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UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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COALITION FOR AFFORDABLE DRUGS (ADROCA) LLC

PETITIONER

V.

ACORDA THERAPEUTICS, INC.

PATENT OWNER

_____

CASE NO.: UNASSIGNED
PATENT NO. 8,440,703
FILED: NOVEMBER 18, 2011
ISSUED: MAY 14, 2013
INVENTORS: ANDREW R. BLIGHT, RON COHEN

TITLE: METHODS OF USING SUSTAINED RELEASE AMINOPYRIDINE COMPOSITIONS

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PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 8,440,703

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I. INTRODUCTION

Petitioner Coalition For Affordable Drugs (ADROCA) LLC ("CFAD"), requests an *Inter Partes* Review ("IPR") of claims 1–52 (collectively, the "Challenged Claims") of U.S. Patent No. 8,440,703 (the "'703 Patent") (Ex. 1001) in accordance with 35 U.S.C. §§ 311–19 and 37 C.F.R. §§ 42.100 *et seq*.

II. GROUNDS FOR STANDING (37 C.F.R. § 42.104(a))

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '703 Patent is available for IPR and that Petitioner is not barred or estopped from requesting IPR challenging the claims of the '703 Patent on the grounds identified in this Petition.

III. MANDATORY NOTICES (37 C.F.R. § 42.8)

A. Real Parties-in-Interest (37 C.F.R. § 42.8(b)(1))

Pursuant to 37 C.F.R. § 42.8(b)(1), Petitioner certifies that Coalition For Affordable Drugs (ADROCA) LLC (CFAD), Hayman Credes Master Fund, L.P. (Credes), Hayman Capital Master Fund, L.P. (HCMF), Hayman Capital Management, L.P. (HCM), Hayman Offshore Management, Inc. (HOM), Hayman Investments, L.L.C. (HI), nXn Partners, LLC (nXnP), IP Navigation Group, LLC (IPNav), J. Kyle Bass, and Erich Spangenberg are the real parties in interest (collectively, RPI). The RPI hereby certify the following information: CFAD is a wholly owned subsidiary of Credes. Credes is a limited partnership. HCMF is a limited partnership. HCM is the general partner and investment manager of Credes and HCMF. HOM is the administrative general partner of Credes and HCMF. HI is

the general partner of HCM. J. Kyle Bass is the sole member of HI and sole shareholder of HOM. CFAD, Credes, and HCMF act, directly or indirectly, through HCM as the general partner and/or investment manager of Credes and HCMF. nXnP is a paid consultant to HCM. Erich Spangenberg is 98.5% member of nXnP. IPNav is a paid consultant to nXnP. Erich Spangenberg is the 98.5% member of IPNav. Other than HCM and J. Kyle Bass in his capacity as the Chief Investment Officer of HCM and nXnP and Erich Spangenberg in his capacity as the Manager of nXnP, no other person (including any investor, limited partner, or member or any other person in any of CFAD, Credes, HCMF, HCM, HOM, HI, nXnP or IPNav) has authority to direct or control (i) the timing of, filing of, content of, or any decisions or other activities relating to this Petition or (ii) any timing, future filings, content of, or any decisions or other activities relating to the future proceedings related to this Petition. All costs associated with this Petition will be borne by HCM, CFAD, Credes and/or HCMF.

B. Related Judicial and Administrative Matters (37 C.F.R. § 42.8(b)(2))

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the ’703 Patent has been the subject of the following lawsuits: *Acorda Therapeutics, Inc. v. Sun Pharm. Indus.*, No. 1-15-cv-00391 (D. Del. filed May 15, 2015); *Acorda Therapeutics, Inc. v. Mylan Pharm. Inc.*, No. 1-14-cv-00139 (N.D. W. Va. filed Aug. 22, 2014); *Acorda Therapeutics, Inc. v. Apotex Corp.*, No. 1-14-cv-00955

(D. Del. filed July 18, 2014); *Acorda Therapeutics, Inc. v. Teva Pharm. USA, Inc.*, No. 1-14-cv-00941 (D. Del. filed July 17, 2014); *Acorda Therapeutics, Inc. v. Mylan Inc.*, No. 1-14-cv-00935 (D. Del. filed July 16, 2014); *Acorda Therapeutics, Inc. v. Accord Healthcare Inc.*, No. 1-14-cv-00932 (D. Del. filed July 15, 2014); *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, No. 1-14-00922 (D. Del. filed July 14, 2014; *Acorda Therapeutics, Inc. v. Alkem Labs. Ltd*, No. 1-14-00917 (D. Del. filed July 11, 2014); *Acorda Therapeutics, Inc. v. Aurobindo Pharma Ltd.*, No. 1-14-cv-00909 (D. Del. filed July 10, 2014); and *Acorda Therapeutics, Inc. v. Actavis Labs. FL Inc.*, No. 1-14-cv-0082 (D. Del. filed July 7, 2014).

In addition to the related judicial matters, on February 10, 2015, Petitioner filed IPR2015-00720 seeking *inter partes* review of U.S. Patent No. 8,663,685; on February 27, 2015, Petitioner filed IPR2015-00817 seeking *inter partes* review of U.S. Patent No. 8,007,826. On August 24, 2015, the Board issued decisions denying institution for both petitions. Simultaneously with this Petition, Petitioner is seeking IPR of U.S. Patent No. 8,007,826, and its child U.S. 8,663,685 Patent; and U.S. Patent No. 8,354,437—the parent of the presently challenged ’703 Patent.

C. Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)) and Service Information (37 C.F.R. § 42.8(b)(4))

Lead counsel is Sarah E. Spires, Reg. No. 61,501. Back-up counsel are Dr. Parvathi Kota, Reg. No. 65,122; and Paul J. Skiermont (*pro hac vice* requested)—all at ADROCA703IPR1@skiermontpuckett.com and of Skiermont Puckett LLP,

2200 Ross Ave. Ste. 4800W, Dallas, Texas 75201, P: 214-978-6600 / F: 214-978-6601. Petitioner consents to electronic service at ADROCA703IPR1@skiermontpuckett.com.

IV. PAYMENT OF FEES (37 C.F.R. § 42.15(A) AND § 42.103)

The required fees are submitted herewith in accordance with 37 C.F.R. §§ 42.15(a) and 42.103(a). If any additional fees are due during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 506293. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of U.S. Patent No. 8,440,703

The ’703 Patent is titled “Methods of Using Sustained Release Aminopyridine Compositions.” (Ex. 1001.) The application, U.S. Patent App. No. 13/299,969 (the “’969 application”) was filed on Nov. 18, 2011, and it is a continuation of U.S. Patent App. No. 11/102,559 (“’559 application”), filed on Apr. 8, 2005 (now U.S. Patent No. 8,354,437), which claims priority to Provisional App. No. 60/560,894, filed on Apr. 9, 2004. (*Id.*)

1. The ’703 Patent Specification

The ’703 Patent purports to describe methods of administering less than 15 mg of a sustained release oral dosage form of 4-aminopyridine (“SR 4-AP” or “fampridine-SR”) twice daily to patients with multiple sclerosis (“MS”) in order to improve certain aspects of lower extremity function. (*Id.* at 3:65–4:19.) These

lower extremity functions are characterized by improvements in walking speed, muscle strength, and muscle tone. (*Id.* at 3:66–4:15.) The ’703 Patent further describes dispersing 4-AP “in a matrix that provides a release profile of 4-[AP] in the blood plasma of the patient extending over a period of at least 6 hours.” (*Id.* at 3:1–3.) The patent discloses that the 4-AP “formulations and compositions of the present invention exhibit a desired release profile that may be described in terms of the average maximum plasma concentration of the drug or active agent at steady state (C_{avSS}),” as “about 15 ng/ml to about 35 ng/ml.” (*Id.* at 8:5–8, 30–31.)

2. **The ’703 Claims**

The ’703 Patent has 52 claims. Claims 1 and 2 are independent claims. Each of the two independent claims describes:

> 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 4-aminopyridine twice daily for a time period of at least two weeks.

(*Id.* at 29:55–67.) Independent **claim 1** requires that the twice daily dosage of 4-AP is “less than 15 milligrams,” and further requires that “the amount of said 4-aminopyridine administered to said patient in each said administering step is the same over said time period.” (*Id.* at 29:58–62.) Independent **claim 2** requires that the twice-daily dosage of 4-AP is “10 milligrams.” (*Id.* at 29:66.)

Dependent claims 3–52 each ultimately depend directly or indirectly from claims 1 or 2, and contain the following additional limitations:

- "the improving lower extremity function in the patient is increasing walking speed of the patient" or simply "the lower extremity function is walking" (claims 3, 32–52);
- "the lower extremity function is lower extremity muscle strength" (claim 4);
- "the lower extremity function is lower extremity muscle tone" (claim 5);
- "initiating treatment of said patient with 4-aminopyridine by orally administering said sustained release composition twice daily to said patient" (claims 6–7, 33);
- "twice daily is about every 12 hours" (claims 8–9, 34);
- "said sustained release composition is a tablet" (claims 10–13);
- "said sustained release composition provides a release profile to obtain a C_{avSS} of about 15 ng/ml to about 35 ng/ml" (claims 14–15, 35–36);
- "said sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient" (claims 16–17, 37–38);
- "said sustained release composition provides a mean T_{max} in a range of about 2 to about 5.2 hours after administration of the sustained release composition to the patient" (claims 18–19, 39–41);

- "said sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours" (claims 20–21, 48–49);
- "said 4-aminopyridine is dispersed in a rate of release controlling polymer" (claims 22–23, 50–51);
- "said sustained release composition comprises a matrix, in which said 4-aminopyridine is uniformly dispersed, that is suitable for controlling the release rate of the 4-aminopyridine" (claims 24–25, 42–43);
- "said patient has relapsing remitting multiple sclerosis" (claims 26–27, 52);
- "said time period is more than two weeks" (claims 28–29, 44–45);
- "said time period comprises twelve weeks" (claims 30–31, 46–47).

3. **Prosecution History of the '703 Patent**

The '969 application included original claims 1–16, which were generally directed to "administering to a patient with multiple sclerosis…twice daily…less than 15 milligrams of 4-aminopyridine" for "increasing walking speed" or "improving lower extremity muscle strength" or "improving lower extremity muscle tone." *See*, *e.g.*, as-filed claims 1, 7, and 12. (Ex. 1002-55–56. [1]) Original claims 17–20 were generally directed to "methods of selecting individuals based on responsiveness to treatment." (*Id.* -56–57.)

[1] All hyphenated references to Exhibit pin-cites are to the Exhibit's Bates-labeled page number.

The Examiner issued a restriction requirement for the applicant to elect Group I (claims 1–16) or Group II (17–20) for further prosecution. (*Id.* -73.) Applicant elected Group I, but cancelled claims 1–20 and replaced them with new claims 21–54. (*Id.* -80–85.) The new claims were similar to original claims 1–16, but included the limitation that the 4-AP composition be administered for "at least two weeks." (*Id.* -80.) The new claims included limitations directed to particular pharmacokinetic parameters and rate-of-release compositions. (*Id.* -81–82.)

The Examiner's first substantive rejection was for obviousness over *Masterson* (Ex. 1008) in view of *Schwid* (Ex. 1009). (Ex. 1002-119.) The rejection stated that *Masterson* taught a method of treating MS patients with low-dose 4-AP (i.e., less than 15 mg), but did not explicitly address "a method of treating the symptoms of multiple sclerosis." (Ex. 1002-119–20.) *Schwid* addressed this limitation because it disclose treating MS patients with 4-AP to improve "muscle speed and lower extremity muscle tone and strength." (Ex. 1002-120.)

The Examiner also found that based on the prior art, SR 4-AP pharmacokinetic parameters would have been obvious to a person of ordinary skill in the art ("POSA"), and it would have been obvious to use a release matrix and to optimize treatment time (such as for at least two weeks):

> Finally, with regards to the treatment period instantly claimed of at least two weeks … treatment regimen is dependent on … the disease condition, the patients age, weight, co-existing conditions and other

> [individually optimized] factors … and it would have been obvious to a person of ordinary skill in the art to optimize the treatment time.

(*Id.* -122–24.)

The applicant did not directly address these arguments, but instead amended independent claim 21, adding: "'wherein the amount of said 4-aminopyridine administered to said patient in each said administering step is the same over said time period,' to make it clear that the 4-aminopyridine dosage amount is a stable amount over said time period." (*Id.* -137.) In view of the amendments, applicant stated "the [prior] art did provide some guidance regarding what dosage of 4-aminopyridine ("4-AP[”]) should be used, and this guidance was to use dosage amounts of 4-AP that were much higher than the less than 15 mg BID [twice daily] of sustained release ('SR') 4-AP that are recited in the instant claims." (*Id.* -138.)

The applicant alleged "secondary considerations of nonobviousness (surprising results, long-felt but unmet need, commercial success) exhibited by the claimed invention" (*Id.* -139), and submitted a declaration from Dr. Blight—one of the listed inventors—setting forth allegedly surprising results. (*Id.* -160.) The applicant also submitted a declaration from Dr. Medori alleging long-felt but unsolved needs, as well as failure by others. (*Id.* -161–63.) Finally, the applicant submitted a declaration from Ms. Sabella alleging commercial success of its product. (*Id.* -164–65.) A Notice of Allowance followed. (Ex. 1047-959.)

B. Effective Priority Date of the ’703 Patent Claims

The ’703 Patent claims the benefit of the ’894 Provisional application (“the Provisional”), filed April 9, 2004 (Ex. 1007.) Nevertheless, at least claims 1–30 and 32–52 are not entitled to the benefit of the Provisional’s filing date. The priority date for those claims is the ’559 application’s filing date: April 8, 2005.

The ’703 Patent’s challenged claims can only receive the benefit of the Provisional’s filing date if its disclosure satisfies the requirements of 35 U.S.C. § 112 ¶1. *New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294-96 (Fed. Cir. 2002). To satisfy written description, a POSA must immediately discern that the Provisional “necessarily discloses” the ’703 Patent’s claim limitations from the four corners of the Provisional at the time is was filed—it is not enough that a POSA could speculate as to modifications to the Provisional’s disclosure that the inventor might have envisioned but failed to disclose—and it is not even enough if such limitations are obvious from the Provisional’s disclosure. *Id*. at 1296. *See also Lockwood v. American Airlines*, 107 F.3d 1565, 1571–72 (Fed. Cir. 1997); *Waldemar Link v. Osteonics Corp*., 32 F.3d 556, 558–59 (Fed. Cir. 1994). Though the Provisional need not use the exact words of later-filed claims, it must contain an equivalent description of the claimed subject matter based on an examination of the Provisional’s words, structures, figures, and diagrams.

Lockwood, 107 F.3d at 1572. For a host of reasons, the Provisional fails to provide adequate written description for the challenged claims.

First, all challenged claims (except claims 30–31 and 46–47) require that 10 mg (or less than 15 mg) 4-AP be administered twice daily, and the claimed time period of administration must be "at least two weeks" or "more than two weeks" (together, the "two-week limitations"). (Ex. 1001 at 29:55–32:43.) The Provisional nowhere discloses a method of improving lower extremity function by administering 10 mg 4-AP, or less than 15 mg 4-AP, for "at least two weeks" or "more than two weeks." Example 11 of the Provisional describes administering 4-AP during a ***12-week*** "treatment period" at 3 different doses (10 mg, 15 mg, 20 mg) to improve lower extremity function in MS patients—and that is the only disclosure in the Provisional where less than 15 mg 4-AP is administered twice daily to MS patients. (Ex. 1007-56.) However, the disclosure of a ***12-week*** "treatment period" to improve lower extremity function in MS patients does not adequately disclose to a POSA that the challenged claims' two-week limitations were necessarily present from the Provisional's disclosure.

Example 11 discloses a "double-blind, placebo-controlled, 20 week, parallel-group study…designed in accordance with the Figure entitled Example 11 Study Design." (Ex. 1007-50.) The Study Design discloses the following time periods: "2-week placebo run-in"; "2-week ***upward titration*** (10/15 mg bid or placebo)";

"12-week stable ***treatment period***"; "1-week downward titration"; and "2-week post treatment follow-up." (Ex. 1007-56; emphasis added.) Example 11 discloses data collected at Visit 4 (end of upward titration period) and not again until Visit 7. The Provisional does not disclose when Visit 7 occurred. However, based on the placement of Visit 7 in the 12-week treatment period figure, a POSA would understand that Visit 7 occurred no earlier than week 4 of the 12-week treatment period. (Ex. 1023 ¶ 41.) Example 11, therefore, "does not disclose *any* data for the first two weeks of the 12-week treatment period, and does not disclose improvement of lower extremity function after the first two weeks of this treatment period." (*Id.* ¶ 42.) A POSA would have inferred from such non-disclosure that "the applicant either collected no data after the first two weeks of the treatment period, or the applicant collected data but did not disclose it because such data did not show lower extremity function improvement." (*Id.* ¶ 43.) As a result, this disclosure is not a full, clear, concise, and exact disclosure of the challenged claims' two-week limitations—and "a POSA would not immediately discern that the Provisional necessarily disclosed the two-week limitations based on reviewing the Provisional." (*Id.* ¶¶ 43, 36.) *New Railhead*, 298 F.3d at 1294–96.

Nor does Example 11's two-week *upward-titration* period *prior* to the stable 12-week "treatment" period support the claimed two-week limitations in the challenged claims. In fact, the Provisional is silent as to precise method of

performing "upward titration (10/15 mg bid or placebo)" for two weeks. (Ex. 1023 ¶¶ 46–47.) However, upon reviewing the Provisional, "a POSA would have understood from experience that the '2-week upward titration' period refers to a standard phrase in the industry that describes the time period during which a dose is introduced and gradually increased to ensure the patient does not have an adverse reaction to the medication." (*Id.* ¶ 44; Ex. 1007-56.) Specifically:

> The figure entitled "Example 11 Study Design" ambiguously alludes to "2-week upward titration (***10/15 mg bid*** or placebo)" without further explanation. (Ex. 1007-56.) At best, a POSA would have understood this disclosure to mean that the "2-week upward titration" period involved administering SR 4-AP BID at a dose of 10 mg for some portion of the 2-week period, following by an upward dose of 15 mg for the remaining portion of the 2-week period, to ensure patients do not have an adverse reaction. Nothing in Example 11 suggests that different treatment groups took different dosages during the upward titration period. And the applicant essentially acknowledges the Provisional's failure to disclose the upward titration method of Example 11 because it ***added at least 15 lines of text*** to the '703 Patent to explain the dosing parameters of the upward-titration period. (Ex. 1001 at 20:3–19.) As noted, that explanation is different from how a person of ordinary skill in the art at the time the Provisional was filed would have understood the Example 11 Study Design.

(Ex. 1023 ¶ 47.) As a result, the "upward titration period of Example 11 does not disclose to a POSA that the two-week limitations of claim 1 and its dependent claims were necessarily present from the Provisional's disclosure, because those claims require administration of ***less than*** 15 mg 4-AP—not the 15 mg disclosed in Example 11's upward titration period." (*Id*.) Those claims also require administering ***the same dose*** of 4-AP for at least two weeks or more than two weeks—"not merely for a portion of the two-week upward titration period as suggested by Example 11's disclosure." (*Id*.) Likewise, "Example 11's upward titration period does not adequately disclose to a POSA that the two-week limitations in '703 Patent claim 2 (and its dependent claims) were necessarily present from the disclosure, because those claims require administration of 10 mg 4-AP for ***at least two weeks or more than two weeks***—not merely for some portion of the two-week upward titration period. (*Id*.) *Lockwood*, 107 F.3d at 1571–72.

Likewise, original claims 1–2 of the Provisional do not satisfy § 112 ¶ 1 for the challenged claims, because those claims are entirely open-ended with respect to duration of dosing. (Ex. 1007-52.) Therefore, from the perspective of a POSA such claims "do not disclose to a POSA that the two-week limitations were necessarily present—because such limitations, or their equivalents, are not disclosed by the original claims based on a POSA's evaluation of the disclosure as a whole."

(Ex. 1023 ¶ 48.) *See Ariad Pharms., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1349-51 (Fed. Cir. 2010) (en banc).

Second, claim 1 and its dependent claims require a dosing of "less than 15 milligrams of 4-aminopyridine twice daily…." (Ex. 1001 at 29:55–32:43.) A POSA would have understood this phrase to encompass the range of "between 0 and 15 milligrams (exclusive of 0 and 15)." *See* Section V.D.1., *infra*. The Provisional does not provide support for "less than 15 milligrams" because it does not adequately describe the full scope of the range "less than 15 milligrams." (Ex. 1023 ¶ 37.) Example 11 of the Provisional "describes a 12-week dosing of 10 mg 4-AP BID. However, other than this 10 mg dosing, the Provisional does not describe any other 4-AP doses in the range 'less than 15 milligrams.'" (*Id*.) Consequently, a POSA considering this *single data point* would not immediately discern that the Provisional necessarily disclosed the full scope of the claimed range of "less than 15 milligrams" 4-AP BID. (*Id*.) *See, e.g., In re Lukach*, 442 F.2d 967, 969 (C.C.P.A. 1971) (patentee not entitled to an earlier application's filing date for a claimed Mw/Mn ratio ranging "from 2.0 to 3.0" based on a "single example" in the priority application disclosing a "Mw/Mn ratio of 2.6"); *Ralston Purina Co. v. Far-Mar-Co.*, 772 F.2d 1570, 1575–76 (Fed. Cir. 1985) (parent application disclosing 25%–27% water does not support broader claims "in the range of 20%–30%"); *Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995)

(disclosed range of 45% to 55% does not provide written description for claimed range of 50% to 60%). *Cf. In re Fisher*, 57 C.C.P.A. 1099, 1108 (C.C.P.A. 1970) (explaining that "a single embodiment" is less likely to support a claimed range broader than the embodiment when claims are directed to physiological activity rather than the more predictable mechanical or electrical arts).

Third, claims 14–15 and 35–36 are unsupported by the Provisional because they require a C_{avSS} range of 15 ng/ml to 35 ng/ml in MS patients receiving 10 mg (or less than 15 mg) 4-AP BID. By contrast, the only C_{avSS} ranges disclosed in the Provisional are in Table 7, which only discloses C_{avSS} ranges of 15.1 ng/ml to **26.5** ng/ml. (Ex. 1007-45.) Because all claimed ranges for claims 14–15 and 35–36 claim up to 35 ng/ml—while the Provisional does not disclose at least the upper range of 26.6 ng/ml–35 ng/ml—claims 14–15 and 35–36 of the '703 Patent cannot claim priority to the Provisional. *See*, *e.g.*, *Chiron Corp. v. Genentech*, Inc., 363 F.3d 1247, 1259 (Fed. Cir. 2004) (claims broader than the specification lack written description where disclosure lacks a specific and useful teaching commensurate with claim scope); *In re Lukach*, 442 F.2d at 969; *Ralston Purina*, 772 F.2d at 1575–76. The written support for the claimed C_{avSS} ranges found in the '703 Patent (Ex. 1001 at 8:21–27) is absent from the Provisional, thus a POSA

would not have immediately discerned that the Provisional necessarily disclosed the full scope of the claimed C_{avSS} ranges. (Ex. 1023, ¶ 49.)[2]

For all of the foregoing reasons, at least claims 1–30 and 32–52 are entitled to a priority date that is no earlier than April 8, 2005.

C. Level of Ordinary Skill in the Art

A POSA as of April 9, 2004—the earliest possible priority date for the '703 Patent—"would have 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, with access to a person having an advanced degree (M.S. or Ph.D.) in pharmaceutics or pharmaceutical formulation, specifically oral sustained release formulations, or at least 5 years of experience in formulating oral sustained release pharmaceutical drug products." (Ex. 1023 ¶ 16.) "A POSA may work as part of a multi-disciplinary team and draw upon not only his or her own skills," but also take advantage of "specialized skills of others on the team." (*Id*. ¶ 17.)

[2] The Provisional purports to incorporate by reference certain documents that cannot provide the missing disclosure because they do not identify where the incorporated material is found. (Ex. 1007, *passim*.) *See Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378 (Fed. Cir. 2007).

D. Claim Construction of Challenged Claims

A claim subject to IPR receives the "broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b); *see In re Cuozzo Speed Techs., LLC*, 778 F.3d 1271 (Fed. Cir. 2015). The broadest reasonable construction of claim language is not one that permits *any* reading, but instead is one that must be made "in light of the specification as it would be interpreted by one of ordinary skill in the art." *In re Am. Acad. of Sci. Tech. Ctr.*, 367 F.3d 1359, 1364 (Fed. Cir. 2004) (quotation omitted).

Unless otherwise noted, Petitioner accepts, for purposes of this IPR only, that the claim terms of the '703 Patent are presumed to take on the ordinary and customary meaning that they would have to a POSA.

1. **"less than 15 milligrams"**

The term "less than 15 milligrams" should be construed to mean "between 0 and 15 milligrams, exclusive of 0 and 15 milligrams." (Ex. 1023 ¶ 52.)

2. **"release profile"**

The term "a release profile" should be construed to mean "a concentration of a drug in a patient's plasma over time." (*See* Ex. 1001 at 7:11–15; Ex. 1023 ¶ 54.)

3. **"matrix"**

The term "matrix" should be construed to mean "a composition which provides for a sustained release of a drug into the plasma of a patient." (*See* Ex. 1001 at 3:19–21, 9:16–19; Ex. 1023 ¶ 56.)

4. **"improving walking"**

Improving walking (claim 32) means "to quantifiably make better a patient's ability to walk." (Ex. 1023 ¶ 58.)

5. **"initiating treatment"**

The phrase "initiating treatment" means "beginning administration of a therapeutic agent or drug." (Ex. 1023 ¶ 60; Ex. 1001 at 13:30–34.)

E. Statement of Precise Relief Requested for Each Claim Challenged

1. Claims for Which Review is Requested

Petitioner requests IPR under 35 U.S.C. § 311 of claims 1–52 of the '703 Patent, and cancellation of these 52 claims as unpatentable.

2. Statutory Grounds of Challenge

Petitioner requests IPR of the '703 Patent claims 1–52 in view of the following references, each of which is prior art to the '703 Patent under 35 U.S.C. §§ 102(a) and (b) or 103. The *S-1* was not cited by the applicant or otherwise introduced to the Examiner during the '703 Patent prosecution, and the Examiner did not rely on any of the prior art in the following chart as the basis of any

rejection in any Office Action. (*See* Exs. 1002, 1046-47, *passim*.) Claims 1–52 are unpatentable under 35 U.S.C. § 103:

Ground	Proposed Rejections for the ’703 Patent	Exhibit Number(s)
1	Claims 1–7, 10–11, 26–33, 44–46, 52 are obvious under 35 U.S.C. § 103 in light of the *S-1*	1003
2	Claims 8–9, 12–21, 34–41, 47–49 are obvious under 35 U.S.C. § 103 in light of the *S-1* in view of *Hayes*	1003, 1005
3	Claims 22–25, 42–43, 50–51 are obvious under 35 U.S.C. § 103 in light of the *S-1* in view of *Juarez*	1003, 1006

F. Overview of the State of the Art and Prior Art References

1. 4-AP History and State of the Art at the Time of the ’703 Patent

The ’703 Patent does not claim the 4-AP compound. (Ex. 1001, *passim*.) Nor does it claim to have pioneered the use of 4-AP to treat MS patients. (*Id*.) The ’703 Patent does not even claim that the oral administration of 10 mg 4-AP (or less than 15 mg) BID to MS patients or the use of sustained release 4-AP are novel, because those teachings were known in the art. (*See, e.g.*, Ex. 1003; Ex. 1005; Ex. 1020.) Instead, the ’703 Patent claims methods of administering 4-AP BID to MS patients for a time period to attain therapeutic objectives such as improving walking. By at least April 9, 2004—the earliest possible priority date for the ’703

Patent—a POSA would have known to apply the claimed methods to achieve those objectives.

The pharmacological properties of 4-AP have been studied for decades. For over 30 years, researchers have shown the effectiveness of 4-AP treatment in MS patients—"an inflammatory demyelinating disease featuring selective destruction of the central nervous system (CNS) myelin." (Ex. 1023 ¶ 18; Ex. 1010-2.) By the 1990s, researchers conducted double-blind studies evaluating the effectiveness of *oral* 4-AP administration in MS patients. (*See generally*, Ex. 1011; 1012.) And by 1991, it was even known in the art that *sustained-release* oral compositions of 4-AP were effective in treating MS. (*See, e.g.*, Ex. 1008, *passim*.)

By April 2004, a POSA would have known that MS is a chronic disease that causes problems with walking and lower extremity muscle function on an ongoing basis, and especially as the disease progresses over time. (Ex. 1023 ¶ 26.) As a result, among the therapeutic objectives of a POSA "seeking to treat MS patients with 4-AP prior to April 2004, were to improve walking, increase walking speed, and increase lower extremity muscle strength and tone." (*Id*. ¶ 27.) By 1987, researchers had measured neurological changes from 7–35 mg of 4-AP in 1–5 mg doses administered every 10–60 minutes, with "motor function (power, coordination, gait)" in 5 out of 12 patients improving "within minutes of drug injection at doses as low as 2 mg." (Ex. 1013-1.) In 1990, Davis *et al*. administered

10–25 mg 4-AP (total doses per individual) to MS patients and observed marked improvements in motor functions, including gait, in doses as low as 10 mg. (Ex. 1014-1.) Polman also found that "4-Aminopyridine was more effective than 3,4-diaminopyridine, especially for ambulation" in patients with MS. (Ex. 1012-3.) Thus, by April 2004, a POSA would have known to use less than 15 mg (e.g., 10 mg) 4-AP to improve lower extremity function in MS patients.

By 1996, the National Multiple Sclerosis Society ("NMSS") had introduced four disease categories for MS: relapsing-remitting, relapsing-progressive, primary-progressive, and secondary-progressive. (Ex. 1023 ¶¶ 21–22; Ex. 1022-2.) Relapsing-remitting MS is the most common form of MS, affecting 85% of patients. (Ex. 1015-1.) A typical MS treatment regimen would almost certainly extend for at least two weeks or even months, because all four disease states require continuous treatment to maintain the benefits of the drug over time. (Ex. 1023 ¶ 28.) For example, *van Diemen* taught administering 4-AP to treat MS disability for at least two weeks, with an efficacy analysis performed only in patients who completed "at least two weeks" of treatment. (Ex. 1011-2–3.) *van Diemen* further teaches a statistically significant estimated effect of 4-AP on the mean EDSS score after 2, 6, and 12 weeks of treatment. (*See id.* at Table 1.)

It is a basic precept in medicine that "physicians always seek to prescribe the lowest effective dose of any medication" to minimize side effects. *Healthcare Grp.*

LP v. Mut. Pharm. Co., 642 F.3d 1370, 1371–72 (Fed. Cir. 2011). Therefore, a POSA would be motivated to combine the elements of the prior art showing that an oral sustained-release tablet of 4-AP at a low dose (e.g., 10 mg BID) would be *effective* in achieving the treatment objectives for an MS patient, while *minimizing* adverse effects, and to sustain treatment for a period of time of at least two weeks to maintain the benefits from treatment. (Ex. 1023 ¶ 29.)

2. **The *S-1* (Ex. 1003)**

The *S-1* constitutes prior art under 35 U.S.C. §§ 102(a) and (b) because it was printed and made publicly available at least as early as September 30, 2003—more than one year before the earliest effective filing date of April 8, 2005 (for claims without provisional priority). (Ex. 1004-9; *see generally*, Ex. 1003.) Even assuming *arguendo* that the priority date is April 9, 2004, the *S-1* would still qualify as prior art against *all* claims under 35 U.S.C. § 102(a). The *S-1* was not art of record during the '703 Patent prosecution. (*See* Ex. 1001-1–10.)

A reference is a "printed publication" if it was "available to the extent that persons interested and ordinarily skilled in the subject matter or art[,] exercising reasonable diligence, can locate it." *Voter Verified, Inc. v. Premier Election Solutions, Inc.*, 698 F.3d 1374, 1380 (Fed. Cir. 2012) (quotation omitted). The touchstone is access. If the *S-1* was accessible to interested persons skilled in the art "it is unnecessary to show that anyone actually inspected the reference." *In re*

Lister, 583 F.3d 1307, 1314 (Fed. Cir. 2009). *See also Constant v. Advanced Micro-Devices, Inc*., 848 F.2d 1560, 1569 (Fed. Cir. 1988) (holding if publication is accessible, "there is no requirement to show that particular members of the public actually received the information.").

As early as 2000, a POSA would have known that Acorda was investigating fampridine [4-AP] "for the potential treatment of spinal cord injuries and multiple sclerosis." (Ex. 1017-1.) This 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. (*See id;* Ex. 1018-1 ("[f]ampridine-SR is also in Phase 2 clinical trials to evaluate safety and efficacy in the treatment of symptoms associated with multiple sclerosis (MS)."); Ex. 1019-1 ("[t]he Company's lead product, Fampridine-SR, is in Phase 3 clinical trials for chronic SCI and Phase 2 for MS.").) Based on such information, a POSA would have been motivated to consult information—particularly public filings such as the *S-1*—relating to Acorda's research. A POSA interested in researching and treating MS would have known that Acorda is active in the field of SR 4-AP research to treat patients with MS, "and would have been motivated to keep apprised of Acorda's research and studies conducted with 4-AP in 2003. A POSA would therefore monitor and seek information about such studies by looking for and accessing statements and publications by researchers and companies

conducting such studies, including Acorda's research and disclosures." (Ex. 1023, ¶¶ 62–63.)

"By law, companies in the United States making an initial public offer of stock must file certain forms with the U.S. Securities and Exchange Commission (SEC)." (Ex. 1016 ¶ 11.) "Since 1996, these public filings have been available online in the SEC's EDGAR (Electronic Data Gathering, Analysis, and Retrieval) system," which endeavors to make the filings publicly available within "a matter of minutes." (*Id*. ¶ 12, n.2.) *See Constant*, 848 F.2d at 1569 ("Evidence of routine business practice can be sufficient to prove that a reference was made accessible before a critical date.") "Included in these disclosures is the S-1 form, which contains basic business and financial information about the issuer." (*Id.* ¶ 11.)

The *S-1* HTML properties establish that, "[t]he SEC received the Acorda Therapeutics filing, including the S-1 form, on 26 September 2003" and "filed it on 29 September 2003." (*Id.* ¶¶ 14–15.) Thus, by at least September 30, 2003, the *S-1* was available to a POSA interested in reviewing information regarding Acorda Therapeutics. (*Id.*) The September 30, 2003 SEC Registration Statement, which provided instructions to the public for obtaining a printed copy of the *S-1* publication via mail, further establishes its public availability. (Ex. 1004-9.)

Lest there be any doubt, Acorda has admitted that the *S-1* is prior art to a European counterpart of the '703 Patent with the same priority date, and that

admission is binding here.[3] Specifically, on September 16, 2014, Acorda responded to an appeal opposing its European Patent No. 1732548 (B9) ("EP '548") (Ex. 1025), and countered an opponent's argument that the *S-1* (the "C27" reference) anticipates EP '548's claims. (Ex. 1026 ¶ 5.19.)[4] In its EPO brief, Acorda repeatedly *admitted* that the *S-1* was prior art to EP '548 (*See e.g., id.* ¶¶ 4.6, 5.27, 6.39, 6.61.) The Federal Circuit has held that a patentee's admissions of a reference's prior art status is "clear and convincing evidence" that the reference is prior art. *See, e.g., Tyler Refrig. v. Kysor Indus. Corp.*, 777 F.2d 687, 690 (Fed. Cir. 1985) (collecting authority). The fact that the admissions occurred during EPO proceedings does not negate Acorda's admissions.[5] *See, e.g., Sentry Prot. Prods. v. Eagle Mfg. Co.*, No. 1:01-cv-2240, 2003 WL 25539702, 2003 U.S. Dist. LEXIS

[3] The EPO's "Espacenet" search tool provides access to "patent family information, telling you if similar patents have been claimed in other countries." (Ex. 1027-2.) Espacenet's bibliographic data for the '703 Patent states it was "also published as" Acorda's opposed "EP1732548 (B9)" patent (Ex. 1028.)

[4] The *S-1* is document C27 in the EPO appeal. (Ex. 1026, Annex A.)

[5] For purposes of Acorda's admissions, the EPO standards for writings as prior art are comparable to the U.S. requirements for prior art printed publications. (*See* Ex. 1021-1 ("everything made available to the public by means of a written… description …before the date of filing of the European patent application.").

27435, at *32–33 (N.D. Ohio Sept. 30, 2003) (collecting authority and finding "[s]everal other cases have held that statements made by a patentee during foreign patent proceedings can constitute admissions"); *Donnelly Corp. v. Gentex Corp.*, 918 F. Supp. 1126, 1134–35 (W.D. Mich. 1996) (finding public use admissions from foreign patent proceedings admissible in U.S. proceedings under FRE 801(d)(2)). Thus, the *S-1* is a prior art printed publication to the challenged claims.

The *S-1* describes clinical trials conducted using a sustained-release ("SR") composition of 4-AP. The reference teaches the effectiveness of the 10–25 mg BID dosing range, stating that "clinical trials indicated that there was evidence of increasing dose-response through the range of 10 to 25 mg twice a day, but that evidence of increasing efficacy at doses higher than 25 mg twice a day was limited, possibly being offset by increased side effects." (Ex. 1003-37.) The *S-1* described using sustained-release fampridine in an MS Phase II clinical trial:

> The current late Phase II clinical trial, MS-F202, was designed, after extensive consultation with a panel of expert MS neurologists and with the FDA, to provide pivotal data for support of an NDA for the use of fampridine-SR in MS. **The clinical trial is also designed to compare three doses of 10, 15 and 20 mg, twice per day, and to assess their relative safety and efficacy over a treatment period of 12 weeks**. The primary endpoint of the study is an improvement in average walking speed using the Timed 25 Foot Walk.

(*Id.* -37, emphasis added.)

The *S-1* also discussed a previously conducted Phase II study, MS-F201, which was completed in 2001. (*Id*.) In that study, "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." *Id.* The MS-F201 Phase II 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" and that "[m]ost 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*.) The *S-1* disclosures teach nearly all claim limitations, as explained in more detail below.

3. ***Hayes* (Ex. 1005)**

Hayes constitutes prior art under 35 U.S.C. §§ 102(a) or (b) to all claims because it was published and accessible by September 2003 (Ex. 1016 ¶¶ 16–21) in the peer-reviewed journal, *Clinical Neuropharmacology*—more than one year before the earliest effective filing date of April 8, 2005, for claims not entitled to provisional priority. (Ex. 1005.) Even assuming *arguendo* an April 9, 2004, priority date, *Hayes* would still be prior art against all claims under 35 U.S.C. § 102(a). *Hayes* was not the basis of any Examiner rejection during the '703 Patent prosecution. (Exs. 1002, 1046-47, *passim*.) Rather, the applicant cited *Hayes* as

prior art evidence *supporting* its claimed pharmacokinetic ranges. (Ex. 1002-151–52, 157.)

Hayes notes that "[c]linical trials have confirmed that administration of fampridine [4-AP] results in symptomatic improvements in patients with SCI and multiple sclerosis." (Ex. 1005-1.) It presents the results of two studies "conducted to determine the pharmacokinetics and safety profile of an oral, sustained-release (SR) formulation of fampridine (fampridine-SR, 10–25 mg) [1] administered as a single dose…and [2] twice daily for 1 week…in patients with chronic, incomplete SCI." (Ex. 1005-1.) Dose administrations occurred every 12 hours. (*Id.* -3.) The doses in each study were 10 mg, 15 mg, 20 mg, and 25 mg. (*Id.* -2.)

Hayes reported that "[s]teady state was achieved by day 5…after twice-daily administration" and recorded pharmacokinetic data in relation to the plasma concentration of the drug. (*Id.* -4.) Figure 1 provides release profile information for the drug, and Table 3 provides pharmacokinetic data. (*Id.* -5, 7.) The data for 10 mg BID showed a C_{avSS} (average plasma concentration at steady state) of 20.8 (± 5.7) ng/mL—a range of 15.1 ng/mL to 26.5 ng/mL (accounting for error), a t_{max} of 10 mg SR 4-AP is 2.7 ± 1.0 hours—a range of 1.7–3.7 hours (accounting for error), and a release profile of 24 hours. (*Id.* -5, 7.)

4. ***Juarez* (Ex. 1006)**

Juarez constitutes prior art under 35 U.S.C. § 102(b) regardless of priority date, because it was published in the *Int'l J. of Pharm.* in 2001, which is more than one year before April 9, 2004. (Ex. 1006-1.) *Juarez* was not the basis of any Examiner rejection during the '703 prosecution. (Exs. 1002, 1046-47, *passim*.)

Juarez teaches the preparation of an oral tablet comprising 4-AP and a rate of release controlling polymer. (Ex. 1006-1–3.) *Juarez* also discloses a sustained release 4-AP composition formulated as a matrix with the polymer hydroxypropyl methylcellulose ("HPMC"). (Ex. 1006-2–3.) *Juarez* further discloses that the purpose of this HPMC matrix is to "prolong delivery with zero-order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect." (*Id*. -2.)

VI. DETAILED EXPLANATION OF THE CHALLENGE

A. Ground 1: Claims 1–7, 10–11, 26–33, 44–46, and 52 are obvious in light of the *S-1* in view of the knowledge of a POSA.

Independent claims 1 and 2 require:

> 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 4-aminopyridine twice daily for a time period of at least two weeks.

(Ex. 1001 at 29:55–67.) Claim 1 further requires that the twice daily dosage of 4-AP is "less than 15 milligrams," while claim 2 requires the dosage to be "10

milligrams." (Ex. 1001 at 29:58, 66.) Claim 1 further requires that "the amount of said 4-aminopyridine administered to said patient in each said administering step is the same over said time period." (Ex. 1001 at 29:58–62.)

The combination of the *S-1* with common knowledge available to a POSA teaches each element of the challenged claims. A POSA would have been motivated to combine the *S-1* with common knowledge in an effort to arrive at low-dose methods for improving lower-extremity functions associated with MS, while minimizing adverse side effects. (Ex. 1023 ¶¶ 62–120.)

1. **Independent claims 1 and 2 are obvious in light of the *S-1* disclosure and the knowledge of a POSA.**

The *S-1* teaches every limitation of claims 1 and 2. The *S-1* describes research into "Fampridine-SR, [which] is a **sustained release, oral tablet** formulation of **fampridine**, suitable for **twice daily dosing**." (Ex. 1003-34 (emphasis added).) Thus, the *S-1* confirms, and a POSA would have understood, that Fampridine-SR is another name for sustained release 4-aminopyridine, or SR 4-AP. (Ex. 1003-34 ("We have a worldwide exclusive license from Elan to its patent for the sustained release formulation of aminopyridines, which includes fampridine"); Ex. 1023 ¶ 39.) The *S-1* also discloses the details of multiple clinical trials in which Fampridine-SR was administered to patients suffering from MS, all with the intended outcome of improving lower-extremity function. (Ex. 1023 ¶¶ 63, 66, 67–68.)

The *S-1* discloses that the "Phase 2 clinical trial of **Fampridine-SR** in **Multiple Sclerosis**, MS-F201…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." (Ex. 1003-37 (emphasis added).) To do so, "subjects received Fampridine-SR in doses increasing from 10 mg to 40 mg **twice per day over eight weeks** of treatment," and "demonstrated that **doses up to 25 mg twice a day**…were associated with statistically **significant improvements in walking speed and leg muscle strength**." (*Id.* -37 (emphasis added).) Significantly, "**[m]ost 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.* (emphasis added).)

In sum, the *S-1* disclosed the results of a completed clinical trial, MS-F201, in which MS patients received 4-AP twice a day orally for 8 weeks, wherein patients exhibited improvements in walking strength and speed within the first 3 weeks. The 4-AP dosing during the first 3 weeks of treatment was 10–25 mg twice per day. "A POSA considering the teachings disclosed in the *S-1* as clinical trial MS-F201 would have understood that low-dose SR 4-AP could be orally administered to MS patients for a short period of time (e.g., several weeks) to achieve an improvement in lower extremity strength and walking speed." (Ex.

1023 ¶ 113.) Further, "common knowledge available at the time would have motivated a POSA to seek similar teachings in which lower doses of 4-AP could be administered to achieve efficacious results." (*Id.* ¶ 115.) *See Tyco Healthcare Grp. LP*, 642 F.3d at 1371–72 ("physicians always seek to prescribe the lowest effective dose of any medication"). The *S-1* provides exactly that teaching.

Following the MS-F201 trial, the *S-1* discloses a second "Phase 2 clinical trial, MS-F202, [that] was designed…to provide pivotal data for support of an NDA for the use of **Fampridine-SR** in **MS**." (Ex. 1003-37 (emphasis added).) According to the *S-1*, this trial, which was "designed to ***compare* three doses of 10, 15, and 20 mg, twice per day**, and to assess their relative safety and efficacy over a treatment period of **12 weeks**. The primary endpoint of the study is an **improvement in average walking speed** using the Timed 25 Foot Walk." (*Id.* -37 (emphasis added).) "In light of this disclosure that a stable 10 mg dose was chosen for MS-F202 following the conclusion of the MS-F201 trial 'designed to determine the optimal dose level of Fampridine-SR,' the '703 Patent's claimed point of novelty over the prior art—its 10 mg (or less than 15 mg) dose—would have been obvious to a POSA." (*Id.* -37; Ex. 1023 ¶ 77.) *See In re Peterson*, 315 F.3d 1325, 1329–30 (Fed. Cir. 2003) ("[W]hen, as here, the claimed ranges are completely encompassed by the prior art, the [obviousness] conclusion is even more compelling than in cases of mere overlap."); *In re Applied Materials, Inc.*, 692

F.3d 1289, 1295 (Fed. Cir. 2012) ("'[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'") (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). Such is the case here because it is a basic precept in the field of medicine that "a POSA would have been motivated to try to use the lowest effective dose to minimize side effects." (Ex. 1023 ¶ 29.) *See Tyco Healthcare Grp. LP*, 642 F.3d at 1371–72 (affirming summary judgment of invalidity on the basis that it would have been obvious to administer a medication at the lowest disclosed efficacious range since "physicians always seek to prescribe the lowest effective dose of any medication," particularly in the case of "patients sensitive to the side effects of" the medication).

Moreover, the *S-1* further discloses that the data from the MS-F202 trial was intended "to support an indication for the **treatment of lower extremity motor dysfunction, characterized by weakness and walking impairment**." (Ex. 1003-37 (emphasis added).) "Based on these statements of intent to rely on this clinical data for NDA submission and drug label indications, a POSA would reasonably expect all doses (10, 15, and 20 mg) of this trial to be successful in treating lower extremity motor dysfunction, and particularly with respect to improving lower extremity muscle strength and walking speed." (Ex. 1023 ¶ 89.) *See In re Montgomery*, 677 F.3d 1375, 1382–83 (Fed. Cir. 2012) (affirming invalidity over a

published clinical protocol "designed to obtain data for submission to regulatory agencies" and so in "an advanced stage of testing designed to secure regulatory approval" in light of Manual of Patent Examining Procedure § 2107.03's statement that, "if an applicant has initiated human clinical trials for a therapeutic product or process, [Patent & Trademark] Office personnel should presume that the applicant has established that the subject matter of that trial is reasonably predictive of having the asserted therapeutic utility").

As the bold typeface above indicates, the *S-1* explicitly discloses every element common to **claims 1 and 2**: "1) improving lower extremity function; 2) in a human[6] multiple sclerosis patient in need thereof; 3) comprising orally administering to said patient; 4) 10 mg (and thus less than 15 mg); 5) of a sustained release composition of 4-aminopyridine (Fampridine-SR); 6) twice daily; 7) for a time period of at least two weeks (i.e., 12 weeks)." *See In re Applied Materials,*

[6] "A POSA would have understood, and the *S-1* confirms, that these Phase 2 clinical trials for MS were conducted in 'human multiple sclerosis patient[s] in need' of treatment." (Ex. 1023 ¶ 68; Ex. 1003-45 ("Human clinical trials…: Phase 2: The drug is administered to a limited subject population to identify possible adverse effects and safety risks, to determine the efficacy of the product for specific targeted diseases and to determine dosage tolerance and optimal dosage.").)

Inc., 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("A prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.") (quotation omitted). (Ex. 1023 ¶ 66.)

With respect to the final element of **claim 1**, "[a] POSA would have understood that the MS-F202 comparison in the *S-1* of 'three doses of 10, 15, and 20 mg, twice a day…over a treatment period of 12 weeks' means that 10 mg of Fampridine-SR was administered twice per day to a first patient group for 12 weeks; hence receiving the ***same* amount** (i.e. 10 mg) of 4-AP at each administration step as **claim 1** requires." (*Id.* ¶ 71 (emphasis added.)

Thus, for at least the foregoing reasons, "[**c]laims 1 and 2** of the '703 Patent would have been obvious to a POSA in light of the *S-1*." (*Id.* ¶ 72.)

2. **Dependent claims 3–7, 10–11, 26–33, 44–46, and 52 are obvious in light of the *S-1* and a POSA's knowledge.**

The dependent claims fail to add any non-obvious limitations. Each element of the dependent claims is disclosed in the *S-1*, or would have been obvious to a POSA in light of the common knowledge in the field.

a. The *S-1* teaches improving lower extremity function, including walking, muscle strength, and muscle tone, as well as increasing the patient's walking speed (claims 3–5, 32).

Claim 3 depends from claim 1 and additionally requires that "the improving lower extremity function in the patient is increasing walking speed of the patient."

(Ex. 1001 at 30:1–3.) **Claim 32** also depends from claim 1, and additionally requires that "the lower extremity function is walking." (Ex. 1001 at 31:15–16.)

The *S-1* disclosure of Fampridine-SR clinical trials "to support an indication for the treatment of lower extremity motor dysfunction, characterized by weakness and walking impairment," measuring "an improvement in average walking speed" and "the effect of the drug on symptoms of the disease, including motor strength, [and] timed walking" satisfies the additional limitations of **claims 3 and 32**. (Ex. 1003-37 (emphasis added).) *See In re Montgomery*, 677 F.3d at 1382–83.

The *S-1* is replete with the researchers' observations that the administration of the sustained-release formulation of fampridine resulted in "improvement in walking speed." (Ex. 1003-30, 33, 35, 37.) In particular, the *S-1* teaches that "[t]he primary endpoint of the study is an improvement in average walking speed using the Timed 25 Foot Walk ("T25-FW"). (*Id*. -37.) The T25-FW "is part of a standardized set of neurological tests, called the Multiple Sclerosis Functional Composite Score, and involves timing the subject completing a 25 foot walk." (*Id.*) In one clinical trial, when the researchers "examined the measurements from individual subjects, and looked at the improvement in walking speed between the baseline period and the average over the first four treatment weeks, [they] found clear differences in the pattern of response between Fampridine-SR and placebo-

treated subjects." (*Id.*) The researchers additionally found that "the Fampridine-SR treated group showed a marked tendency for improvement in speed." (*Id.*)

A patient's score on the T25-FW, used as a primary measure of improvement in the studies disclosed in the *S-1*, is indicative of not just walking speed, but also other aspects of walking. (Ex. 1023 ¶ 93.) "Applying this knowledge to the *S-1*, a POSA would have concluded—based on a reasonable expectation—that the administration of 10 mg BID of sustained release 4-AP" in the reference resulted in the **claim 3** improved walking speed and **claim 32** improved walking. (*Id.* ¶ 94.) Therefore, these claims would have been obvious to a POSA. (*Id.*)

Claim 4 depends from claim 1 and additionally requires that "the lower extremity function is lower extremity muscle strength." (Ex. 1001 at 30:4–5.) **Claim 5** depends from claim 1 and additionally requires that "the lower extremity function is lower extremity muscle tone." (Ex. 1001 at 30:6–7.)

As noted above, the *S-1* discloses Fampridine-SR clinical trials "to support an indication for the <u>treatment of lower extremity motor dysfunction</u>, characterized by <u>weakness</u>," and measuring "the effect of the drug on symptoms of the disease, including <u>motor strength</u>." (Ex. 1003-37 (emphasis added).) In light of this *S-1* disclosure regarding improving lower extremity weakness and motor strength, it would have been obvious to a POSA that such improvements would naturally also

improve "lower extremity muscle tone," satisfying **claim 5**. (Ex. 1023 ¶¶ 97–98.) *See Perfect Web Techs., Inc. v. InfoUSA, Inc.*, 587 F.3d 1324, 1329 (Fed. Cir. 2009) ("*KSR* expanded the sources of information for a properly flexible obviousness inquiry to include … background knowledge, creativity, and common sense of the person of ordinary skill."); *In re Montgomery*, 677 F.3d at 1382–83.

A POSA would have understood "weakness" in this context to refer to both muscle strength and tone. (Ex. 1023 ¶ 97.) Muscle tone, as a POSA would have known, refers to a muscle's resistance to passive stretch during a resting state. (*Id.*) Lower extremity weakness in an MS patient implies both deficient muscle tone and strength. (*Id.*) Therefore, the *S-1's* disclosure of treating lower extremity motor dysfunction, characterized by weakness, implies an indication directed to improvements in muscle strength and muscle tone. (*Id.* ¶¶ 97–98.) Thus, a POSA would have found "it obvious to apply the methods disclosed in the *S-1* to achieve the additional elements of **claims 4 and 5**." (*Id.* ¶ 98 (emphasis added).)

b. The *S-1* teaches "initiating treatment of said patient with 4-aminopyridine by orally administering said sustained release composition twice daily to said patient" (claims 6–7, 33).

Claim 6 depends from claim 1, claim 7 depends from claim 2, and claim 33 depends from claim 32—described above in Section VI.A.2.a. Each of **claims 6–7 and 33** requires "initiating treatment." (Ex. 1001 at 30:8–15, 31:18–21.)

A POSA would have understood that "initiating treatment" refers to administering a therapeutic agent or drug to a patient. "Because the *S-1* discloses initiating treatment of MS patients in the MS-F202 trial by administering to the patient doses of 10 mg BID of fampridine-SR, a POSA would have understood this to mean that patients initiated treatment with a 10 mg BID dose as indicated." (Ex. 1023 ¶ 76.) Thus, the additional limitations of **claims 6–7 and 33** would have been obvious to a POSA in light of the *S-1* disclosure. (*Id.* ¶ 77.)

c. The *S-1* teaches that the sustained release 4-AP is a tablet (claims 10–11).

Claim 10 depends from claim 1, and claim 11 depends from claim 2. Each of **claims 10–11** requires that "said sustained release composition is a tablet." (Ex. 1001 at 30:20–23.)

The *S-1* explicitly discloses the limitations of **claims 10–11**, stating that "Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1003-29 (emphasis added).) "Therefore, these claims would have been obvious to a POSA in light of the *S-1* disclosure." (Ex. 1023 ¶ 102.)

d. The *S-1* teaches or suggests treatment of a patient with relapsing remitting multiple sclerosis (claims 26–27, 52).

Claim 26 depends from claim 1, claim 27 depends from claim 2, and claim 52 depends from claim 32—described above in Section VI.A.2.a. Each of **claims**

26–27 and 52 requires that "said patient has relapsing remitting multiple sclerosis." (Ex. 1001 at 31:3–6, 32:42–43.)

The *S-1*'s general disclosure of using "Fampridine-SR in Multiple Sclerosis" meets the limitation of **claims 26–27 and 52**. (Ex. 1003-37.) As the patentee acknowledged during prosecution, "[m]ultiple sclerosis has been commonly classified into four (4) clinical phenotypic subtypes: Relapsing Remitting (RR), Secondary Progressive (SP), Primary Progressive (PP), and Progressive Relapsing (PR)." (Ex. 1002-154 n.15; Ex. 1023 ¶ 21.) A POSA in April 2004 also would have appreciated the MS subtypes, and understood that RR is the most common MS subtype. (Ex. 1023 ¶¶ 21–22.) "Because the *S-1* does not specify which MS subtype it is intended to treat, or teach away from treating any particular subtype, a POSA would have been motivated to utilize the *S-1*'s disclosed methods to treat RRMS patients." (*Id.* ¶ 120.) *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) ("'When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.'") (quoting *KSR Int'l Co.*, 550 U.S. 398, 421 (2007)). Therefore, these claims would have been obvious to a POSA in light of the *S-1* disclosure. (Ex. 1023 ¶ 120.)

e. The *S-1* teaches the administration of sustained release 4-AP for "more than two weeks" and "twelve weeks" (claims 28–31, 44–46)

Claim 28 depends from claim 1, claims 29 and 45 depend from claim 2, and claim 44 depends from claim 32—as described in Section VI.A.2.a. Each of **claims 28–29 and 44–45** requires that "said time period is more than two weeks." (Ex. 1001 at 31:7–10, 32:18–22.) **Claim 45** requires that the "lower extremity function is walking," which the *S-1* teaches as described in Section VI.A.2.a.

Claim 30 depends from claim 1, claim 31 depends from claim 2, claim 46 depends from claim 32—described above in Section VI.A.2.a. Each of **claims 30–31 and 46** requires the additional limitation that "said time period comprises twelve weeks." (Ex. 1001 at 31:11–14, 32:23–24.)

The *S-1* disclosure of a "treatment period of 12 weeks" meets the open-ended limitation of "said time period is more than two weeks" recited in **claims 28–29 and 44–45**, as well as the limitation "said time period comprises twelve weeks," recited in **claims 30–31 and 46**. (Ex. 1003-37.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295. Therefore, these claims would have been obvious to a POSA in light of the *S-1* disclosure. (Ex. 1023 ¶¶ 103–114.)

B. Ground 2: Claims 8–9, 12–21, 34–41, and 47–49 are obvious in light of the *S-1* in view of *Hayes* and the knowledge of a POSA.

Dependent claims 8–9, 12–21, 34–41, and 47–49 fail to add any additional non-obvious elements. The claims upon which those claims depend (claims 1–2, and 32) are obvious for at least the reasons described with respect to Ground 1.

Each of claims 8–9, 12–21, 34–41, and 47–49 would have been obvious to a POSA over the *S-1* in further view of *Hayes* and common knowledge available to a POSA. (Ex. 1023 ¶¶ 121–71.) A POSA would have been motivated to combine the *S-1* with common knowledge and publications like *Hayes*—which focuses on the same 10 mg BID doses of SR 4-AP oral tablets disclosed in the *S-1*—"to further understand and apply the methods disclosed in the *S-1* to treat patients suffering from MS and its associated conditions." (*Id.* ¶ 125.) In particular, "a POSA considering the effectiveness of the clinical trials disclosed in the *S-1* implementing oral low-dose SR 4-AP twice daily would have been motivated to look to the teachings of *Hayes*—disclosing the use of the same oral low-dose SR 4-AP—in an effort to achieve effective blood plasma pharmacokinetics." (*Id.*) The particular relevance of the *Hayes* teachings to the pending claims was explicitly acknowledged by the applicant during prosecution of the '703 Patent. (Ex. 1002-151–52, 157.)

1. **The *S-1* and *Hayes* combination teaches "twice daily is about every 12 hours" (claims 8–9, 34).**

Claim 8 depends from claim 1, claim 9 depends from claim 2, and claim 34 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1. Each of **claims 8–9 and 34** requires that "twice daily is about every 12 hours." (Ex. 1001 at 30:16–19, 31:22–24.)

"A POSA would have known that the most preferable administration of the dosings '10, 15, and 20 mg [4-AP], twice per day' described in the *S-1* is about every 12 hours," as **claims 8–9 and 34** require. (Ex. 1003-37; Ex. 1023 ¶ 145; Ex. 1044 ¶ 51.) "The spacing of doses at 12 hour intervals is even more important and likely to occur in a clinical trial setting such as that disclosed in the *S-1*, because researchers can standardize their administration of a drug by using the 12-hour mark" as the designated dosing time. (Ex. 1023 ¶ 145; Ex. 1044 ¶ 51.) Indeed, the *S-1* discloses that the administration of Fampridine SR to spinal cord injury patients "every 12 hours produced peak concentrations of Fampridine-SR." (Ex. 1003-36.)

Additionally, *Hayes* discloses a study in which 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] were asked to take their medication at 12-hour intervals, at approximately 8:00 AM and 8:00 PM." (Ex. 1005-2–3

(emphasis added).) Thus, **claims 8–9 and 34** would have been obvious over the *S-1* in view of *Hayes*. (Ex. 1023 ¶ 144; Ex. 1044 ¶ 50.)

2. **The *S-1* and *Hayes* combination teaches "wherein said sustained release composition is a tablet" (claims 12–13).**

Claim 12 depends from claim 8—described above in Section VI.B.1., and claim 13 depends from claim 9—also described above in Section VI.B.1. Each of **claims 12–13** requires that "said sustained release composition is a tablet." (Ex. 1001 at 30:24–27.)

As explained above in Section VI.A.2.c., the *S-1* discloses the "said sustained release composition is a tablet" limitations of **claims 12–13**, stating that "Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1003-29 (emphasis added).) *Hayes* also discloses this limitation, stating that "a sustained-release tablet formulation of fampridine (fampridine-SR) has been developed." (Ex. 1005-2.) "Thus, these claims would have been obvious to a POSA in light of the *S-1* and *Hayes*." (Ex. 1023 ¶ 148; Ex. 1044 ¶ 54.)

3. **The *S-1* and *Hayes* combination teaches that sustained release 4-AP "provides a release profile to obtain a C_{avSS} of about 15 ng/ml to about 35 ng/ml" (claims 14–15, 35–36).**

Claim 14 depends from claim 1, claims 15 and 36 depend from claim 2, and claim 35 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1. Each of **claims 14–15 and 35–36** requires that "said sustained release composition provides a release profile to obtain a C_{avSS} of about 15 ng/ml to

about 35 ng/ml." (Ex. 1001 at 30:28–33, 31:25–31.) **Claim 36** further requires the additional limitation that the "lower extremity function is walking," which is taught by the *S-1* for reasons discussed in Section VI.A.2.a. with respect to Ground 1.

The *S-1* teaches or suggests each and every element of claims 1, 2, and 32. Additionally, *Hayes* discloses the pharmacokinetic ranges recited in dependent **claims 14–15 and 35–36**. *See also Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (affirming obviousness because "an obvious formulation cannot become nonobvious simply by administering it to a patient and claiming the resulting serum concentrations.") (citation omitted).

At the least, claims 14–15 and 35–36 are obvious over the combination of the *S-1* and *Hayes*. In fact, the applicant conceded as much during the prosecution of the '703 Patent. During examination, applicant's basis for patentability relied squarely on the known "pharmacokinetics of SR 4-AP." (Ex. 1002-151.) Specifically, the applicant cited "[t]he pharmacokinetics of SR 4-AP reported by [*Hayes*]" as being reliable data points for demonstrating the *in vivo* pharmacokinetics recited in the claims of the '703 Patent. (Ex. 1002-151.) The applicant further admitted that "[*Hayes*] at Table 3 on p. 191 teaches that in

patients with spinal cord injury[7] [the[C_{avSS}…(in ng/ml) w[as] as follows, for 10 mg BID, 15 mg BID, 20 mg BID and 25 mg BID SR 4-AP":

	10 mg BID	15 mg BID	20 mg BID	25 mg BID
C_{avSS}	20.8±5.7	31.0±7.2	39.4±9.3	53.3±14.5

(Ex. 1002-151–52.) By acknowledging the reliability of the pharmacokinetic data points reported in *Hayes*, the applicant essentially admitted that the pharmacokinetic limitations recited in the claims of the '703 Patent are obvious in view of the prior art. In particular, the reported C_{avss} of 20.8 (±5.7) in *Hayes* for 10 mg BID administration of 4-AP falls squarely within the claimed range of "C_{avSS} of about 15 ng/ml to about 35 ng/ml."

"A POSA also would have known that the 10 mg BID sustained release 4-AP disclosed in the *S-1* would have the same pharmacokinetics as both *Hayes* and

[7] During prosecution, the applicant admitted that one of ordinary skill "'would expect the same pharmacokinetics in MS patients as in patients with spinal cord injury, because these disabilities were and are not expected to affect metabolism of half-life of 4-AP, which is largely renally cleared.'" (Ex. 1002-151.) Drs. Pleasure and Polli agree. (Ex. 1023 ¶ 136; Ex. 1044 ¶ 42.)

the claimed invention."[8] (Ex. 1023 ¶ 137; Ex. 1044 ¶ 43.) "A POSA looking to optimize a stable dose regimen of sustained release 4-AP would have been motivated to look to both the *S-1* and *Hayes*, as they provide guidance regarding the clinical effects of 10, 15, and 20 mg BID doses, as well as the plasma concentrations resulting from those doses, respectively." (Ex. 1023 ¶ 124; Ex. 1044

[8] Although "the *S-1* teaches administration of 10 mg BID SR 4-AP for twelve weeks and *Hayes* teaches administration of 10 mg BID SR 4-AP for 6 ½ days, a POSA would have understood that the pharmacokinetics for the two administrations would have been the same because the C_{avSS} was measured at steady state, and *Hayes* discloses that '[s]teady state was achieved by day 5 (4 days of fampridine-SR dosing) after twice-daily administration of fampridine-SR.'" (Ex. 1005-4; Ex. 1023 ¶ 139; Ex. 1044 ¶ 45.) "Steady state refers to the pharmacokinetic situation where the drug plasma profile is the same, resulting in stable treatment efficacy of 4-AP, due to overall intake of a drug being equal to drug elimination. Prior to that point, because there are overall increasing or decreasing levels of drug in the system, any observed efficacy could correspondingly change." (Ex. 1044 ¶ 35; Ex. 1023 ¶ 129.) Similarly, "[a] POSA also would have understood that the *S-1* and the *Hayes* study each used similar formulations and dosing, and thus would have had the same T_{max}." (Ex. 1044 ¶ 44; Ex. 1023 ¶¶ 137–38.)

¶ 55.) A POSA would find further motivation to combine the references to assess the safety of sustained release 4-AP. (*Id.*; Ex. 1003-37 ("The clinical trial is also designed to compare three doses of 10, 15, and 20 mg, twice per day, and to assess their relative safety and efficacy"); Ex. 1005-2 ("This paper describes 2 open-label, single-center studies designed to examine the pharmacokinetics and safety profile of fampridine-SR".).) *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (holding that "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed").

Thus, as demonstrated by Table 3 of *Hayes*, a POSA would have known that "the C_{avSS} of 10 mg sustained release 4-AP at steady state was 20.8±5.7"—a range of 15.1–26.5 when accounting for error—"rendering obvious the pharmacokinetic limitations of **claims 14–15 and 35–36** when combining the teachings of *Hayes* with the 10 mg BID dosing regimen of sustained release 4-AP described in the *S-1*." (Ex. 1023 ¶ 154; Ex. 1044 ¶ 60.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295.

4. **The *S-1* and *Hayes* combination teaches a mean T_{max} in a range of about 2 to about 5.2 or 6 hours after SR 4-AP administration (claims 16–19, 37–41).**

Claim 16 depends from claim 1, claims 17 and 38 depend from claim 2, and claim 37 depends from claim 32—described above in Section VI.A.2.a. with

respect to Ground 1. Each of **claims 16–17 and 37–38** requires that "said sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient." (Ex. 1001 at 30:34–41, 31:32–40.)

Claim 18 depends from claim 1, claims 19 and 41 depend from claim 2, claim 39 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1—and claim 40 depends from claim 34—described above in Section VI.B.1. Each of **claims 18–19 and 39–41** requires that "said sustained release composition provides a mean T_{max} in a range of about 2 to about 5.2 hours after administration of the sustained release composition to the patient." (Ex. 1001 at 30:42–49, 31:41–32:9.)

Claims 38 and 41 further require that the "lower extremity function is walking," which is as the *S-1* teaches as discussed in Ground 1, Section VI.A.2.a.

For reasons similar to those stated above with respect to the C_{avSS} pharmacokinetic parameter, the *S-1* teaches or suggests each and every element of that claims from which **claims 16–19 and 37–41** depend. Additionally, *Hayes* discloses the steady state t_{max} pharmacokinetic ranges for sustained release 4-AP. *See also Santarus, Inc.*, 694 F.3d at 1354. During prosecution, the applicant admitted that *Hayes* teaches the "t_{max} of SR 4-AP in fasting patients given 15 or 20 mg BID is about 3h." (Ex. 1002-151.) And in Table 3, for 10 mg BID sustained

release 4-AP, *Hayes* teaches that the t_{max} is 2.7 ± 1.0 hours. (Ex. 1005-7.) A t_{max} of 2.7 hours falls squarely within the claimed ranges of "about 2 to about 5.2 hours" and "about 2 to about 6 hours." Thus, the combination of the *S-1* and *Hayes* teaches each and every limitation of claims 16–19 and 37–41.

Moreover, there is nothing non-obvious about the full scope of the claimed t_{max} range. (Ex. 1023 ¶¶ 138, 164; Ex. 1044 ¶ 70.) "A POSA considering *Hayes* would have known that the t_{max} of 10 mg sustained release 4-AP is 2.7 ± 1.0 hours," providing for a range—accounting for error—of 1.7–3.7 hours, "which overlaps substantially with the claimed t_{max} ranges." (Ex. 1023 ¶ 164; Ex. 1044 ¶ 70.) For at least this additional reason, **claims 16–19 and 37–41** are obvious over the *S-1* and *Hayes*. (*Id.*)

5. **The *S-1* and *Hayes* combination teaches a release profile extending over at least 6 hours (claims 20–21, 48–49).**

Claim 20 depends from claim 1, claims 21 and 49 depend from claim 2, and claim 48 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1. Each of claims **20–21 and 48–49** requires that "said sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours." (Ex. 1001 at 30:50–57, 32:28–36.)

For reasons similar to those stated above with respect to the C_{avSS} pharmacokinetic parameter, the *S-1* teaches or suggests each and every element of

claims 20–21, 48–49. Additionally, *Hayes* discloses the steady state pharmacokinetic ranges recited in **claims 20–21 and 48–49**. *See Santarus, Inc.*, 694 F.3d at 1354. Specifically, *Hayes* discloses in Figure 1 B, copied below, that a 10 mg BID dose of SR 4-AP has a release profile (as defined in Section V.D.2.) extending over 24 hours:

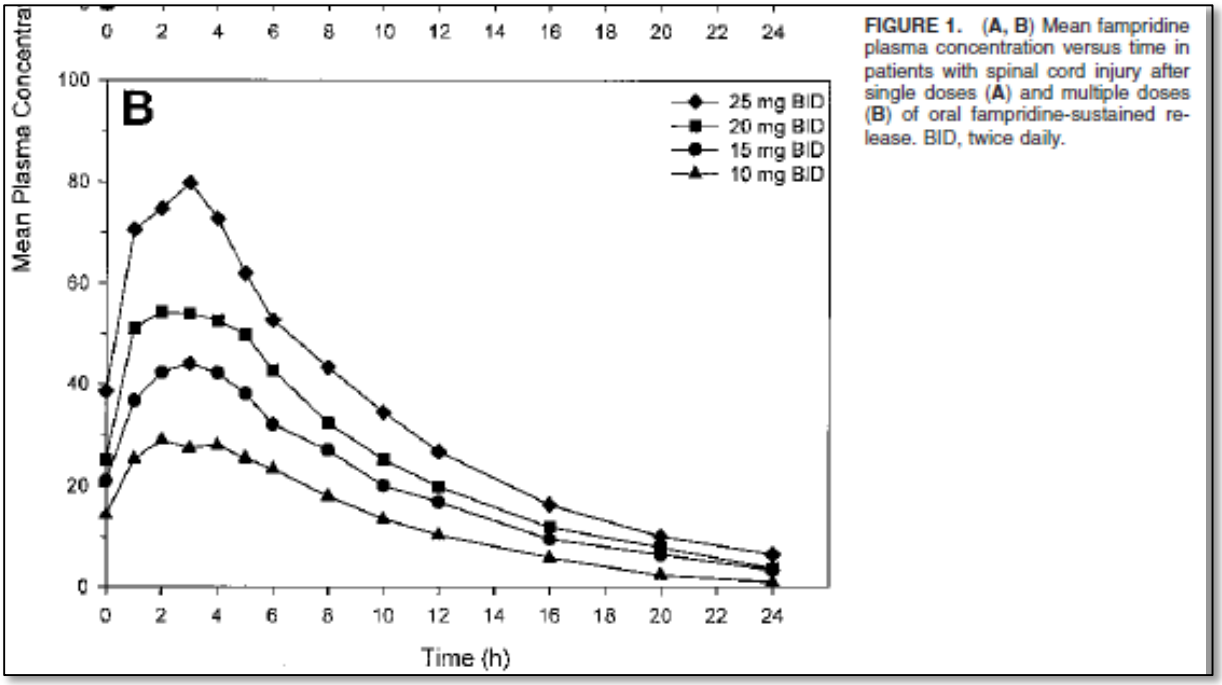

FIGURE 1. (**A**, **B**) Mean fampridine plasma concentration versus time in patients with spinal cord injury after single doses (**A**) and multiple doses (**B**) of oral fampridine-sustained release. BID, twice daily.

(Ex. 1005-5.) Thus, according to Figure 1 of *Hayes*, a POSA would have known that "the release profile of the 10 mg sustained release 4-AP described in the *S-1* and *Hayes* extends over 24 hours, rendering obvious the additional pharmacokinetic limitations of **claims 20–21 and 48–49** when combining the teachings of *Hayes* with the 10 mg BID dosing regimen of sustained release 4-AP in the *S-1*." (Ex. 1023 ¶ 169; Ex. 1044 ¶ 75.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295.

6. The *S-1* and *Hayes* combination teaches administration of sustained release 4-AP for "more than two weeks" and "twelve weeks" (claim 47).

Claim 47 depends from claim 40—described above in Section VI.B.4—and additionally requires administration of SR 4-AP for "twelve weeks," and that "the lower extremity function is walking." (Ex. 1001 at 32:25–27.)

As explained above in Section A.2.e., the *S-1* disclosure of a "treatment period of 12 weeks" meets the open-ended limitation "said time period is more than two weeks" limitation recited in **claim 47**. (Ex. 1003-37.) *See In re Applied Materials, Inc.*, 692 F.3d at 1295.

As explained above in Section A.2.a., the *S-1* disclosure of SR 4-AP clinical trials "to support an indication for the treatment of lower extremity motor dysfunction, characterized by weakness and walking impairment," measuring "an improvement in average walking speed" and "the effect of the drug on symptoms of the disease, including motor strength, [and] timed walking" meets the additional limitation of **claim 47**. (Ex. 1003-37 (emphasis added).) *See In re Montgomery*, 677 F.3d at1382–83. Therefore, claim 47 would have been obvious to a POSA in light of the *S-1* and *Hayes*. (Ex. 1023 ¶ 171.)

C. Ground 3: Claims 22–25, 42–43, and 50–51 are obvious in light of the *S-1* in view of *Juarez* and the knowledge of a POSA.

Dependent claims 22–25, 42–43 and 50–51 fail to add any non-obvious limitations. The claims upon which those claims depend (claims 1–2 and 32) are

obvious for at least the reasons set forth above with respect to Ground 1. Claims 22–25, 42–43 and 50–51 are obvious over the *S-1* in view of *Juarez*.

"A POSA would have been motivated to combine the *S-1* with common knowledge and publications like *Juarez*—which focuses on optimizing the same SR 4-AP oral tablets disclosed in the *S-1*"— in an effort to further understand and apply the methods disclosed in the *S-1* "to treat patients suffering from MS and its associated conditions." (Ex. 1023 ¶¶ 172–92; Ex. 1044 ¶ 76.)

1. **The *S-1* and *Juarez* combination teaches "controlling the release rate" of the 4-AP by dispersing it in a rate of release controlling polymer, such as a matrix in which the 4-AP is uniformly dispersed (claims 22–25, 42–43, and 50–51).**

Claim 22 depends from claim 1, claims 23 and 51 depend from claim 2, and claim 50 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1. Each of **claims 22–23 and 50–51** requires that "said 4-aminopyridine is dispersed in a rate of release controlling polymer." (Ex. 1001 at 30:58–61, 32:37–41.)

Claim 24 depends from claim 1, claims 25 and 43 depend from claim 2, and claim 42 depends from claim 32—described above in Section VI.A.2.a. with respect to Ground 1. Each of **claims 24–25 and 42–43** requires that "said sustained release composition comprises a matrix, in which said 4-aminopyridine is uniformly dispersed, that is suitable for controlling the release rate of the 4-aminopyridine." (Ex. 1001 at 30:62–31:2, 32:10–18.) Claims 43 and 51 also recite

"wherein the lower extremity function is walking," an obvious limitation for the reasons discussed in Section VI.A.2.a.

"A POSA reading the *S-1* would have known that one of the methods available to control the rate of release of a drug," such as would be necessary for the sustained release 4-AP disclosed in the *S-1*, would be the use of a hydrophilic polymer-formed matrix to control rate of release" as in **claims 22–23 and 50–51**. (Ex. 1023 ¶ 182; Ex. 1044 ¶ 86.) A POSA also would have known that, for such a matrix to function properly, "the drug whose release rate was being controlled should be uniformly dispersed in this matrix, as in **claims 24–25 and 42–43."** (Ex. 1023 ¶ 183; Ex. 1044 ¶ 87.)

Juarez discloses this claimed matrix. (Ex. 1006-1–3.) A POSA working with a sustained release form of 4-AP, as disclosed in *S-1*, would have been motivated to look to *Juarez*, because *Juarez* teaches how to use a polymer-formed matrix to provide a sustained-release composition of 4-AP that could maintain desirable "*in vivo* plasma concentrations and thus a constant pharmacological effect." (Ex. 1023 ¶ 173; Ex. 1044 ¶ 77.) *See KSR Int'l Co.*, 550 U.S. 398, 420.

Specifically, *Juarez* teaches preparation of an oral tablet comprising 4-aminopyridine and a rate of release controlling polymer. (Ex. 1006-1–2.) *Juarez* indicates that "[t]ablets of the model drug 4-aminopyridine with hydroxypropyl methylcellulose [HPMC] were prepared with different proportions of polymer

content." (*Id.* -1.) *Juarez* discloses that the purpose of this HPMC matrix is "for controlling the release of soluble drugs from solid dosage forms," and to "prolong delivery with zero-order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect," as in **claims 22–23 and 50–51**. (*Id*. -1–2.) A POSA would have understood that *Juarez* teaches that 4-aminopyridine could be readily and easily formulated into a useful rate of release controlling polymer, more commonly known as a sustained release composition, using universally known compounds such as HPMC. (Ex. 1023 ¶ 191; Ex. 1044 ¶ 94.) Therefore, these claims would have been obvious to a POSA. (Ex. 1023 ¶¶ 183, 184–91; Ex. 1044 ¶ 94.) *Juarez* also teaches forming the matrix:

> Ten grams of each different formula were prepared by gently mixing in a mortar the corresponding proportions of 4-aminopyridine and HPMC for 20 min. Each mixture was moistened with 2 ml of distilled water, kneaded for 5 min and sifted using a sieve number 12. The resulting granulations were dried at 40ºC for 3 h in beds with a thickness up to 5 mm.

(Ex. 1006-3.) A POSA would have understood that these mixing instructions would result in "the 4-AP being *uniformly* dispersed in the matrix, such that the matrix 'is suitable for controlling the release rate of the 4-aminopyridine' as in **claims 24–25 and 42–43**." (Ex. 1023 ¶ 192; Ex. 1044 ¶ 95.) Therefore, these claims would have been obvious to a POSA applying *Juarez* to the *S-1* regime. (Ex. 1023 ¶ 192; Ex. 1044 ¶ 95.)

VII. ANY SECONDARY CONSIDERATIONS ARE INSUFFICIENT TO OVERCOME THE OBVIOUSNESS OF CLAIMS 1–52

During prosecution of the ’703 Patent, the applicant submitted declarations stating that the claimed inventions were nonobvious in light of secondary considerations. However, these declarations fail to overcome the particularly strong evidence of obviousness presented above. The crux of the secondary considerations discussed in the declarations was “that there were no notable differences among the 10 mg BID, 15 mg BID, and 20 mg BID treatment groups with respect to improving walking” and this “comparable efficacy of the 10 mg BID dosage of SR 4-AP as compared to the 15 mg and 20 mg BID dosages…is surprising and unexpected.” (Ex. 1002-172.) The declarants argued that this result was surprising because of an “understanding in the field…that there was a dose-benefit correlation for 4-AP’s clinical effects, *i.e.*, the higher the dose the greater the therapeutic benefit.” (*Id.* -173.) However, the results described are neither unexpected nor surprising in view of the disclosures in the prior art that render the treatment methods obvious. (Ex. 1023 ¶ 194.)

First, the declarants’ assertion that the results were unexpected is incorrect. The Blight Declaration data is “consistent with the expected dose-benefit correlation.” (*Id.* ¶ 195.) For example, improvement in walking *did* increase with the dosage, albeit in small increments (1–2 percentage points). Even though the increase was not *statistically* significant, it showed an upward trend, and where the

dosage difference was slight to begin with—a mere 5 to 10 mg compared with studies in which up to 50–60 mg of 4-AP had been administered—such small increases would be expected. (*Id.*) The Federal Circuit's opinion in *Galderma Labs. LP v. Tolmar Inc.* is particularly instructive. 737 F.3d 731, 739 (Fed. Cir. 2013). The court found unexpected results insufficient for nonobviousness, because the unexpected result—the lack of a percent increase in the prevalence of side effects—constituted "only a difference in degree from the prior art results" rather than a "difference in kind." *Id.* Here, applicant's argument regarding the lack of significant improvement from one dose to another is a difference in degree. Any "evidence of superior efficacy does nothing to undercut the showing that there was a reasonable expectation of success with the [] dose, even if the level of success may have turned out to be somewhat greater than would have been expected." *Hoffmann-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1334 (Fed. Cir. 2014).

Second, the Medori declaration touts Ampyra's approval as "an MS treatment effective to treat all four forms (subtypes) of MS…Ampyra® was the first FDA-approved drug indicated for improving walking in patients with MS, and it remains the only drug approved for this purpose." (Ex. 1002-161–62.) However, none of the claims of the '703 Patent require that a covered drug be an MS treatment effective to treat all four forms (subtypes) of MS. By contrast, the only subtype required by *only two* of the patent's 52 claims is the most common

subtype—relapsing remitting multiple sclerosis. *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1385 (Fed. Cir. 2015) ("secondary consideration actually results from something other than what is both claimed and novel in the claim, so there is no nexus to the merits of the claimed invention.")

Third, none of the declarations establish a ***nexus*** between the alleged secondary considerations and the particular limitations of the challenged patent claims. (*See* Ex. 1002-169–345; Ex. 1046, *passim*, Ex. 1047, *passim*.) The *S-1* and *Hayes* disclose the claimed dosing of 10 mg BID. Although the claims also require a treatment period of at least two weeks (which the *S-1* also discloses), none of the declarations attribute a treatment period of at least two weeks to the success of 4-AP. (*See id.*) Nor was there evidence that any long-felt need allegedly solved by Ampyra was due to treatment for at least 2 weeks. (*See id.*) The Medori declaration points to other MS drugs, like "Nerispirdine," which failed to enter Phase III clinical trials. (Ex. 1046-34.) However, there is no showing that an "at least two weeks" regimen of 10 mg (or less than 15 mg) sustained release 4-AP or the pharmacokinetic parameters recited in the claims were—or could have been—the particular elements that rendered Ampyra successful where other MS drugs failed.

Fourth, although secondary considerations must be taken into account, they do not control obviousness. Where a strong prima facie obviousness showing exists, the Federal Circuit repeatedly finds even relevant secondary considerations

supported by substantial evidence may not dislodge the primary conclusion of obviousness. *See, e.g.*, *Bayer Healthcare Pharms. Inc. v. Watson Pharms. Inc*., 713 F.3d 1369, 1376 (Fed. Cir. 2013) (secondary considerations "d[id] not overcome the express teachings of multiple references"); *Allergan Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013) (rejecting secondary considerations, including evidence of unexpected results from the claimed drug combinations).

VIII. CONCLUSION

Petitioner respectfully requests IPR of claims 1–52 of the '703 Patent.

Respectfully submitted,

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CERTIFICATE OF SERVICE

I hereby certify that on September 2, 2015, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 8,440,703, including all exhibits, was served via FedEx, overnight delivery, upon the following:

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