2017-2078, 2017-2134

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.

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

PETITION FOR REHEARING EN BANC

Jane G. Wasman
Anthony Michael
ACORDA THERAPEUTICS, INC.
420 Saw Mill River Road
Ardsley, NY 10502
(914) 347-4300
jwasman@acorda.com
amichael@acorda.com

Bruce M. Wexler
Attorney of Record
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000
brucewexler@paulhastings.com

Counsel for Appellant Acorda Therapeutics, Inc.

Additional Counsel:

Stephen B. Kinnaird
Igor V. Timofeyev
PAUL HASTINGS LLP
875 15th Street, N.W.
Washington, D.C. 20005
(202) 551-1700
stephenkinnaird@paulhastings.com
igortimofeyev@paulhastings.com

CERTIFICATE OF INTEREST

Pursuant to Federal Circuit Rule 47.4, counsel of record for Appellant Acorda Therapeutics, Inc. certifies the following:

1. Full name of the party represented by me:	2. Name of the real party in interest represented by me:	3. Parent corporations and publicly held companies that own 10% or more of the stock in the party represented by me:
Acorda Therapeutics, Inc.	Acorda Therapeutics, Inc.	BlackRock, Inc.

4. The names of all law firms and the partners or associates that appeared for the party represented by me in the trial court or are expected to appear in this Court (and who have not or will not enter an appearance in this case) are:

Arnold & Porter Kaye Scholer LLP:
Aaron Stiefel, Daniel DiNapoli, Jeffrey Martin, Soumitra Deka, and Sylvia Becker

Morris, Nichols, Arsht & Tunnell LLP:
Jack B. Blumenfeld, Maryellen Noreika,* and Jeremy A. Tigan

5. The title and number of any case known to counsel to be pending in this or any other court or agency that will directly affect or be directly affected by this Court's decision in the pending appeal. *See* Fed. Cir. R. 47.4(a)(5) and 47.5(b).

Acorda Therapeutics, Inc. v. Micro Labs. Ltd.,
No. 17-CIV-03724 (filed on May 24, 2017).

*No longer with the firm.

Dated: October 24, 2018

/s/Bruce M. Wexler
Bruce M. Wexler
Counsel for Appellant
Acorda Therapeutics, Inc.

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STATEMENT OF COUNSEL

Based on my professional judgment, I believe (1) the panel decision is contrary to the following decisions of the Supreme Court and this Court: *Graham v. John Deere Co.*, 383 U.S. 1 (1966); *In re Cyclobenzaprine*, 676 F.3d 1063 (Fed. Cir. 2012); and *Merck Sharp & Dohme Corp. v. Hospira, Inc.*, 874 F.3d 724 (Fed. Cir. 2017) ("*Merck II*"); and (2) this appeal requires an answer to a precedent-setting question of exceptional importance:

> Whether the "blocking-patent" doctrine of *Merck & Co. v. Teva Pharmaceuticals USA, Inc.*, 395 F.3d 1364 (Fed. Cir. 2005) ("*Merck I*"), which weakens the inference of non-obviousness from a pharmaceutical drug's commercial success based on a preexisting patent and prior FDA regulatory exclusivity, may properly be expanded to negate other objective indicia of non-obviousness, even where such indicia are found to exist as a matter of fact?

/s/ Bruce M. Wexler

Counsel for Appellant Acorda Therapeutics, Inc. ("Acorda")

INTRODUCTION

Acorda invented the first safe and effective treatment to improve walking in multiple sclerosis ("MS") patients, using the century-old toxic compound 4-aminopyridine ("4-AP") that had never before been approved for pharmaceutical use. Breaking from the prior art, which taught escalating 4-AP to the highest tolerable dose, Acorda discovered a new protocol consisting of a single low, fixed 10 mg/twice-daily dose of sustained-release 4-AP to improve walking in MS

patients. The district court found that Acorda's drug Ampyra®, which had sales of $1.7 billion through 2015, enjoyed commercial success attributable to the patented invention. The district court also found that Acorda's invention satisfied a "long-felt, unmet need for a method of treating walking in MS patients," and that competitors had tried and failed to meet that need. While deeming the objective evidence of non-obviousness "significant" and "convincing," Appx87-88, the district court discounted its fact findings under a misapplication of the *Merck I* "blocking-patent" doctrine.

A divided panel of this Court affirmed in an opinion that radically expands the controversial *Merck I* "blocking-patent" doctrine in conflict with this Court's later decision in *Merck II*. As originally articulated in *Merck I*, the doctrine tempers an inference of non-obviousness from a drug's *commercial success* where a preexisting patent, *together with an existing FDA regulatory exclusivity*, precludes others from entering the market. *Merck I*, 395 F.3d at 1376-77. *Merck II* clarified that a dominating compound patent does not, without more, diminish commercial success. 874 F.3d at 730-31. Here, the panel majority—over Judge Newman's dissent—extended this doctrine (in a case not involving prior regulatory exclusivity) beyond commercial success to negate other, powerful objective indicia of non-obviousness: long-felt need and the failure of others. The majority unmoored the "blocking-patent" doctrine from its premise—that an

inference of non-obviousness from commercial success is weak where the marketplace is foreclosed to others. And because the majority affirmed even where the district court found convincing objective evidence of non-obviousness, the new doctrine would extend to any improvement patent so long as an infringer can point to some earlier dominating patent. As Judge Newman warned in dissent, "[t]he consequences of this new legal theory are large," and would significantly discourage pharmaceutical innovation. Dissenting Op. 1-2.

STATEMENT OF THE CASE

1. MS is a complex degenerative neurological disease that impedes muscle coordination and motoring functions. Its symptoms vary greatly from patient to patient and even within individual patients, making discovery of treatments highly unpredictable.

The active ingredient in Acorda's invention, 4-AP, was discovered in 1902 and known to be toxic, causing seizures and other serious adverse effects. The source of 4-AP's toxicity—the blocking of potassium flow in nerve impulse transmissions—also held out the therapeutic promise of improving neural function. Because the mechanism was the same, researchers believed that therapeutic effect occurred near the toxicity threshold. Accordingly, as the district court found, there was "consistent use of titration" in the 4-AP art, Appx75, with studies starting at a

low dosage with no anticipated effect, and escalating incrementally to the highest dose tolerable by a patient.

Elan Corporation PLC ("Elan") pioneered a sustained-release formulation of 4-AP, and in 1991 obtained U.S. Patent No. 5,540,938 ("the Elan Patent"). The patent claimed sustained-release compositions of a family of compounds, including 4-AP, and their administration to treat neurological diseases, including MS. The Elan Patent did not claim a specific dosage or walking therapy, and taught upward titration to a maximum tolerable dose.

In 1997, Elan conducted the largest, most rigorously controlled clinical study administering 4-AP to MS patients. The study failed to demonstrate therapeutic effect and, according to its co-author, created "a huge amount of skepticism and doubt" about 4-AP's efficacy. Appx829. Following this failure, Elan abandoned independent 4-AP development.

2. Acorda was founded in 1993 as a small company willing to take risk to develop therapies for spinal cord injury ("SCI") and neurological disease. Acorda focused on 4-AP, obtaining an exclusive license to the Elan Patent in 1997 for SCI treatments, and expanding it to MS after Elan's large study failed. There was no evidence of any other company's interest in the Elan Patent.

Acorda's first 4-AP MS trial, testing eye muscle movement, failed in 1999. Acorda's second clinical study, using upward titration to evaluate the safety and

tolerability of escalating doses, failed in 2000 as to all but one secondary endpoint. Acorda's reports of that study (the Goodman references) indicated a statistically significant effect on walking only over the entire 20-80 mg escalating dose range, and did not express efficacy for any single dose level (and indeed the study lacked power to do so).

Acorda persisted, and in 2003 carried out a large (non-prior art) clinical study, using titration, to test various 4-AP doses. The study initially failed to show improved walking. Acorda hypothesized, however, that MS's variable symptoms might mask 4-AP's positive effects. Applying a novel "responder" analysis to the study data, Acorda discovered that 4-AP's therapeutic effect did not increase with dosage levels, and a stable 10 mg/twice-daily dose could safely improve walking in MS patients.

Acorda thereafter filed for patents narrowly claiming a method of increasing walking speed in MS patients by administering a 10 mg/twice-daily dosage of sustained-release 4-AP for at least two weeks, with no titration, and achieving specific blood-serum levels. After granting priority review, the FDA in 2010 approved Ampyra®—the first FDA-approved drug to treat walking in MS patients and the first using 4-AP as the active ingredient. Ampyra® achieved considerable commercial success, with sales of $1.7 billion through 2015, and increasing thereafter, and high rates of patient satisfaction. Appx34-35; Appx82.

3. Appellees sought FDA approval for generic versions of Ampyra®. Acorda and Alkermes Pharma Ireland Limited (the Elan Patent owner) filed suit, and Appellees stipulated to infringement.

After a three-day bench trial, the district court ruled that the Elan Patent was not obvious, but the Acorda Patents were. The court acknowledged that the prior art "may have generally suggested that 4-AP would be more effective in higher doses"; taught "consistent use of titration" because of safety concerns; and "did not specifically support stable dosing," but nevertheless found the claimed 10 mg/twice-daily dosing regimen obvious to try. Appx71-73; Appx75-76.

With regard to objective indicia of non-obviousness, the court expressly found that Ampyra® enjoyed commercial success attributable to Acorda's invention. Appx79-83. The court also found that Ampyra® satisfied a "long-felt, unmet need for a method of treating walking in MS patients," and that Elan and Sanofi-Aventis had tried and failed to develop a walking therapy. Appx85-87. Nonetheless, the district court discounted this "convincing evidence" because the Elan Patent "blocked" the field of Acorda's invention. Appx79-87.

4. On appeal, a divided panel affirmed. Even though Goodman did not establish the efficacy of any individual dosage, the panel majority found that Goodman narrowed safe dosage options to 25 mg/twice daily and below, and thus "'10 mg/twice daily would have been an attractive starting point for a person of

skill in the art'" and obvious to try. Op. 37 (alterations and citation omitted). Despite no support in the prior art for stable dosing of the required minimum two weeks without titration, the majority determined that such an artisan would abandon titration for this single low dose. Op. 34-35.

Turning to objective indicia, the majority acknowledged that Acorda established "commercial success, failure of others, and long-felt but unmet need," but affirmed the district court's judgment. Op. 50. It conceded that, under this Court's precedents, "the mere existence … of blocking patents does not, without more, 'necessarily detract from evidence of commercial success of a product or process.'" Op. 48 (quoting *Merck II*, 874 F.3d at 731). The majority nevertheless held that since other entities "would not have access to" Elan's 4-AP formulation, and "securing freedom from blocking patents in advance is likely important to pharmaceutical research investments," the "blocking effect of the Elan patent" negated the evidence of commercial success, long-felt need, *and* failure of others. Op. 51-56.

5. Judge Newman dissented. She differed sharply with the majority on the prior art, observing that it "shows … 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." Dissenting Op. 14. She found "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." *Id.* at 13. Given the decades of failure by other 4-AP researchers, Judge Newman concluded 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," despite a "recognized need for a stable, non-toxic dosage protocol." *Id.* at 21.

Judge Newman also highlighted the majority's "flawed reasoning," *id.* at 2, with respect to objective indicia of non-obviousness. "[T]he Elan Patent did not block research on 4-AP, did not block other possible treatments for multiple sclerosis," and so "d[id] not block the [Appellees] from developing a competitive treatment for multiple sclerosis." *Id.* at 15. The dissent faulted the majority's failure to mention that Elan—the "blocking" patent owner—abandoned 4-AP development "after years of failures," *id.* at 3, and disputed the majority's "peculiar conclusion" that "Elan's failure 'is not particularly relevant to the expectation of success.'" *Id.* at 23 (quoting Op. 40-41). "Elan had undertaken an immense investment, including clinical trials, in the hope that its extended-release concept would solve the problems encountered by others." *Id.*

In Judge Newman's assessment, the majority "misappl[ied] the concept of 'blocking patent'" when it "h[e]ld 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." *Id*. As explained, "a prior patent would not have categorically precluded others from further developing the technology," given the statutory safe harbor of § 271(e)(1), the knowledge provided in the patents, and the right to conduct research on patented subject matter." *Id.*

ARGUMENT

I. The Panel's Expansion of the "Blocking-Patent" Doctrine To Nullify the Objective Indicia of Long-Felt Need and Failure of Others Sets a Dangerous and Unsupported Precedent.

The Supreme Court and this Court have long recognized that the objective indicia of non-obviousness "play a critical role in the obviousness analysis [and] enable[] the court to avert the trap of hindsight." *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013) (internal quotation marks and citation omitted); *Graham v. John Deere Co.*, 383 U.S. 1, 17-18 (1966); *Apple Inc. v. ITC*, 725 F.3d 1356, 1375 (Fed. Cir. 2013) (Reyna, J., concurring-in-part and dissenting-in-part). In *Merck I*, this Court articulated a new doctrine, under which a court may reduce the weight given to the objective indicium of commercial success where a preexisting patent, together with the FDA's regulatory exclusivity, precluded "market entry by others." 395 F.3d at 1376-77; *see also Merck II*, 874 F.3d at 730-31.

The "blocking patent" doctrine was tied to the probative function of commercial success as an indicium of non-obviousness: "Commercial success is

relevant 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 I*, 395 F.3d at 1376. Where "others were legally barred from commercially testing" the purportedly obvious idea because of the preexisting patent and the regulatory exclusivity, and "could only exhort [the patent owner] to try it," the court may conclude that "the inference of non-obviousness … from evidence of commercial success … is weak." *Id.* at 1377. The Court has since invoked the *Merck I* "blocking-patent" doctrine in *Syntex (U.S.A.) LLC v. Apotex, Inc.*, 407 F.3d 1371, 1383 (Fed. Cir. 2005); *Galderma Laboratories, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 740 (Fed. Cir. 2013); and *Merck II*, 874 F.3d at 730-31, solely with respect to commercial success.

Its application to commercial success has been subject to significant debate. Three judges dissented from the Court's original articulation of the doctrine, observing that commercial success "is not negatived by any inability of others to test various formulations because of the existence of another patent. … The panel's rule is especially unsound in the context of an improvement patent, as here, because it holds in effect that commercial success for an improvement is irrelevant when a prior patent dominates the basic invention." *Merck & Co. v. Teva Pharm. USA, Inc.*, 405 F.3d 1338, 1339 (Fed. Cir. 2005) (Lourie, J., dissenting from denial of rehearing en banc). And in *Merck II*, this Court made clear that prior FDA

regulatory exclusivity was critical to the application of the doctrine in *Merck I*. *See* 874 F.3d at 730-31.

The panel majority here for the first time extended the "blocking-patent" doctrine beyond commercial success, and with no prior regulatory exclusivity, using it to negate other objective indicia of non-obviousness recognized to be powerful checks on hindsight—long-felt need and the failure of others. Op. 54-56. This expansion is unsound. Commercial success corroborates non-obviousness by demonstrating that a knowledgeable and unbiased marketplace recognized the invention as a substantial advance over prior art. Otherwise, if the invention were obvious, it would "have been brought to market sooner, in response to market forces." *Merck I*, 395 F.3d at 1376. By contrast, long-felt need and the failure of others are not inherently affected by a "blocking" patent; they corroborate the invention's non-obviousness by "demonstrat[ing] both that a demand existed for the patented invention, and that others tried but failed to satisfy that demand." *In re Cyclobenzaprine*, 676 F.3d 1063, 1082 (Fed. Cir. 2012) (citing cases). These separate indicia of non-obviousness, *see Graham*, 383 U.S. at 17-18, speak to the invention's non-obviousness independently of commercial success.

The inquiry into long-felt need and failure of others can consider noncommercial research and research performed outside the United States, as occurred here. The panel majority dismissed this factor because the foreign

research involving 4-AP here preceded the "blocking" patent. Op. 52. But the timing does not negate that foreign research can and did occur. The district court and the majority did not and could not find that the Elan Patent blocked research outside the United States—markets accounting for a large amount of global pharmaceutical sales, where 4-AP research had in fact occurred. *See* OECD Health Policy Studies, *Pharmaceutical Pricing Policies in a Global Market* 58 & tbl.2.2 (2008). Neither precedent nor logic justifies the majority's troubling new rule in which the existence of a "blocking patent" negates fact findings of long-felt but unmet need and failures of others.

The panel also dismissed the research "safe harbor" of 35 U.S.C. § 271(e)(1) for work in the United States, reasoning that it would not "eliminate infringement liability for the eventual reward-collecting activity of generally marketing the product." Op. 52. At most, that risk might affect the evaluation of commercial success (even though a researcher with serious interest could have approached Elan or Acorda for commercial rights), but it does not affect long-felt need and failures of others. Research proceeds even without commercialization, and any printed publication can serve as an invalidating reference (as a post-"blocking-patent" publication in fact did in *Merck I*, *see* 395 F.3d at 1375, 1377). There is no requirement under long-felt need or failure of others that the inventor *practice* a solution (thereby risking infringement). Indeed, preexisting patent rights do not

bar attempts to solve long-felt but unmet needs, especially in the medical field where academic institutions and independent researchers do much of the work, driven by patient need. *See, e.g.*, J.P. Walsh, A. Arora, and W.M. Cohen, *Working Through the Patent Problem*, 299 Science 1021 (2003) (noting that "almost none of [the survey's] respondents reported worthwhile projects being stopped because of issues of access to IP rights to research tools"). Here, because no record evidence was presented to support this new theory, the majority decision creates a dangerous legal rule.

The majority's rejection of evidence of the failure of others is similarly untenable. "[T]here can be little better evidence negating an expectation of success than actual reports of failure." *In re Cyclobenzaprine*, 676 F.3d at 1081 (internal quotation marks and citation omitted). Here, the district court discounted Sanofi-Aventis's failed attempt to develop an MS walking therapy with another potassium-channel blocker (nerispirdine) based on unsupported speculation that "Sanofi-Aventis likely did not use 4-AP because of the blocking effect of the Elan patent," Op. 55 (internal quotation marks omitted), even though the record evidence instead was that Sanofi-Aventis selected nerispirdine to avoid 4-AP's toxicity. Appx727. The panel found no clear error: *i.e.*, that the mere presence of a blocking patent on the specific composition used in the invention negated the failure of others.

That holding conflicts directly with precedent. The relevant inquiry is whether Sanofi-Aventis and Acorda "share[d] a central common goal: to create a therapeutically effective product"; the fact that [Acorda] "took a materially different approach and succeeded" demonstrates non-obviousness. *In re Cyclobenzaprine*, 676 F.3d at 1081-82; *see also Eli Lilly & Co. v. Zenith Goldline Pharm., Inc.*, 471 F.3d 1369, 1375, 1378-80 (Fed. Cir. 2006) (failure of others based on different compounds); *Alco Standard Corp. v. TVA*, 808 F.2d 1490, 1500-01 (Fed. Cir. 1986) (failure of others where a competitor "had pursued other solutions to the problem," using different technology); *Knoll Pharm. Co. v. Teva Pharm. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004). "Evidence that others were going in different ways is strong evidence that the [inventor's] way would not have been obvious." *In re Cyclobenzaprine*, 676 F.3d at 1082 (internal quotation marks and citation omitted). Because courts may consider failures attempting different compounds or methods (and thus *a fortiori* different compounds with the same mechanism of action, like nerispirdine), the blocking-patent doctrine is irrelevant to the "failure of others" indicium. The district court's "implicit finding that securing freedom from blocking patents in advance is likely important to pharmaceutical research investments," Op. 53, is false where other companies have conducted post-patent research addressing the problem solved by the inventors but failed.

The panel also erroneously extended *Merck I* when it dismissed Elan's failure. Elan abandoned 4-AP because, after its large clinical trial failed, it did not expect such efforts to succeed. Appx596 (281:13-19). The panel adjudged this failure not probative because it preceded the Goodman references and one other (Schwid, a small study sponsored by Elan that also reported the failure of Elan's trial). Op. 55; Op. 40-41; Appx6681. But Elan's failure paved the way for Acorda to obtain a license to the Elan patent and eventually invent Ampyra®. Dissenting Op. 23. To apply the "blocking patent" doctrine where *the holder* of the "blocking" patent itself chose not to pursue further research is a severe disincentive to continued efforts at innovation after another's failure.

II. The Panel's Transformation of the "Blocking-Patent" Doctrine Jeopardizes Innovative Pharmaceutical Patents and Improvement Patents Generally.

Given the posture of this appeal—where the court affirmed the nullification of factual findings of objective indicia based on an expanded blocking-patent doctrine—the mere presence of a "blocking" patent now negates objective indicia, even absent evidence of actual blocking. For instance, the majority reasoned that "[t]he risk of [infringement] liability" under the dominant patent "would have provided an independent incentive … not to develop the invention of the Acorda Patents," citing nothing but the license sought and obtained by Acorda (the patentee). Op. 51. The panel also discarded evidence that the Elan formulation

patent did not bar all use of 4-AP, and that others conducted research using that compound, but did not succeed. The panel did not even remand the case for findings as to whether (and to what extent) the pre-existing patent contributed to the commercial success of Acorda's invention and its ability to solve a long-standing therapeutic need where others consistently failed.

This analysis clearly contravenes this Court's recent blocking-patent precedent. In *Merck II*, the Court emphasized that "evidence of commercial success should not have been discounted simply because of the existence of another patent of which [the patentee] was the exclusive licensee," and noted the importance of regulatory exclusivity in *Merck I* (absent here); it held that "multiple patents do not necessarily detract from evidence of commercial success of a product or process, which speaks to the *merits of the invention*." 874 F.3d at 730-31 (emphasis in original).

Here, by contrast, and notwithstanding the absence of regulatory exclusivity, the panel rejected what even the district court found to be "significant" and "convincing" indicia of non-obviousness based on "the implicit finding that securing freedom from blocking patents in advance is likely important to pharmaceutical research investments." Op. 53. This generic "implicit finding" could be made in *every* case where a preexisting patent arguably covers (at least in part) the claimed invention. Because "most inventions represent improvements on

some existing article, process, or machine," *Gen. Elec. Co. v. Wabash Appliance Corp.*, 304 U.S. 364, 368 (1938), the majority's erroneous decision would inhibit biopharmaceutical innovation.

The majority's extension of the blocking-patent doctrine effectively eviscerates objective evidence of non-obviousness for most inventions that could be characterized as a species within some earlier genus. For such patents, objective indicia are often a crucial check against the insidious hindsight. The majority ruling, contrary to precedent, deters risk-taking, particularly for new drugs using previously unapproved or unsuccessful compounds.

Obviousness commands that a court undertake a unitary analysis of both prior art and objective indicia, *In re Cyclobenzaprine*, 676 F.3d at 1079, and "objective indicia of failure of others and longfelt need are particularly telling" where (as here) the patent requires therapeutically effective treatment, *id.* at 1083. The district court itself acknowledged this was a close case, Appx89, and the dissent showed that, even if Goodman eliminated doses above 25 mg/twice-daily as unsafe, Acorda's invention was not "obvious to try" because the prior art gave no reasonable expectation that Acorda's specific 10 mg dosing protocol would improve walking. *See* Dissenting Op. 17-24 (citing *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009)) (the prior art must give "direction as to which of many possible choices is likely to be successful"). But for the panel's improper broad

"blocking-patent" doctrine, the convincing evidence of objective indicia should have defeated Appellees' obviousness challenge; at least, the panel should have remanded the case for consideration of those indicia without negation by the Elan Patent. This Court should not permit the majority's artificial blocking-patent rule to distort the law of obviousness.

CONCLUSION

This Court should grant rehearing en banc and reverse the judgment below.

October 24, 2018

Respectfully submitted,

/s/Bruce M. Wexler

Jane G. Wasman
Anthony Michael
ACORDA THERAPEUTICS, INC.
420 Saw Mill River Road
Ardsley, NY 10502
(914) 347-4300
jwasman@acorda.com
amichael@acorda.com

Bruce M. Wexler
Attorney of Record
PAUL HASTINGS LLP
200 Park Avenue
New York, NY 10166
(212) 318-6000
brucewexler@paulhastings.com

Stephen B. Kinnaird
Igor V. Timofeyev
PAUL HASTINGS LLP
875 15th Street, N.W.
Washington, D.C. 20005
(202) 551-1700
stephenkinnaird@paulhastings.com
igortimofeyev@paulhastings.com

Counsel for Appellant Acorda Therapeutics, Inc.

October 24, 2018

ADDENDUM

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

BRUCE M. WEXLER, Paul Hastings LLP, New York, NY, argued for plaintiff-appellant. Also represented by STEPHEN BLAKE KINNAIRD, IGOR VICTOR TIMOFEYEV, Washington, DC; GARRARD R. BEENEY, WENYING ANGELA CHANG, STEPHEN J. ELLIOTT, Sullivan & Cromwell LLP,

New York, NY; ANTHONY MICHAEL, JANE G. WASMAN, Acorda Therapeutics, Inc., Ardsley, NY.

MARYELLEN NOREIKA, Morris, Nichols, Arsht & Tunnell LLP, Wilmington, DE, for plaintiff-appellee. Also represented by JEREMY A. TIGAN.

CHARLES B. KLEIN, Winston & Strawn LLP, Washington, DC, argued for defendants-cross-appellants. Defendants-cross-appellants Roxane Laboratories, Inc., Teva Pharmaceuticals USA, Inc. also represented by ANDREW CURTIS NICHOLS; BRYCE COOPER, GEORGE C. LOMBARDI, REID SMITH, Chicago, IL.

ROBERT FLORENCE, Parker Poe Adams & Bernstein LLP, Atlanta, GA, for defendant-cross-appellant Mylan Pharmaceuticals Inc. Also represented by MICHEAL L. BINNS, KAREN L. CARROLL.

SARAH ANNE KAGAN, Banner and Witcoff, Ltd., Washington, DC, for amicus curiae Biotechnology Innovation Organization. Also represented by MELISSA A. BRAND, LISA MEREDITH HEMMENDINGER; HANSJORG SAUER, Biotechnology Innovation Organization, Washington, DC.

SCOTT E. KAMHOLZ, Covington & Burling LLP, Washington, DC, for amicus curiae Pharmaceutical Research and Manufacturers of America. Also represented by BRIANNE BHARKHDA; DAVID EVAN KORN, Pharmaceutical Research and Manufacturers Association of America, Washington, DC.

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

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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.

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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

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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.

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." 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 result-

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

ing 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

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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).

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 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 aminopyridines may provide a new approach to the symptomatic treatment of [multiple sclerosis]." *Id.* at S118.[4] As to

[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

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 ("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.

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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,

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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]").

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

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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.

[sustained-release]." J.A. 6684. Schwid concludes that, in the reported study, "4AP [sustained-release] improved motor function in [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.

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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., *Pharmaco-*

kinetic 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

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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,

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

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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.

was completed, Acorda conducted a post-hoc analysis 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.

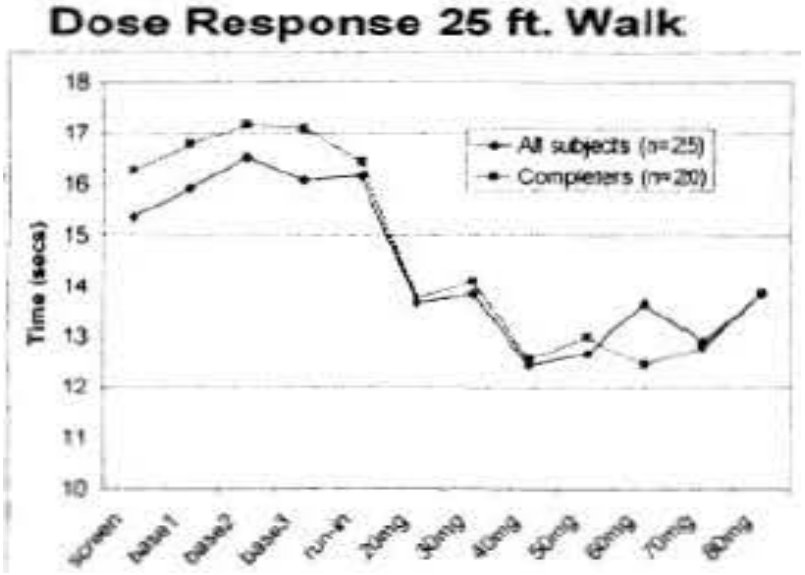
J.A. 6372.

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.*

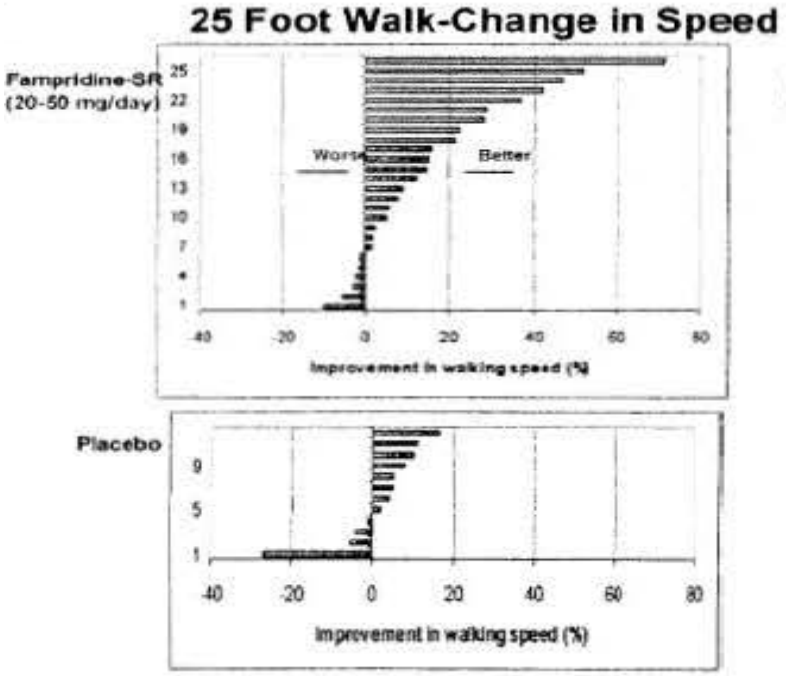
As to the results concerning efficacy, the Goodman Poster includes a graph of a dose-response curve for the 25-foot walk:



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

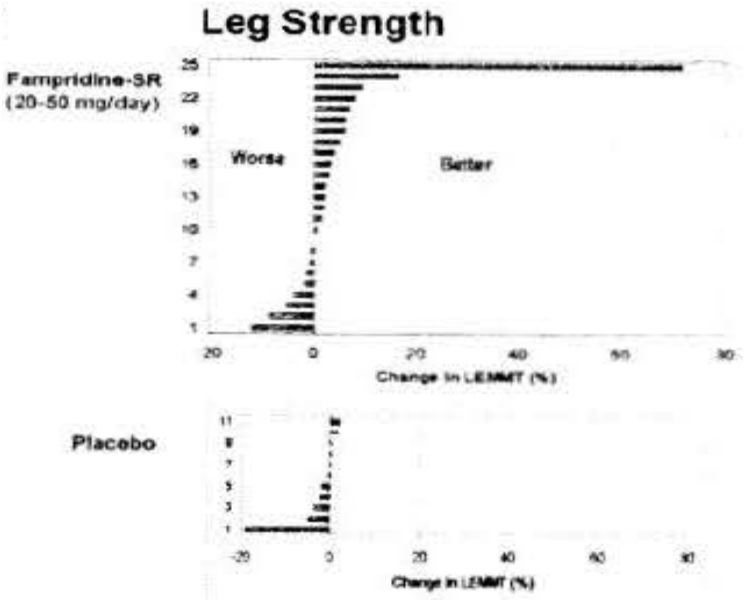
between 12 and 14 seconds for a "stable clinical effect at 20 to 40" mg/day in the "flat part of the dose response curve").

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.

4

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]

5

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

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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.

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

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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.

patent was a "blocking patent" for the claimed 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 court

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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.

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 expectation 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 nonobviousness. *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

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[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.

novo and its underlying factual findings for clear error. *In re Cyclobenzaprine 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: similar). 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 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

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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.

(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 obvious-

ness. *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 other 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 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 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

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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).

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 of skill may not have known the details of the formulation used in

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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.

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 im-

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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).

provement 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 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.

2

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).

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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.

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 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 improve-

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

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ments 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, 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).

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-Avenits 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 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 non-technical 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-cv-00922-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 succeeded where many others had

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[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.

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-aminopyridine, and the

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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.

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

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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.

that side effects of 4-AP "precluded 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

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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.

study examined the 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 the understood need to target

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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.

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*

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

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treatment of multiple sclerosis, 48 Neurology 817 (1997), J.A. 6681-84.

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.

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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.

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 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.

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[11] 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), 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.

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 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.

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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.

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 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 expec-

tation 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.

CERTIFICATE OF SERVICE

I, Bruce M. Wexler, hereby certify that on October 24, 2018, the foregoing Petition for Rehearing En Banc of Appellant Acorda Therapeutics, Inc. was filed using the Court's CM/ECF system and served on the parties' counsel of record via ECF.

/s/Bruce M. Wexler
Bruce M. Wexler
Counsel for Appellant
Acorda Therapeutics, Inc.

CERTIFICATE OF COMPLIANCE WITH TYPE-VOLUME LIMITATION, TYPEFACE REQUIREMENTS AND TYPE STYLE REQUIREMENTS

1. This petition for en banc rehearing complies with the type-volume limitation of Federal Rules of Appellate Procedure 32(a)(7)(B) and 40(b)(1).

The petition contains 3,899 words, excluding the parts of the brief exempted by Federal Rule of Appellate Procedure 32(a)(7)(B)(iii).

2. This petition complies with the typeface requirements of Federal Rule of Appellate Procedure 32(a)(5) and the type style requirements of Federal Rule of Appellate Procedure 32(a)(6).

The brief has been prepared in a proportionally spaced typeface using MS Word 2013 in a 14 point Times New Roman font.

Dated: October 24, 2018

/s/Bruce M. Wexler
Bruce M. Wexler
Counsel for Appellant
Acorda Therapeutics, Inc.