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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 No.: Not yet assigned
Patent No. 8,007,826
Filed: December 13, 2004
Issued: August 30, 2011
Inventors: Andrew R. Blight, Ron Cohen
Title: SUSTAINED RELEASE AMINOPYRIDINE COMPOSITION

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 8,007,826

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I. INTRODUCTION

Petitioner Coalition For Affordable Drugs (ADROCA) LLC ("CFAD") requests an *Inter Partes* Review (IPR) of Claims 1–3, 5–8, and 10–41 of U.S. Patent No. 8,007,826 (the '826 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 '826 Patent is available for *Inter Partes* Review, and that Petitioner is not barred or estopped from requesting *Inter Partes* Review challenging the Claims of the '826 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 '826 Patent is the subject of several judicial matters that may affect, or may be affected by a decision in this proceeding: *Acorda Therapeutics, Inc. v. Mylan Pharms. Inc.*, No. 1:14-cv-00935 (D. Del); *Acorda Therapeutics, Inc. v. Mylan,* No. 1:14-cv-00139 (N.D.W.Va.); *Acorda Therapeutics, Inc. v. Accord and Intas,* No. 1:14-cv-00932 (D. Del.); *Acorda Therapeutics, Inc. v. Actavis,* No. 1:14-cv-00882 (D. Del.); *Acorda Therapeutics, Inc. v. Alkem,* No. 1:14-cv-

00917 (D. Del.); *Acorda Therapeutics, Inc. v. Apotex,* No. 1:14-cv-00955 (D. Del.); *Acorda Therapeutics, Inc. v. Aurobindo,* No. 1:14-cv-00909 (D. Del.); *Acorda Therapeutics, Inc. v. Roxane,* No. 1:14-cv-00922 (D. Del.); *Acorda Therapeutics, Inc. v. Teva,* No. 1:14-cv-00941 (D. Del.). 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, which was filed as a continuation of the presently challenged '826 Patent. The Patent Owner's Preliminary Response in IPR2015-00720 has not yet been filed.

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 Ki O, Reg. No. 68,952 (ki.o@skiermontpuckett.com). Back-up counsel are Sarah E. Spires, Reg. No. 61,501, sarah.spires@skiermontpuckett.com; Dr. Parvathi Kota, Reg. No. 65,122, parvathi.kota@skiermontpuckett.com; and Paul J. Skiermont (*pro hac vice* requested), paul.skiermont@skiermontpuckett.com; all 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.

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). To the extent any additional fees are required to complete this Petition, the Patent Office is hereby authorized by the undersigned to charge Deposit Account No. 506293 for such fees. Any overpayment or refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of the '826 Patent

1. The '826 Patent

The '826 Patent, entitled "Sustained Release Aminopyridine Composition," describes a method of improving walking in a human afflicted with multiple sclerosis (MS). (*See* Ex. 1001.) The '826 Patent describes oral administration of a sustained release composition containing 10 mg of 4-Aminopyridine (4-AP) twice daily (*i.e.,* BID) having various pharmacokinetic parameters, such as administering 4-AP to obtain an in-vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml (Ex. 1001 at 8:5-17) and a mean T_{max} from about 1 to about 6 hours, or about 2 to about 5.2 hours after administration (*Id.* at 6:27–29).

The '826 patent has 41 claims with seven independent claims. Claims 1, 6, 11, 17, 31, 36, and 37 are the independent claims. Claims 1–3, 5–8, and 10–41 are challenged in the present Petition. Each of the 7 independent claims recite administration of 10 mg of 4-AP twice daily. The table below lists the distinguishing claimed elements of each of the 7 independent claims.

Claim Element	Claim 1	Claim 6	Claim 11	Claim 17	Claim 31	Claim 36	Claim 37
for a time period of at least two weeks or greater than two weeks,	**At least two weeks**		**Greater than two weeks**	**Greater than two weeks**	**Greater than two weeks**	**At least two weeks**	**Greater than two weeks**
whereby an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} ratio of							

1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human	**X**	**X**	**X**	**X**		**X**	
T_{max} in a range of about 1 to about 6 hours					**X**		
a mean T_{max} in a range of about 2 to about 5.2 hours after administration							**X**
pharmaceutically acceptable excipient			**X**	**X**			
DEPENDENT CLAIMS	2–3, 5, 13, 18–22	7–8, 10, 23-29	12, 14–16	30	32–35		38–41

2. Summary of '826 Patent Prosecution History Pertinent Events

The '826 patent was filed as Application No. 11/010,828 on December 13, 2004. (Ex. 1004.) According to the FDA's "Orange Book", and based on the USPTO's final patent term adjustment calculation, the '826 Patent expires in 2027. (Ex. 1003.) The '826 patent file history is over 2,000 pages and references over 430 U.S. and foreign patents and non-patent literature documents. A summary of pertinent events follows.

The '826 patent application was filed with original named inventors Andrew R. Blight and Sean Cunningham. (Ex. 1004 at Application Data Sheet.) The Applicant petitioned to have Sean Cunningham removed as an inventor, and the petition was granted on January 5, 2009 (Exs. 1013–1015.) Ron Cohen was added as an inventor in an Amendment and Response to Final Office Action and Request for Continued

Examination dated December 10, 2009. (Ex. 1039.) Of the 23 originally filed claims, the Applicant cancelled claims 12–14 and withdrew Claims 1–8 and 18–23 on May 21, 2008 in response to a restriction requirement. (Ex. 1005.) None of these claims included a limitation directed to the length of SR 4-AP administration.

The Examiner issued a non-final Office Action rejecting the remaining claims on June 6, 2008. (Ex. 1006.) The Examiner rejected claims 9–11 and 15–17 as anticipated by Hayes et al. (Clinical Neuro-pharmacology 26(4), 185-192). (Ex. 1006 (citing Hayes 2003 (Ex. 1029)). The Examiner noted that "[a]ccording to one study in Hayes et al, 10-25 mg of fampridine was administered twice daily for one week to 16 patients with chronic spinal cord injury (abstract)." (Ex. 1006 at 5.) The Examiner also rejected claims 9–11, 15–17 as obvious over Masterson (U.S. Pat. No. 5,580,580 (Masterson '580). (*See* Ex. 1010 for Masterson '580.)

Applicant responded on December 8, 2008 by amending Claim 9, adding Claims 24–41, and traversing the prior rejections. (Ex. 1047.) After an interview with the Examiner, Applicant submitted a Supplemental Amendment and Response on April 2, 2009 to the non-final office action dated December 8, 2008. (Ex. 1048.) Applicant cancelled claims 1–29 and 36–38, amended claims 30–33 and 39–40, and added new claims 42–47. (*Id.*) Applicant also submitted declarations by Andrew R. Blight (Ex. 1011) and David Lawrence (Ex. 1012) attempting to distinguish Masterson '580 and purporting to support secondary considerations of non-obviousness. None of these claims included a limitation directed to the length of SR 4-AP administration.

The Examiner issued a Final Office Action on June 10, 2009, rejecting all claims. (Ex. 1040.) After the Examiner considered Applicant's arguments and declarations, Claims 30–35 and 39–47 were again rejected over Masterson '580. (*Id.*) Applicant responded December 10, 2009, with a Request for Continued Examination by cancelling Claims 1–47 and adding new Claims 48–69. (Ex. 1039.)

The Examiner issued a non-final Office Action rejecting all claims on May 25, 2010. (Ex. 1041.) In the rejection, the Examiner stated that one claim set was obvious over van Diemen et al. (Clinical Neuropharmacology, 1993), another claim set was obvious over van Diemen et al. in view of Bever et al. (Neurology, 1994); and a third claim set was obvious over Masterson, van Diemen et al., and Bever et al. (*Id.*)

On November 24, 2010, Applicants submitted an amendment and response (Ex. 1018) with two declarations by Dr. Rosella Medori (Ex. 1016) and Lauren Sabella (Ex. 1017). Applicants' November 24, 2010 amendment and response introduced independent claims for the first time containing a limitation requiring the 4-AP administration for "at least two weeks." (Ex. 1018 at 4–9.) Neither the Sabella nor Medori declarations anywhere mention a period of treatment that is two weeks or greater; nor do the declarations anywhere mention the claimed pharmacokinetic parameters, such as C_{avSS}, C_{max}, C_{min}, or a mean T_{max}. (Exs. 1017 and 1018, *passim*.)

Applicants' November 24, 2010 response discussed the Goodman reference (Ex. 1030). (*See* Ex. 1018 at 25–26.) Applicant argued that Goodman's dose response curve "showed increasing benefit in the 20–50 mg/day range, and doses above 50 mg

added little benefit and increased adverse effects. This guided [a person of ordinary skill in the art] to use a dose of approx. 50 mg/day (25 mg BID)." (*Id.*) (A reproduction of the dose response curve is provided as Ex. 1052.)

The Examiner issued a Notice of Allowance on April 18, 2011, and stated the following, in part, in the Reasons for Allowance:

> The closest prior art is Schwid et al, Hayes et al (2003a), and Bevers (1994a). Schwid provides guidance to use 4-aminopyridine that achieves at least 60 ng/ml in a patient. However, Table 3 in Hayes indicates that one would need roughly twice the amount of 4-aminopyridine (more than 20 mg) to achieve Schwid's serum level. Thus, Schwid teaches a higher dosage of sustained release 4-aminopyridine than the instant claims. Furthermore, there is a lack of predictability in the prior art that the dosage recited in the instant claims would improve walking.

(Ex. 1020.) The Hayes 2003 reference (Ex. 1029) in the Examiner's Reasons for Allowance is a different reference from the Hayes 2001 document (Ex. 1031) relied upon in this Petition. **No prior art reference relied on in the present Petition formed the basis of any Examiner rejection during prosecution of the application that issued as the '826 Patent**.

3. Effective Priority Date of the '826 Patent Claims

The '826 Patent application was filed December 13, 2004. The Patent impermissibly claims priority to the following U.S. Provisional Patent Applications:

- Application No. 60/528,760 ('760 provisional), filed Dec. 11, 2003 (Ex. 1022);
- Application No. 60/528,592 ('592 provisional), filed Dec. 11, 2003 (Ex. 1023);

- Application No. 60/528,593 ('593 provisional), filed Dec. 11, 2003 (Ex. 1024);
- Application No. 60/560,894 ('894 provisional), filed Apr. 9, 2004 (Ex. 1025).

At a minimum, Claims 1–3, 5–8, 10–30, and 36 cannot claim priority to any of the earlier-filed provisional applications. The priority date for those challenged claims of the '826 Patent is the same as the Patent's filing date—December 13, 2004.

First, Claims 1–3, 5–8, 10–30, and 36 cannot claim priority to *any* of the four provisionals. This is because *none* of the provisionals disclose the entire breadth of the claimed pharmacokinetic ranges claimed in claims 1–3, 5–8, 10–30, and 36. *See New Railhead Mfg., L.L.C. v. Vermeer Mfg. Co.*, 298 F.3d 1290, 1294 (Fed. Cir. 2002) ("the specification of the provisional must contain a written description of the invention and the manner and process of making and using it, in such full, clear, concise, and exact terms to enable an ordinarily skilled artisan to practice the invention claimed in the nonprovisional application.") (quotation omitted).

Specifically, claims 1–3, 5–8, 10–30 and 36 all require the pharmacokinetic range of C_{avSS} of 15 ng/ml to 35 ng/ml. By contrast, the only pharmacokinetic ranges disclosed in the provisionals are in Table 7 of the '894 provisional. (Ex. 125 at 45.) That table, however, merely discloses ranges encompassing a C_{avSS} of 15.1 ng/ml to **26.5** ng/ml. (*Id.*) Because all claimed ranges for claims 1–3, 5–8, 10–30, and 36 claim up to 35 ng/ml, while the provisionals do not disclose the range of 26.6 ng/ml – 35 ng/ml, those claims are not entitled to claim priority to any of the provisionals. *See,*

e.g., Waddington N. Am., Inc. v. Sabert Corp., No. 9-4883, 2011 U.S. Dist. LEXIS 29772, at *17–18 (D.N.J. Mar. 22, 2011) ("claiming ranges broader than those disclosed in the patent fails the written description requirement," which "prevent[s] an applicant from claiming more than he actually invented"). Similarly, the support for the claimed pharmacokinetic ranges, found in the '826 Patent at 6:55–8:43, is absent from all of the provisionals. Thus, at the time of the provisionals, the Applicant had not yet discovered or disclosed the full scope of the claimed pharmacokinetic ranges. *See LizardTech v. Earth Res. Mapping, Inc.*, 424 F.3d 1336, 1345–48 (Fed. Cir. 2005).

Claims 32 and 38, in addition to previously discussed claims 1–3, 5–8, 14, 17, 20–26, and 29–30, require a C_{maxSS}:C_{minSS} ratio of **1.0 to 3.5**. Yet disclosures in Table 7 of the '894 provisional only discloses a C_{maxSS}:C_{minSS} ratio of **1.3–4.3**. (Ex. 125 at 45.) Because all claimed ranges for claims 1–3, 5–8, 10–14, 17, 20–26, and 29–30 claim a C_{maxSS}:C_{minSS} ratio beginning at **1.0**, while the provisionals do not disclose the ratio range of 1.0–1.2, claims 1–3, 5–8, 10–14, 17, 20–26, and 29–30 of the '826 Patent are not entitled to claim priority to any of the provisionals. *See, e.g., Eiselstein v. Frank*, 52 F.3d 1035, at 1039–40 (Fed. Cir. 1995) (specification describing nickel content of 45%–50% does not support broader claim for 50% to 60%); *Ralston Purina Co. v. Far-Mar-Co.*, 772 F.2d 1570, 1575–76 (Fed. Cir. 1985) (parent application disclosing 25%–27% water in soybean mixture does not support broader claims to "at least 20%," "between 20% and 40%," or "in the range of 20%–30%").

Even obvious changes and extensions to the disclosed ranges are insufficient for entitlement to the provisional priority dates. *See In re Huston*, 308 F.3d 1267, 1277 (Fed. Cir. 2002) ("Entitlement to a filing date does not extend to subject matter which is not disclosed, but would be obvious over what is expressly disclosed.").

Further, the publications that the provisionals purport to incorporate by reference also cannot provide the missing disclosure. The Federal Circuit instructs that to incorporate material by reference, "the host document must identify **with detailed particularity** what specific material it incorporates and **clearly indicate where** that material is found in the various documents." *Zenon Envtl., Inc. v. U.S. Filter Corp.*, 506 F.3d 1370, 1378 (Fed. Cir. 2007) (quotation omitted). The provisionals' purported incorporations contain no identification of the material incorporated or where that material is found. (*See* Exs. 1022–1025.)

Second, even absent the provisionals' failed disclosures, *none* of the claims of the '826 Patent can claim priority to any of the three provisionals filed in 2003 because the '826 Patent does not share a common inventor with the first three provisionals—a statutory requirement for claiming the benefit of priority. *See* 35 U.S.C. § 120 (pre-AIA version) "An application … which is filed by an inventor or inventors named in the previously filed application shall have the same effect, as to such invention, as though filed on the date of the prior application … or on an application similarly entitled to the benefit of the filing date of the first application") (emphasis added); (37 C.F.R. § 1.78(c)(1) ("[e]ach prior-filed application must name

the inventor or a joint inventor named in the later-filed application as the inventor or a joint inventor."). The provisionals filed in 2003 all list Sean Cunningham as the sole inventor. (Ex. 1038.) However, Applicants *removed* Mr. Cunningham as an inventor of the application during prosecution of the '826 Patent. (*See* Exs. 1013–1015.) When the Applicant removed Cunningham—the sole inventor of the three December 2003 provisionals—it forfeited any claim of priority to them by statute. The '826 Patent does *not* share a common inventor to the provisionals filed in 2003, and so *cannot* claim priority to them. *See In re NTP, Inc.*, 654 F.3d 1268, 1277 (Fed. Cir. 2011) (Under § 120, a patent is entitled to the priority date of an earlier filed application if … the applications have **at least one common inventor**.").

B. Level of Skill in the Art

"Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field." *Custom Accessories Inc. v. Jeffrey-Allan Industries Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). Petitioner submits an expert declaration from Dr. Pleasure, Professor of Neurology and the Glenn W. Johnson, Jr. Memorial Endowed Chair of Neurology at the University of California, San Francisco School of Medicine. (Pleasure Decl. ¶ 3 (Ex. 1026).) Based on the above factors, Dr. Pleasure attests that "a person of ordinary skill in the art (POSA) in connection with the '826 patent would have an M.D. or Ph.D. in neuroscience or 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." (Pleasure Decl. ¶ 16 (Ex. 1026).) Petitioner also submits an expert declaration from Dr. Polli, Professor of Pharmaceutical Sciences and Ralph F. Shangraw/Noxell Endowed Chair in Industrial Pharmacy and Pharmaceutics at the University of Maryland School of Pharmacy. (Ex. 1027.) Dr. Polli adopted the same definition of a POSA. (Polli Decl. ¶ 11 (Ex. 1027).)

C. Claim Construction

In an IPR, "[a] claim in an unexpired patent shall be given its broadest reasonable construction in light of the specification of the patent in which it appears." 37 C.F.R. § 42.100(b). Petitioner is not required to define every claim term; thus any claim term not specifically discussed will have its ordinary and customary meaning. Fed. Reg., Vol. 77, No. 157, p. 48700 (Aug. 14, 2012) (see Comment 35). Where the construction of specific terms is not necessary to resolve issues before the Board, the Board can refrain from construing those terms. *Leo Pharmaceutical Products, Ltd. v. Rea*, Appeal No. 2012–1520, slip opinion, August 12, 2013, p. 10 (Fed. Cir. 2013). Petitioner submits that the Board need not construe any terms other than the one discussed below.

The term "sustained release composition" (Claims 1, 4–6, 9–11, 17, 22, 29, 30–32, 34, 36, 37, 38, 40) should be construed to mean a formulation "designed to release a therapeutically effective amount of drug or other active agent such as a polypeptide or a synthetic compound over an extended period of time, with the result being a reduction in the number of treatments necessary to achieve the desired therapeutic effect." (Ex. 1001 at 5:33–38.)

D. Statements of Precise Relief Requested for Each Claim Challenged

1. Claims for which Review is Requested

Petitioner requests IPR and cancellation of Claims 1–3, 5–8, and 10–41 of the '826 Patent under 35 U.S.C. § 311. The precise relief requested by Petitioner is that each of Claims 1–3, 5–8, and 10–41 of the '826 Patent be found unpatentable as obvious in view of the prior art.

2. Statutory Grounds of Challenge

Inter partes review of the '826 Patent is requested in view of the following references, each of which is prior art to the '826 Patent under 35 U.S.C. § 103(a):

Ground	Rejection for the '826 Patent	Exhibit Number(s)
1	Claims 1–3, 5–8, 10–30, and 36, are invalid because they are obvious under 35 U.S.C. § 103(a) over the Acord S-1 reference ("S-1") in view of Hayes et al. ("Hayes 2001") and	1028, 1031

	common knowledge available to those of skill in the art.	
2	Claims 31–35, and 37–41 of the '826 Patent are obvious under 35 U.S.C. § 103(a) over Goodman in view of the Hayes 2001 and common knowledge available to those of skill in the art.	1030, 1031

E. Overview of State of the Art Providing Motivation to Combine for All Grounds in the Petition

3. 4-AP History and the State of the Relevant Art of the '826 Patent

The '826 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 patients suffering from multiple sclerosis. (*Id.*) The '826 Patent does not even claim that the oral administration of 10 mg BID of 4-AP compound to MS patients or the use of slow-release versions of 4-AP are novel, because those teachings were known in the prior art. (*See, e.g.*, Exs. 1030, 1031.) Instead, the '826 Patent simply attempts to claim methods of administering 4-AP (BID) for a certain period of time to attain certain pharmacokinetic profiles. As set forth herein, those pharmacokinetic profiles were known to a (POSA) for the dosing claimed.

The pharmacological properties of 4-AP have been studied for over 90 years. In 1924, researchers first described the pharmacological properties of aminopyridine

compounds and, specifically, the excitatory effect of 4-AP on the central nervous system. For more than 30 years, researchers have been able to show the effectiveness of 4-AP treatment in patients suffering from multiple sclerosis. (*See* Ex. 1032.) Even in the 1990s, researchers conducted double-blind studies evaluating the effectiveness of oral 4-AP administration in multiple sclerosis patients. (*See* Exs. 1033, 1034.)

More than 10 years prior to the earliest priority date of the '826 Patent, researchers had extensively studied the use of 4-AP in MS patients. (*See* Ex. 1036.) By 1987, researchers had measured neurological changes associated with 7 to 35 mg of 4-AP in 1 to 5 mg doses administered every 10 to 60 minutes, with "motor function (power, coordination, gait)" in 5 out of 12 patients improving "minutes within injection at doses as low as 2 mg." (*Id.*) In 1990, Davis et al. administered 10 to 25 mg of 4-AP to MS patients improving motor functions including gait. (Ex. 1037.)

Dr. Pleasure attests that MS is "an inflammatory demyelinating disease featuring selective destruction of the central nervous system (CNS) myelin." (Pleasure Decl. ¶ 17 (Ex. 1026).) Dr. Pleasure cites the New England Journal of Medicine describing MS (*Id.* ¶ 22, quoting Ex. 1035) in support of his testimony that "a POSA as of December 2002 would have known that MS is a long-lasting, chronic disease, with patients experiencing problems walking on an ongoing basis and especially as the disease progresses with time." (Ex. 1026 ¶ 24.) Dr. Pleasure further states prior to December 2002, "it was well known to a POSA that difficulty in walking was a common and chronic symptom in MS patients." (*Id.* ¶ 23, citing Ex. 1008 at 2454.)

This fact provided a POSA with motivation "to treat such patients for a sustained period of at least two weeks and even longer with agents such as SR 4-AP shown to alleviate symptoms, such as walking difficulties, associated with MS, and thus to improve MS patients' walking, increase MS patients' walking speed, and increase MS patients' lower extremity muscle strength." (*Id.* ¶ 24.)

The claims of the '826 patent are obvious because the methods listed in the challenged claims were known in the art at the time of the alleged invention. The prior art taught orally administering 10 mg SR 4-AP twice per day for periods greater than two weeks, and taught that this dose was effective to improve walking in MS patients, while avoiding the side effects of higher daily doses. (*See* Exs. 1028, 1030 *passim*.)

The claimed pharmacokinetic parameters were likewise well known from the prior art. (Polli Decl. ¶¶ 14–16, 19–24 (Ex. 1027 (citing Exs. 1009, 1031, 1043)).) In particular, Dr. Polli explains that a POSA before the time of the invention would have understood that SR 4-AP doses of 10 mg BID exhibited the following pharmaco-kinetic data: "(1) a T_{max} of 2.7 hours (±1.0 hr), (2) a sustained-release profile extending over at least 6 hours, and also over at least 12 hours, and (3) a steady state average 4-aminopyridine plasma concentration of 20.8 ng/mL (±5.7 ng/mL)." (Polli Decl. ¶ 19 (Ex. 1027 (citing Ex. 1031)).) Moreover, "a POSA would know that steady state plasma concentrations of the 4-aminopyridine were achieved within only 5 days, during administration of the 10 mg BID dose." (*Id.* ¶ 20 (citing Ex. 1031).)

4. Summary of the Prior Art References

a. The Acorda SEC S-1 Reference (Ex. 1028)

The S-1 constitutes prior art under 35 U.S.C. § 102(b) to Claims 1–3, 5–8, 10–30, and 36 because it was filed on September 29, 2003 (Ex. 1028 at 39), which is more than one year before the earliest effective filing date of December 13, 2004 for Claims 1–3, 5–8, 10–30, and 36. And even if the date of invention was December 2003 (it was not), the S-1 would be prior art against all claims under 35 U.S.C. § 102(a). The S-1 was published in the September 30, 2003 issue of the SEC Digest, which informs the general public of S-1 filings. (Ex. 1046 at 9.) The SEC Digest publication provides the public with instructions about how they can obtain a copy, and also notes its availability on the SEC website (referencing Acorda's S-1). (*Id.*) The S-1 was not the basis of any Examiner rejection.

The S-1 acknowledges the effectiveness of the 10 and 25 mg BID dosing range, stating "subject and clinician reports and clinical measures in these non-blinded 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. 1028 at 44.) The S-1 described using fampridine-SR 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.* at 45, emphasis added.) The S-1 also discussed a previous 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 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.* at 46.)

b. The Hayes 2001 Reference (Ex. 1031)

Hayes 2001 constitutes prior art under 35 U.S.C. § 102(b) against all challenged claims because it was published on Sept. 30—October 3, 2001 (a fact admitted by the '685 patent applicants in an October 31, 2011 IDS, see Ex. 1049, at Reference No. C148). That date is more than one year prior to the earliest effective priority date, even if that date is December 2003. Hayes 2001 was not the basis of any Examiner rejection during the '826 prosecution history. (Transcriptions of the original Hayes

2001 (Ex. 1031) is included as Ex. 1050 for ease of reading as Ex. 1050 and a reproduction of Table 2 and Dose Response Curve of Hayes 2001 are provided as Exs. 1051-52.)

Hayes 2001 notes the importance of SR 4-AP for treating patients with MS, and cites Polman (Ex. 1034) for its disclosure that 4-AP "improves sensory and motor function in patients with…multiple sclerosis." (*Id.* at 2.) Patients in the Hayes 2001 study received 10, 15, 20 or 25 mg doses of SR fampridine, BID, for one week. (*Id.*) Steady state plasma concentrations were achieved by day 5. (*Id.* at 3.)

Table 2 provides pharmacokinetic data on SR 4-AP administration. (*Id.* at 4.) The data for 10 mg BID (i.e., 20 mg/day total) set forth in the table was: C_{avSS} (average plasma concentration at steady state): 20.8 (±5.7) ng/mL; T_{max} (time to reach maximum plasma concentration at steady state): 2.7(±1.0) hours. (*Id.*) Figure 1 shows the mean plasma concentration at each dose of fampridine over time. (*Id.*) At 10 mg BID fampridine remains in plasma at about 22 ng/mL at 6 hours after administration, at about 10 ng/mL at 12 hours after administration, and does not approach 0 ng/mL until about 20 hours after administration. (*Id.* at Figure 1.)

Moreover, it was within the knowledge of a POSA that a number of prior art studies and applications teach and disclose long-term administration of 4-AP for treatment of MS. For example, Hayes cites to a prior art publication by Polman et al., "4-Aminipyridine is Superior to 3,4, diaminopyridine in the Treatment of Patients with Multiple Sclerosis," Archives Neurol., 51: 1139–96 (Nov. 1994). (Ex. 1034.)

Polman constitutes prior art under 35 U.S.C. § 102(b) because it was published in 1994, more than one year prior to December 11, 2003, the earliest priority date of the '826 patent. Polman was not the basis of any rejection during the '826 patent prosecution.

Polman teaches a method of improving walking in a human multiple sclerosis patient in need thereof: "To compare the efficacy and toxicity of 4-aminopyridine and 3,4 diaminopyridine in patients with multiple sclerosis. … 4-Aminopyridine was more effective than 3,4-diarninopyri.dine, especially for ambulation" wherein ambulation is walking. (Ex. 1034, Abstract.) Polman's method comprised orally administering to said patient a composition of 10–35 milligrams daily of 4-aminopyridine for a time period of at least two weeks. "Responders to treatment with 4-aminopyridine (10 patients) participated in a comparative study of 6 weeks duration with 4-aminopyridine and 3,4-diaminopyri dine according to a randomized, double-blind, double crossover design." (*Id.* at Abstract.)

Polman disclosed, "[w]e recently completed a randomized, double-blind, placebo-controlled, crossover study of 12 weeks of oral treatment that demonstrated that 4-aminopyridine is superior to placebo and improved disability in certain patients with MS." (*Id.* at 1136.) Polman further disclosed that, "[p]atients were treated for 6 weeks and received one bottle of medication for each week. The first and the last bottles of medication always contained 4-aminopyridine." (*Id.* at 1137.) Further, there was a cross-over randomization wherein two consecutive bottles of the remaining

four contained 3,4-diaminopyridine. (*Id.*) In this way, patients had a double crossover; they were randomized to receive 3,4-diaminopyridine either during weeks 2 and 3, or during weeks 3 and 4, or during weeks 4 and 5.

Therefore, the patients receiving the 3,4-diaminopyridine in weeks 4 and 5 had, by definition, received 4-aminopyridine for at least four weeks—weeks 1, 2, 3, and 6. Polman concludes by teaching the efficacy of prolonged usage of 4-AP: "The finding that in the patients who used 4-aminopyridine for intervals varying from 6 to 30 months (mean, 19 months) before participating in this study the blinded crossovers induced clear changes in favor of 4-aminopyridine points to a continued efficacy of 4-aminopyridine during prolonged usage." (***Id***. at 1139.)

As another example of a POSA's knowledge concerning the length of 4-AP therapy to treat MS, Polman cites to a prior art publication by van Diemen et al., "The effect of 4-aminopyridinc on the clinical signs in multiple sclerosis: a randomized, placebo-controlled, double-blind, cross-over study," Annals Neurol., 32:123–130 (1992). (Ex. 1033.) van Diemen constitutes prior art under 35 U.S.C. § 102(b) because it was published in 1992, more than one year prior to December 11, 2003, the earliest possible priority date of the '826 patent. van Diemen was not the basis of any Examiner rejection during the '826 patent prosecution.

van Diemen teaches administering 4-AP to treat MS disability for at least two weeks; and specifically, for twelve weeks. (***Id.*** at 124.) Efficacy analysis was performed

only in patients who completed "at least two weeks" of a treatment period. (*Id.* at 125.) van Diemen teaches a statistically significant estimated effect of 4-AP on the mean EDSS score after 2, 6, and 12 weeks of treatment (*see* Table 1).

c. The Goodman Reference (Ex. 1030)

Goodman constitutes prior art under 35 U.S.C. § 102(b) because it was published at least as early as September 18–21, 2002 (a fact admitted by the '826 Patent applicants in a November 24, 2010 Information Disclosure Statement, *see* Ex. 1019 at Reference No. C84) (Ex. 1042.) This date is more than one year prior to the earliest possible effective priority date for claims 31–35 and 37–41, even if that date is December 2003. Goodman was not the basis of any Examiner rejection during the '826 prosecution history.

Goodman discloses data, results, and conclusions from a placebo-controlled double-blind dose ranging study of SR 4-AP (also referred to as fampridine-SR) in MS patients. (Ex. 1030 at Abstract.) Goodman notes that the primary aim of its study was to determine the safety and tolerability of escalating doses of an oral SR formulation of 4-AP. (*Id.*) A secondary aim was "to explore efficacy over a broad dose range using measures of fatigue and motor function." (*Id.*) Evidence of efficacy and dose response included "Standard MS measurements, including timed walk, lower extremity muscle strength . . ." (*Id.* at Objectives.)

The Goodman study administered multiple doses of fampridine-SR (one week each of 20 mg/day (10 mg BID), 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day, 70

mg/day, and 80 mg/day). (*Id.* at Objectives.) Each dose, in the form of a single tablet, was administered twice daily (i.e., BID)—every 12 hours. (*Id.* at Overview of Study Design.) Goodman's results showed improvement in a timed 25–foot walk as compared with control at a total daily dose of 20 mg and 30 mg (each about 13.5 secs), 40 mg and 50 mg (about 12.5 secs), 60 mg (about 13.5 secs), 70 mg (about 13 secs), and 80 mg (about 14 secs). (*Id.* at Dose Response 25 ft. Walk.) These results demonstrated a statistically significant (p=.04) improvement in walking speed following doses of at least 20 mg/day. (*Id.* at Results Summary.) Goodman further observed a "significant benefit in lower extremity strength." (*Id.* at Conclusions.)

Goodman's study concludes that it demonstrated "[e]vidence of dose-response in 20–40 mg/day range." (*Id.* at Conclusions.) However, the study cautioned that "[a]t doses above 40 mg/day, more severe adverse events were reported, including cases of seizure . . . ." (*Id.* at Results Summary.) Similarly, Goodman concluded that there was "[l]ittle added benefit, and increased risk, at doses above 50 mg/day." (*Id.* at Conclusions.)

VI. DETAILED EXPLANATION OF CHALLENGE

A. Ground 1: Challenged Claims 1–4, 5–8, 10–30 and 36 are invalid under 35 U.S.C. § 103(a) as obvious over S-1 in view of Hayes 2001 and a POSA's knowledge of the art.

As supported by the declarations from Dr. Pleasure and Dr. Polli, the challenged claims are invalid under 35 U.S.C. § 103(a) as obvious over the S-1 (Ex. 1028) in view of Hayes 2001(Ex. 1031) and a POSA's knowledge of the art.

Challenged claims 1–3, 5, 11–22, 24–30 and 36 are directed to methods of improving walking in MS patients by administering a sustained release oral formulation of 10 mg 4-AP twice daily (i.e., BID) for at least two weeks, or greater than two weeks. (*See* Ex. 1001.) Claims 6–8 and 10 do not require that the administration be maintained for an extended period of time. Claim 23 recites a maintenance period of "at least a week."

The S-1 expressly teaches the oral administration of a sustained-release formulation of 10 mg 4-AP twice daily for a period of greater than two weeks. (Ex. 1028.) In particular, the S-1 describes several clinical trials (e.g., MS-F201, MS-F202) in which the drug fampridine-SR was orally administered to patients suffering from MS. (*Id.*) The S-1 confirms that fampridine-SR is a sustained-release composition containing 4-aminopyridine as the active ingredient. (*Id.* at 3.) At the time of filing, the S-1 reported that one particular clinical trial, MS-F202, was in "late Phase II" and 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." (id. at 45, emphasis added). Such "pivotal data" would be derived from the comparison of three different dosing regimens of "**10, 15, and 20 mg, twice per day**, and [] assess their relative safety and efficacy over a treatment period of 12 weeks." (*Id.*, emphasis added). The S-1 further provides that "[t]he primary endpoint of the study is an improvement in average walking speed using the Timed 25 Foot Walk." (*Id.*, emphasis added). It was also noted that the resulting

measurements would be used specifically "to support an indication for the treatment of lower extremity motor dysfunction, characterized by weakness and walking impairment." (*Id.*, emphasis added). "[I]f an applicant has initiated human clinical trials for a therapeutic product or process, [Patent] 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." *In re Montgomery* 102 USPQ2d at 1886, citing MPEP § 2107.03 8th ed., rev. 6, Sept. 2007.

In summary, the S-1 teaches, *inter alia*, the oral administration of 10 mg SR 4-AP twice daily (i.e., BID) to MS patients for a stable administration period of greater than two weeks (i.e., 12 weeks) demonstrating an improvement in walking speed and lower extremity muscle strength. "It would have been obvious to a POSA to administer 10 mg SR 4-AP, BID for more than 12 weeks, based on the Acorda S-1's disclosure of successful 12 week Phase II and Phase III clinical trials, and the knowledge of a POSA regarding the benefits of extended regimens for the treatment of chronic diseases such as MS." (Pleasure Decl. ¶ 33 (Ex. 1026).) *See also In re Montgomery* (finding it is not necessary for a clinical trial to actually have been conducted in order for a reference, which discusses or suggests a clinical trial, to invalidate a claim to a method encompassing that trial).

Additionally, challenged claims 1–3, 5–8, 10–30 and 36 also require the achievement of certain *in vivo* pharmacokinetic parameters attributed to oral

administration of 10 mg 4-AP twice daily. (Ex. 1001 at Claims.) Specifically, independent claims 1, 6, 11, 17, and 36 of the '826 Patent recite the *in vivo* pharmacokinetic range "C_{maxSS}:C_{minSS} ratio or 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml." Claims 2–3, 5, 7–8, 10, 12–14, 20–26, 29, and 30 depend directly or indirectly from those claims and, thus, require the pharmacokinetic range limitation recited therein. Claims 15, 18, and 27 also depend directly or indirectly from the independent claims, but recite the narrower *in vivo* pharmacokinetic range "C_{maxSS}:C_{minSS} ratio or 1.5 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml." Dependent claims 16, 19, 28 recite the narrower range "C_{maxSS}:C_{minSS} ratio or 2.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml."

Hayes 2001 explicitly teaches these pharmacokinetic parameters for the claimed 10 mg SR 4-AP BID dosing. (Ex. 1031, *passim*.) Hayes 2001 reports that the mean pharmacokinetics for the twice-daily 10 mg dosing regimen includes a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3. (*Id.* at 4, Table 2.) Consequently, the pharmacokinetics reported in Hayes 2001 for the 10 mg SR 4-AP BID oral regimen fall within each of the pharmacokinetic ranges recited in claims 1–3, 5–8, 10–30 and 36 of the '826 Patent. A POSA would have been motivated to combine the S-1's sustained multi-week dosing SR 4-AP at 10 mg BID with a reasonable expectation of success because "both references are concerned with the administration and safety of sustained release dosages of 4-AP." (Pleasure Decl. ¶ 40 (Ex. 1026); *see also* Polli Decl. ¶ 41 (Ex. 1027).) Further, a POSA would have been motivated to combine the

references because "the similar dosing compositions, formulations, and regimens, disclosed by both would have exhibited similar pharmacokinetics. . . . useful for improving walking, walking speed, and lower extremity muscle strength in patients with multiple sclerosis because similar dosing regimens and levels would result in similar pharmacokinetics." (Polli Decl. ¶¶ 42–43 (Ex. 1027).)

Hayes 2001 does not specifically indicate a treatment period of two weeks or more. But Dr. Pleasure attests that based on Hayes 2001, a POSA would have had knowledge of a number of studies and references teaching long-term administration of 4-AP to treat MS. (Pleasure Decl. ¶¶ 45–46 (Ex. 1026 (citing Exs. 1033, 1035)).) For example, the Hayes 2001 reference cites Polman, which teaches a POSA about studies "that administered 4-aminopyridine for between 6–30 months, and for a six week time period, and specifically touted its benefit as a 'superior' drug (compared to other aminopyridines) for prolonged administration, which would have specifically motivated a POSA to administer the 4-aminopyridine for at least two weeks." (Pleasure Decl. ¶ 45 (Ex. 1026).) Likewise, Polman cites the van Diemen 1992 reference (Ex. 1033), which "teaches administering 4-AP to treat MS disability for at least two weeks; and specifically, for twelve weeks." (Pleasure Decl. ¶ 46 (Ex. 1026 (citing Ex. 1033 at 124)).) van Diemen's dose administration is striking in its similarity to the '826 specification. (*Compare* Ex. 1033 at 124, *with* Ex. 1001 at 6:37–48.)

Moreover, it is noted that Hayes 2001 further teaches that "[s]teady state was achieved by day 5 (4 days of fampridine-SR dosing) after twice-daily administration of

fampridine-SR." (*Id.* at 3.) Hayes 2001 ultimately concludes that orally administered fampridine-SR was well tolerated, absorbed and eliminated slowly, and reached steady state after 4 days. (*Id.*) Hayes 2001 presents data, results, and conclusions from an "open label, 4-week study conducted to investigate the pharmacokinetics and safety of multiple oral doses of fampridine-SR (sustained release 4-aminopyridine)" having the claimed pharmacokinetic parameters. (Ex. 1031 at 2, 3.) Patients in the Hayes 2001 study received 10, 15, 20 or 25 mg doses of fampridine, BID for one week. (*Id.*) Steady state plasma concentrations were achieved by day 5. (*Id.* at 3.)

Table 2 of Hayes 2001 provides pharmacokinetic data for the study. (*Id.* at Table 2.) The data for 10 mg BID (i.e., 20 mg/day total) as set forth in that table is as follows: C_{avSS}: 20.8 (±5.7) ng/mL; T_{max}: 2.7(±1.0) hours. (*Id.*) Figure 1 teaches mean plasma concentrations for each dose of 4-AP over time. (*Id.* at Figure 1.) The 10 mg BID dosing shows that 4-AP attains a steady state concentration in the plasma at about 22 ng/mL at 6 hours after administration, at about 10 ng/mL at 12 hours after administration, and does not approach 0 ng/mL until after about 20 hours following administration. (*Id.* at 4.)

Thus, although not explicitly disclosed in the S-1, a POSA considering Hayes 2001 and common knowledge at the time of the alleged invention would have understood that the S-1 methods would have exhibited *in vivo* pharmacokinetics falling within the ranges required by claims 1–3, 5–8, 10–30 and 36. Dr. Polli testifies that a

POSA would have understood that these pharmacokinetic parameters would exist in the clinical studies referenced in the S-1. (Polli Decl. ¶ 42 (Ex. 1027).)

First, with regard to MS-F202, the S-1 expressly teaches orally administering a sustained release dose of 10 mg of fampridine-SR, BID for 12 weeks. (Ex. 1028 at 45.) ***Second***, "because it was known in the art that fampridine-SR achieves a steady state in vivo at 5 to 8 days, a POSA would reasonably expect the fampridine-SR to have the same pharmacokinetic properties at the end of two weeks—as claimed as in the '826 patent—as during the every-four-week test periods disclosed in the S-1." (Polli Decl. ¶ 29 (Ex. 1027).)

Further, the recited pharmacokinetic parameters are obvious from the combination of S-1 and Hayes 2001 that teach the claimed compound, dose, regimen, and pharmacokinetic parameters. A property that is obvious from a combination of the prior art, even if previously unknown, does not render the combination nonobvious. *See, e.g.*, *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. To hold otherwise would allow any formulation — no matter how obvious — to become patentable merely by testing and claiming an inherent property.") (citation omitted); *Allergan Inc. v. Sandoz, Inc.*, 726 F.3d 1286, 1294 n.1 (Fed. Cir. 2013) (suggesting that where evidence establishes a claimed limitation is the

necessary result of a claimed administration it does not render an otherwise obvious claim nonobvious).

"At the least, a POSA would be motivated to try to produce variations that would optimize the release of 4-AP into a patient." (Pleasure Decl. ¶ 43 (Ex. 1026).) *See Bayer Schering Pharma AG v. Barr Labs., Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (affirming invalidity on the basis of "obvious to try," and explaining that an invention may be found obvious if it would have been obvious to a person having ordinary skill to try a course of conduct) (internal quotations omitted).

Thus, it would have been obvious to a POSA to administer SR 4-AP at a 10 mg BID for the treatment of MS as described in the S-1 and claimed in the '826 Patent to achieve a C_{avSS} of 20.8 ng/mL (+ 5.7) and a C_{maxSS}:C_{minSS} ratio of 2.3, as disclosed in Hayes 2001 and claimed in Claims 1–3, 5–8, 10–30 and 36. (*See* Polli Decl. ¶ 44 (Ex. 1027).) For at least those reasons, a POSA would have had the skill and motivation to combine the teachings of the S-1 and Hayes 2001 at the time of the alleged invention.

Claims 5, 10, 11, and 17 further recite a pharmaceutically acceptable excipient. Dr. Polli testifies that "POSA would understand that a sustained release formulation contains at least one pharmaceutically acceptable excipient in addition to the active pharmaceutical ingredient (4-aminopyridine)." (Polli Decl. ¶ 53 (Ex. 1027.) Claims 29 and 30 merely limit their respective claims to "a tablet"— as disclosed in the S-1 and within the general knowledge of the art. (S-1 describes tablets purchased from Elan).

1. Claim Chart for Ground 1 – S-1 and Hayes 2001

U.S. Pat. No. 8,007,826	The S-1 and Hayes 2001
Claim 1. A method for maintaining a therapeutically effective concentration of 4-aminopyridine in order to improve walking in a human with multiple sclerosis in need thereof, said method comprising:	The S-1 teaches a method for maintaining a therapeutically effective concentration of 4-aminopyridine in order to improve walking in a human with multiple sclerosis in need thereof: "We are currently conducting two Phase 3 clinical trials in people with SCI for the reduction of muscle stiffness, referred to as spasticity, and one late Phase 2 clinical trial in people with MS for the improvement of walking speed" using "Fampridine-SR for the treatment of spasticity in SCI in 2004 and for the treatment of lower extremity motor dysfunction in people with MS." (Ex. 1028 at 3.) "We hold an exclusive, worldwide license to three issued U.S. patents from Elan relating to timed delivery formulations of a family of aminopyridine compounds, including fampridine" (Ex. 1028 at 54.) "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 [and m]ost of the improvement in strength and walking speed was apparent within the first week." (Ex. 1028 at 46.)
orally administering to the human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day; and thereafter,	The S-1 teaches orally administering to the human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day: "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." (Ex. 1028 at 45.) A "Phase 2 clinical trial of Fampridine-SR in Multiple Sclerosis, MS-F201 … subjects received Fampridine-SR in doses increasing from 10 mg to 40 mg twice per day over eight weeks of treatment." (Ex. 1028 at 45.)

<table>
<tr><td></td><td>A “Phase 2 clinical trial, MS-F202, was designed … 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.” (Ex. 1028 at 45.)</td></tr>
<tr><td>maintaining administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks,</td><td>The S-1 teaches maintaining administration of 4-aminopyridine by orally administering to a human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks:

“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.” (Ex. 1028 at 46.)

A “Phase 2 clinical trial, MS-F202, was designed … 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.” (Ex. 1028 at 45.)</td></tr>
<tr><td>whereby an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a $C_{avSS}$of 15 ng/ml to 35 ng/ml are obtained in the human.</td><td>Hayes 2001 teaches an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} ratio of between 1.0 to 3.5 and a $C_{avSS}$of between 15 ng/ml to 35 ng/ml obtained in the human:

Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031:

Table 2. Summary of Fampridine-SR Pharmacokinetics
<table>
<tr><td>Parameter</td><td>10 mg b.i.d. (N=15)</td><td>10 mg b.i.d. (N=15)</td><td>20 mg b.i.d. (N=14)</td><td>25 mg b.i.d. (N=14)</td></tr>
<tr><td>C_{maxSS},</td><td>32.2 ±</td><td>46.7 ±</td><td>60.1 ±</td><td>87.2 ±</td></tr>
</table></td></tr>
</table>

	ng/mL	8.9	10.5	15.0	29.0
	C_{minSS}, ng/mL	14.0 ± 4.4	23.5 ± 9.1	27.3 ± 10.0	41.3 ± 15.2
	C_{avSS}, ng/mL	20.8 ± 5.7	31.0 ± 7.2	39.4 ± 9.3	53.3 ± 14.5
	t_{max}, h	2.7 ± 1.0	3.2 ± 0.9	3.1 ± 1.2	2.6 ± 0.9

(Ex.1051 - Reproduction of Table 2 of Ex.1031)

A "study was conducted to investigate the pharmacokinetics and safety of multiple oral doses of fampridine-SR (sustained-release 4-aminopyridine) … Study participants received multiple oral doses of fampridine-SR (10, 15, 20, or 25 mg b.i.d.) for 1 week." (Ex. 1031 at 2.)

"Steady state plasma concentrations increased with increasing doses and were achieved by Day 5." (Ex. 1031 at 3.)

"Compared with the IR formulation of fampridine, the SR formulation used in this study demonstrated slower absorption, lower maximum plasma concentration, and a longer period of elevated plasma levels. All doses of fampridine-SR were generally well tolderated." (Ex. 1031 at 6.)

"Summary of Fampridine-SR Pharmacokinetics…10 mg b.i.d…. Tmax h 2.7 (1.0) [hours]." (Ex. 1031 at 4, Table 2.)

See also Pleasure Decl. ¶¶ 32, 59 (Ex. 1026).

See also Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).

Claim 2. The method of claim 1, whereby an increase in walking speed is obtained in	The S-1 teaches an increase in walking speed is obtained by a human: *See* discussion in Claim 1 above.

said human.	"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 [and m]ost of the improvement in strength and walking speed was apparent within the first week." (Ex. 1028 at 46.)
Claim 3. The method of claim 1, whereby an improvement in lower extremity muscle strength is obtained in said human.	The S-1 teaches an improvement in lower extremity muscle strength is obtained in a human: *See* discussion in Claim 1 above. "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 [and m]ost of the improvement in strength and walking speed was apparent within the first week." (Ex. 1028 at 46.)
Claim 5. The method of claim 1, wherein the sustained release composition further comprises a pharmaceutically acceptable excipient.	The S-1 teaches that the sustained release composition further comprises a pharmaceutically acceptable excipient: "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
Claim 6. A dosing regimen method for providing a 4-aminopyridine at a therapeutically effective concentration in order to improve walking in a human with multiple sclerosis in need thereof, said method comprising:	The S-1 teaches A dosing regimen method for providing a 4-aminopyridine at a therapeutically effective concentration in order to improve walking in a human with multiple sclerosis in need thereof: *See* discussion in Claim 1 above. "We are currently conducting two Phase 3 clinical trials in people with SCI for the reduction of muscle stiffness, referred to as spasticity, and one late Phase 2 clinical trial in people with MS for the improvement of walking speed" using "Fampridine-SR for the treatment of spasticity in SCI in 2004 and for the treatment of lower extremity motor dysfunction in people with MS." (Ex. 1028 at 3.)

initiating administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day without a prior period of 4-aminopyridine titration, and then,	The S-1 teaches initiating administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a day without a prior period of 4-aminopyridine titration: *See* discussion in Claim 1 above. "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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027).
maintaining administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily; without a subsequent period of 4-aminopyridine titration,	The S-1 teaches maintaining administration of 4-aminopyridine by orally administering to said human a sustained release composition of 10 milligrams of 4-aminopyridine twice daily; without a subsequent period of 4-aminopyridine titration: *See* discussion in Claim 1 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027).
whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031.

	See also Pleasure Decl. ¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 24 (Ex. 1027).
Claim 7. The method of claim 6, whereby an increase in walking speed is obtained in said human.	*See* discussion in Claim 2 above.
Claim 8. The method of claim 6, whereby an improvement in lower extremity muscle strength is obtained in said human.	*See* discussion in Claim 3 above.
Claim 10. The method of claim 6, wherein the sustained release composition further comprises a pharmaceutically acceptable excipient.	*See* discussion in Claim 5 above. *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
Claim 11. A method for maintaining a therapeutically effective concentration of 4-aminopyridine in a human with multiple sclerosis in need of an improvement in walking, in order to improve walking in the human, said method comprising:	The S-1 teaches a method for maintaining a therapeutically effective concentration of 4-aminopyridine in a human with multiple sclerosis in need of an improvement in walking, in order to improve walking in the human: *See* discussion in Claim 1 above. "We are currently conducting two Phase 3 clinical trials in people with SCI for the reduction of muscle stiffness, referred to as spasticity, and one late Phase 2 clinical trial in people with MS for the improvement of walking speed" using "Fampridine-SR for the treatment of spasticity in SCI in 2004 and for the treatment of lower extremity motor dysfunction in people with MS." (Ex. 1028 at 3.)
orally administering twice daily to the human a sustained release composition	The S-1 teaches orally administering twice daily to the human a sustained release composition comprising a pharmaceutically acceptable excipient and 4-aminopyridine, the 4-aminopyridine consisting of 10

comprising a pharmaceutically acceptable excipient and 4-aminopyridine, the 4-aminopyridine consisting of 10 milligrams of 4-aminopyridine, for one day; and thereafter,	milligrams of 4-aminopyridine, for one day: *See* discussion in Claims 1 and 5 above. "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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027). "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
maintaining twice daily administration for a time period of greater than two weeks of a sustained release composition comprising a pharmaceutically acceptable excipient and 4-aminopyridine, the 4-aminopyridine consisting of 10 milligrams of 4-aminopyridine;	The S-1 teaches maintaining twice daily administration for a time period of greater than two weeks of a sustained release composition comprising a pharmaceutically acceptable excipient and 4-aminopyridine, the 4-aminopyridine consisting of 10 milligrams of 4-aminopyridine: *See* discussion in Claims 1 and 5 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027). "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
whereby an in vivo 4-aminopyridine	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35

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

See discussion in Claim 1 above.

Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031.

See also Pleasure Decl. ¶¶ 32, 59(Ex. 1026).

See also Polli Decl. ¶¶ 25–28, 30, 24 (Ex. 1027).</td></tr>
<tr><td>12. The method of claim 11, wherein an improvement in lower extremity muscle strength is obtained in said human.</td><td>See discussion in Claim 3 above.</td></tr>
<tr><td>13. The method of claim 1, further comprising a step of determining the C_{maxSS}:C_{minSS} ratio or the C_{avSS}.</td><td>The S-1 teaches a clinical trial to provide support for an NDA:

A “Phase 2 clinical trial, MS-F202, was designed … to provide pivotal data for support of an NDA for the use of Fampridine-SR in MS.” (Ex. 1028 at 45.)

Hayes 2001 teaches a step of determining the C_{maxSS}:C_{minSS} ratio or the C_{avSS}:

Table 2. Summary of Fampridine-SR Pharmacokinetics
<table>
<tr><th>Parameter</th><td>10 mg b.i.d. (N=15)</td><td>10 mg b.i.d. (N=15)</td><td>20 mg b.i.d. (N=14)</td><td>25 mg b.i.d. (N=14)</td></tr>
<tr><td>C_{maxSS}, ng/mL</td><td>32.2 ± 8.9</td><td>46.7 ± 10.5</td><td>60.1 ± 15.0</td><td>87.2 ± 29.0</td></tr>
<tr><td>C_{minSS}, ng/mL</td><td>14.0 ± 4.4</td><td>23.5 ± 9.1</td><td>27.3 ± 10.0</td><td>41.3 ± 15.2</td></tr>
<tr><td>C_{avSS}, ng/mL</td><td>20.8 ± 5.7</td><td>31.0 ± 7.2</td><td>39.4 ± 9.3</td><td>53.3 ± 14.5</td></tr>
</table></td></tr>
</table>

	<table><tr><td></td><td></td><td></td><td></td><td></td></tr><tr><td>**t_{max}, h**</td><td>2.7 ± 1.0</td><td>3.2 ± 0.9</td><td>3.1 ± 1.2</td><td>2.6 ± 0.9</td></tr></table> (Ex.1051 - Reproduction of Table 2 of Ex.1031) *See also* Polli Decl. ¶¶ 31, 50–51 (Ex. 1027).
14. The method of claim 11, wherein the twice daily administration comprises b.i.d. administration or administration at 12-hour intervals.	The S-1 teaches the twice daily administration comprises b.i.d. administration or administration at 12-hour intervals: *See* discussion in Claim 1 above. "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." (Ex. 1028 at 45.)
15. The method of claim 11, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.5 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
16. The method of claim 11, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026).

	See also Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
17. A method to improve walking by a human with multiple sclerosis in need thereof, said method comprising:	The S-1 teaches a method to improve walking by a human with multiple sclerosis in need thereof: *See* discussion in Claim 1 above. "We are currently conducting two Phase 3 clinical trials in people with SCI for the reduction of muscle stiffness, referred to as spasticity, and one late Phase 2 clinical trial in people with MS for the improvement of walking speed" using "Fampridine-SR for the treatment of spasticity in SCI in 2004 and for the treatment of lower extremity motor dysfunction in people with MS." (Ex. 1028 at 3.)
orally administering twice daily for one day to the human a sustained release composition of 10 milligrams of 4-aminopyridine and an agent selected from the group consisting of one or more additional active ingredients, one or more pharmaceutically acceptable excipients and a combination thereof; and thereafter,	The S-1 teaches orally administering twice daily for one day to the human a sustained release composition of 10 milligrams of 4-aminopyridine and an agent selected from the group consisting of one or more additional active ingredients, one or more pharmaceutically acceptable excipients and a combination thereof: *See* discussions in Claims 1 and 5 above. "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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027). "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
maintaining twice daily administration of 4-aminopyridine by orally administering twice daily to said human a sustained release composition	The S-1 teaches maintaining twice daily administration of 4-aminopyridine by orally administering twice daily to said human a sustained release composition of 10 milligrams of 4-aminopyridine and an agent selected from the group consisting of one or more additional active ingredients, one or more pharmaceutically acceptable excipients and a combination thereof for a time period of greater than two

of 10 milligrams of 4-aminopyridine and an agent selected from the group consisting of one or more additional active ingredients, one or more pharmaceutically acceptable excipients and a combination thereof for a time period of greater than two weeks;	weeks: *See* discussions in Claims 1 and 5 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.) *See also* Polli Decl. ¶ 39 (Ex. 1027). "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶¶ 16, 53 (Ex. 1027).
whereby an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained and there is an improvement in walking by the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. The S-1 teaches an improvement in walking by the human. "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 [and m]ost of the improvement in strength and walking speed was apparent within the first week." (Ex. 1028 at 46.) *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).

18. The method of claim 1, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.5 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.5 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
19. The method of claim 1, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
20. The method of claim 1 wherein the maintaining step comprises maintaining for a period of more than two weeks.	The S-1 teaches the method of claim 1 wherein the maintaining step comprises maintaining for a period of more than two weeks: *See* discussion in Claim 1 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.)
21. The method of claim 1 wherein the	The S-1 teaches maintaining a therapeutically effective concentration of 4-aminopyridine for a period twelve

maintaining step comprises maintaining for a period of more than twelve weeks.	weeks: A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.) *See also* Pleasure Decl. ¶¶ 24, 66–68, 33 (Ex. 1026).
22. The method of claim 1 wherein said sustained release composition is a tablet.	The S-1 teaches that the sustained release composition is a tablet: "Our lead product candidate, Fampridine-SR, is an oral, small molecule drug, contained in a sustained release tablet form." (Ex. 1028 at 35.) *See also* Polli Decl. ¶ 13 (Ex. 1027).
23. The method of claim 6 wherein the maintaining step comprises maintaining for a period of at least a week.	The S-1 teaches the method of claim 6 wherein the maintaining step comprises maintaining for a period of at least a week: *See* discussion in Claim 6 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.)
24. The method of claim 6 wherein the maintaining step comprises maintaining for a period of at least two weeks.	The S-1 teaches the method of claim 1 wherein the maintaining step comprises maintaining for a period of at least two weeks: *See* discussion in Claim 6 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.)
25. The method of claim 6 wherein the maintaining step comprises maintaining for a period of more than two weeks.	The S-1 teaches the method of claim 1 wherein the maintaining step comprises maintaining for a period of more than two weeks: *See* discussion in Claim 6 above. A "Phase 2 clinical trial, MS-F202, was designed … 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." (Ex. 1028 at 45.)
26. The method of claim 6 wherein the maintaining step comprises maintaining for a period of more than twelve weeks.	*See* discussion in Claim 21 above. *See also* Pleasure Decl. ¶¶ 24, 66–68, 33 (Ex. 1026).
27. The method of claim 6, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.5 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 1.5 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 6 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
28. The method of claim 6, whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.0 and a C_{avSS} of 15 ng/ml to 35 ng/ml are obtained in the human.	Hayes 2001 teaches that whereby an in vivo C_{maxSS}:C_{minSS} ratio of 2.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 6 above. Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS}

	of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 30, 34 (Ex. 1027).
29. The method of claim 6 wherein said sustained release composition is a tablet.	*See* discussion in Claim 22 above.
30. The method of claim 17 wherein said sustained release composition is a tablet.	*See* discussion in Claim 22 above.
36. A method to improve walking in a patient with multiple sclerosis in need thereof by use of a sustained release composition of 4-aminopyridine,	The S-1 teaches a method to improve walking in a patient with multiple sclerosis in need thereof by use of a sustained release composition of 4-aminopyridine *See* discussion in Claim 1 above. "We are currently conducting two Phase 3 clinical trials in people with SCI for the reduction of muscle stiffness, referred to as spasticity, and one late Phase 2 clinical trial in people with MS for the improvement of walking speed" using "Fampridine-SR for the treatment of spasticity in SCI in 2004 and for the treatment of lower extremity motor dysfunction in people with MS." (Ex. 1028 at 3.) "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." (Ex. 1028 at 45.)
where sustained indicates that the composition achieves an in vivo 4-aminopyridine C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS}	Hayes 2001 teaches where sustained indicates that the composition achieves an in vivo C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 and a C_{avSS} of 15 ng/ml to 35 ng/ml are maintained in the human: *See* discussion in Claim 1 above.

of 15 ng/ml to 35 ng/ml in a human, said method comprising:	Hayes 2001 teaches a C_{maxSS} of 32.2 ng/mL (+ 8.9), C_{minSS} of 14.0 ng/mL (+ 4.4), and a C_{avSS} of 20.8 ng/mL (+ 5.7), whereby the C_{maxSS}:C_{minSS} ratio is 2.3 in Table 2 of Ex. 1031. *See also* Pleasure Decl. ¶¶ 32, 59 (Ex. 1026). *See also* Polli Decl. ¶¶ 25–28, 60, 34 (Ex. 1027).
orally administering twice daily for one day to the patient an amount of the sustained release composition having only 10 milligrams of 4-aminopyridine; and thereafter, maintaining twice daily administration of 4-aminopyridine by orally administering to said patient an amount of the sustained release composition having only 10 milligrams of 4-aminopyridine for a time period of at least two weeks.	The S-1 teaches orally administering twice daily for one day to the patient an amount of the sustained release composition having only 10 milligrams of 4-aminopyridine; and thereafter, maintaining twice daily administration of 4-aminopyridine by orally administering to said patient an amount of the sustained release composition having only 10 milligrams of 4-aminopyridine for a time period of at least two weeks: *See* discussion in Claim 1 above. "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." (Ex. 1028 at 45.) *See also* Pleasure Decl. ¶¶ 24, 66–68 (Ex. 1026).

B. Ground 2: Claims 31–35 and 37–41 are invalid under 35 U.S.C. § 103(a) as being obvious over Goodman in view of Hayes 2001 and in view of a POSA at the time.

Goodman, when combined with the Hayes 2001 reference, discloses each element of Claims 31–35 and 37–41. Goodman discloses an optimal dosage of 10 mg SR 4-AP, BID, for the treatment of MS. (Ex. 1028 at Abstract.) Although Goodman does not explicitly recite a dosage period of "at least two weeks" or a mean T_{max}

within the ranges required by Claims 31 and 37, Hayes 2001 discloses administering 10 mg SR 4-AP, BID for one week exhibiting a mean T_{max} within the claimed ranges. (Ex. 1031 at Table 2.) As Dr. Pleasure testifies, a POSA would have been motivated to combine the two references "as both references are concerned with the administration and safety of sustained release dosages of 4-AP," and, as a result, would have viewed the alleged invention as obvious. (Pleasure Decl. ¶ 40)(Ex. 1026).)

Goodman's results indicated patient results of a timed 25-foot walk at 10 mg BID and 15 mg BID for a total daily dose of 20 mg and 30 mg (about 13.5 seconds improvement against baseline); 20 mg BID and 25 mg BID for a total daily dose of 40 mg and 50 mg (about 12.5 seconds improvement against baseline); 30 mg BID for a total daily dose of 60 mg (about 13.5 seconds improvement against the baseline), 35 mg BID for a total daily dose of 70 mg (about 13 seconds improvement against the baseline); and 40 mg BID for a total daily dose of 80 mg (about 14 seconds improvement against the baseline). (*See Id.* at "Dose Response 25 ft. Walk.") These results demonstrated a statistically significant (p=.04) improvement in walking speed following doses of at least 20 mg/day. (*Id.* at Results Summary.) Goodman further observed a "significant benefit in lower extremity strength." (*Id.* at Conclusions.)

"A review of Goodman shows that the greatest benefit was seen with the first dose step of the drug. Any further benefit with increased dosage in walking speed, again, was not shown to be statistically significant, and a POSA would have considered the dosing efficacy as between 10-40 mg BID to be substantially

equivalent." (Pleasure Decl. ¶ 65 (Ex. 1026).) Accordingly, "Goodman shows that there are undesirable side effects associated with higher doses of SR 4-aminopyridine—above 40 mg/day (20 mg BID), teaching a POSA to select a dose no greater than 40 mg/day (20 mg BID)." (Pleasure Decl. ¶ 57 (Ex. 1026).)

Goodman's study concluded that there was "[e]vidence of dose-response in 20–40 mg/day range." (Ex. 1030 at Conclusions.) However, the study cautioned that "[a]t doses above 40 mg/day (i.e., twice daily at 20 mg), more severe adverse events were reported, including cases of seizure …" (*Id.* at Results Summary.) Similarly, the study concluded that there was "[l]ittle added benefit, and increased risk, at doses above 50 mg/day." (*Id.* at Conclusions.) Thus, while the study purportedly covers a 10 mg to 40 mg BID dosing range, Goodman clearly teaches that the optimal dosing in terms of dose response and safety covers a 10 mg to 20 mg BID range. *See Abbott Labs v. Andrx Pharms., Inc.*, 452 F.3d 1331, 1345 (Fed. Cir. 2006) (finding substantial question of invalidity because the combination of references for "the reduction of systemic side effects would not be surprising and would not be unexpected").

A secondary aim of Goodman was "to explore efficacy over a broad dose range using measures of fatigue and motor function." (*See* Ex. 1008 at Abstract.) After studying this efficacy, Goodman disclosed a dose response curve demonstrating that there are no significant increases in efficacy between 10 mg BID and 25 mg BID. (*Id.*) Thus, in light of Goodman's dose response curve, Dr. Pleasure attests that "POSA desiring to address mobility issues (*e.g.*, difficulty walking) in MS patients, and aware of

the efficacy in MS patients of an oral SR 4-aminopridine formulation dosed at between 10 and 20 mg BID, as disclosed in Goodman, would have been motivated to administer 10 mg BID of the SR formulation to MS patients in need of therapy." (Pleasure Decl. ¶ 30 (Ex. 1026).)

Goodman further taught a finite number of doses that were most desirable from the perspective of efficacy and avoidance of side effects, i.e., 20 mg/day (10 mg BID), 30 mg/day and 40 mg/day. (*See* Ex. 1008.) Based on the information available to one of ordinary skill in the art as of December 2002, Dr. Pleasure attests that a POSA would have known that a 10 mg BID would provide the best chance for efficacy while avoiding side effects, in light of the insignificant differences in mobility from 10 mg BID to 20 mg BID or higher. (*See* Pleasure Decl. ¶ 57 (Ex. 1026).) *See Tyco Healthcare Grp. LP v. Mut. Pharm. Co.*, 642 F.3d 1370, 1371–72 (Fed. Cir. 2011)(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).

Although Goodman does not explicitly disclose a dosing regimen of at least two weeks or twelve weeks, a POSA would have a reasonable "expectation that the improvements in walking observed after administration of the LED for one week could be extended by continuing the administration for two weeks or longer." (Pleasure Decl. ¶ 68 (Ex. 1026).) *See Hoffmann La Roche, Inc. v. Apotex Inc.*, 748 F.3d

1326, 1332 (Fed. Cir. 2014) (affirming finding that 150 mg monthly dose was obvious to try, in view of disclosed weekly doses of 35 mg, 40 mg, 45 mg, or 50 mg, because "[t]here was a need to solve the problem of patient compliance by looking to less-frequent dosing regimens. And…there were only a finite number of identified, predictable solutions.") (quotations omitted). Specifically, "a POSA would have recognized that the administration of an effective amount of SR 4-aminopyridine would need to be continued beyond a single week in MS patients, and into multiple weeks, in order to provide the MS patients with needed ongoing relief for their chronic mobility (e.g., walking) problems." (Pleasure Decl. ¶ 66 (Ex. 1026).) *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012) (finding substantial question of validity "'[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability'") (quoting *KSR*, 550 U.S. at 417).

Thus, "[d]ue to this chronic condition, a POSA would have recognized that patients afflicted with MS would be appropriate candidates for the administration of 4-aminopyridine—not only for a short period of time such as one week, but on an ongoing basis." (Pleasure Decl. ¶ 61 (Ex. 1026).) *See Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367–68 (Fed. Cir. 2007) (holding that where, as here, "one skilled in the art would have had a reasonable expectation of success at the time the invention was made, and merely had to verify that expectation. [ ] The experimentation needed, then, to arrive at the subject matter claimed in the [ ] patent was 'nothing more than

routine' application of a well-known problem-solving strategy, and…'the work of a skilled [artisan], not of an inventor.'") (citation omitted).

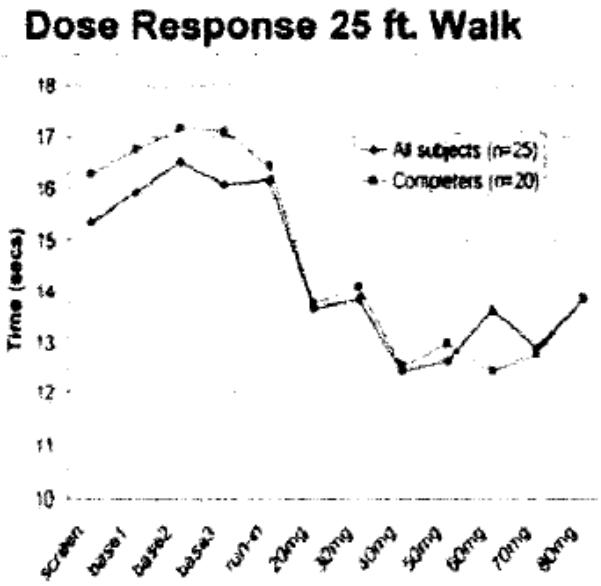
Dr. Pleasure's declaration establishes "that MS is a long-lasting, chronic disease, with patients experiencing problems walking on an ongoing basis and especially as the disease progresses with time. A POSA would understand that such ongoing problems require sustained therapy." (Pleasure Decl. ¶ 24 (Ex. 1026).) Because MS is a chronic illness affecting mobility, ongoing therapies that would extend to at least two weeks are well within the range that a POSA would have investigated at the time of the alleged invention (Pleasure Decl. ¶ 34 (Ex. 1026).)

Although Goodman does not explicitly describe the T_{max} data recited in Claims 31–35 and 37–41, the Hayes 2001 reference disclose such data as set forth in detail, *infra*, at pages 28-32. As with the S-1, a POSA would have been motivated to combine Goodman's SR 4-AP at 10 mg BID dosing with a reasonable expectation of success because "both references are concerned with the administration and safety of sustained release dosages of 4-AP." (Pleasure Decl. ¶ 54 (Ex. 1026); *see also* Polli Decl. ¶ 25 (Ex. 1027).) Further, a POSA would have been motivated to combine the references because "the similar dosing compositions, formulations, and regimens, disclosed by both would have exhibited similar pharmacokinetics. . . . and thus useful for improving walking, walking speed, and lower extremity muscle strength in patients with multiple sclerosis because similar dosing regimens and levels would result in similar pharmacokinetics." (Polli Decl. ¶¶ 26–27 (Ex. 1027).)

The Hayes 2001 data correspond to the pharmacokinetic parameters recited in Claims 31 and 37. (*See* Ex. 1001.) Thus, a POSA would conclude that, in view of Hayes 2001, at 10 mg BID, the T_{max} at 2.7(±1.0) hours, Goodman's administration of 10 mg BID would yield the same T_{max} results. (Polli Decl. (Ex. 1027 ¶¶ 2–3).) *See In re Kao*, 639 F.3d 1057, 1070 (Fed. Cir. 2011) (finding an inherent property of a compound used in a claimed method did not render the obvious claimed method nonobvious even though the property was unknown in the prior art).

1. Claim Chart for Ground 2 – Goodman and Hayes 2001

U.S. 8,007,826	**Goodman and Hayes 2001**
31. A method of increasing walking speed in a human multiple sclerosis patient in need thereof comprising	Goodman teaches a method of increasing walking speed in a human multiple sclerosis patient in need thereof: "Significant improvement in walking speed was observed in the fampridine treated group." (Ex. 1030 at Results Summary.) "That the primary aim of the study was to determine the safety and tolerability of escalating doses of an SR formulation of Fampridine given orally to patients with MS." (*See* Ex.1030 at Abstract.) "Significant improvement in walking speed was observed in the fampridine treated group." (Ex. 1030 at Results Summary.) "Average improvement in walking speed during the low dose period (20-50 mg/day) include >20% increase for 9 of the 25 subjects." (Ex. 1030 at Results Summary.)
orally administering to said patient a sustained release composition of	Goodman teaches orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of a week:

10 milligrams of 4-aminopyridine twice daily for a time period of greater than two weeks,	"Determine safety of multiple doses of fampridine-SR (one week each of 20 mg/day, 30 mg/day, 40 mg/day, 50 mg/day, 60 mg/day 70 mg/day, and 80 mg/day" (Ex. 1030 at Objectives.) "[S]tarted with a placebo run for the first week, 20 mg/day (10 mg BID) the second week, and then increased in wekly increments of 10 mg up to 80 mg/d during week 8." (Ex. 1030 at Abstract.)  (*Id.* at Dose Response 25 Ft. Walk graph.) "Evidence of dose-response in 20-40 mg/day range. Little added benefit, and increased AEs at doses above 50 mg/day." (*Id.* at Conclusions) "At doses above 40 mg/day, more severe adverse events were reported" (*Id.* at Results Summary.) *See also* Pleasure Decl. ¶¶ 24, 56–68 (Ex. 1026).
wherein said sustained release composition provides a mean T_{max} in a range of about 1 to about 6 hours after administration of the	Hayes 2001 teaches wherein said sustained release composition provides a mean T_{max} in a range of about 1 to about 6 hours after administration of the sustained release composition to the patient: A "study was conducted to investigate the

<table>
<tr>
<td>sustained release composition to the patient.</td>
<td>pharmacokinetics and safety of multiple oral doses of fampridine-SR (sustained-release 4-aminopyridine) … Study participants received multiple oral doses of fampridine-SR (10, 15, 20, or 25 mg b.i.d.) for 1 week." (Ex. 1031 at 2.)

Table 2 of Hayes 2001 indicates "Fampridine-SR Pharmacokinetics…10 mg b.i.d…. T_{max} h 2.7 (1.0) [hours]." (Ex. 1031 at 3.)

"Steady state plasma concentrations increased with increasing doses and were achieved by Day 5." (Ex. 1031 at 3.)

"Compared with the IR formulation of fampridine, the SR formulation used in this study demonstrated slower absorption, lower maximum plasma concentration, and a longer period of elevated plasma levels. All doses of fampridine-SR were generally well tolderated." (Ex. 1031 at 6.)

See also Polli Decl. ¶¶ 29, 31–32 (Ex. 1027).</td>
</tr>
<tr>
<td>32. The method of claim 31 wherein the sustained release composition elicits a C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 when administered b.i.d. or administered at 12-hour intervals to a human.</td>
<td>Hayes 2001 teaches wherein the sustained release composition elicits a C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 when administered b.i.d. or administered at 12-hour intervals to a human:

Hayes 2001 teaches a C_{maxss} of 32.2 ng/mL (± 8.9) and a C_{minss} of 14.0 ng/mL (± 4.4), whereby the C_{maxSS}:C_{minSS} ratio is 2.3. (Ex. 1031 at Table 2.)

Table 2. Summary of Fampridine-SR Pharmacokinetics
<table>
<tr><td>Parameter</td><td>10 mg b.i.d. (N=15)</td><td>10 mg b.i.d. (N=15)</td><td>20 mg b.i.d. (N=14)</td><td>25 mg b.i.d. (N=14)</td></tr>
<tr><td>C_{maxSS}, ng/mL</td><td>32.2 ± 8.9</td><td>46.7 ± 10.5</td><td>60.1 ± 15.0</td><td>87.2 ± 29.0</td></tr>
<tr><td>C_{minSS},</td><td>14.0 ±</td><td>23.5 ±</td><td>27.3 ±</td><td>41.3 ±</td></tr>
</table>
</td>
</tr>
</table>

	<table><tr><td>**ng/mL**</td><td>4.4</td><td>9.1</td><td>10.0</td><td>15.2</td></tr><tr><td>**C_{avSS}, ng/mL**</td><td>20.8 ± 5.7</td><td>31.0 ± 7.2</td><td>39.4 ± 9.3</td><td>53.3 ± 14.5</td></tr><tr><td>**t_{max}, h**</td><td>2.7 ± 1.0</td><td>3.2 ± 0.9</td><td>3.1 ± 1.2</td><td>2.6 ± 0.9</td></tr></table> (Ex.1051 - Reproduction of Table 2 of Ex.1031) Table 2 of Hayes 2001 indicates "Fampridine-SR Pharmacokinetics…10 mg b.i.d." (Ex. 1031 at 3.)
33. The method of claim 31 wherein said time period is twelve weeks.	Goodman teaches wherein said time period is eight weeks: "[S]tarted with a placebo run for the first week, 20 mg/day (10 mg BID) the second week, and then increased in wekly increments of 10 mg up to 80 mg/d during week 8." (Ex. 1030 at Abstract.) *See also* Pleasure Decl. ¶¶ 60–68 (Ex. 1026).
34. The method of claim 31 wherein said sustained release composition is a tablet.	*See* Polli Decl. ¶ 13 (Ex. 1027).
35. The method of claim 31 wherein the step of administering comprises b.i.d. administering or administering at 12-hour intervals.	Goodman teaches wherein the step of administering comprises b.i.d. administering or administering at 12-hour intervals: "[S]tarted with a placebo run for the first week, 20 mg/day (10 mg BID) the second week, and then increased in wekly increments of 10 mg up to 80 mg/d during week 8." (Ex. 1030 at Abstract.) Hayes 2001 teaches wherein the step of administering comprises b.i.d. administering or administering at 12-hour intervals: Table 2 of Hayes 2001 indicates "Fampridine-SR Pharmacokinetics…10 mg b.i.d." (Ex. 1031 at 3.)
37. A method of increasing walking speed	Goodman teaches a method of increasing walking speed in a human multiple sclerosis patient in need thereof:

in a human multiple sclerosis patient in need thereof comprising	"Significant improvement in walking speed was observed in the fampridine treated group." (Ex. 1030 at Results Summary.)
orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of greater than two weeks,	Goodman teaches orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of a week: "[S]tarted with a placebo run for the first week, 20 mg/day (10 mg BID) the second week, and then increased in wekly increments of 10 mg up to 80 mg/d during week 8." (Ex. 1030 at Abstract.) *See also* Pleasure Decl. ¶¶ 24, 56–68 (Ex. 1026).
wherein said sustained release composition provides a mean T_{max} in a range of about 2 to about 5.2 hours after administration of the sustained release composition to the patient.	*See* discussion above regarding Claim 31. *See also* Polli Decl. ¶¶ 29, 31, 33 (Ex. 1027).
38. The method of claim 37 wherein the sustained release composition elicits a C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 when administered b.i.d. or administered at 12-hour intervals to a human.	Hayes 2001 teaches wherein the sustained release composition elicits a C_{maxSS}:C_{minSS} ratio of 1.0 to 3.5 when administered b.i.d. or administered at 12-hour intervals to a human: *See* discussion above regarding Claim 32. Hayes 2001 teaches a C_{maxss} of 32.2 ng/mL ($\pm$ 8.9) and a C_{minss} of 14.0 ng/mL ($\pm$ 4.4), whereby the C_{maxSS}:C_{minSS} ratio is 2.3. (Ex. 1031 at Table 2.) Table 2 of Hayes 2001 indicates "Fampridine-SR Pharmacokinetics…10 mg b.i.d." (Ex. 1031 at 3.)
39. The method of claim 37 wherein said time period is twelve weeks.	*See* discussion above regarding Claim 33.
40. The method of claim	*See* Polli Decl. ¶ 13 (Ex. 1027).

37 wherein said sustained release composition is a tablet.	
41. The method of claim 37 wherein the step of administering comprises b.i.d. administering or administering at 12-hour intervals.	*See* discussion above regarding Claim 35.

VII. ANY SECONDARY CONSIDERATIONS ARE INSUFFICIENT TO OVERCOME THE OBVIOUSNESS OF CLAIMS 1–3, 5–8, 10–41

Applicant has the burden of establishing the existence and sufficiency of such secondary considerations, as well as their nexus and commensurateness with the claims. (*Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992); *Galderma Labs., L.P. v. Tolmar, Inc.*, 737 F.3d 731 (Fed. Cir. 2013) (stating "[w]here there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.). Although secondary considerations must be taken into account, they do not control the obviousness conclusion. *See Newell Cos., Inc. v. Kenney, Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). And in cases where a strong prima facie obviousness showing exists, the Federal Circuit has repeatedly held that even relevant secondary considerations supported by substantial evidence may not dislodge the

primary conclusion of obviousness. *See, e.g., Leapfrog Enters. Inc. v. Fisher-Price Inc.*, 485 F.3d 1157, 1162 (Fed. Cir. 2007).

During prosecution, four expert declarations were introduced by applicant to prove secondary considerations. (Exs. 1011, 1012, 1016, 1017 (declarations of Blight, Lawrence, Sabella, Medori). None of the declarations establish a nexus between the alleged secondary considerations and the '826 patent claims. (*Id.)* Several prior art references, such as S-1 and Goodman, disclose the same dosing of 10 mg BID. Most of the claims include the limitation of a period of treatment that is at least two weeks or longer. None of these declarations attribute a treatment period of at least two weeks to the success of 4-AP. *Id.* Nor was there any evidence that any long felt need allegedly resolved by Amprya was due to treatment for at least 2 weeks. *Id.* None of the declarations mentioned $C_{avSS,}$ nor C_{maxSS} to C_{minSS} ratio, nor mean T_{max} of 4-AP after administration. *Id.* Thus, no evidence provided by any of the declarations attributes any secondary considerations to the pharmacokinetic properties recited in the independent claims of the '826 patent. *Id.*

Applicant additionally submitted a declaration by Blight in support of "surprising results" to show that its scientific findings were unexpected. (Ex. 1011.) Blight's declaration states that the fact that "it was surprising that a 10 mg dose was as effective as a 20 mg dose is further evidence[d] by the recognition in the art of 4-AP's narrow therapeutic window and the bias in the art toward using larger dosage amount than those recited in the instant claims." (*Id.* at 8.) To support conclusions of

unexpected results, the evidence asserted as unexpected must actually have been obtained. *See, e.g., In re Klosak*, 455 F.2d 1077, 1080 (CCPA 1973). And the evidence must include a comparison with the closest prior art. *See., e.g., In re Merchant*, 575 F.2d 865, 869, (CCPA 1978). **But Goodman disclosed that dosages at 10 mg BID were as effective as 15 mg BID.** (Ex. 1030 at Abstract.) Thus, one of ordinary skill in the art "would not have considered the effectiveness of dosages of 10 mg Ampyra BID without dose escalation to be surprising." (Pleasure Decl. ¶ 71 (Ex. 1026).)

Further, there exists no independent data that describes the unexpected result from the claimed period of treatment when compared to shorter treatments. (*See* Ex. 1001.) Superiority of, or difference in results, if not shown to be unexpected, is insufficient. *See, e.g., In re Dill*, 604 F.2d 1356, 1361 (CCPA 1979).

Applicant additionally submitted a declaration by Medori dated November 15, 2010. (Ex. 1016) Medori points to other MS drugs, like "Nerispirdine," which failed to enter Phase III of clinical trials. (*Id.* ¶ 16.) However, there is no showing that an "at least two weeks" regimen of 4-AP or the pharmacokinetic parameters recited in the claims could have been the solutions to a failed MS drug. If anything, Ampyra's success was to be expected since Goodman, Hayes 2001, and the S-1 had all previously demonstrated the success of the same dosing regimen in MS patients. (Pleasure Decl. ¶ 74, 75 (Ex. 1026).)

For the foregoing reasons, Petitioner respectfully requests *inter partes* review of Claims 1–3, 5–8, 10–41 of U.S. Patent No. 8,007,826.

Respectfully submitted, February 27, 2015

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CERTIFICATE OF SERVICE

I certify that on February 27, 2015, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 8,007,826, including all exhibits (1001–1052), was served via FEDEX, overnight delivery, upon the following:

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