Trials@uspto.gov
571.272.7822

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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

COALITION FOR AFFORDABLE DRUGS (ADROCA) LLC,
Petitioner,

v.

ACORDA THERAPEUTICS, INC.,
Patent Owner.

Case IPR2015-01850
Patent 8,440,703 B2

Before MICHAEL P. TIERNEY, LORA M. GREEN, and JACQUELINE WRIGHT BONILLA, *Administrative Patent Judges*.

TIERNEY, *Administrative Patent Judge*.

DECISION
Institution of *Inter Partes* Review
37 C.F.R. § 42.108

I. INTRODUCTION

Coalition for Affordable Drugs (ADROCA), LLC ("Petitioner"), filed a Petition requesting an *inter partes* review of claims 1–52 of U.S. Patent 8,440,703 B2 (Ex. 1001, "the '703 patent"). Paper 2 ("Pet."). Patent Owner, Acorda Therapeutics, Inc., ("Patent Owner") filed a Preliminary Response. Paper 10 ("Prelim. Resp.").

We have jurisdiction under 35 U.S.C. § 314. The standard for instituting an *inter partes* review is set forth in 35 U.S.C. § 314(a), which provides:

> THRESHOLD.—The Director may not authorize an inter partes review to be instituted unless the Director determines that the information presented in the petition filed under section 311 and any response filed under section 313 shows that there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.

Upon consideration of the Petition and Preliminary Response, we conclude that the information presented in the Petition demonstrates that there is a reasonable likelihood that Petitioner would prevail in challenging claims 1–52 as unpatentable. Pursuant to 35 U.S.C. § 314, we hereby authorize an *inter partes* review to be instituted as to claims 1–52 of the '703 patent.

A. Related Proceedings

The claims of the '703 patent are said to have issued from a continuation application of U.S. Application 11/102,559, filed April 8, 2005, which issued as U.S. Pat. 8,354,437 B2. Ex. 1001. The '437 patent has been challenged in related *inter partes* review proceeding IPR2015-01858. Pet. 3. Additionally, Petitioner notes that two additional Acorda patents

have been challenged, IPR2015-01853 (U.S. Pat. 8,007,826 B2) and IPR2015-01857 (U.S. Pat. 8,663,685 B2). *Id*. at 2–3.

B. The ’703 Patent

The ’703 is directed to a sustained release oral dosage of an aminopyridine pharmaceutical composition that can be used to treat individuals affected with neurological disorders. Ex. 1001, 1:14–16. The most preferred aminopyridine is 4-aminopyridine (“4-AP” or “fampridine”). *Id*. at 1:35–41, 2:29–32. According to the ’703 patent, its pharmaceutical composition can be used to treat spinal cord injury, multiple sclerosis (“MS”), Alzheimer’s disease and amyotrophic lateral sclerosis (“ALS”). *Id*. at 2:23–27. The composition is said to maximize the therapeutic effect while minimizing side effects. *Id*. at 1:17–18.

In one embodiment of the ’703 patent, the composition is administered to patients with MS to increase their walking speed. *Id*. at 3:65–4:3. The composition is administered twice daily in an amount of less than about 15 milligrams of aminopyridine, preferably about 10 to 15 milligrams of aminopyridine. *Id*. at 2:2–5. In other embodiments, the composition is said to improve lower extremity muscle tone and lower extremity muscle strength in patients with MS. *Id*. at 4:6–19. The ’703 states that in responsive patients (approximately 37%), “treatment with fampridine at doses of 10–20 mg produced a substantial and persistent improvement in walking.” *Id*. at 29:23–26.

C. Illustrative Claims

The ’703 patent contains fifty-two claims, all of which are challenged by Petitioner. All fifty-two claims are directed to methods of improving

lower extremity function in an MS patient in need thereof. Claims 1 and 2 are the only independent claims. Claims 1 and 2 are illustrative of the challenged claims and are reproduced below:

> 1. A method of improving lower extremity function in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of less than 15 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, wherein the amount of said 4-aminopyridine administered to said patient in each said administering step is the same over said time period.
>
> 2. A method of improving lower extremity function in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks.

D. Prior Art Relied Upon

Petitioner relies upon the following prior art:

Acorda Therapeutics, Inc., Registration Statement Under the Securities Act of 1933 (Form S-1) (Sept. 26, 2003) ("S-1") (Ex. 1003).

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*, Clinical Neuropharmacology, Vol. 26, No. 4, 185–92 (2003) ("Hayes") (Ex. 1005).

Haydee Juárez et al., *Influence of Admixed Carboxymethylcellulose on Release of 4-Aminopyridine from Hydroxypropyl Methylcellulose Matrix Tablets*, 216 Int'l J. Pharm., 115–25 (2001) ("Juarez") (Ex. 1006).

Petitioner contends that the challenged claims are unpatentable under 35 U.S.C. § 103 based on the following specific grounds (Pet. 19–60):

Reference(s)	Basis	Claims challenged
S-1	§ 103	1–7, 10, 11, 26–33, 44–46, 52
S-1 in light of Hayes	§ 103	8, 9, 12–21, 34–41, 47–49
S-1 in light of Juarez	§ 103	22–25, 42, 43, 50, 51

E. Level of Ordinary Skill in the Art

Petitioner's declarants, Drs. Samuel J. Pleasure and James Polli, testify that, a person of ordinary skill in connection with the '703 patent would have had an M.D. or Ph.D. in neuroscience or a related field with an understanding of pharmacokinetics and at least some experience in providing drug therapy to MS patients. Ex. 1023 ¶ 16, Ex. 1044 ¶ 13. Additionally, Drs. Pleasure and Polli testify that a person of ordinary skill in the art would have had access to a person having an advanced degree in pharmaceutics or pharmaceutical formulation, specifically oral sustained release formulations, or at least five years of experience in formulating sustained oral release drug products and may work as part of a multi-disciplinary team. Ex. 1023 ¶¶ 16–17; Ex. 1044 ¶¶ 13–14. At this stage of the proceeding, Patent Owner does not dispute this recitation of the level of ordinary skill in the art. We adopt the level of ordinary skill in the art identified by Drs. Pleasure and Polli as it is consistent with the prior art of record. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (the prior art itself can reflect the appropriate level of ordinary skill in the art).

II. ANALYSIS

A. Claim Interpretation

In an *inter partes* review, the Board interprets claim terms in an unexpired patent according to the broadest reasonable construction in light of the specification of the patent in which they appear. 37 C.F.R. § 100(b); *In re Cuozzo Speed Techs., LLC*, 793 F.3d 1268, 1278–79 (Fed. Cir. 2015), *cert. granted sub nom. Cuozzo Speed Techs., LLC v. Lee*, 136 S. Ct. 890 (mem.) (2016). Under that standard, and absent any special definitions, we give claim terms their ordinary and customary meaning, as would be understood by one of ordinary skill in the art at the time of the invention. *See In re Translogic Tech., Inc.*, 504 F.3d 1249, 1257 (Fed. Cir. 2007). Any special definitions for claim terms must be set forth with reasonable clarity, deliberateness, and precision. *See In re Paulsen*, 30 F.3d 1475, 1480 (Fed. Cir. 1994).

Petitioner identifies several claim terms in the challenged claims and provides definitions for those terms. Pet. 18–19. Patent Owner contends that Petitioner has failed to provide an explanation as to why the identified claim terms require construction and why the Board should depart from the plain and ordinary meaning of the terms. Prelim. Resp. 17, n.4.

We agree with Patent Owner and determine that it is unnecessary to construe explicitly the claim terms for purposes of this Decision. *See Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) ("[C]laim terms need only be construed 'to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

B. Section 103 Obviousness Challenge

Petitioner raises three (3) challenges based on 35 U.S.C. § 103. Generally, Petitioner contends that the challenged claims represent a combination of known prior art elements (sustained release 4-AP, dosed twice daily to MS patients) for their known use (improve lower extremity function) to achieve a predictable result (improvements in walking speed, muscle strength and muscle tone). Pet. 20–21. Patent Owner opposes Petitioner's assertions. Prelim. Resp. 7–26. Based on the current record, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing claims 1–52 are unpatentable as obvious over the cited art.

1. Background on Obviousness

An invention is not patentable under 35 U.S.C. § 103 if it is obvious. *KSR Int'l Co. v. Teleflex Inc*., 550 U.S. 398, 427 (2007). Under § 103:

> [T]he scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined.

Graham v. John Deere Co., 383 U.S. 1, 17 (1966). In addressing the findings of fact, "[t]he combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results." *KSR*, 550 U.S. at 416. As explained in *KSR*:

> If a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill.

Id. at 417. Accordingly, a central question in analyzing obviousness is "whether the improvement is more than the predictable use of prior art elements according to their established functions." *Id.*

2. S-1: Claims 1–7, 10, 11, 26–33, 44–46, and 52

S-1 is an Acorda prospectus SEC filing that describes Acorda's initial public offering of common stock and Acorda's desire to list their common stock on the Nasdaq National Market. Ex. 1003, 2[1]. S-1 describes Acorda as a late-stage biopharmaceutical company dedicated to identification, development and commercialization of therapies that improve neurological function. *Id*. at 5. Acorda's therapies are focused on treating people suffering from spinal cord injury, multiple sclerosis and related disorders of the nervous system. *Id*. The S-1 states that Fampridine-SR is Acorda's lead product candidate and that laboratory studies have shown that fampridine improves impulse conduction in nerve fibers that have been damaged, such as in the case of MS. *Id*. at 6. Fampridine-SR was developed by and manufactured for Acorda by Elan. *Id*. at 34.

Fampridine-SR is described as suitable for twice daily dosing for both SCI (spinal cord injury) and MS. *Id*. at 34. S-1 states that it is believed that Fampridine-SR represents a "fundamental shift in the treatment of both SCI and MS because it may improve neurological function rather than only treating the symptoms or slowing the progression of these diseases." *Id*. Specifically, S-1 teaches that fampridine is able to block exposed myelin

[1] We cite exhibit page numbers as indicated by Petitioner on the bottom right of Exhibit 1003, rather than page numbers designed in the S-1 itself.

potassium channels in MS patients, thereby permitting the axons in nerve fibers to transmit nerve impulses again. *Id*.

S-1 states that clinical trials of Fampridine-SR have demonstrated improved neurological function in people with chronic SCI or MS. *Id*. at 6. S-1 states that eight clinical trials have been conducted with Fampridine-SR for SCI and six clinical trials for MS. *Id*. S-1 further states that in Phase 2 clinical trials, treatment with Fampridine-SR has been associated with a variety of neurological benefits in people with SCI or MS. *Id*. S-1 also states that Acorda was conducting a late Phase 2 clinical trial in people with MS for the improvement of walking speed. *Id*. According to S-1, Acorda has performed clinical trials of Fampridine-SR in chronic SCI and MS to establish the "pharmacokinetics, safety, and optimal dosing of the drug, as well as to assess its efficacy." *Id*. at 34. S-1 states that clinical trials of Fampridine-SR therapy have shown "a statistically significant improvement in walking speed and leg strength" in MS patients. *Id*. at 35.

S-1 describes the design and results of a clinical trial designated "MS-F201" as follows:

> In 2001, we completed a double-blind Phase 2 clinical trial of Fampridine-SR in Multiple Sclerosis, MS-F201. The clinical trial was designed to determine the optimal dose level of Fampridine-SR and to evaluate possible ways in which to measure the effect of the drug on symptoms of the disease, including motor strength, timed walking, and self-reported fatigue. The clinical trial involved a total of 36 MS subjects in four major academic MS research centers. A total of 25 subjects received Fampridine-SR in doses increasing from 10 mg to 40 mg twice per day over eight weeks of treatment, and 11 subjects were given placebo over the same period. This treatment period was preceded by a series of baseline evaluations over the course of four weeks to allow the subjects to become adjusted to the clinic visits and allow the various

> measurements to stabilize. A one week blinded treatment with placebo preceded the first drug administration to look for potential placebo effects on the various outcome measures.
>
> The clinical trial demonstrated that doses up to 25 mg twice a day were well tolerated, and were associated with statistically significant improvements in walking speed and leg muscle strength. Most of the improvement in strength and walking speed was apparent within the first three weeks of the Fampridine-SR treatment, at doses from 10 to 25 mg twice a day.

Id. at 37. S-1 also describes a current late Phase 2 clinical trial, "MS-F202," that was designed, based on extensive consultations with expert MS neurologists and the FDA, to provide support for an NDA for the use of Fampridine-SR in MS. *Id*. The MS-F202 trial was designed to "compare three doses of 10, 15 and 20 mg, twice per day and assess their relative safety and efficacy over a treatment period of 12 weeks." *Id*. at 37. The primary endpoint of the MS-F202 trial involved timing subjects completing a 25 foot walk. *Id*. The trial enrolled approximately 200 subjects in 24 major MS centers in July 2003 and was to conclude by the end of March 2004. *Id*.

Petitioner contends that claims 1–7, 10, 11, 26–33, 44–46, and 52 are obvious over the teachings of the S-1 reference. Pet. 30–42. Patent Owner disagrees. Prelim. Resp. 8–24. Generally, Patent Owner contends that S-1 is not statutory prior art and that S-1 fails to teach or suggest the dosing regimen recited in the challenged claims. These issues will be discussed in detail below.

a. S-1 is Statutory Prior Art

"The determination of whether a reference is a 'printed publication' under 35 U.S.C. § 102(b) involves a case-by-case inquiry into the facts and circumstances surrounding the reference's disclosure to members of the public." *In re Klopfenstein*, 380 F.3d 1345, 1350 (Fed. Cir. 2004). "The 'printed publication' bar is grounded on the principle that once an invention is in the public domain, it is no longer patentable by anyone." *Id*. at 1349 (quoting *In re Hall*, 781 F.2d 897, 899 (Fed. Cir. 1986)) (internal brackets removed).

Thus, "public accessibility" is "the touchstone" in determining whether a reference is a printed publication. *In re Hall*, 781 F.2d at 899. "A given reference is 'publicly accessible' upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art exercising reasonable diligence, can locate it." *SRI Int'l, Inc. v. Internet Sec. Sys., Inc*., 511 F.3d 1186, 1194 (Fed. Cir. 2008) (quoting *Bruckelmyer v. Ground Heaters, Inc.*, 445 F.3d 1374, 1378 (Fed. Cir. 2006)). Further, one accessibility has been shown, it is unnecessary to show that anyone inspected the reference. *In re Lister*, 583 F.3d. 1307, 1314 (Fed. Cir. 2009).

Petitioner contends that S-1 is prior art under 35 U.S.C. §§ 102(a) and 102(b) as it was printed and made publically available at least as of September 30, 2003, which is more than one year before

the earliest effective filing date of the April 8, 2005.[2] Pet. 23. Petitioner relies upon the testimony of Dr. Bennett, who testifies that the S-1 HTML properties demonstrate that the SEC received the Acorda Therapeutics filing, including the S-1 form, on September 26, 2003 and made the S-1 available to the public on September 29, 2003. Pet. 25, Ex. 1016 ¶¶ 14–15.

Petitioner states that a person of ordinary skill in the art would have known that Acorda was investigating fampridine [4-AP] "for the potential treatment of spinal cord injuries and multiple sclerosis." Pet. 24, citing Ex. 1017, 1. According to Petitioner, Acorda's investigations had received attention in prominent publications in the field as well as general news sources from 2002 until the date of the S-1 filing. Pet. 24, citing Ex. 1018, 1, Ex. 1019, 1. Petitioner contends that a person of ordinary skill in the art interested in researching and treating MS would have known that Acorda was active in the field of SR 4-AP research. Pet. 24. Dr. Pleasure testifies that one of ordinary skill in the art, aware of Acorda's activities, would have been motivated to be kept apprised of Acorda's research

[2] The '703 patent issued from an application claiming benefit of U.S. Provisional Application No. 60/560,894, filed April 9, 2004. Ex. 1001. Petitioner contends that the '703 patent is not entitled to the filing date of the provisional application, and that the '703 patent has an effective filing date of April 8, 2005. Pet. 10–17. Patent Owner did not address Petitioner's arguments, but reserved the right to challenge Petitioner's allegations should the Board institute a trial. Prelim. Resp. 9, n.2. For purpose of this Decision we need not determine whether the '703 patent is entitled to priority benefit of the provisional application as the S-1 prospectus is statutory prior art under either effective filing date.

and studies and would have monitored and sought information about such studies by looking for and accessing statements and publications by researchers and companies conducting such studies, including Acorda's clinical trial research and disclosures, such as Acorda's S-1. Ex. 1023 ¶¶ 62–63.

Patent Owner contends that Petitioner has failed to demonstrate the public accessibility of S-1 as Petitioner has not demonstrated that S-1 was indexed or cataloged in the SEC's EDGAR database in a way that one could have searched for the filing other than by looking under the name Acorda. Prelim. Resp. 11. Additionally, Patent Owner characterizes Dr. Pleasure's testimony as "conclusory and inherently implausible." Prelim. Resp. 14. Specifically, Patent Owner states:

> Dr. Pleasure in essence asserts that one of skill in the art would have reviewed the entirety of every available statement of any person or company that has been involved in MS research, based on the mere possibility that it might contain a description of the company's (or individual's) current research. (*See* Ex. 1023, Pleasure Decl., ¶¶ 62–63). But he cites nothing in support of the notion that one of skill in the art would engage in such a massive undertaking and, in fact, does not state that he himself (or anyone else of skill in the art) would have done such a thing.

Prelim. Resp. 14.

The SEC requires S-1 filings through the EDGAR filing system so that investors may use the S-1 information to consider the merits of an offering and make educated investment decisions. Ex. 1016 ¶¶ 11–12. A prospectus is one of the main documents used by an investor to research a company prior to an initial public offering. Ex. 1003, 4. Patent Owner has not explained sufficiently on this record why a prospectus in the SEC's

EDGAR database is sufficiently accessible to investors, but not to the public interested in the art. Nor does Patent Owner explain sufficiently why the SEC's identification of Acorda by name and document type on the EDGAR database does not catalog the S-1 filings meaningfully.

On this record, we determine that Dr. Pleasure's testimony has merit, consistent with the purposes of S-1 filings. *Cf. Eli Lilly v. Barr Labs.*, 251 F.3d 955, 969 (Fed. Cir. 2001) (listing a company's 10-K as part of "the panoply of evidence to support the recognition of an inherent biological function of a compound" that a party provided). Subsequent to institution, Patent Owner will have an opportunity to cross-examine Dr. Pleasure regarding his testimony, and object to evidence under 37 C.F.R. § 42.64(b).

Based on the evidence of record, we credit Dr. Pleasure's testimony and hold that there is sufficient evidence of record before us, to demonstrate that a person of ordinary skill in the art would have been aware of Acorda's clinical trials and would have monitored and sought information about such studies by looking for and accessing statements and publications by Acorda and its researchers. On this record, and for purposes of this decision, we hold that S-1 is a printed publication.

S-1 is Acorda's own document. Acorda will have a full opportunity during the trial phase to submit declaratory evidence from a person knowledgeable about the publication of the S-1 document and the information it contains regarding the Fampridine-SR MS clinical trials.

b. S-1 Teaches or Suggests All the Elements of Claims 1–7, 10, 11, 26–33, 44–46, and 52

Petitioner argues that claims 1–7, 10, 11, 26–33, 44–46, and 52 are unpatentable as obvious over S-1. As set forth in its Petition and

Dr. Pleasure's testimony and claim chart, Petitioner asserts that S-1 teaches or suggests each limitation of the claims to one of ordinary skill in the art. Pet. 30–42; Claim Charts for '703 S-1 Petition, Exs. 1023, 1043. For example, Petitioner relies upon S-1's teaching that Fampridine-SR (4-aminopyridine) is an oral, sustained-release tablet having 10, 15 or 20 mg that can be administered orally twice daily to a human having MS for a period of at least two weeks to improve lower extremity function, including walking. Ex. 1003, 34–38; Ex. 1023 ¶¶ 66–72. Having reviewed the arguments and evidence, we are persuaded that Petitioner has shown sufficiently that each limitation of the challenged claims is taught or suggested to one of ordinary skill in the art by S-1.

According to Patent Owner, nothing in S-1 teaches or suggests the dosage regimen set forth in the challenged claims. Prelim. Resp. 19. We disagree. As noted by Petitioner, S-1 states that in the MS-F201 trial "25 subjects received Fampridine-SR in doses increasing from 10 mg to 40 mg twice per day over eight weeks of treatment." Ex. 1003, 37.

Patent Owner contends that the MS-F201 trial was not designed to, and did not, evaluate efficacy at any particular dose. Prelim Resp. 20. S-1 specifically states that the MS-F201 clinical trial "demonstrated that doses up to 25 mg twice a day were well tolerated, and were associated with statistically significant improvements in walking speed and leg muscle strength." Ex. 1003, 37.

Patent Owner contends that one skilled in the art could not infer the safety or efficacy of the twice daily 10 mg dosage in particular. Prelim. Resp. 20. S-1 identifies dosages from 10 mg up to 25 mg as

well tolerated and associated with statistically significant improvement in walking speed and muscle strength. Ex. 1003, 37. Dr. Pleasure testifies that one of ordinary skill in the art would have understood that 10 mg dose of fampridine was part of the both the MS-F201 and MS-F202 study and would have been obvious to one of ordinary skill in the art based on the statements made concerning the benefits achieved by providing such a dosage. Ex. 1023 ¶¶ 66–87. We credit Dr. Pleasure's testimony as it is consistent with the express statements contained in S-1.

Patent Owner contends that one of ordinary skill in the art would not have assumed that the MS-F202 study would be a success. Pet. 21–23. As to predictions of the success of the MS-F202 study, the design of the MS-F202 study with its doses of 10, 15, and 20 mg, is consistent with the S-1 statements that the MS-F201 study demonstrated that "doses up to 25 mg twice a day were well tolerated, and were associated with statistically significant improvements in walking speed and leg muscle strength." Ex. 1003, 37.

Patent Owner also contends that the post-filing outcome MS-F202 study belies any notion that there was an expectation of success in showing the efficacy of the claimed 10 milligram twice a day dosage. Prelim. Resp. 24. In particular, Patent Owner states that only by using an "innovative responder analysis" was the efficacy of the 10 mg dosage revealed. *Id*. An invention is not patentable if it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the claimed invention pertains. Accordingly, the pertinent knowledge is that possessed at the time of the invention and Patent Owner has not persuaded us that

its post-filing results are relevant to the knowledge possessed at the time of the invention.

Based upon the evidence of record, we credit Dr. Pleasure's testimony as it is consistent with the express statements contained in S-1. On this record, we hold that one of ordinary skill in the art would have combined the known elements 10 mg dosage, twice daily for more than 2 weeks, in an MS patient for the stated purpose of improving lower extremity function, including improvement in walking speed and muscle strength. Accordingly, we determine that Petitioner has established a reasonable likelihood that it would prevail in showing that claims 1–7, 10, 11, 26–33, 44–46, and 52 are unpatentable as obvious over S-1.

3. S-1 in light of Hayes: Claims 8, 9, 12–21, 34–41, and 47–49
4. S-1 in light of Juarez: Claims 22–25, 42, 43, 50, and 51

Hayes is entitled "Pharmacokinetic Studies of Single and Multiple Oral Doses of Fampridine-SR (Sustained-Release 4-Aminopyridine) in Patients With Chronic Spinal Cord Injury." Ex. 1005, 1.[3] Hayes states that "[t]wo studies were conducted to determine the pharmacokinetics and safety profile of an oral, sustained-release (SR) formulation of fampridine (fampridine-SR, 10–25 mg) administered as a single dose (n = 14) and twice daily for 1 week (n = 16) in patients with chronic, incomplete SCI," i.e., spinal cord injury. *Id*. at 1, Abstract.

[3] We cite exhibit page numbers as indicated by Petitioner on the bottom right of Exhibit 1005, rather than page numbers designed in Hayes itself.

Hayes discloses that "[c]linical trials have confirmed that administration of fampridine results in symptomatic improvements in patients with SCI and multiple sclerosis." *Id*. at 1 (citations omitted). Hayes discusses its "first study [that] evaluated single oral doses of fampridine-SR (10 mg, 15 mg, 20 mg, and 25 mg) in 14 patients with SCI," and its "second study [that] examined multiple oral doses (10 mg, 15 mg, 20 mg, and 25 mg, twice daily, each given for 1 week) of fampridine-SR in 16 patients with SCI." *Id*. at 2.

In relation to the second study, Hayes discloses that 16 patients "received doses of orally administered fampridine-SR tablets at each dose level (10, 15, 20, and 25 mg) twice daily for 6 consecutive days and then once daily on the seventh day," and "[d]osing at each level was performed in an ascending manner over 4 weeks with no intervening washout period." *Id*. Thus, at one point, patients received 10 mg of fampridine-SR tablets twice daily for six days as part of this study.

In relation to a number of measured pharmacokinetic parameters in the second study, as presented in Figure 1B and Table 3, Hayes states that "[s]teady state was achieved by day 5 (4 days of fampridine-SR dosing) after twice-daily administration of fampridine-SR." *Id*. at 4. Figure 1B presents the mean fampridine plasma concentration versus time over 24 hours for each dosage, including 10 mg, given twice daily. *Id*. at 5. Table 3 presents the "Mean (±standard deviation) pharmacokinetic parameters of fampridine-SR after multiple-dose administration" for each dosage, including 10 mg given twice daily. Such parameters for the 10 mg dosage twice daily dosage include: C_{maxss}, ng/mL of 32.2 ± 8.9, C_{minss}, ng/mL of 14.0 ± 4.4, C_{avss}, ng/mL of 20.8 ± 5.7, and t_{max}, h of 2.7 ± 1.0. *Id*. at 7.

Juarez describes the use of mixtures of polymers to achieve a variety of release properties. Ex. 1006. In particular, Juarez describes testing the matrix release behavior of tablets of 4-aminopyridine with hydroxypropyl methylcellulose ("HPMC"). *Id*. at 2. Juarez states that the purpose of the HPMC matrix is to "prolong delivery with zero-order kinetics to maintain a constant in vivo plasma concentration, and with this to maintain a constant pharmacological effect." *Id*. at 2.

Petitioner cites Hayes for its teaching of pharmacokinetic properties of fampridine-SR, and Juarez for its teaching of optimizing the release properties of fampridine (4-aminopyridine) using polymer matrices. Pet. 42–56.

According to Petitioner, a person of ordinary skill in the art would have had reason to look to Hayes' teachings with the SR 4-AP tablets disclosed in S1 to achieve effective blood plasma pharmacokinetics. Pet. 43, Ex. 1023 ¶¶ 121–171, Ex. 1044 ¶¶ 28–75. Further, Petitioner contends that a person of ordinary skill in the art would have had reason to look to Juarez's teaching of polymer matrices in order to optimize the delivery of fampridine in S-1 as both references describe the SR 4-AP oral tablets. Pet. 54, Ex. 1023 ¶¶ 172–192, Ex. 1044 ¶¶ 76–95. For example, according to Petitioner, one of ordinary skill in the art following Juarez's mixing instructions would result in a 4-AP being uniformly dispersed in a matrix that is suitable for controlling the release of 4-AP. Pet. 54–56, Ex. 1044 ¶ 95.

Patent Owner contends that Hayes and Juarez fail to remedy the deficiencies of S-1. Prelim. Resp. 25. In particular, Patent Owner states that Hayes does not speak to the efficacy of the dosing regime

and Juarez does not describe clinical data or using 4-AP in MS patients. *Id*.

Based on the record presented, we credit the testimony of Dr. Pleasure and Dr. Polli, as their testimony is consistent with the teachings of the prior art of record and find that Petitioner has demonstrated that one of ordinary skill in the art would have had reason to combine the teachings of S-1 and Hayes, and S-1 and Juarez, as all three references describe the use of delayed release fampridine. We conclude, on this record, that Petitioner has provided sufficient and credible evidence to demonstrate that one skilled in the art would have combined the references for the purpose of forming a polymeric delayed release tablet with of 4-AP to maintain *in vivo* plasma concentrations (S-1 and Juarez) and the purpose of achieving Hayes' extended release profile with 4-AP (S-1 and Hayes).

III. CONCLUSION

For the foregoing reasons, we determine that the information presented in the Petition, notwithstanding the Preliminary Response, establishes that there is a reasonable likelihood that Petitioner would prevail in demonstrating unpatentability of claims 1–52. The Board has not yet made a final determination of the patentability of any of claims 1–52 of the '703 patent.

IV. ORDER

Accordingly, it is

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–52 of the '703 patent on the following grounds:

Reference(s)	Basis	Claims challenged
S-1	§ 103	1–7, 10, 11, 26–33, 44–46, 52
S-1 in light of Hayes	§ 103	8, 9, 12–21, 34–41, 47–49
S-1 in light of Juarez	§ 103	22–25, 42, 43, 50, 51

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

PETITIONER:

Sarah E. Spires
Parvathi Kota
SKIERMONT PUCKETT LLP
ADROCA703IPR1@skiermontpuckett.com

PATENT OWNER:

Gerald Flattmann
Naveen Modi
PAUL HASTINGS LLP
CFAD-Acorda-IPR@paulhastings.com

Soumitra Deka
Kaye Scholer LLP
Soumitra.Deka@kayescholer.com