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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. 8,663,685
Filed: July 20, 2011
Issued: March 4, 2014
Inventors: Andrew R. Blight, Ron Cohen
Title: SUSTAINED RELEASE AMINOPYRIDINE COMPOSITION

PETITION FOR *INTER PARTES* REVIEW
OF U.S. PATENT NO. 8,663,685

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I. INTRODUCTION

Petitioner Coalition For Affordable Drugs (ADROCA) LLC ("CFAD") requests an *Inter Partes* Review ("IPR") of claims 1–8 of U.S. Patent No. 8,663,685 ("the '685 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 '685 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 '685 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 of the costs associated with this Petition will be borne by HCM, CFAD, Credes and/or HCMF.

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

Pursuant to 37 C.F.R. § 42.8(b)(2), Petitioner states that the '685 patent is the subject of several 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.).

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 refund of fees may also be deposited in this Deposit Account.

V. IDENTIFICATION OF CHALLENGE

A. Overview of the '685 Patent

i. The '685 Patent and Related Applications

The '685 patent issued on March 4, 2014, from U.S. Patent Application No. 13/187,158, filed July 20, 2011, (Ex. 1001), which is a continuation of U.S. Patent Application No. 11/010,828, filed December 13, 2004, now U.S. Patent 8,007,826 (Ex. 1002). The '685 patent claims priority to four U.S. Provisional Patent Applications: Application No. 60/528,760, filed December 11, 2003 (Ex. 1028), Application No. 60/560,894 (Ex. 1029), filed April 9, 2004, Application No. 60/528,592 (Ex. 1030), filed December 11, 2003, and Application No. 60/528,593 (Ex. 1031), filed December 11, 2003.

The '685 patent is entitled "Sustained Release Aminopyridine Composition" and describes a method of improving walking in a human afflicted with multiple sclerosis ("MS"). (*See* Ex. 1001.) The '685 patent further describes various pharmacokinetic parameters and dosing regimens associated with the administration of this SR oral formulation, such as T_{max}, "release profile[s]," average plasma concentrations, dispersal of the drug based on a rate-of-release-controlling polymer, and administration intervals. (*Id.* at col. 13, ll. 7–28.) The '685 patent claims the administration of an oral, sustained release ("SR") composition comprising 10 mg of 4-aminopyridine and one or more pharmaceutically-acceptable excipients twice daily for a time period of at least two weeks. (*Id.* at Claims.) The specification teaches an

escalating dosing regimen: "For example, at the commencement of treatment the active agent is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. The dose administered may then be increased by amounts of at least 5-15 mg/day until a therapeutic dose is reached." (Ex. 1001, at 6:37–48.) The specification also discloses treatment for multiple weeks in Example 8, which is an 8-week study. (*Id.* at col. 25, 26.)

ii. The '685 Patent Claims

The '685 patent includes 8 claims with claim 1 being the only independent claim. Each of claims 1–8 are challenged in the present petition.

Independent Claim 1 is directed to a method of improving walking in a human multiple sclerosis patient comprising orally administering a sustained release composition of 10 mg 4-aminopyridine twice daily for at least two weeks. Independent claim 1 recites:

> A method of improving walking in a human multiple sclerosis patient in need thereof comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily for a time period of at least two weeks, wherein the sustained release composition further comprises one or more pharmaceutically acceptable excipients.

(*See* Ex. 1001, at 27:22–28.) Claims 2–8 depend directly or indirectly from claim 1.

Claim 2 depends from claim 1 and recites that the sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient. (*Id.* at 28:1–4.)

Claim 3 depends from claim 2 and recites that the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours. (*Id.* at 28:5–8.)

Claim 4 depends from claim 3 and recites that the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least about 12 hours. (*Id.* at 28:9–12.)

Claim 5 depends from claim 1 and recites that the sustained release composition provides an average plasma concentration at steady state in humans in the range of about 15 ng/ml to about 35 ng/ml. (*Id.* at 28:13–17.)

Claim 6 depends from claim 1 and recites that the 4-aminopyridine is dispersed in a rate of release controlling polymer. (*Id.* at 28:18–19.)

Claim 7 depends from claim 1 and recites that the sustained release composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. (*Id.* at 28:20–23.)

Claim 8 depends from claim 1 and recites that the step of administering comprises b.i.d. administering or administering at 12 hour intervals. (*Id.* at 28:24–26.)

iii. The '685 Patent Prosecution History

The application that ultimately issued as the '685 patent contained a preliminary amendment dated July 20, 2011, cancelling all 23 of its original claims, and added 10 new claims all directed to methods of improving walking in MS patients. (*See* Ex. 1022.)

On October 31, 2011, June 7, 2012, and October 1, 2012, Applicants filed three separate Information Disclosure Statements (IDS) listing, in total, thirty-three United States patent documents, fourteen foreign patent documents, and at least four hundred and twenty three (423) non-patent literature documents totaling 470 references. (*See* Exs. 1014–1016.) In the IDS submitted October 31, 2011, one of the 423 non-patent documents Applicants submitted was Reference C148: Hayes et al., 2001, "Open-label, multiple-dose study to determine the pharmacokinetics and safety of fampridine-sr (sustained-release 4-aminopyridine) in patients with chronic spinal cord injury," presented to the American Neurological Association, Chicago, Illinois, Sept. 30–Oct. 3, 2001. (*See* Ex. 1014, at Sheets 9–10 of 23.) Another of the 423 non-patent documents Applicants submitted was reference C416: a poster entitled "Placebo-controlled double-blinded dose ranging study of fampridine-SR in multiple sclerosis," by Goodman et al., presented at a conference from September 18–21, 2002. (*See* Ex. 1016, at Sheet 1 of 2.)

On December 17, 2012, the Examiner issued a first office action, and rejected the pending claims over the doctrine of obviousness-type double patenting in view of

recently issued claims in Applicant's U.S. Patent No. 8,007,826, copending application No. 11/102,559 (now U.S. Patent No. 8,354,437), copending application No. 13/410,388, and copending application No. 13/299,969 (now U.S. Patent No. 8,440,703). (*See* Ex. 1017, at 2–6.)

The Applicants responded on March 18, 2013, and filed four terminal disclaimers against the identified patent and applications and requested that the double patenting rejections be withdrawn. (*Id.* at 2–5.) A Notice of Allowance was mailed on April 25, 2013. The Examiner's Reasons for Allowance states that "claims 24–33 are methods of use claims, corresponding to the methods of use claims which ha[ve] been found to be novel and unobvious and ha[ve] been allowed and issued" in the '826 patent. (*See* Ex. 1023, at 2.)

On October 2, 2013, Applicants filed a petition to withdraw the application from issuance and a Request for Continued Examination in order to submit a fourth IDS with twelve additional references for consideration by the Examiner. (Ex. 1024.) In response, on October 18, 2013, the Examiner again issued a Notice of Allowance, stating in the Reasons for Allowance that the newly submitted references "do not teach nor provide adequate motivation to arrive at the instantly claimed methods." (*See* Ex. 1025, at 2–3.) An updated Notice of Allowance was issued on November 14, 2013, to reflect Applicants' amendment canceling pending claims 32 and 33.

On January 13, 2014, Applicants yet again filed a petition to withdraw the application from issuance and a Request for Continued Examination in order to

submit a fifth IDS with thirteen additional references for consideration. (*See* Ex. 1026.) In response, on January 22, 2014, the Examiner again issued a Notice of Allowance, stating in the Reasons for Allowance that the newly submitted references "do not teach nor provide adequate motivation to arrive at the instantly claimed methods." (*See* Ex. 1027, at 2.) The '685 patent issued on March 2, 2014. The Examiner never entered a substantive rejection against any of the pending claims—no prior art was cited by the Examiner during the prosecution of the '685 patent in any Office Action. (*See* Ex. 1001.)

iv. Summary of Selected Prosecution History of the Parent '826 Patent

The '685 patent issued from a child continuation application of the parent '826 patent. The Applicant filed the application that issued as the '826 parent on December 13, 2004, over six years prior to filing the application for the '685 patent. None of the prior art cited in any office action rejection in the '826 file history is used in any of the Petition's grounds challenging the '685 patent claims. But given that the '685 Reasons for Allowance refers to the '826 claims, Petitioner here provides a brief summary of the prosecution history of the parent '826 patent.

The '826 file history is over 2,000 pages. However, the vast majority of the file history is irrelevant to the issued claims of either the parent '826 or the challenged '685 patent because most of the file history is directed to pending claims that were cancelled and never issued. Applicant filed its '826 application on December 13, 2004, with 23 claims. On June 21, 2008, Applicant withdrew claims 1–8 and 18–23 in

response to a restriction requirement. The withdrawn claims were directed to a sustained release tablet, a therapeutic composition, and a sustained release composition. (See Ex. 1038, at pg. 2.)

The Examiner issued two office action rejections during the '826 prosecution. In response to the first rejection dated December 8, 2008, the Applicant withdrew several claims, amended pending claims, added new claims, and removed one of the two inventors from the application. (Ex. 1039) On May 25, 2010, the Examiner again rejected all pending claims. (Ex. 1040, at 1.) In response to this rejection, on November 24, 2010, the Applicant withdrew certain claims, amended others, added new claims, added a new second inventor to the application, and submitted two declarations purporting to support commercial success and long-felt need. (Ex. 1041.) After an interview and certain Examiner amendments, the claims that were first submitted on November 24, 2010—nearly six years after filing the application—issued as the '826 patent. The '826 Reasons for Allowance reveal that the claims issued over three references (Schwid, Hayes 2003, and Bevers 194)—none of which are at issue in the instant Petition. (Ex. 1042, at 2.) The Reasons for Allowance do not cite, rely upon, or even acknowledge Applicant's declarations directed to alleged commercial success and long-felt need. (*Id.*)

B. Level of Skill in the Art

The level of skill in the art at the time of the invention may be derived from a review of the relevant prior art. 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. (Ex. 1013.) Dr. Pleasure attests that "a person of ordinary skill in the art would have been 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 (Master of Science or Ph.D.) in pharmaceutics or pharmaceutical formulation, specifically oral sustained release formulations, or at least 5 years of experience in formulating oral sustained release pharmaceutical drug products." (Ex. 1013, Pleasure Decl. ¶ 23.)

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. 1035.) Dr. Polli adopted the same definition of a person of ordinary skill. (*Id.*, ¶ 11.)

C. Claim Construction of Challenged Claims

In an *inter partes* review, "[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). This means that the words of the claim are given

their plain meaning unless that meaning is inconsistent with the specification. *In re Zletz*, 893 F.2d 319, 321 (Fed. Cir. 1989).[1]

For the purpose of *inter partes* review, the analysis herein presumes that the claim terms take on their broadest reasonable interpretation in view of the specification of the '685 patent. The specific terms for which a broadest reasonable construction should be applied are as follows:

1. Release Profile

The term "a release profile" (claims 3–4) should be construed to mean "a concentration of a drug in a patient's plasma over time." (Ex. 1001, col. 6, ll. 24–27.)

2. Matrix

The term "matrix" should be construed to mean "a composition which provides for a sustained release of a drug into the plasma of a patient." (*See* Ex. 1001, at col. 9, ll. 15–17; Ex. 1035, ¶ 34.)

[1] Terms should be construed to have a special meaning only when the Patent Owner amends the claims pursuant to 35 U.S.C. § 112, to make them expressly correspond to that meaning. *See* 77 Fed. Reg. 48764 at II.B.6 (Aug. 14, 2012).

D. Statements of Precise Relief Requested for Each Claim Challenged

i. Claims for which Review is Requested

Petitioner requests IPR and cancellation of claims 1–8 of the '685 patent under 35 U.S.C. § 311. The precise relief requested by Petitioner is that each of claims 1–8 of the '685 patent be found unpatentable as obvious in view of the prior art.

ii. Statutory Grounds of Challenge

Inter partes review of the '685 patent is requested in view of the following references, each of which is prior art to the '685 patent under 35 U.S.C. §§ 102(a) and (b) or 103. The prior art cited in the following chart were not referenced in any Office Action by the Examiner. Claims 1–8 are unpatentable under 35 U.S.C. § 103:

Ground	Proposed Rejection for the '685 patent	Exhibit Number(s)
1	Claims 1–8 are invalid under 35 U.S.C. § 103(a) as obvious over the publication entitled "Placebo-controlled double-blinded dose ranging study of fampridine-SR in multiple sclerosis" by Goodman et al. ("the Goodman Poster") (Ex. 1008), in view of Hayes et al., "Open-label, multiple-dose study to determine the pharmacokinetics and safety of fampridine-SR (sustained-	1008, 1009, 1032, 1007

	release 4-aminopyridine) in patients with chronic spinal cord injury," presented to the American Neurological Association, Chicago, IL, Sept. 30–Oct. 3, 2001 (poster) ("Hayes") (Ex. 1009) and knowledge of a person of ordinary skill in the art, as evidenced at least by the Polman reference (Ex. 1032) cited in Hayes, and by the van Diemen reference (Ex. 1007) cited Polman.	
2	Claims 1–4 and 6–8 are obvious under 35 U.S.C. § 103(a) over the Goodman Poster (Ex. 1008), in view of United States Patent 5,540,938 to Masterson et al. ("Masterson") (Ex. 1010).	1008, 1010
3	Claims 6 and 7 are invalid under 35 U.S.C. § 103(a) as obvious over the Goodman Poster (Ex. 1008) in combination with Juarez (Ex. 1018).	1008, 1018

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

i. 4-AP History and the State of the Relevant Art as of December 2002

4-aminopyridine (also referred to as fampridine or "4-AP") is an organic compound that has been the subject of intensive medical research for nearly 100 years. 4-AP is a derivative of pyridine with an amino substitution in the 4-position. (*See* Ex. 1009.) 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. 1005.) Placebo-controlled, double-blind studies evaluating the effectiveness of oral 4-AP administration in multiple sclerosis patients also were conducted in the early 1990s. (*See* Exs. 1007, 1008, 1032.) Published research from such studies clearly demonstrated that administering 4-AP to patients suffering from multiple sclerosis was an effective treatment. (*Id.*) Clinical endpoints measured in these studies included lower extremity functions and timed walk and 4-AP treatment clearly demonstrated an improvement in multiple sclerosis patients. (*See* Ex. 1008.)

Dr. Pleasure attests that MS is "an inflammatory demyelinating disease featuring selective destruction of the central nervous system ("CNS") myelin. (Ex. 1035, ¶ 16.) Dr. Pleasure further cites and quotes from the New England Journal of Medicine describing MS in support of his testimony that "[i]t is my opinion that a

POSA at the time of the invention 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. 1013 ¶¶ 21-22, quoting Ex. 1019 at 1430.) For many patients afflicted with MS, ambulatory difficulties, such as walking, are chronic, long-term conditions, and thus require ongoing, sustained therapies. (*Id.*)

The use of 4-AP in MS patients was well studied over 10 years prior to the earliest priority date of the '685 patent. (*See* Ex. 1020.) As early as 1987, the neurological changes associated with administration of 4-AP were measured with 7 to 35 mg of 4-AP in 1 to 5 mg doses, every 10 to 60 minutes, and "motor function (power, coordination, gait)" in 5 out 12 patients improved "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 twenty MS patients and motor functions (power, coordination, and gait) were improved in 9 of the 13 that were studied in particular for motor functions. (Ex. 1021.)

The Applicants of the '685 patent do not contend that they invented the 4-AP compound. (Ex. 1001, *passim*.) Nor do they claim to have pioneered the use of 4-AP to treat patients suffering from multiple sclerosis. (*Id.*) The mode of action of 4-AP on demyelinating diseases was well understood long before the relevant priority date of the '685 patent, and studies on the use of 4-AP on MS patients were well known in the art, as described in detail below. The '685 patent does not even claim original dosing. (*Id.*) Instead, the '685 patent simply attempts to claim a method of

administering 4-AP twice a day for at least two weeks. (*Id.*) Not only was that specific dosing regimen known in the prior art at the time of the alleged invention, but the prior art also taught that administering 10 mg twice per day was effective at improving walking in MS patients, while avoiding side effects attendant to higher daily doses. (*See* Ex. 1008, *passim*.)

Moreover, as discussed extensively below, Dr. Pleasure testifies that "it would have been obvious to one of ordinary skill in the art without undue experimentation to treat such patients for a period of at least two weeks (or longer) with agents shown to alleviate symptoms associated with MS. (Ex. 1013, ¶ 22.) *See also In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012) ("'[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.'") (quoting *In re Aller*, 220 F.2d 454, 456 (CCPA 1955)). It would have been obvious to a POSA to extend the dosing regimen, for chronic diseases like MS, from a time period of 1 week to two weeks or more. (Ex. 1013 ¶ 41.) In fact, administering at least 2 weeks of 10 mg 4-AP BID to a person with MS in need of improved walking is not just one of a long list of things a POSA would have been motivated to do in view of the prior art—it is the ***first*** thing a POSA was motivated to do: i.e., select the lowest known efficacious dose (10 mg BID) for use over an extended treatment period (measured in weeks not days).

ii. Summary of the Petition's Prior Art References

1. The Goodman Refence (Ex. 1008)

The Goodman reference 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 '685 patent applicants in an October 1, 2012 IDS, see Ex. 1043, at Reference No. C416). This date is more than one year prior to December 11, 2003, the earliest possible effective filing date for the claims of the '685 patent. The Goodman Poster was not the basis of any Examiner rejection during the '685 prosecution history.

The Goodman Poster discloses data, results, and conclusions from a placebo-controlled double-blinded dose ranging study of SR 4-aminopyridine (also referred to as fampridine-SR) in MS patients. The Goodman Poster notes that the primary aim of this study is to determine the safety and tolerability of escalating doses of an oral SR formulation of 4-aminopyridine. (Ex. 1008, at "Abstract.") A secondary aim "is to explore efficacy over a broad dose range using measures of fatigue and motor function." (*Id.* at "Abstract.") Evidence of efficacy and dose response include "Standard MS measurements, including timed walk, lower extremity muscle strength . . ." (*Id.* at "Objectives.")

Multiple doses of fampridine-SR were administered (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.") The results indicated improvement in 25–foot walk over 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.") The improvement in walking speed associated with doses of at least 20 mg/day was statistically significant (p=.04). (*Id.* at "Results Summary.") A "significant benefit in lower extremity strength" also was observed. (*Id.* at "Conclusions.")

The study concludes that there was demonstrated "[e]vidence of dose-response in 20–40 mg/day range." 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.") In this same regard, the study concluded that there was "[l]ittle added benefit, and increased risk, at doses above 50 mg/day." (*Id.* at "Conclusions.")

2. The Hayes Reference (Ex. 1009)

Hayes constitutes prior art under 35 U.S.C. § 102(b) because it was published on Sept. 30—October 3, 2001, more than one year prior to December 11, 2003 (a fact admitted by the '685 patent applicants in an October 31, 2011 IDS, see Ex. 1033, at Reference No. C148). This date is more than one year prior to December 11, 2003, the earliest possible effective filing date for the claims of the '685 patent. Hayes was not the basis of any Examiner rejection during the '685 prosecution history.

The Hayes reference – a poster entitled "Open-label, multiple-dose study to determine the pharmacokinetics and safety of fampridine-SR (sustained release 4-aminopyridine) in patients with chronic spinal cord injury," by Hayes et al.—was

presented to the American Neurological Association, in Chicago, IL, September 30-October 3, 2001. (*Id.* at 7.) Like the Goodman Poster, Hayes 2001 notes the importance of 4-AP for treatment of patients with MS, and cites Polman (Ex. 1039) for its disclosure that 4-AP "improves sensory and motor function in patients with…multiple sclerosis." (*Id.* at 2.) Polman, in turn, cites van Diemen (Ex. 1007) for the similar proposition that 4-AP has "been shown to improve symptoms in patients with MS." (*Id.* at 1138.)

Hayes 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)." (Ex. 1009, pp. 2, 3.) The doses of fampridine administered during the study were 10, 15, 20 or 25 mg BID for one week, in an ascending manner. (*Id.*) Steady state plasma concentrations were achieved by Day 5. (Ex. 1009, p. 3.)

Table 2 provides Fampridine-SR pharmacokinetic data. The data for 10 mg BID (i.e., 20 mg/day total) as set forth in that table is as follows: Cave: 20.8 (±8.9) ng/mL; Tmax: 2.7(±1.0) hours. (Ex. 1009, p. 4.) Figure 1 shows the mean plasma concentration for each dose of fampridine over time. The 10 mg BID dosing shows that fampridine remains 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 about 20 hours after administration. (Ex. 1009, p. 4.) This study noted that the SR formulation did demonstrate slower absorption and lower

Cmax relative to the immediate release formulation, and a longer period of elevated plasma levels. (Ex. 1009, pp. 5, 6.)

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," Arch. Neurol., 51: 1139–96 (Nov. 1994). (Ex. 1032.) 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 '685 patent. Polman was not the basis of any rejection during the '685 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. 1032, 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," *Ann. Neurol.,* 32: 123-130 (1992).

(Ex. 1007.) 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 priority date of the '685 patent. van Diemen was not the basis of any Examiner rejection during the '685 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.) The starting dose of the treatment was 10 to 15 mg/day in two to three divided doses, and the dose was then elevated by an additional 5 to 15 mg/day at weeks 2 and 6, respectively. (*Id.*) Thus, a patient starting with a dose of 10 mg/day or 15 mg/day, would receive 20 mg/day when the dose was elevated by 10 mg/day or 5 mg/day, respectively. 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).

3. U.S. Patent No. 5,540,938 ("Masterson") (Ex. 1010)

The Masterson patent constitutes prior art under 35 U.S.C. § 102(b) because it issued and was published on July 30, 1996, more than one year prior to December 11, 2003, the earliest possible effective filing date for the claims of the '685 patent. Masterson was not the basis of any Examiner rejection during the '685 patent prosecution.

Masterson issued July 30, 1996, and entitled "Formulations and their use in the treatment of neurological diseases"—discloses a 4-AP formulation for twice daily

administration, which releases the 4-AP over at least a 12-hour period at a rate sufficient to achieve therapeutically effective blood levels at 12-24 hours after administration. (*Id.* at 2:32-42.) Masterson teaches a polymer matrix formed by blending 4-AP, an excipient, and a polymer to form a homogenous powder for controlling the release rate of the 4-AP into the blood stream. (*Id.* at 2:33-42, 6:24-26.)

Masterson teaches formulations for twice-daily administration which can maintain therapeutically effective blood plasma levels for over 12 hours with peak plasma levels (Tmax) occurring between 1 and 10 hours, and especially between 2 and 8 hours, may be provided by preparing cores formed from a powder mixture containing 4-aminopyridine, an excipient and polymeric materials, a major portion of which is a pharmaceutically acceptable water soluble polymer. (*Id.* at 4:16-35.) Illustrative water soluble polymers include, among others, hydroxypropyl methylcellulose ("HPMC"). (*Id.* at 4:36-40.)

Alternatively, formations are described in which the active agent, pharmaceutically acceptable excipient(s) and polymeric materials (e.g., HPMC) provide an active core. This active core is formed by blending these ingredients, shaping the blend into a core, and applying the remainder of the blend with a polymer binding solution to form a layered structure on the core. (*Id.* at 6:13-38.)

4. Juarez (Ex. 1018)

The Juarez reference constitutes prior art under 35 U.S.C. § 102(b) because it was published in 2001, more than one year prior to December 11, 2003, the earliest

possible effective filing date for the claims of the '685 patent. Juarez was not the basis of any Examiner rejection during the '685 patent prosecution.

The Juarez reference from the 2001 International Journal of Pharmaceutics—entitled "Influence of admixed carboxymethylcellulose on release of 4-aminopyridine from hydroxypropyl methylcellulose matrix tablets," by Juarez et al.—discloses a sustained release 4-AP composition formulated as a matrix with the polymer HPMC. (*Id.* at 116-17.)

Juarez teaches the preparation of a tablet designed for oral administration comprising 4-aminopyridine and a rate of release controlling polymer. Specifically, Juarez indicates that "[t]ablets of the model drug 4-aminopyridine with hydroxypropyl methylcellulose were prepared with different proportions of polymer content as well as with different proportions of admixed carboxymethylcellulose. …" (*Id.* at Abstract.) Juarez further discloses that the purpose of this HPMC matrix is to "prolong delivery with zero-order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect." (*Id.* at 116.)

VI. DETAILED EXPLANATION OF CHALLENGE

A. Ground 1: Claims 1–8 are invalid under 35 U.S.C. § 103(a) as obvious over Goodman (Ex. 1008), in view of Hayes (Ex. 1009) and a POSA's knowledge.

As supported by the declarations from Dr. Pleasure and Dr. Polli, claims 1–8 each would have been obvious to a person of skill in the art over the Goodman

Poster, in view of the Hayes Poster and a POSA's knowledge of the art as of December 2002.

i. Claims 1 and 8 are Obvious under Ground 1

Challenged claims 1 and 8 are directed to methods of treating MS patients by administering an extended release formulation of 10 mg 4-AP BID for a time period of at least two weeks. (*See* Ex. 1001.) Although Goodman only explicitly discloses administration of an extended release formulation of 10 mg 4-AP BID for 11 days (one week and four days), it taught the administration of treatment for several weeks with increasing doses. Thus, it would have been obvious to one of ordinary skill in the art at the time to extend the treatment at the 10 mg BID dose to two or more weeks. (Ex. 1013 ¶ 53.) *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: 'When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.'") (quoting *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 421 (U.S. 2007)).

Goodman discloses detailed data, results, and conclusions from a placebo-controlled double-blinded dose ranging study of SR 4-aminopyridine (also referred to as sustained release 4-AP or fampridine-SR) in MS patients.

Goodman notes that the primary aim of this study was to determine the safety and tolerability of escalating doses of an oral sustained release formulation of 4-aminopyridine. (*See* Ex. 1008, at "Abstract.") A secondary aim was "to explore efficacy over a broad dose range using measures of fatigue and motor function." (*Id.* at "Abstract.") Evidence of efficacy and dose response included "Standard MS measurements, including timed walk, [and] lower extremity muscle strength . . . ." (*Id.* at "Objectives.")

To accomplish these objectives, Goodman discloses that multiple doses of SR 4-aminopyridine were administered "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." (*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 indicated patient improvement in a timed 25-foot walk compared with baseline at a 10 mg BID and 15 mg BID for a total daily dose of 20 mg and 30 mg (each improved about 13.5 seconds against the baseline), 20 mg BID and 25 mg BID for a total daily dose of 40 mg and 50 mg (about 12.5 seconds against the baseline), 30 mg BID for a total daily dose of 60 mg (about 13.5 seconds against the baseline), 35 mg BID for a total daily dose of 70 mg (about 13 seconds against the

baseline), and 40 mg BID for a total daily dose of 80 mg (about 14 seconds against the baseline). (*See id.* at "Dose Response 25 ft. Walk.") The improvement in walking speed associated with doses of at least 20 mg/day was statistically significant (p=.04) compared with the control. (*Id.* at "Results Summary.") A "significant benefit in lower extremity strength" also was observed. (*Id.* at "Conclusions.") Although there is general improvement in mobility speed from 20 mg BID to 40 mg BID, there is no improvement, and in fact, a decrease in improvement speeds from 10 mg BID compared to 15 mg BID. (*Id.* at Dose Response 25 Ft. Walk graph.) Accordingly, a person skilled in the art would have found that lower dosages at 10 mg BID were as successful as 15 mg BID—and a POSA would have also learned that the benefits to walking from higher doses was marginal. (*See* Ex. 1013 ¶ 33.)

The study concluded that there was 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 (i.e. twice daily at 20 mg), more severe adverse events were reported, including cases of seizure . . . ." (*Id.* at "Results Summary.") In this same regard, the study concluded that there was "[l]ittle added benefit, and increased risk, at doses above 50 mg/day." (*Id.* at "Conclusions.")

Just as important as Goodman's disclosure of a 10 mg BID of 4-AP is the disclosure of the range between 10 mg to 40 mg BID. (*Id.* at Abstract.) A person of ordinary skill in the art would have begun studies on dosing starting at 10 mg BID in light of Goodman because customary practice in the industry was to start at the

lowest accepted range in order to attempt to minimize potential adverse side effects of the drug. (*See* Ex. 1013 ¶ 34.) As noted, Goodman also discloses that undesirable side effects were indeed noted at higher dosing regimens. Therefore one of ordinary skill in the art at the time of Goodman would have been motivated to administer doses of sustained release 4-AP no higher than 20 mg BID in order to minimize the adverse side effects Goodman describes. (*See* Ex. 1013 ¶ 32.)

Further, although Goodman doesn't explicitly disclose a regimen for a time period of "at least two weeks," a person of ordinary skill in the art would have been motivated to test durations for periods far past two weeks in chronic illnesses, such as MS. (Ex. 1013 ¶ 36.) *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.'") (quoting *KSR Int'l Co. v. Teleflex*, 550 U.S. 398, 421 (2007)).

At 10 mg BID, Dr. Pleasure testifies that a POSA knew from Goodman that the side effects from administering 4-AP would be minimized when compared to higher doses, because of the adverse side effects at 40 mg BID. (Ex. 1013 ¶ 40.) He further testifies that a person of ordinary skill in the art would have seen from the Goodman results that doses of 10 mg BID fampridine-SR showed statistically significant improvement in walking speed as compared to baseline and also resulted in

fewer side effects. (*Id.*, ¶ 28.) *See also 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 POSA would have fully expected this trend to continue upon extending the treatment for multiple weeks in MS, a chronic illness. (Ex. 1013, ¶ 36.) *See Sciele Pharma, Inc. v. Lupin Ltd.*, 684 F.3d 1253, 1259 (Fed. Cir. 2012) (finding substantial question of validity because "'[i]f a person of ordinary skill can implement a predictable variation, § 103 likely bars its patentability'") (*KSR*, 550 U.S. at 418).

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.") A dose response curve disclosed by Goodman in support of the conclusion shows that there are no significant increases in efficacy between 10 mg BID and 25 mg BID. (*Id.*) Thus, upon considering the actual dose response curve, Dr. Pleasure attests that a POSA would have reasonably concluded that the difference in efficacy from doses of 10 mg BID to 20 mg BID was insignificant. (*See* Ex. 1013 ¶ 28.)

Goodman 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/day BID would provide the best chance to avoid side

effects considering the insignificant differences in mobility from 10 mg/day BID to 20 mg/day BID or higher. (*See* Ex. 1013 ¶ 28.) *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 the challenged claims include a limitation that the treatment duration be for "at least two weeks," considering the chronic nature of MS, a person of ordinary skill in the art at that time would have needed to do little, if any, experimentation to arrive at the conclusion that the lowest dosage of 10 mg BID would be beneficial to the patient, and such benefit would extend in duration from one week to multiple weeks. (*See* Ex. 1013 ¶ 53.) *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,…[t]he 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 in chronic illnesses, drug treatments lasting multiple weeks are common. (Ex. 1013 ¶¶ 44-46, citing Exs. 1032, 1007.)

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 prior to December 2002. (*Id.* ¶¶ 35, 36.) Further, Dr. Pleasure testifies that a POSA prior to December 2002 would have recognized that those 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 for an ongoing basis, including two weeks and more. (*Id.* at ¶36.) *See Sciele Pharma, Inc.*, 684 F.3d at 1259 (Fed. Cir. 2012) (The obviousness analysis entails 'an expansive and flexible approach.'…"There need not be 'precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.'") (quoting *KSR*, 550 U.S. at 418).

Thus, a POSA prior to December 2002 "would have had both a reason to continue the administration of SR 4-aminopyridine at the relatively low dose level noted previously (10 mg BID) over a course of multiple weeks, and more than a reasonable expectation that this dosage regimen would provide enhanced mobility in MS patients," (e.g., improved walking) over that same time period based on the prior art clinical studies which demonstrated the efficacy of this regimen in those patients. (Ex. 1013 ¶ 45.) *See also KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 416–17 (2007) (holding that where a straightforward combination of references "[s]imply arranges old elements with each performing the same function it had been known to perform

and yields no more than one would expect from such an arrangement, the combination is obvious.") (internal quotations and citations omitted).

Further, Dr. Pleasure attests that a POSA would have knowledge of a number of studies and references teaching long-term administration of 4-AP to treat MS. The Hayes 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." (Ex. 1013, ¶ 43.) Likewise, Polman cites the van Diemen 1992 reference (Ex. 1007), which "teaches administering 4-AP to treat MS disability for at least two weeks; and specifically, for twelve weeks." (Ex. 1013, ¶ 44, citing Ex. 1007 at 124.) van Diemen's disclosure of dose administration is striking in its similarity to the '685 specification. (Compare Ex. 1007 at 124, *with* Ex. 1001 at 6:37–48.)

ii. Claims 2–7 are Obvious under Ground 1

Goodman does not explicitly disclose the pharmacokinetic parameters disclosed in claims 2–7. However, the Hayes reference when combined with Goodman discloses each and every element of claims 2–7.

The Hayes reference 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)." (Ex. 1009

at 2, 3.) The doses of fampridine-SR administered during the study were 10, 15, 20 or 25 mg BID for one week, in an ascending manner. (*Id.*) Steady state plasma concentrations were achieved by Day 5. (*Id.* at 3.)

Table 2 of Hayes provides pharmacokinetic data. The data for 10 mg BID (*i.e.*, 20 mg/day total) as set forth in that table is as follows: C_{ave}: 20.8 (±5.7) ng/mL; T_{max}: 2.7(±1.0) hours. (*Id.* at Table 2.) Figure 1 teaches mean plasma concentrations for each dose of AP over time. (*Id.* at Figure 1.) The 10 mg BID dosing shows that 4-AP attains a steady state 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.)

These data correspond to the pharmacokinetic parameters recited in claims 3 and 4. (*See* Ex. 1001.) Claim 3 requires a release profile of 4-aminopyridine extended over at least 6 hours—Figure 1 reports that fampridine remains in the plasma at about 22 ng/mL at 6 hours after administration, and thus meets the requirement of claim 3. (*See* Ex. 1009, at 4.) Claim 4 requires a release profile of 4-aminopyridine extended over at least 12 hours—Figure 1 reports that measurable amounts of 4-aminopyridine remains in the plasma at 12 hours after administration which meets the claim requirement. (*See* Ex. 1001.)

Under Hayes, these pharmacokinetic results are demonstrated from administering the composition at a dose of 10 mg BID, irrespective of the duration of the dosing duration (one week, two weeks, or longer). (*See* Ex. 1009, at pg. 3)

Although the pharmacokinetic characteristics of the administration of sustained release 4-AP as set forth in claims 2–5 were not specifically mentioned in Goodman, Dr. Polli testifies that the Hayes reference establishes that one of ordinary skill in the art would have known that 10 mg BID achieves the claimed pharmacokinetic parameters. (Ex. 1035 ¶¶ 24-26.) It would have been obvious to one of ordinary skill in the art that the similar dosing compositions, formulations, and regimens disclosed by both Goodman and Hayes would have exhibited similar pharmacokinetics over similar periods of time (T_{max}) without undue experimentation. (*Id.*) *See Santarus, Inc. v. Par Pharm., Inc.*, 694 F.3d 1344, 1354 (Fed. Cir. 2012) (affirming obviousness where "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).

Thus, as the above evidence including Dr. Polli's declaration establish, the claim limitations in claims 2 through 7 would have been obvious to a person skilled in the art based on Goodman, in view of Hayes. (*See* Ex. 1035 ¶¶ 24-32.) This evidence is specified in further detail in the following claim chart.

iii. Ground 1 Claim Chart Showing Exemplary Citations from Goodman (Ex. 1008), in view of Hayes (Ex. 1009) and POSA knowledge.

Element	Prior Art of Goodman and Hayes
1pre. A method of improving walking in a	Goodman (Ex. 1008) teaches a method of improving walking in a human multiple sclerosis patient in need thereof.

human multiple sclerosis patient in need thereof	Ex. 1008 at Abstract ("The primary aim of this trial was to determine the safety and tolerability of escalating doses of a sustained release (SR) formulation given orally to patients with MS."); *see also* Ex. 1008 at Methods ("this study looked at measures such as timed ambulation (the Timed 25 Foot Walk component of the Multiple Sclerosis Functional Composite, MSFC."); *see also* Ex. 1008 at Results Summary ("Significant improvement in walking speed was observed in the fampridine treated group (P=0.04*)."). The method of improving walking in a human multiple sclerosis patient in need thereof was also within the knowledge of one of skill in the art at the time of the invention, as evidenced by Polman (Ex. 1032, cited by Hayes) and van Diemen (Ex. 1007, cited by Polman). Polman also teaches a method of improving walking in a human multiple sclerosis patient in need thereof. Ex. 1032 at Abstract ("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-diarninopyridine, especially for ambulation" wherein ambulation is walking.).
1a. comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily	Goodman teaches orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."); *see also* Ex. 1008 at Objectives ("Determine safety of multiple doses of fampridine-SR (one week each of 20 mg/day…"); *see also* Ex. 1008 at Abstract ("dose escalation protocol started…20 mg/day (10mg po BID) the second week…"); *see also* Ex. 1008 at Overview of Study Design ("Study Visit 1, 10 mg q

	12h. Doses shown are individual doses, to be taken q12h. Each fampridine-SR and placebo dose will be in the form of single tablet.").
1b. for a time period of at least 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 one week. *See, supra*, at claim 1b. Goodman does not specifically teach administering for a period of at least two weeks. The method of orally administering for a time period of at least two weeks was within the knowledge of one of skill in the art at the time of the invention, as evidenced by Polman (Ex. 1032, cited by Hayes) and van Diemen (Ex. 1007, cited by Polman): Polman (Ex. 1032) at Abstract: ("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."); *see also* Ex. 1032 at 1136 ("We 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."); *see also* Ex. 1032 at 1137 ("Patients 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."); *see also* *Id.* ("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, for example, the patients receiving the 3,4-diaminopyridine in weeks 4 and 5 had, by definition, received 4-aminopyridine for at least weeks 1, 2, 3, and 6."); *see also* Ex. 1032 at 1139 ("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."); *see also* Ex. 1032 at 1136 ("12 weeks of oral treatment"); *see also* Pleasure Decl. ¶ 22 ("a POSA at the time of the invention 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. Therefore it would have been obvious to one of ordinary skill in the art without undue experimentation to treat such patients for a period of at least two weeks (or longer) with agents shown to alleviate symptoms associated with MS."); *see also* Pleasure Decl. ¶ 53 ("A person of ordinary skill around December 2002 would have known MS is a long-lasting, continuing disease, with patients experiencing problems walking on an ongoing basis. Therefore, it would have been obvious to one of ordinary skill in the art without undue experimentation to administer the SR 4-aminopyridine compositions as disclosed and tested in Goodman for a period of at least two weeks (or longer) to such patients in order to alleviate the symptoms associated with MS. Moreover, a POSA would have been particularly motivated to select the lowest effective dosage (LED) described in Goodman, i.e. 10 mg BID, with the 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."); *see also* van Diemen (Ex. 1007) at 124 ("All patients were treated with both 4-AP and placebo for 12 weeks…The starting dose of the treatment was 10 to 15 mg/day in two to three divided doses, and the dose was then elevated by an additional 5 to 15 mg/day at weeks 2 and 6, respectively."); *see also* Ex. 1007 at 125 ("The analyses of efficacy were performed only in patients who completed at least two weeks of a treatment period.") Ex. 1007 at 126, Table 1 ("EDSS (after 2 wk), Estimated Effect of 4-AP -0.15, 95% Confidence Interval (-0.29, -0.00), *p* Value 0.043").

1c. wherein the sustained release composition further comprises one or more pharmaceutically acceptable excipients.	Goodman teaches the sustained release composition further comprises one or more pharmaceutically acceptable excipients, but does not specifically teach the sustained release composition further comprises one or more pharmaceutically acceptable excipients. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."); *see also* Polli Decl. ¶ 21 ("by definition, a sustained release formulation contains at least one pharmaceutically acceptable excipient in addition to the active pharmaceutical ingredient (4-aminopyridine). This would have to be so in order for the formulation to function as a sustained release composition as intended.").
Element	Prior Art
2. The method of claim 1, wherein said sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient.	Both Goodman and Hayes teach administering a sustained release 4-aminopyridine 10 mg formulation twice daily. Goodman does not specifically teach the pharmacokinetic parameters recited in claims 2-5, but these parameters are set forth in Hayes (Ex. 1009). Goodman, *see* analysis of claim 1b. Hayes (Ex. 1009) at Abstract ("an open-label, 4-week single-center 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."); *see also* Ex. 1009 at 4, Table 2 ("Summary of Fampridine-SR Pharmacokinetics…10 mg b.i.d…. T_{max} h 2.7 (1.0) [hours]."); *see also* Ex. 1009 at Pharmacokinetics ("[s]teady-state plasma concentrations … were achieved by day 5."); *see also* Pleasure Decl. ¶ 46 ("it would have been obvious to orally administer SR 4-aminopyridine at a regimen of 10 mg BID to MS patients with difficulty walking."); *see also*

	Polli Decl. ¶ 26 ("for the SR 4-aminopyridine formulations administered in Hayes 2001 and in Goodman, it would have been understood by a POSA that the similar dosing compositions, formulations, and regimens, disclosed by both would have exhibited similar pharmacokinetics. This understanding would have been based on the literature available to a POSA."); *see also* Polli Decl. ¶ 27 ("It would have been obvious to one of ordinary skill in the art at the time of the invention that the pharmacokinetics detailed in Hayes 2001 would be inherent in the method of administration taught by Goodman and so useful for treating multiple sclerosis as similar dosing regimens and levels would result in similar pharmacokinetics."); *see also* Polli Decl. ¶ 28 ("it would have been obvious to one of ordinary skill in the art at the time of the invention that the Tmax of 2.7 (±1.0) hours after administration of 10 mg BID sustained release 4-aminopyridine, disclosed in Hayes 2001, would be inherent in the method of administration taught by Goodman, and so useful for treating multiple sclerosis as similar dosing regimens and levels would result in similar pharmacokinetics.").
Element	Prior Art
3. The method of claim 2, wherein the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours.	Hayes (Ex. 1009) teaches the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending at least 6 hours. Ex. 1009 at Figure 1 (For 10 mg b.i.d,dosing, detectable plasma concentrations of 4-aminopyridine are reported over the course of at least 20 hours after administration of the sustained release composition.); *see also* Ex. 1009 at Pharmacokinetics ("[s]teady-state plasma concentrations … were achieved by day 5."); *see also* Polli Decl. ¶ 29 ("it would have been obvious to one of ordinary skill in the art at the time of the invention that, upon administration of 10 mg BID sustained release 4-aminopyridine, the release profile of the 4-aminopyridine showing about 22 ng/mL remaining in the plasma at 6 hours after administration, disclosed in Hayes 2001,

	would be inherent in the method of administration taught by Goodman, and so useful for treating multiple sclerosis as similar dosing regimens and levels would result in similar pharmacokinetics.").
Element	Prior Art
4. The method of claim 3, wherein the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 12 hours.	Hayes (Ex. 1009) teaches the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending at least 12 hours. Ex. 1009 at Figure 1 (For 10 mg b.i.d,dosing, detectable plasma concentrations of 4-aminopyridine are reported over the course of at least 20 hours after administration of the sustained release composition.); *see also* Ex. 1009 at Pharmacokinetics ("[s]teady-state plasma concentrations … were achieved by day 5."); *see also* Polli Decl. ¶ 30 ("it would have been obvious to one of ordinary skill in the art at the time of the invention that, upon administration of 10 mg BID sustained release 4-aminopyridine, the release profile of the 4-aminopyridine showing about 10 ng/mL remaining in the plasma at 12 hours after administration, disclosed in Hayes 2001, would be inherent in the method of administration taught by Goodman, and so useful for treating multiple sclerosis as similar dosing regimens and levels would result in similar pharmacokinetics.").
Element	Prior Art
5. The method of claim 1, wherein the sustained release composition provides an average plasma concentration at steady state in humans in the range of about 15 ng/ml to	Both Goodman and Hayes teach administering a sustained release 4-aminopyridine 10 mg formulation twice daily. Goodman does not specifically teach the sustained release composition provides an average plasma concentration at steady state in humans in the range of about 15 ng/ml to about 35 ng/ml, but this is set forth in Hayes (Ex. 1009). Goodman, *see* analysis of claim 1b. Hayes (Ex. 1009) at Abstract ("an open-label, 4-week single-center study was conducted to investigate the pharmacokinetics and safety of multiple oral doses of fampridint-SR (sustained-release 4-aminopyridine)…Study participants received multiple oral doses of

about 35 ng/ml.	fampridine-SR (10, 15, 20, o4 25 mg b.i.d.) for 1 week."); *see also* Ex. 1009 at Table 2 (Average plasma concentration at steady state (C_{avSS}) was reported to be 20.8 ng/ml for 10 mg b.i.d. dosing.); *see also* Ex. 1009 at Pharmacokinetics ("[s]teady-state plasma concentrations … were achieved by day 5."); *see also* Polli Decl. ¶ 31 ("it would have been obvious to one of ordinary skill in the art at the time of the invention that, upon administration of 10 mg BID sustained release 4-aminopyridine, the average plasma concentration at steady state in humans (Cavss) of 20.8 (±5.7) ng/mL, disclosed in Hayes 2001, would be inherent in the method of administration taught by Goodman, and so useful for treating multiple sclerosis as similar dosing regimens and levels would result in similar pharmacokinetics.").
Element	Prior Art
6. The method of claim 1, wherein the 4-aminopyridine is dispersed in a rate of release controlling polymer.	Goodman teaches a sustained release composition, but not specifically wherein the 4-aminopyridine is dispersed in a rate release controlling polymer. Hayes inherently teaches that the 4-aminopyridine is dispersed in a rate of release controlling polymer. Ex. 1009 at Abstract ("sustained-release 4-aminopyridine"); *see also* Ex. 1009 at Figure 1 (For 10 mg b.i.d dosing, detectable plasma concentrations of 4-aminopyridine are reported over the course of at least 20 hours after administration of the sustained release composition.); *see also* Polli Decl. ¶ 32 ("it would have been obvious to one of ordinary skill in the art at the time of the invention to homogenously disperse 4- aminopyridine in a matrix of HPMC to control the release rate of the 4-aminopyridine—a technique well-known in the art—while practicing the method of Goodman for treating MS.").
Element	Prior Art
7. The method of claim 1,	Goodman teaches a sustained release composition as above, but not specifically wherein the composition comprises a matrix in

wherein the sustained release composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine.	which the 4-aminopyridine is homogenously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."). Hayes inherently teaches that the 4-aminopyridine is dispersed in a rate of release controlling polymer: Ex. 1009 at Abstract ("sustained-release 4-aminopyridine"); *see also* Ex. 1009 at Figure 1 (For 10 mg b.i.d dosing, detectable plasma concentrations of 4-aminopyridine are reported over the course of at least 20 hours after administration of the sustained release composition.); *see also* Polli Decl. ¶ 32 ("it would have been obvious to one of ordinary skill in the art at the time of the invention to homogenously disperse 4- aminopyridine in a matrix of HPMC to control the release rate of the 4-aminopyridine—a technique well-known in the art—while practicing the method of Goodman for treating MS.").
Element	Prior Art
8. The method of claim 1, 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. Ex. 1008 at Overview of Study Design ("Study Visit 1, 10 mg q 12h. Doses shown are individual doses, to be taken q12h."); *see also* Ex. 1008 at Abstract ("dose escalation protocol started…20 mg/day (10mg po BID) the second week…").

B. Ground 2: Claims 1–4 and 6–8 are invalid under 103(a) as obvious over Goodman (Ex. 1008) in view of Masterson (Ex. 1010) and POSA knowledge.

Claims 1 and 8 are obvious in light of Goodman and a POSA's knowledge of the state of the art as evidenced by Polman and van Diemen. And even though

Goodman does not explicitly disclose the pharmacokinetic parameters of claims 2–4, a rate controlling polymer of claim 6 or homogeneously dispersed polymer that is suitable for controlling the release rate of the 4-aminopyridine of claim 7, the use of these rate controlling polymers was well known in the art, and Dr. Polli testifies that it would have been obvious to a POSA to combine them with Goodman in view of Masterson. (*See* Ex. 1035 ¶¶ 43, 46.) *See Par Pharm., Inc. v. TWi Pharms., Inc.*, 773 F.3d 1186, 1197 (2014) (stating that "the motivation to combine does not have to be explicitly stated in the prior art, and can be supported by testimony of an expert witness regarding knowledge of a person of skill in the art at the time of invention"). Masterson is a prior art reference that discloses a matrix core that uses the same type of release control polymer as matrices with the administration of 4-AP, and one of ordinary skill in the art would have applied the same type of release control polymer to Goodman to achieve the predictable result of a slower release. (*See* Ex. 1035, ¶19.)

Masterson discloses a pharmaceutical formulation comprising a mono- or di-aminopyridine (*e.g.*, 4-aminopyridine) for administration on a once- or twice-daily basis which releases the aminopyridine over not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours after administration. (*See* Ex. 1010, at col. 2, ll. 32–42.)

Formulations for "twice-daily administration which can maintain therapeutically effective blood plasma levels for over 12 hours with peak plasma levels (T_{max}) occurring between 1 and 10 hours, and especially between 2 and 8 hours," were

provided by preparing a powder mixture containing 4-aminopyridine, an excipient, and polymeric materials, a major portion of which was a pharmaceutically acceptable water soluble polymer. (*Id.* at col. 4, ll. 16–35.) Illustrative water soluble polymers include, among others, hydroxypropyl methylcellulose ("HPMC"). (*Id.* col. 4, ll. 36–40.) Goodman teaches a sustained release composition, but does not explicitly show how the 4-aminopyridine is dispersed with a rate release controlling polymer.

However, Masterson (Ex. 1010) teaches that 4-aminopyridine (col 1: 52–61; col 2: 33–42) is dispersed using a rate of release controlling polymer (col 3:2–6; col 6:15–18). Thus, it would have been obvious to one of ordinary skill in the art to combine the teachings of Goodman with Masterson because they both sought to control the release of drug throughout a longer period. *See Tyco Healthcare Grp. LP v. Ethicon Endo-Surgery, Inc.*, 774 F.3d 968, 112 U.S.P.Q.2d (BNA) 1979, 1987(Fed. Cir. 2014) ("When a claimed invention involves a combination of elements, however, any need or problem known in the relevant field of endeavor at the time of invention can provide a reason to combine.").

Furthermore, Goodman specifically references fampridine-SR as the particular form of 4-AP used for oral administration to MS patients. Dr. Polli attests that fampridine SR comprises a 'matrix' formulation and is a standard matrix-type SR formulation at the time of the invention. (*See* Ex. 1035, ¶ 20.) Thus, one of ordinary skill in the art would have understood that Goodman incorporated its own release control matrix to control the release rate of the 4-AP active ingredient. (*Id.* at 23.)

Goodman discloses a fampridine SR at a dosage regimen in MS patients at 10 mg BID. Although Goodman does not explicitly disclose descriptions of a rate-controlling polymer, Dr. Polli explains that the matrix type SR formulation of Goodman includes polymeric materials that provide release control for the drug. (*See* Ex. 1035, ¶ 45.) The Masterson formulations include "active agent, pharmaceutically acceptable excipient(s), and polymeric materials" (*e.g.,* HPMC) that provide an active core. (Ex. 1010, at col. 6, ll. 12–21.) This active core is formed by blending these ingredients, shaping the blend into a core, and coating the remainder of the blend with a polymer binding solution to form a layered structure on the core. (*Id.* at col. 6, ll. 13–38.)

Masterson teaches that formulations for twice-daily administration which can maintain therapeutically effective blood plasma levels for over 12 hours with peak plasma levels (T_{max}) occurring between 1 and 10 hours, and especially between 2 and 8 hours, may be provided by preparing cores formed from a powder mixture containing 4-aminopyridine, an excipient and polymeric materials, a major portion of which is a pharmaceutically acceptable water soluble polymer. (*Id.* at col. 4, ll. 16- 35.) Illustrative water soluble polymers include, among others, hydroxypropyl methylcellulose ("HPMC"). (*Id.* at col. 4, ll. 36–40.) Thus, in addition to claims 2 through 4, Goodman in view of Masterson discloses rate-controlling polymers as claimed in claims 6 and 7, and those challenged claims are obvious. (Ex. 1035, ¶ 45.) The following detailed claim chart identifying the specific prior art evidence and relevant expert testimony

establishes the obviousness of Claims 1-4 and 6-8 from Goodman in view of Masterson.

i. Claim Chart for Ground 2 Showing Exemplary Citations in Goodman (Ex. 1008) and Masterson (Ex. 1010).

Element	Prior Art
1pre. A method of improving walking in a human multiple sclerosis patient in need thereof	Goodman teaches a method of improving walking in a human multiple sclerosis patient in need thereof. Ex. 1008 at Abstract ("The primary aim of this trial was to determine the safety and tolerability of escalating doses of a sustained release (SR) formulation given orally to patients with MS."); *see also* Ex. 1008 at Methods ("this study looked at measures such as timed ambulation (the Timed 25 Foot Walk component of the Multiple Sclerosis Functional Composite, MSFC."); *see also* Ex. 1008 at Results Summary ("Significant improvement in walking speed was observed in the fampridine treated group (P=0.04*).").
1a. comprising orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily	Goodman teaches orally administering to said patient a sustained release composition of 10 milligrams of 4-aminopyridine twice daily. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."); *see also* Ex. 1008 at Objectives ("Determine safety of multiple doses of fampridine-SR (one week each of 20 mg/day…"); *see also* Ex. 1008 at Abstract ("dose escalation protocol started…20 mg/day (10mg po BID) the second week…"); *see also* Ex. 1008 at Overview of Study Design ("Study Visit 1, 10 mg q 12h. Doses shown are individual doses, to be taken q12h. Each fampridine-SR and placebo dose will be in the form of single tablet.").

	Masterson teaches a sustained release composition of 4-aminopyridine twice daily. Ex. 1010 at 16:44-49 ("Active 4-AP beads/pellets were formulated according to the procedure set out in Example 1. These active pellets were coated according to the procedure set out in Example 2, however, the application of coats was such as to provide a form of 4-AP suitable for twice daily administration.").
1b. for a time period of at least 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 one week. *See, supra*, at claim 1b. Goodman does not specifically teach administering for a period of at least two weeks. While Masterson does not specifically teach a time period of at least two weeks, it does indicate the sustained release formulation is preferable for "long term therapy". Ex. 1010 at 2:8-10 ("In the use of a drug for long-term therapy it is desirable that the drug be formulated so that it is suitable for once- or twice-daily administration to aid patient compliance."); *see also* Ex. 1010 at 2:22-25 ("It is an object of the present invention to provide preparations suitable for the long-term administration of a mono or di-aminopyridine active agent."); *see also* Ex. 1010 at 14:5-10 ("the active agent is preferably administered at a dose less than 15 mg/day until a tolerable state is reached. Suitably when said tolerable state is reached, the dose administered is increased by amounts of at least 5-15 mg/day until said therapeutic dose is reached. The active agent is preferably 4-aminopyridine…"); *see also* Pleasure Decl. ¶ 22 ("a POSA at the time of the invention 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. Therefore it would have been obvious to one of ordinary skill in the art without undue experimentation to treat such patients for a period of at least two weeks (or longer) with agents shown to alleviate

	symptoms associated with MS."); *see also* Pleasure Decl. ¶ 53 ("A person of ordinary skill around December 2002 would have known MS is a long-lasting, continuing disease, with patients experiencing problems walking on an ongoing basis. Therefore, it would have been obvious to one of ordinary skill in the art without undue experimentation to administer the SR 4-aminopyridine compositions as disclosed and tested in Goodman for a period of at least two weeks (or longer) to such patients in order to alleviate the symptoms associated with MS. Moreover, a POSA would have been particularly motivated to select the lowest effective dosage (LED) described in Goodman, i.e. 10 mg BID, with the 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.")
1c. wherein the sustained release composition further comprises one or more pharmaceutically acceptable excipients.	Goodman teaches the sustained release composition further comprises one or more pharmaceutically acceptable excipients, but does not specifically teach the sustained release composition further comprises one or more pharmaceutically acceptable excipients. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."); *see also* Polli Decl. ¶ 21 ("by definition, a sustained release formulation contains at least one pharmaceutically acceptable excipient in addition to the active pharmaceutical ingredient (4-aminopyridine). This would have to be so in order for the formulation to function as a sustained release composition as intended.").
Element	Prior Art
2. The method of claim 1, wherein said sustained release	Goodman does not specifically recite said sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to

composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient.	the patient. Masterson teaches a sustained release composition provides a mean T_{max} in a range of about 2 to about 6 hours after administration of the sustained release composition to the patient. Ex. 1010 at col 4:17-21 ("Pharmaceutical formulations according to the invention for twice-daily administration can maintain therapeutically effective blood levels substantially over 12 hours with peak plasma levels occurring between 1 and 10 hours, more especially between 2 and 8 hours."); *see also* Polli Decl. ¶ 43 ("a POSA at the time of the invention considering the teachings of Goodman and Masterson would reasonably expect that the administration of 10 mg BID of sustained release 4-AP to MS patients for a time period of at least two weeks would result in a mean T_{max} in a range of about 2 to about 6 hours after administration.")
Element	Prior Art
3. The method of claim 2, wherein the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours.	Masterson teaches the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 6 hours. Ex. 1010 at col 2:33-42 ("According to the invention there is provided a pharmaceutical formulation comprising a mono- or di-aminopyridine for administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following administration."); *see also* Polli Decl. ¶ 45 ("It would have been obvious to POSA at the time of the invention that the sustained release formulation disclosed by Masterson could have been readily adapted to practice the method of Goodman for treating MS patients in order to yield a release profile of the 4-AP extending over at least 6 or 12 hours because Masterson specifically disclose a formulation of a

	sustained release compound that achieves this rate of release.").
Element	Prior Art
4. The method of claim 3, wherein the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 12 hours.	Masterson teaches the sustained release composition is capable of providing, upon administration to the patient, a release profile of the 4-aminopyridine extending over at least 12 hours. Ex. 1010 at 2:33-42 ("According to the invention there is provided a pharmaceutical formulation comprising a mono- or di-aminopyridine for administration on a once- or twice-daily basis, said formulation including said mono- or di-aminopyridine active agent in a carrier effective to permit release of said mono- or di-aminopyridine at a rate allowing controlled absorption thereof over, on the average, not less than a 12 hour period and at a rate sufficient to achieve therapeutically effective blood levels over a period of 12-24 hours following administration."); *see also* Polli Decl. ¶ 45 ("It would have been obvious to POSA at the time of the invention that the sustained release formulation disclosed by Masterson could have been readily adapted to practice the method of Goodman for treating MS patients in order to yield a release profile of the 4-AP extending over at least 6 or 12 hours because Masterson specifically disclose a formulation of a sustained release compound that achieves this rate of release.").
Element	Prior Art
6. The method of claim 1, wherein the 4-aminopyridine is dispersed in a rate of release controlling polymer.	Goodman does not specifically recite the 4-aminopyridine is dispersed in a rate of release controlling polymer. Masterson teaches the 4-aminopyridine is dispersed in a rate of release controlling polymer. Ex. 1010 at 2:65-3:9 ("water insoluble polymer and optionally a minor proportion of a pharmaceutically acceptable film-forming, water soluble polymer, the number of layers in said membrane and the ratio of said water soluble to water insoluble polymer, when said water soluble polymer is present, being effective to permit release of said mono- or di-aminopyridine from said pellet at a rate allowing controlled absorption thereof over, on the average, not

	less than a 12 hour period following oral administration"); *see also* Ex. 1010 at 6:24-26 ("The active core is formed by blending mono- or diaminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder."); *see also* Polli Decl. ¶ 46 ("It would have been obvious to POSA at the time of the invention that the polymer matrix disclosed by Masterson could have been readily adapted to practice the method of Goodman for treating MS patients because Goodman teaches a sustained release 4-AP formulation and Masterson describes how a sustained release 4-AP formulation could be made by homogeneously dispersing 4-AP in a release controlling polymer matrix."
Element	Prior Art
7. The method of claim 1, wherein the sustained release composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine.	Goodman teaches a sustained release composition as above, but not specifically wherein the composition comprises a matrix in which the 4-aminopyridine is homogenously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. Ex. 1008 at Background and Study Rationale ("a sustained release oral formulation of Fampridine (Fampridine-SR) was developed."). Masterson teaches a sustained release composition, but not specifically wherein the composition comprises a matrix in which the 4-aminopyridine is homogenously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. Ex. 1010 at 5:47-49 ("The mono- or di-aminopyridine and pharmaceutically acceptable excipient(s) are blended to form a homogeneous powder."); *see also* Ex. 1010 at 6:24-26 ("The active core is formed by blending mono- or diaminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder."); *see also* Ex. 1010 at 6:15-18 ("The active core is suitably formed by

	blending the mono- or diaminopyridine, pharmaceutically acceptable excipient(s) and polymeric material to form a homogeneous powder."); *see also* Polli Decl. ¶ 46 ("It would have been obvious to POSA at the time of the invention that the polymer matrix disclosed by Masterson could have been readily adapted to practice the method of Goodman for treating MS patients because Goodman teaches a sustained release 4-AP formulation and Masterson describes how a sustained release 4-AP formulation could be made by homogeneously dispersing 4-AP in a release controlling polymer matrix."
Element	Prior Art
8. The method of claim 1, wherein the step of administering comprises b.i.d. administering or administering at 12 hour intervals.	Goodman teaches the step of administering comprises b.i.d. administering or administering at 12 hour intervals, as above. Ex. 1008 at Overview of Study Design ("Study Visit 1, 10 mg q 12h. Doses shown are individual doses, to be taken q12h."); *see also* Ex. 1008 at Abstract ("dose escalation protocol started…20 mg/day (10 mg po BID) the second week…"). Masterson also teaches the step of administering comprises b.i.d. administering or administering at 12 hour intervals. Ex. 1010 at col 4:17-19 ("Pharmaceutical formulations according to the invention for twice-daily administration can maintain therapeutically effective blood levels substantially over 12 hours.").

C. Ground 3: Claims 6–7 are invalid under 35 U.S.C. § 103(a) as obvious over Goodman (Ex. 1008) in view of Juarez (Ex. 1018).

Goodman and a POSA's knowledge render claim 1 obvious for the detailed reasons previously set forth. Claims 6 and 7 each depend from claim 1. Although Goodman does not explicitly disclose the rate-controlling polymer of claim 6 or a "matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for

controlling the release rate of the 4-aminopyridine" of claim 7, the use of controlled release polymers as described in claims 6 and 7 was well known in the art—and specifically for 4-AP. (*See* Ex. 1018, *passim*.)

Juarez uses matrices to control the release of the active ingredient in a tablet. (*Id.*) Juarez tested Tablets of 4-aminopyridine with hydroxypropyl methylcellulose prepared with different proportions of polymer content as well as with different proportions of admixed carboxymethylcellulose (CMC) in the range up to 35% (based on the total polymer content). (*Id.* at Abstract.) Dr. Polli's declaration explains that a POSA would understand that "the Juarez document teaches very clearly that 4-aminopyridine could be readily and easily formulated into a useful rate of release controlling polymer, more commonly known as a sustained release composition, using universally known compounds such as HPMC. One of ordinary skill in the art, upon reading the Juarez document, would have understood that the Juarez document discloses 4-aminopyridine formulated into a rate of release controlling polymer and even further that composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine." (Ex. 1035, ¶ 38.)

Dr. Polli further attests that "a POSA would have been motivated to combine Goodman with Juarez in an effort to provide a sustained-release composition of 4-AP for oral administration in an effort to maintain desirable *in vivo* plasma concentrations to maintain a constant pharmacological effect." (*Id.*, ¶ 39.)

Juarez showed that decreasing release constant values show a logarithmic relationship with increasing values of the exponent n. (Ex. 1018 at 121.) This indicates that zero-order release occurs with sufficiently reduced release rate. (*Id.*) Or in other words, there were no significant increases in dissolution when then controlled release polymer was used with reduced release rates. (*Id.*) As such, one of ordinary skill in the art would have understood that the polymer release means used in the dosages of 10 mg of 4-AP BID were predictable and obvious. (*See* Ex. 1035, ¶¶ 40-41.) *See Tyco Healthcare Group LP*, 774 F.3d 968, 112 U.S.P.Q.2D (BNA) at 1986 ("Claims would have been obvious if they are nothing more than a combination of familiar elements that yield predictable results.").

Thus, Dr. Polli's testimony and the Juarez reference establish that a person of ordinary skill in the art would have been motivated to combine the references of Goodman and Juarez to yield the predictable result of a release-controlled drug claimed in claims 6 and 7. (Ex. 1035, ¶¶ 33-41.)

i. Claim Chart for Ground 3 Showing Exemplary Citations in Goodman (Ex. 1008) and Juarez (Ex. 1018).

Element	Prior Art
6. The method of claim 1, wherein the 4-aminopyridine is dispersed in a rate of release controlling polymer.	Goodman teaches a sustained release composition, but not specifically wherein the 4-aminopyridine is dispersed in a rate release controlling polymer. Juarez (Ex. 18) teaches the preparation of a tablet designed for oral administration comprising 4-aminopyridine and a rate of release controlling polymer. Ex. 18 at Abstract ("[t]ablets of the model drug 4-aminopyridine

	with hydroxypropyl methylcellulose were prepared with different proportions of polymer content as well as with different proportions of admixed carboxymethylcellulose. …"); *see also* Ex. 18 at 116 ("purpose of an orally administered hydrophilic matrix is generally to prolong delivery with zero-order kinetics to maintain a constant in vivo plasma drug concentration, and with this to maintain a constant pharmacological effect."); *see also* Polli Decl. ¶ 40 ("it would have been obvious to a POSA at the time of the invention that 4-aminopyridine formulated into a rate of release controlling polymer using compounds such as HPMC, disclosed in Juarez, could have been readily adapted to maintain desirable in vivo plasma concentrations for maintaining a constant pharmacological effect while practicing the method of Goodman for treating MS."); *see also* Polli Decl. ¶ 39 ("it would have been obvious to a POSA to combine Goodman with Juarez, and reasonably expect that the desired pharmacokinetic properties could be achieved by dispersing 4-AP in a rate of release controlling polymer.")
Element	Prior Art
7. The method of claim 1, wherein the sustained release composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine.	Goodman teaches a sustained release composition, but not specifically wherein the composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. Juarez teaches the preparation of a tablet designed for oral administration, wherein the composition comprises a matrix in which the 4-aminopyridine is homogeneously dispersed that is suitable for controlling the release rate of the 4-aminopyridine. Ex. 18 at Abstract ("[t]ablets of the model drug 4-aminopyridine with hydroxypropyl methylcellulose were prepared with different proportions of polymer content as well as with different proportions of admixed carboxymethylcellulose. …"); *see also* Ex. 18 at 118 ("[d]issolution data for the release of 4-aminopyridine from <u>matrices</u> containing 80 mg/tab. of HPMC.") (emphasis added); *see also*

	Ex. 18 at 118-19 (reporting various regression parameters for dissolution curves of 4-AP/Metolose ("HPMC")/carboxymethyl cellulose ("CMC") formulations, as well as release profiles for tablets comprising 4-AP dispersed in a matrix.); *see also* Polli Decl. ¶ 39 ("a POSA would have been motivated to combine Goodman with Juarez in an effort to provide a sustained-release composition of 4-AP dispersed in a matrix for oral administration in an effort to maintain desirable *in vivo* plasma concentrations to maintain a constant pharmacological effect."); *see also* Polli Decl. ¶ 41 ("it would have been obvious to a POSA at the time of the invention to homogenously disperse 4-aminopyridine in a matrix of HPMC to control the release rate of the 4-aminopyridine, as disclosed in Juarez, to maintain desirable in vivo plasma concentrations for maintaining a constant pharmacological effect while practicing the method of Goodman for treating MS.").

VII. ANY SECONDARY CONSIDERATIONS ARE INSUFFICIENT TO OVERCOME A FINDING THAT CLAIMS 1–8 ARE OBVIOUS

The Applicants submitted no evidence showing secondary considerations of non-obviousness during prosecution of the '685 patent. The Applicant has the burden of establishing the existence and sufficiency of such secondary considerations, as well the burden of establishing nexus commensurate with the claims. *See Ex parte Gelles*, 22 USPQ2d 1318, 1319 (Bd. Pat. App. & Inter. 1992). They did not do so during prosecution of the challenged claims—and did not even do so during prosecution of the parent '826 patent when the Applicants attempted to put forth evidence of secondary considerations in support of claims not challenged here.

The purported secondary considerations raised in the '826 parent patent prosecution history fail to even mention any treatment duration of "at least two

weeks," nor was there any connection to alleged secondary considerations related to extended treatments of 4-AP to MS patients. An Interview Summary dated November 10, 2010 describes a Today show episode video recording that was shown to the Examiner. Applicant claimed that "Ampyra can be considered a break-through, not only because it targets walking ability, but also because it is an oral drug." (Ex. 1041 (citing the video at 4:18, 4:58, 5:48).) Notably absent from this explanation is the dose amount, or a dosing regimen for "at least [a] two week" period—the allegedly novel aspect of the sole independent claim of the '685 patent. Oral drugs targeting the walking ability of MS patients were well-known in the prior art more than a decade before the '685 patent, as explained in detail in the instant Petition's grounds for obviousness. Thus, there was no connection between the puffery on the Today show and the claims of the '685 patent.

The Applicants also submitted a declaration by Andrew R. Blight in the parent prosecution that allegedly showed the "surprising results" to show that their scientific findings were unexpected in overcoming the obviousness rejection. (See Ex. 1044.) Blight's declaration states that "it was surprising that a 10 mg dose was as effective as a 20 mg dose is further evidence 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." **But as previously established, Goodman disclosed that dosages at 10 mg/day BID were just as effective as 20 mg/day BID.** One of ordinary skill in the art would not have considered doses of 10 mg/day

BID to be surprising in light of Goodman. (*See generally* Ground 1.) 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). Moreover, the evidence must include a comparison with the closest prior art. (*See, e.g., In re Merchant*, 575 F.2d 865, 869 (CCPA 1978). The Applicant had no evidence for either of these requirements.

There exists no independent data that describes the unexpected result from an "at least two week" 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).

In any event, the Examiner of the parent patent did not cite, rely on, or even mention secondary considerations as a factor for issuing the parent claims. Thus, the burden is on the Patent Owner to come forward with such evidence in the event trial is instituted and it is not Petitioner's burden to address *potential* secondary considerations where no evidence or nexus was put forth during prosecution of the challenged claims, and when the Examiner of the parent application did not make any findings related to secondary considerations.

VIII. CONCLUSION

Thus, for all of the foregoing reasons, Petitioner respectfully requests *inter partes* review of claims 1–8 of U.S. Patent No. 8,663,685.

Respectfully submitted, February 10, 2015

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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 IPR NO. Unassigned
U.S. Patent 8,663,685

COALITION FOR AFFORDABLE DRUGS (ADROCA) LLC'S POWER OF ATTORNEY
(*INTER PARTES* REVIEW OF U.S. PATENT NO. 8,663,685)

CERTIFICATE OF SERVICE

I hereby certify that on February, 10, 2015, a copy of this Petition for *Inter Partes* Review of U.S. Patent No. 8,663,685, including all exhibits (1001–1043), were served via FEDEX, overnight delivery, upon the following:

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