novartis Pharma AG an FTO analysis of "[t]he ability to *perform a particular commercial activity* (e.g. commercialize a product, provide a service, perform a manufacturing process or use a product) *without* 'infringing' 3rd party's valid IP [intellectual property] rights," explaining that "[i]dentifying possible 3rd party IP rights posing risks as soon as possible is essential"); Saharsh Davuluri, *Generic Drugs – The Freedom to Operate*, Neutland Labs. Ltd. (Aug. 2, 2014), https://www.neulandlabs.com/blog/2014/08/02/generic-drugs-the-freedom-to-operate/ ("A Freedom to Operate analysis is crucial – and is best performed *before* embarking down the product development path."). In so stating, we do not prejudge what evidence in another case might demonstrate.

[18] Amici point out that pharmaceutical improvements (new formulations, new combinations, and new indications of previously marketed drugs) are not uncommon: 23 were approved by the FDA and launched in 2016. Biotech. Innovation Org. Br. at 20 (citing A.I. Graul et al., *The year's new drugs & biologics 2016: Part I*, 53 Drugs of Today 27, 28 (2017)). But amici do not specify whether the approved applications for those improvements are held by the owners (or licensees) of any original blocking patents or by competing entities. *See* Chie Hoon Song & Jeung-Whan Han, *Patent cliff and strategic switch: exploring strategic design possibilities in the pharmaceutical industry*, 5 SpringerPlus 692,

Acorda offers no more persuasive basis for challenging the district court's findings of the weakness of Acorda's evidence of the failure of others and long-felt but unmet need as evidence of non-obviousness. *Dist. Ct. Op.* at *39–40. As to the former, the district court found that Sanofi-Aventis experimented with another potassium-channel blocker and was unsuccessful, and "Sanofi-Aventis likely did not use 4-AP because" of the blocking effect of the Elan patent. *Id.* at *39. Acorda has not shown clear error in that finding. Acorda also points to the failure of Elan's 1994 study. But the district court reasonably found that "Elan's failure is not particularly probative" because the Elan study preceded publications that would render the invention

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698–99 (2016) (noting that some of the best ways for a pharmaceutical company to avoid the "patent cliff" of losing the monopoly on its brand-name drug from patent expiration is through a product-line extension (new formulations, new combinations), new indications, or a follow-on product). For example, among the examples from 2016 listed in the Graul article are Ilaris, Ezetrol, and Inegy, *see* Graul, *The year's new drugs & biologics*, 53 Drugs of Today at 56, 57, which involve improvements (new indications) on drugs previously approved for other indications for marketing by the same company that submitted the application for the new indication. *See Product Update: New indication for Inegy*, The Pharmaceutical Journal (Mar. 1, 2016), https://www.pharmaceutical-journal.com/news-and-analysis/notice-board/new-indication-for-inegy/20200796.article?firstPass=false (Merck sells the drug Inegy (ezetimibe/simvastatin) for both old and new indications); U.S. Food & Drug Admin., U.S. Dep't of Health & Human Servs., *FDA News Release: FDA approves expanded indications for Ilaris for three rare diseases* (Sept. 23, 2016), https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm522283.htm (Ilaris (canakinumab) sold by Novartis for old and new indications); Joel Levy, *MHRA approves new indication for MSD's Ezetrol*, Pharmafile (Feb. 26, 2016), http://www.pharmafile.com/news/503098/mhra-approves-new-indication-msd-s-ezetrol (Merck (MSD) sells Ezetrol (ezetimibe) for both old and new indications).

obvious to those of skill in the art (Schwid and Goodman) as of the 2004 priority date. *Dist. Ct. Op.* at *40; *see Graham*, 383 U.S. at 36 ("The [1956] Scoggin invention . . . rests upon exceedingly small and quite nontechnical mechanical differences in a device which was old in the art. At the latest, those differences were rendered apparent in 1953 by the appearance of the Livingstone patent [invalidating prior art], and unsuccessful attempts to reach a solution to the problems confronting Scoggin made before that time became wholly irrelevant."); *see also* Note, *Subtests of "Nonobviousness,"* 112 U. Pa. L. Rev. at 1174 ("In receiving evidence of unsuccessful research, courts must take care that such research was conducted under the same state of the art as that which confronted the patentee. It may be that an intervening innovation made that which the patentee accomplished obvious even though it was not obvious to prior unsuccessful researchers." (internal reference omitted)). By 1997, the art expressly explained why improvement of multiple sclerosis symptoms with 4-AP was promising despite the failed 1994 Elan study. *See*, *e.g.*, J.A. 6681 (1997 Schwid article states that the EDSS score was "an inadequate outcome variable" for the Elan study, reports a significant improvement in timed gait, and concludes that "4AP [sustained-release] improved motor function in [multiple sclerosis] patients.").

As to long-felt but unmet need, the district court discounted its finding of such need in light of the evidence of blocking by the Elan patent. *Dist. Ct. Op.* at *40. We see no clear error. While not dispositive, the evidence of blocking we have discussed is pertinent, in this case, to the factual question of long-felt but unmet need—at least as to the period after the issuance of the Elan patent in 1996.

III

The defendants cross-appealed the district court's ruling that the Elan patent is not invalid and the resulting injunction. Because the injunction terminated by its terms on the date of expiration of the Elan patent (July 30, 2018), and no retrospective liability is at issue, the cross-appeal is dismissed as moot. *See* Fed. R. App. P. 41(b), (c); 16AA Charles A. Wright & Arthur R. Miller, *Federal Practice and Procedure* § 3987 (4th ed. 2018); *cf.* Defs.' Br. 61 ("the Court need not reach the cross-appeal unless the Court intends to issue a decision before August 2018").

IV

We affirm the district court's ruling that the asserted claims of the Acorda patents are invalid and dismiss the defendants' cross-appeal as moot.

AFFIRMED

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ACORDA THERAPEUTICS, INC.,
Plaintiff-Appellant

ALKERMES PHARMA IRELAND LIMITED,
Plaintiff-Appellee

v.

ROXANE LABORATORIES, INC., MYLAN PHARMACEUTICALS INC., TEVA PHARMACEUTICALS USA, INC.,
Defendants-Cross-Appellants

2017-2078, 2017-2134

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-00882-LPS, 1:14-cv00922-LPS, 1:14-cv-00935-LPS, 1:14-cv-00941-LPS, Chief Judge Leonard P. Stark.

NEWMAN, *Circuit Judge*, dissenting.

The court today holds that the new Acorda treatment for multiple sclerosis, Ampyra®, achieved after decades of failed research, was obvious. For this discovery, where a relatively small pharmacological difference produced long-sought medical benefits, it is essential that the correct law and analysis of obviousness are applied.

The district court observed that the objective indicia, viz. commercial success, long-felt but unmet need, failure of others, and copying, could change the result,

yet discounted its weight on the theory that the patentee had a "blocking" patent. Adopting this flawed reasoning, my colleagues hold that this new treatment for multiple sclerosis was obvious. However, it is apparent that there is not clear and convincing evidence of obviousness.

The consequences of this new legal theory are large, as the amici curiae advise. Had the court's approach to the law of obviousness been in effect when Acorda took up the study of 4-aminopyridine after decades of failures by others, it is questionable whether this new treatment for multiple sclerosis would have been discovered and pursued. The loser is the afflicted public.[1]

From my colleagues' continuation of this error, and their erroneous conclusions, I respectfully dissent.

I

The Decades of Failures

As the court reports, 4-AP has "for several decades" been the "focus of research regarding the treatment of multiple sclerosis." Maj. Op. at 5. Starting in the 1980s or earlier, scientists in several countries tried and failed to provide safe and effective application of 4-AP. My colleagues agree, as do the Defendants who initiated these Hatch-Waxman proceedings, that the Acorda Patents describe novel technology, and that a safe and effective formulation for 4-AP was not previously known. The Acorda inventors suc-

[1] The FDA gave the Acorda product expedited approval, in view of the public need for relief of multiple sclerosis. Appellant's Br. at 23.

ceeded where many others had failed. The panel majority treats these past failures simply as invalidating prior art.

The court recognizes that the Acorda Patents are directed to a new, effective treatment to relieve the "walking impairment" of multiple sclerosis.[2] However, the court holds that Acorda merely "add[ed] further, more specific requirements to the Elan Patent's claimed methods." Maj. Op. at 3. The court does not mention that Elan, after years of failures, abandoned its attempts to use 4-AP to treat multiple sclerosis and licensed the sustained-release patent to Acorda.

The record shows that many scientists in many institutions studied and eventually abandoned 4-AP as a treatment prospect for multiple sclerosis. These abandoned studies constitute the prior art on which the district court and my colleagues rely for obviousness of the Acorda Patents. However, the experimentation with 4-AP shows just the opposite – it shows that work with 4-AP was abandoned due to the inability to balance the compound's potential effectiveness with its toxicity.

To review obviousness of the Acorda Patents, I start with the cited references, whose chronology illustrates the initial encouragement followed by failed attempts to apply the neurological properties of 4-

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[2] The symptoms of multiple sclerosis include "walking impairment, visual difficulty, fatigue, bladder dysfunction, tingling or pain, sexual dysfunctions, balance problems, and cognitive changes," with "weakness in the legs and/or alterations in walking among the most common symptoms." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 1:14-cv-00882-LPS, 2017 WL 1199767 (D. Del. Mar. 31, 2017) (Dist. Ct. Op.) at *2.

aminopyridine, and the eventual abandonment of this product despite some positive observations.

A. The Stefoski Study

In 1987, Stefoski et al. reported a one-day test of the effects of 4-AP on vision and gait in twelve multiple sclerosis patients.[3] They reported that, following intravenous injection of 7 to 35 mg of 4-AP, in 1 to 5 mg doses every ten to sixty minutes, "[v]ision improved in 7 patients, oculomotor function in 5, and motor function (power, coordination, gait) in 5," stating that there were "no serious side effects," and "transient therapeutic benefit in selected patients." Stefoski et al. at 71. My colleagues rely on this publication for rendering obvious Acorda's improvement in walking, while downplaying the "serious side effects" including seizures reported by Bever[4] and others, and the criticism of the small sample size and the brief duration of these one-day tests.

B. The Davis Study

In 1990, Davis and Stefoski reported a study of fifteen patients using an orally-administered formulation of 4-AP.[5] They concluded that the results "suggest a safe and effective therapeutic window for orally administered 4-AP," but they cautioned that similar studies had found that side effects of 4-AP "precluded

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[3] Dusan Stefoski et al., *4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis*, 21 Annals of Neurology 71 (1987), J.A. 6697.

[4] Christopher T. Bever, Jr., *The Current Status of Studies of Aminopyridines in Patients with Multiple Sclerosis*, 36 Annals of Neurology S118 (1994) ("Bever II"), J.A. 6172.

[5] Floyd A. Davis et al., *Orally Administered 4-Aminopyridine Improves Clinical Signs in Multiple Sclerosis*, 27 Annals of Neurology 186 (1990), J.A. 6327.

its clinical use," and that "MS patients have an increased risk of seizures." Davis et al. at 191.

These studies were criticized by Bever as "limited because they did not use a randomized treatment design, were not double blinded, and relied on outcome measures that were not widely accepted." Bever II at S119. Although my colleagues cite Davis' reports of "mild to marked improvements," Maj. Op. at 5, they do not mention the risk of seizures as warned by Davis, or Bever's criticisms.

While the panel majority states that Davis reported "no serious or bothersome side effects, including seizures" at doses up to 25 mg, *id.*, Elan, which relied on Davis' research team, Dist. Ct. Op. at *4, terminated its development of 4-AP based on toxicity and seizures, and licensed its sustained release patent to Acorda. Nonetheless, my colleagues hold that the Davis studies contributed to the obviousness of the Acorda Patents, ignoring the problems that were reported, and the abandonment of 4-AP by these researchers.

C. The Van Diemen study

The panel majority also relies on a study conducted in the Netherlands and published in 1993 by Van Diemen.[6] The publication reports the effect of escalating doses of 4-AP, measured by the Kurtzke expanded disability status scale (EDSS) that is frequently used as a benchmark to measure symptoms in multiple sclerosis patients. The study examined the

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[6] Harriët A. M. Van Diemen et al., *4-Aminopyridine in Patients with Multiple Sclerosis: Dosage and Serum Level Related to Efficacy and Safety*, 16 Clinical Neuropharmacology 195 (1993), J.A. 7037.

effect on eye function of intravenous and oral administration of 4-AP for up to 12 weeks.

My colleagues report that eye functioning was benefited, but ignore the report of side effects, including nausea and dizziness, at the "escalated" dosages needed to produce improvement in eye function. Van Diemen et al. at 200, 203.

D. The Polman study

Polman[7] describes an unblinded study of the treatment with 4-AP of thirty-one multiple sclerosis patients, some of whom had been involved in an earlier study. Twenty-three patients were treated with 4-AP for longer than six months. The new patients were given an upward titration dosing plan in accordance with the tolerability by the patient, up to a maximum dose (based on patient weight) over four to eight weeks. Polman measured efficacy based on subjective reports from the patients during clinic visits.

The Van Diemen and Polman references were relied on by the district court as teaching "stable dosing," but they involve stable dosing only after titration to the highest tolerable dose for each individual patient. Both Van Diemen and Polman describe using a titration scheme up to the maximum amount based on the patient's weight. Dist. Ct. Op. at *12–13. These references only teach stable dosing after the maximum tolerable dose has been determined for each patient, after upward titration. Goodman, *post*, also reports an "increasing benefit" for doses up to 50 mg/day if such doses can be tolerated. These sources all show

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[7] Chris H. Polman et al., *4-Aminopyridine in the Treatment of Patients with Multiple Sclerosis*, 51 Archives of Neurology 292 (1994), J.A. 6654.

the understood need to target higher doses to the extent they can be tolerated. *See* Goodman Poster (reporting increasing benefit as dosage was increased from 20mg to 50mg).[8]

Polman reported that "[i]mprovements in fatigue and ambulation were mentioned quite often by the patients." Polman et al. at 295. However, two patients in the Polman study experienced seizures and discontinued participation. *Id.* at 294–5. My colleagues cite Polman's report of "favorable response to the medication," Maj. Op. at 7 (citing *id.* at 293), but downplay Polman's conclusion that there was little quantifiable benefit of the therapy using the primary EDSS benchmark, my colleagues stating that the side effects were not troublesome, despite the reports of seizures. Maj. Op. at 8–9.

E. Additional studies reported by Bever

The Bever II reference reports additional studies, as follows:

> Two double-blind, placebo-controlled crossover trials of DAP have recently been completed. Carter and associates, using 3-week treatment periods and doses up to 80 mg/day, found subjective improvement in 48% of patients on DAP but only 24% on placebo. Although this difference was not statistically significant, treatment-related differences were found in sensitivity to thermal challenge.

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[8] Dist. Ct. Op. at *14 ("The Goodman Poster is a poster presented at the September 2002 annual meeting of the America Committee for Treatment and Research in Multiple Sclerosis, held in Baltimore, Maryland."), J.A. 6497–504.

Bever II at S120 (citing JL Carter et al., *A double-blind, placebo-controlled crossover trial of 3,4-diaminopyridine in the symptomatic treatment of multiple sclerosis*, 34 Annals of Neurology 272 (1993)).

These studies further illustrate the uncertain state of the art at that time, and the "differences" and "sensitivity" that led to abandonment of development of 4-AP. These studies did not lead to any proposed treatment of multiple sclerosis, despite the accumulating knowledge concerning 4-AP. My colleagues mention the toxic effects including seizures, encephalopathy, and hepatitis, but skip over their importance. However, it is apparent that others did not ignore their importance, for no proposed product, no proposed treatment, resulted from these studies.

F. The abandoned Elan studies

The manifestations and miseries of multiple sclerosis are powerful, and Elan Corporation entered the field to pursue the idea that sustained-release formulations of 4-AP might relieve the toxic effects and provide "therapeutically effective blood levels throughout a given treatment period." U.S. Patent No. 5,540,938 (the "Elan Patent") at col.2, l.15. In 1991 Elan filed the patent application leading to the Elan Patent, which described and claimed sustained-release formulations of 4-AP. Elan undertook major efforts to develop a treatment for multiple sclerosis using sustained-release formulations. Reports of these unsuccessful efforts were published.

Schwid[9] reports a failed clinical trial in 1994, described as a six-week, 161-patient placebo-controlled

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[9] Steven R. Schwid et al., *Quantitative assessment of sustained-release 4-aminopyridine for symptomatic* treatment *of multiple sclerosis*, 48 Neurology 817 (1997), J.A. 6681-84.

study of the administration of sustained-release 4-AP to multiple sclerosis patients. The results were measured using the EDSS benchmark, and included measures of walking disability including gait and speed. The conclusion was that there was no improvement over the placebo. Schwid et al. at 817.

Another Elan study of ten patients, also reported by Schwid, stated that nine of these patients showed an improvement in speed of walking. Schwid discussed that the mean serum level of 4-AP during the study 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." *Id.* at 819– 20. The study reported 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 [sustained-release] than placebo," while all patients with serum levels above 60 ng/ml demonstrated improvement in timed gait, grip strength, and five of six improving by their own subjective impression. *Id.* at 819–20. In contrast, the Acorda Patents are directed to a serum range of about 15-35 ng/ml, which Schwid described as unlikely to produce therapeutic effect.

The 17.5 mg dose used by Schwid was stated to be ineffective in a number of respects, including the EDSS benchmark. Schwid et al. at 817. Schwid suggested that further research should be conducted, but this does not convert Schwid's reported failures into a teaching of the path to success. My colleagues state that Schwid reported "promising" results, Maj. Op. at 55, but do not mention Schwid's conclusion that 4-AP was not effective at the doses that were necessary to limit toxicity, or the lack of improvement over placebo. Instead, my colleagues suggest that Schwid contributed to obviousness because Schwid suggested that,

since the EDSS benchmark had failed, it might be useful to look at "more sensitive, quantitative measures." Maj. Op. at 13–14 (quoting Schwid, J.A. 6681). Thus the panel majority concludes that these studies rendered obvious the Acorda success that had eluded Schwid.

Elan also sponsored studies at the University of Maryland, published by Bever et al.[10] Bever summarized that the "lower serum concentration range of 30 to 59 ng/ml may . . . be adequate for inducing improvement of some neurologic deficits," Bever I at 1058, quoted at Maj. Op. at 10; but the panel majority ignores that the study did not show any improvement on the EDSS benchmark or on an ambulation benchmark, *id.* at 1056–57, and treats the Bever report of "increased side effects," including a grand mal seizure, as a throwaway, Maj. Op. at 10.

These studies surely added to the body of knowledge, but they did not produce a usable product. Although these studies used Elan's sustained-release formulations, the effort was eventually abandoned. The record is consistent in showing that Elan, like the others who had studied 4-AP, had been unable to achieve an effective product free of toxicity and serious side effects.

G. The Hayes report of early Acorda studies

Hayes[11] reports Acorda's activity, starting in 1993 and investigating use of 4-AP for treatment of spinal

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[10] Christopher T. Bever, Jr. et al., *The effects of 4-aminopyridine in multiple sclerosis patients: Results of a randomized*, *placebo-controlled*, *double-blind*, *concentration-controlled*, *crossover trial*, 44 Neurology 1054 (1994) ("Bever I"), J.A. 6180.

[11] Keith C. Hayes et al., *Pharmacokinetic Studies of Single and Multiple Oral Doses of Fampridine-SR* (*Sustained-Release 4-*

cord injury. The first of these studies evaluated single doses of sustained-release 4-AP in fourteen patients with spinal cord injury, and the second study examined multiple doses of sustained-release 4-AP in sixteen patients with spinal cord injury. Dist. Ct. Op. at *15 (citing Hayes et al. at 186). The Hayes publication stated that all patients in both studies experienced at least one adverse event, such as dizziness, hypotension, or nausea. Hayes et al. at 188, 191.

H. The Solari review article

Solari[12] is a review of medical knowledge related to 4-AP, including reports on clinical trials conducted with MS patients. From the studies in its analysis, Solari tabulated that 54% of the multiple sclerosis patients taking 4-AP or diaminopyridine experienced improved motor functions, compared to 7% of placebo. Solari et al., J.A. 7204. Solari concluded that its "review of trials found there is not enough evidence about the safety of these drugs or whether benefits are certain." Solari et al., J.A. 7218.

II

The Acorda Studies

As outlined *supra*, Acorda began research with 4-AP in 1993 for treatment of spinal cord injury. As reported by Hayes, successful results were not obtained. Dr. Ron Cohen, the founder of Acorda, turned to study of multiple sclerosis. Dr. Cohen testified that he took on the "daunting challenges" of seeking an effective

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Aminopyridine) *in Patients With Chronic Spinal Cord Injury*, 26 Clinical Neuropharmacology 185 (2003), J.A. 6433.

[12] Alessandra Solari et al., *Aminopyridines for symptomatic treatment in multiple sclerosis* (*Review*), Cochrane Database of Systematic Reviews, Issue 4 (2002), J.A. 7204.

treatment for multiple sclerosis, with knowledge of the failures of Elan and others. Appellant's Br. at 13 (citing J.A. 596–97).

Acorda scientists conducted research over the ensuing six years, and published their results as experience accumulated and knowledge evolved. These publications are treated as prior art to the Acorda Patents.

A. Acorda's initial failures

Acorda's initial publications reported that the multiple sclerosis population receiving various experimental 4-AP treatments showed some improvement in walking speed and lower extremity muscle strength, but "did not show that any individual dosage had a statistically significant effect versus placebo." Appellant's Br. at 15; *see* Goodman Poster, n.9 *ante*. Dr. Goodman was the lead clinical investigator for Acorda, and the lead author for the published results of Acorda's MS-F201 study,[13] a randomized double-blind placebo-controlled study with the aim of "determin[ing] the safety and tolerability of escalating doses of a sustained-release ('SR') formulation given orally to patients with MS." Goodman I at S116.

Goodman I states that the MS-F201 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)." *Id.* at S117. It further states that "[d]ose response curves showed increasing benefit in both measures in

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[13] Andrew Goodman et. al., *Placebo-Controlled Double-blinded Dose Ranging Study of Fampridine-SR in Multiple Sclerosis*, 8 Multiple Sclerosis S116 (P308) (July 2002), ("Goodman I") J.A. 6370.

the 20 to 50 mg/day range." *Id.* However, two participants withdrew due to seizures. *Id.*

The Goodman Poster reported that the MS-F201 study demonstrated "statistically significant improvements in the timed 25-foot walk and manual muscle test relative to placebo." Dist. Ct. Op. at *15. However, the Poster also stated that a greater improvement in fatigue was reported by the placebo group as compared to the 4-AP treated group, and referred to the withdrawal of two subjects due to seizure. Goodman Poster, J.A. 6502. Dr. Goodman testified at trial that "[a]ll of the prespecified analyses failed except for the lower extremity manual muscle test." J.A. 604 (289:24–5). He stated that the result of the timed walk "was not at all significant," and was consistent with the failed Elan study. J.A. 605 (290:5).

The district court found that the Goodman Poster established 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." Dist. Ct. Op. at *33. Acorda states that "the district court's conception that the Goodman Poster teaches anything about a 10 mg BID dose of 4-AP as the sole individual dose of an MS treatment protocol—as opposed to merely the starting point of an escalating dosing scheme—is impermissible hindsight." Appellant's Br. at 38. Acorda is correct that the Goodman Poster does not suggest this low-dose formulation with a reasonable expectation of success, but reports increasing benefit as dosage was increased from 20 to 50 mg.

Acorda correctly states that the Elan work and these initial Acorda studies show, if anything, that 4-AP treatment requires upward titration to determine the maximum tolerable dose for individual patients

since efficacy can only be achieved at higher doses, and that these studies do not provide any reason to believe that a low dose would be effective. Goodman I reported an "increasing benefit in both measures in the 20-50 mg/day range," referring to mobility and lower extremity strength. Goodman I at S117.

In 2003, Acorda conducted a 206-patient clinical study, designated MS-F202. The study employed upward titration to successively higher doses, starting at dosages of 10 mg of sustained-release 4-AP twice-daily. The highest tolerable dose was then continued for 12 weeks. It was concluded that no treatment group showed improvement over placebo, over the 12-week testing period. Dist. Ct. Op. at *9.

The low dose protocol developed by Acorda is not suggested in the prior art. Although the goal was a stable dose without individual titration, no study, no reference reported successful results using the low dose of the Acorda Patents, or even suggested that it should be tried. The panel majority's contrary theory is devoid of support.

B. Acorda's analytical breakthrough

Acorda analyzed the MS-F202 results, focusing on "patients in the study who, after treatment, showed a 'meaningful difference' from their before-treatment baseline—*i.e.* the 'responders,'" and learned that the therapeutic effect of 4-AP did not increase with increase in dosage, as prior reports and Acorda's own research had suggested. Appellant's Br. at 19. Dr. Cohen testified that they "were extremely surprised" because "[e]verything that we had come to expect throughout the program told us that we should be seeing more and more efficacy the higher the dose went as long as the patients were tolerating it and that

turned out not to be the case." J.A. 614 (299:5–9). This contradicted the teachings of all of the earlier studies. Only the courts find it obvious.

Acorda then conducted additional clinical studies at the lower dosages, and established that a twice-daily sustained-release 10 mg dose produced improvement in walking gait and speed, while avoiding the toxicity and seizures of higher dosages. Acorda filed a provisional patent application on April 9, 2004, directed to this treatment. Acorda continued its studies, and after a total of twelve years of investigation and development, Acorda in 2010 obtained FDA approval for a product for improving the walking impairment in multiple sclerosis patients. This product has the brand name Ampyra®. The Acorda Patents are directed to and limited to the twice-daily administration of 10 mg doses of sustained-release 4-AP formulation.

The district court, affirmed by my colleagues, held the Acorda Patents invalid on the ground of obviousness. The district court ruled that the evidence of long-felt need, failure of others, unexpected results, and commercial success are irrelevant because the Elan Patent was a "blocking" patent. However, the Elan Patent did not block research on 4-AP, did not block other possible treatments for multiple sclerosis, and did not affect the Defendants' development and copying and Hatch-Waxman challenge to the Elan and Acorda patents. The court's theory of "blocking" is unrelated to whether the Acorda product meets a long-felt need in treating multiple sclerosis, for the Elan and Acorda patents do not block the Defendants from developing a competitive treatment for multiple sclerosis. The patents that support Acorda's eventual success do not block others from using and learning from Acorda's teachings, experimenting with and

comparing with Acorda's product, and engaging in competitive activity.

III
The District Court's Analysis

The Defendants conceded infringement, and the district court found the Acorda Patents invalid on the ground of obviousness. The district court determined that four claim elements were common to the Acorda Patents, then found that each of these elements is present in a separate reference, and held that a person of ordinary skill in this field would obviously have selected and combined these elements to produce the Acorda product and method.

The district court did not find any motivation or suggestion in the prior art as to which elements to select and combine, and did not find any teaching or suggestion that such selection and combination would be likely to succeed in treating the walking impairment of multiple sclerosis. Acorda attributes the district court's rulings to "hindsight bias" and incorrect statements of law by the Defendants. Indeed, without the hindsight knowledge of Acorda's success, there is no teaching or suggestion of this selection and combination or its likelihood of success.

A. The selected claim elements

The district court selected four aspects of the Acorda claims, as follows: (1) the use of 4-AP to improve walking in multiple sclerosis patients; (2) the use of a 10 mg twice-daily sustained release dose; (3) the use of stable dosing without upward titration; and (4) the specific pharmacokinetic parameters achieved. The court concluded that "a POSA would have been motivated to combine these limitations with a reasonable expectation of success." Dist. Ct. Op. at *29.

However, the question is not whether these four elements, if combined, would produce a successful treatment. The question is whether the prior art contains a suggestion or motivation to select these four elements from the decades of inconclusive prior art, with a reasonable expectation that the selection would eliminate the failures of the prior art. *See*, *e.g.*, *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litig.*, 676 F.3d 1063, 1068–69 (Fed. Cir. 2012) ("a party seeking to invalidate a patent as obvious must 'demonstrate "by clear and convincing evidence 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."" (quoting *Procter & Gamble Co. v. Teva Pharms. USA*, *Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009))); *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) (prior art does not provide a reasonable expectation of success where the art may suggest "vary[ing] all parameters or try[ing] each of numerous possible choices until one possibly arrived at a successful result, where the prior art gives either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful." (quoting *In re O'Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). The years of studies and failures weigh heavily against the simplistic post hoc predictability accepted by the court.

The district court analyzed the purported obviousness of each of the four limitations, as follows.

1. Improvement in walking

The district court found that several references showed improved walking upon treatment with 4-AP. The court framed the question as whether a POSA

would have "a reasonable expectation that 4-AP could be successfully used as claimed to treat (*i.e.*, achieve therapeutically-effective blood levels in) even a single patient." Dist. Ct. Op. at *30. The court referred to Schwid's analysis of the early Acorda studies as showing "a statistically significant improvement in . . . timed gait, which was found to be improved in nine out of 10 patients, in comparison to the placebo group." *Id.*

However, the early Acorda studies all stated concern about toxicity, particularly seizures, at the dosages that these studies showed were needed to obtain relief. No witness suggested that these early studies taught or suggested that a low dosage formulation would be effective.

2. The dosage of 10 mg twice daily

The district court concluded that this dosage was an obvious choice, because the prior art evaluated doses ranging from 10 mg to 80 mg. Dist. Ct. Op. at *32. However, the prior art contains no suggestion, indeed no hint, that a 10 mg twice-daily sustained-release formulation would be effective. All of the early references demonstrated the need for upward titration, showing that higher doses are needed for efficacy, with individual titration to determine the highest tolerable dose before seizures occurred. The district court cited the Goodman Poster as showing that toxicity increased at higher dosages, and as providing "[e]vidence of dose-response in [the] 20-40 mg/day range." Dist. Ct. Op. at *32. However, the studies reported by Goodman did not provide a safe and efficacious product, but depended on individual titration to establish individual dosages at the highest tolerable level.

The district court held that it was obvious to use the 10 mg dose, despite the general showing of ineffectiveness of the 10 mg dose. Dist. Ct. Op. at *33. It is not disputed that the general teaching was that doses higher than 10 mg were needed for therapeutic effect. It cannot reasonably be viewed as obvious that a dosage that was described in the prior art as ineffective, is in fact the optimum dosage.

3. Stable dosing without upward titration

The district court found that the prior art, particularly the Van Diemen and Polman references, taught the use of uniform dosing of 4-AP, and "included reports of safe and effective long-term use of stable dosing of immediate-release 4-AP." Dist. Ct. Op. at *34. The district court further found that the prior art's "consistent use of titration . . . did not undermine the other evidence in the prior art that supports finding that a POSA would have had a reasonable expectation of success with stable dosing." *Id*. Only hindsight can construct the Acorda formulation from these inapt teachings, for the references cited by the district court require upward titration to select the highest tolerable dose, for low stable doses were ineffective.

The panel majority, seeking to fill this gap, asserts that "[t]he prior art is not limited to titrated dosing," Maj. Op. at 34, citing Polman and Schwid. However, Polman involved titration, and reported that therapeutic doses required in excess of 40 mg for minimal quantifiable benefit. *See* Polman et al. at 295 (stating that the reported improvements generally did not result in significant changes to the EDSS benchmark). In addition, Schwid suggested the need for a far higher dose, only maintained stable dosing for a week, and did not report meaningful success in treating multiple sclerosis. Schwid et al. at 817.

4. Pharmacokinetic limitations

For the fourth limitation, the district court found that the claimed pharmacokinetic serum levels were disclosed by Hayes, for "[i]t is undisputed that the Hayes researchers used the Ampyra® formulation in their study." Dist. Ct. Op. at *35. The district court considered Acorda's argument that "there is nothing in the prior art identifying the pharmacokinetic values recited in the claims as being effective to improve walking or increase walking speed in MS patients," *id.*, and found that "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." Dist. Ct. Op. at *36.

The Defendants argue that even if the serum level in the Acorda Patents is not obvious based on the Hayes reference, the claimed range is inherent in the dosage of 4-AP, citing *Santarus*, *Inc. v. Par Pharm.*, *Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012), where the court held that reciting the blood serum concentration resulting from a dosage form did not impart patentability to known dosage forms. Acorda responds that the prior art did not teach or suggest that any specific blood serum levels would improve walking in multiple sclerosis patients. No such teaching or suggestion appears anywhere in the record. Hayes does not relate its serum analysis to efficacy in improving gait or walking speed in persons afflicted with multiple sclerosis.

The district court referred to Acorda's statement at trial, that "[i]t was known in the art that a sustained release formulation of 10 megs BID could achieve" the claimed pharmacokinetic values. Dist.

Ct. Op. at *35 n.39 (citing J.A. 1108–1109). The district court found that there was a reasonable expectation of success with regard to the pharmacokinetic parameters because these parameters are inherent in the claimed dosing. *Id.* The court did not find, and the prior art does not establish, that this pharmacokinetic range was known to have a beneficial effect on walking speed and gait in persons afflicted with multiple sclerosis.

B. The combination of elements

The district court found a reasonable expectation of success on combination of the four claim elements, stating that "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," Dist. Ct. Op. at *33. The court concluded that:

> 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.

Dist. Ct. Op. at *40.

Acorda is correct that there was no suggestion in the prior art that the claimed combination should be tried, and there is no hint of a reasonable expectation of success. Acorda points to the decades of failure of others to develop a safe and effective treatment for multiple sclerosis using 4-AP, despite its known toxicity. The district court's selection of separate limitations from separate sources, and retrospectively fitting them into the Acorda template, is achieved only with the hindsight knowledge of Acorda's eventual

success. *See Sanofi-Synthelabo v. Apotex, Inc.*, 550 F.3d 1075, 1086 (Fed. Cir. 2008) ("The determination of obviousness is made with respect to the subject matter as a whole, not separate pieces of the claim."). Here, only the Acorda Patents teach the combination that successfully treats this multiple sclerosis impairment while avoiding toxicity and seizures.

Acorda's path to successfully harness the neurological benefits of 4-AP eluded the many scientists studying multiple sclerosis. Although the district court acknowledged the known adverse effects of 4-AP including seizures, Dist. Ct. Op. at *41 (stating that "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"), nonetheless the court found that a person of ordinary skill would have had a reasonable expectation of success with the Acorda product. The recognized need for a stable, non-toxic dosage protocol does not render the solution obvious if it is eventually discovered. The record does not show any teaching or suggestion of success of the formulation in the Acorda Patents.

Nor does the record support a finding of "obvious to try." Such a finding requires that a person of ordinary skill would not only have selected these specific elements from various discarded experiments, but also "would have had a reasonable expectation of success in doing so." *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). It is clear that the prior art does not provide a reasonable expectation of success of the Acorda Patents' specific dosage and protocol.

IV
The Objective Indicia of Unobviousness

The objective indicia "may often be the most probative and cogent evidence in the record . . . . It is to be considered as part of all the evidence, not just when the decisionmaker remains in doubt after reviewing the art." *Stratoflex*, *Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983). The district court, affirmed by the panel majority, err in discounting the undisputed evidence of commercial success, long-felt need, failure of others, unexpected results, and copying.

The district court discussed the objective indicia, and concluded that they did not "outweigh" the conclusion of obviousness. The district court found that Ampyra® could be considered a commercial success "[g]iven the strength of Ampyra®'s sales, and the absence of any evidence that its sales are disappointing given its limited indication and patient population." Dist. Ct. Op. at *38. However, the court concluded that this commercial success did not weigh heavily because "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." *Id.*

Commercial success is measured against the products available for the same purpose, not against infringing copies of the patented product. Defendants do not contend that they are precluded from providing or developing other treatments for multiple sclerosis. The Acorda product met a long-felt need, for which the failure of others, despite decades of experimenting with the neurological properties of 4-AP, is evidence of the unobviousness of the Acorda achievement. Such evidence is an important aid to a court that is

attempting to divine whether the patentee's discovery was obvious in accordance with law.

Concerning failure of others, the panel majority states that Elan's failure "is not particularly relevant to the expectation of success." Maj. Op. at 40–41. This is a peculiar conclusion, for Elan had undertaken an immense investment, including clinical trials, in the hope that its extended-release concept would solve the problems encountered by others. Elan eventually gave up. Nonetheless, my colleagues find that Acorda's success was obvious to them.

The district court and my colleagues also misapply the concept of "blocking patent," and hold that because a patent provides the right to exclude infringers, the indicia of commercial success, long-felt need, failure of others, and copying are diminished. However, as the Pharmaceutical Research and Manufacturers of America, as amicus curiae, reminds us, "a prior patent would not have categorically precluded others from further developing the technology," pointing to the statutory safe harbor of § 271(e)(1), the knowledge provided in the patents, and the right to conduct research on patented subject matter. Br. of Amicus Curiae at 4.

The objective indicia of unobviousness are measured against the state of the science and in the commercial context. Here the unexpected success and its human benefits are not disputed. The district court was advised that the Patent Trial and Appeal Board sustained the validity of the Acorda Patents in inter partes review, at *Coalition for Affordable Drugs* (*ADROCA*), *LLC v. Acorda Therapeutics*, *Inc.*, 2017 WL 950736 (P.T.A.B. Mar. 9, 2017). Although the majority reports this event, as did the district court, its

consequences are not explored, including issues of privity, estoppel, and finality.

CONCLUSION

Obviousness of the Acorda Patents was not established by clear and convincing evidence. The prior art did not provide a suggestion to select the specific elements and limitations of the Acorda formulation, and did not suggest that such selection and combination would have a reasonable expectation of success in relieving the walking impairment of multiple sclerosis. From my colleagues' contrary holding, I respectfully dissent

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APPENDIX B

IN THE UNITED STATES DISTRICT COURT FOR THE DISTRICT OF DELAWARE

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

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MEMORANDUM OPINION

March 31, 2017
Wilmington, Delaware

/s/ Leonard P. Stark

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 record in this case and the applicable law, the Court concludes that: (1) Defendants have stipulated that their proposed

[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)

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)

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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.

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 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

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

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 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)

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[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.

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

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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)

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-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 7374)

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-Ami-

nopyridine 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 1025 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.*)

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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)

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)

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

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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)

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 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

[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)

> 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 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.* IN 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

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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)

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 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,

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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)

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 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 sus-

tained-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.*)

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)

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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)

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)

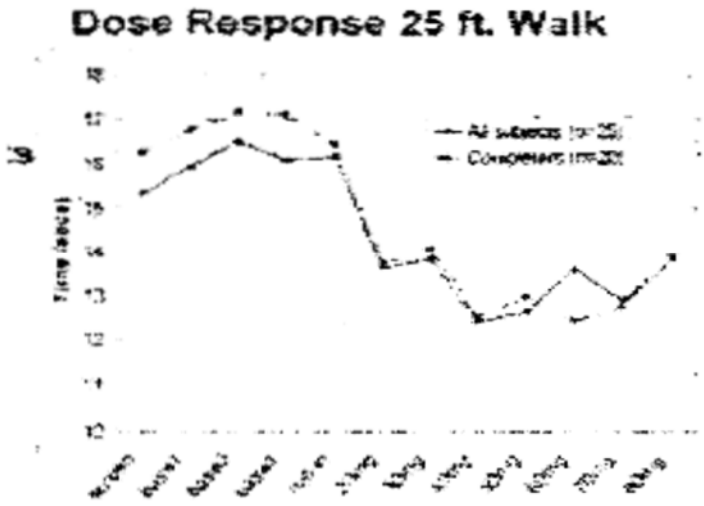
123. Like Goodman I, the Goodman Poster reports results from the MS-F201 study. (Goodman Tr. at 479-80)

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]

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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

h. Solxari

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

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tables is identical to a table disclosed in Hayes. (Kibbe Tr. 223:25-224:15)

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 in-

surance 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 38–890)

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 in 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]

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[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

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).

A defendant's burden to prove obviousness is "especially difficult when the prior art [on which the

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and defendant's definitions and court's analysis was same under either definition).

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 Intl 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

[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)

previously construed the term "therapeutically effective blood levels" as meaning "blood levels sufficient to produce a therapeutic effect." (D.I. 195 at 6)

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

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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)

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 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 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

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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)

[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)

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).

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

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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

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

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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)

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,

34345, 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 nontoxic. (*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 sus-

tained-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 infor-

[21] Dr. Peroutka further noted that, although the Uges study size was small, a POSA would be encouraged by the consistency

mation 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.

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

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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)

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

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 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 for-

mulating 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)

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.

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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)

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 [']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

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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.

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 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]

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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

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 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*

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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.

[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)

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 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, predefined 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)

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 Good-

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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)

man, 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 con-

sistent 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]

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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 4647) 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.

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 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 (IA] 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

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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)

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]

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

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[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)

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 reasona-

ble 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

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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.

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 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*

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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.*)

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 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."))

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.

[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.")

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 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 non-obviousness "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]

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 perform-

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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 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.

ing 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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[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

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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)

(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 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.

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

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 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 109899. 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 51315) 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.

APPENDIX C

Note: This disposition is nonprecedential.

UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

ACORDA THERAPEUTICS, INC.,
Plaintiff-Appellant

ALKERMES PHARMA IRELAND LIMITED,
Plaintiff-Appellee

v.

ROXANE LABORATORIES, INC., MYLAN PHARMACEUTICALS INC., TEVA PHARMACEUTICALS USA, INC.,
Defendants-Cross-Appellants

2017-2078, 2017-2134

Appeals from the United States District Court for the District of Delaware in Nos. 1:14-cv-00882-LPS, 1:14-cv00922-LPS, 1:14-cv-00935-LPS, 1:14-cv-00941-LPS, Chief Judge Leonard P. Stark.

ON PETITION FOR REHEARING EN BANC

Before PROST, *Chief Judge*, NEWMAN, DYK, MOORE, O'MALLEY, REYNA, WALLACH, TARANTO, CHEN, HUGHES, and STOLL, *Circuit Judges*.

PER CURIAM.

O R D E R

Appellant Acorda Therapeutics, Inc. filed a petition for rehearing en banc. A response to the petition was invited by the court and filed by Appellee Alkermes Pharma Ireland Limited and Cross-Appellants Mylan Pharmaceuticals Inc., Roxane Laboratories, Inc. and Teva Pharmaceuticals USA, Inc. The petition was first referred as a petition for rehearing to the panel that heard the appeal, and thereafter the petition for rehearing en banc was referred to the circuit judges who are in regular active service.

Upon consideration thereof,

IT IS ORDERED THAT:

The petition for panel rehearing is denied.

The petition for rehearing en banc is denied.

The mandate of the court will issue on January 11, 2019.

FOR THE COURT

January 4, 2019
Date

/s/ Peter R. Marksteiner
Peter R. Marksteiner
Clerk of Court

APPENDIX D

CONSTITUTIONAL AND STATUTORY PROVISIONS INVOLVED

U.S. Const., art. I, § 8, cl. 8.

The Congress shall have power, * * *

To promote the Progress of Science and useful Arts, by securing for limited Times to Authors and Inventors the exclusive Right to their respective Writings and Discoveries[.]

* * *

35 U.S.C. § 101. Inventions patentable

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

35 U.S.C. § 102. Conditions for patentability; novelty

(a) NOVELTY; PRIOR ART.—A person shall be entitled to a patent unless—

(1) the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention; or

(2) the claimed invention was described in a patent issued under section 151, or in an application for patent published or deemed published under section 122(b), in which the patent or application, as the case may be, names another inventor and was effectively filed before the effective filing date of the claimed invention.

(b) EXCEPTIONS.—

(1) DISCLOSURES MADE 1 YEAR OR LESS BEFORE THE EFFECTIVE FILING DATE OF THE CLAIMED INVENTION.—A disclosure made 1 year or less before the effective filing date of a claimed invention shall not be prior art to the claimed invention under subsection (a)(1) if—

(A) the disclosure was made by the inventor or joint inventor or by another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(B) the subject matter disclosed had, before such disclosure, been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor.

(2) DISCLOSURES APPEARING IN APPLICATIONS AND PATENTS.—A disclosure shall not be prior art to a claimed invention under subsection (a)(2) if—

(A) the subject matter disclosed was obtained directly or indirectly from the inventor or a joint inventor;

(B) the subject matter disclosed had, before such subject matter was effectively filed under subsection (a)(2), been publicly disclosed by the inventor or a joint inventor or another who obtained the subject matter disclosed directly or indirectly from the inventor or a joint inventor; or

(C) the subject matter disclosed and the claimed invention, not later than the effective filing date of the claimed invention, were owned by the same person or subject to an obligation of assignment to the same person.

(c) COMMON OWNERSHIP UNDER JOINT RESEARCH AGREEMENTS.—Subject matter disclosed and a claimed invention shall be deemed to have been owned by the same person or subject to an obligation of assignment to the same person in applying the provisions of subsection (b)(2)(C) if—

(1) the subject matter disclosed was developed and the claimed invention was made by, or on behalf of, 1 or more parties to a joint research agreement that was in effect on or before the effective filing date of the claimed invention;

(2) the claimed invention was made as a result of activities undertaken within the scope of the joint research agreement; and

(3) the application for patent for the claimed invention discloses or is amended to disclose the names of the parties to the joint research agreement.

(d) PATENTS AND PUBLISHED APPLICATIONS EFFECTIVE AS PRIOR ART.—For purposes of determining whether a patent or application for patent is prior art to a claimed invention under subsection (a)(2), such patent or application shall be considered to have been effectively filed, with respect to any subject matter described in the patent or application—

(1) if paragraph (2) does not apply, as of the actual filing date of the patent or the application for patent; or

(2) if the patent or application for patent is entitled to claim a right of priority under section 119, 365(a), 365(b), 386(a), or 386(b), or to claim the benefit of an earlier filing date under section 120, 121, 365(c), or 386(c), based upon 1 or more prior filed applications for patent, as of the filing date of the earliest such application that describes the subject matter.

35 U.S.C. § 103. Conditions for patentability; non-obvious subject matter

A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, 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. Patentability shall not be negated by the manner in which the invention was made.

35 U.S.C. § 282. Presumption of validity; defenses

(a) IN GENERAL.—A patent shall be presumed valid. Each claim of a patent (whether in independent, dependent, or multiple dependent form) shall be presumed valid independently of the validity of other claims; dependent or multiple dependent claims shall be presumed valid even though dependent upon an invalid claim. The burden of establishing invalidity of a patent or any claim thereof shall rest on the party asserting such invalidity.

(b) DEFENSES.—The following shall be defenses in any action involving the validity or infringement of a patent and shall be pleaded:

(1) Noninfringement, absence of liability for infringement or unenforceability.

(2) Invalidity of the patent or any claim in suit on any ground specified in part II as a condition for patentability.

(3) Invalidity of the patent or any claim in suit for failure to comply with—

(A) any requirement of section 112, except that the failure to disclose the best mode shall not be a basis on which any claim of a patent may be canceled or held invalid or otherwise unenforceable; or

(B) any requirement of section 251.

(4) Any other fact or act made a defense by this title.

(c) NOTICE OF ACTIONS; ACTIONS DURING EXTENSION OF PATENT TERM.—In an action involving the validity

or infringement of a patent the party asserting invalidity or noninfringement shall give notice in the pleadings or otherwise in writing to the adverse party at least thirty days before the trial, of the country, number, date, and name of the patentee of any patent, the title, date, and page numbers of any publication to be relied upon as anticipation of the patent in suit or, except in actions in the United States Court of Federal Claims, as showing the state of the art, and the name and address of any person who may be relied upon as the prior inventor or as having prior knowledge of or as having previously used or offered for sale the invention of the patent in suit. In the absence of such notice proof of the said matters may not be made at the trial except on such terms as the court requires. Invalidity of the extension of a patent term or any portion thereof under section 154(b) or 156 because of the material failure—

(1) by the applicant for the extension, or

(2) by the Director,

to comply with the requirements of such section shall be a defense in any action involving the infringement of a patent during the period of the extension of its term and shall be pleaded. A due diligence determination under section 156(d)(2) is not subject to review in such an action.