IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Mylan Laboratories Ltd.
Petitioner,

v.

Janssen Pharmaceutica NV
Patent Owner.

U.S. Patent No. 9,439,906 to Vermeulen *et al.*
Issue Date: September 13, 2016
Title: Dosing Regimen Associated with Long Acting Injectable Paliperidone Esters

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Inter Partes Review No.: IPR2020-00440

Petition for *Inter Partes* Review of U.S. Patent No. 9,439,906 Under 35 U.S.C. §§ 311-319 and 37 C.F.R. §§ 42.1-.80, 42.100-.123

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1003	Abstracts of the Annual Meeting of the American Society for Clinical Pharmacology and Therapeutics, 83 Supp. 1 Clin. Pharmacol. & Therapeutics S31, PI-74 and PI-75 (Mar. 2008) ("Cleton")
1004	L. Citrome, Paliperidone: quo vadis?, Int. J. Clin. Pract. 61(1):653-662 (Apr. 2007) ("Citrome")
1005	U.S. Patent No. 6,555,544 ("the '544 patent")
1006	Formulary Drug Reviews – Paliperidone, Hospital pharmacy 42(7):637-647 July 2007 ("Paliperidone Formulary")
1007	N. Washington, C. Washington, C. Wilson. Physiological Pharmaceutics: Barriers to Drug Absorption. (2001), pages 26-29 ("Physiological Pharmaceutics")
1008	U.S. Patent No. 6,495,534 ("the '534 patent")
1009	J.M. Kane, et al. Guidelines for depot antipsychotic treatment in schizophrenia. B. Eur. Neuropharmacol. 8(1):55-65 (1995) ("Kane")
1010	N. Marder, et al. Pharmacokinetics of long-acting injectable neuroleptic drugs: clinical implications. Psychopharmacology. 98:433-439 (1989) ("Marder")
1011	M.E. Aulton. Pharmaceutics: The Science of Dosage Form Design (2002), Chapter 19 ("Aulton")
1012	Comparison of the '276 and the '918 provisional application specifications ("Specification Comparison")

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1013	U.S. Patent No. 5,254,556 (“the ’556 patent”)
1014	U.S. Patent No. 7,449,184 (“the ’184 patent”)
1015	R. Urso, P. Blardi, G. Giorgi. A short introduction to pharmacokinetics, Rev. Med. Pharmacol. Sci. 6: 33-44 (2002) (“Urso”)
1016	U.S. Provisional Application No. 61/014,918 (“the ’918 provisional”)
1017	U.S. Provisional Application No. 61/120,276 (“the ’276 provisional”)
1018	Excerpt of ’906 Patent Prosecution History (“6-12-2016 Amendment and Response”)
1019	’906 Patent Prosecution History
1020	L. Ereshefsky, et al., Future of Depot Neuroleptic Therapy: Pharmacokinetic and Pharmacodynamic Approaches. J. Clin. Psychiatry, 45(5):50-59 (1984) (“Ereshefsky”)
1021	Goodman & Gilman’s, The Pharmacological Basis of Therapeutics (2001), Chapter 1 (“Goodman & Gilman”)
1022	D. Waller & A. Renwick, Principles of Medical Pharmacology (1994) (“Principles of Medical Pharmacology”)
1023	U.S. Patent No. 6,818,633 (“the ’633 patent”)
1024	Ansel *et al.*, Pharmaceutical Dosage Forms and Drug Delivery Systems 8th ed. (2005) (“Added Substances”)
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1030	INVEGA SUSTENNA® Label ("INVEGA LABEL")
1031	ClinicalTrials.gov, A Safety and Tolerability Study of Paliperidone Palmitate Injected in the Shoulder or the Buttock Muscle in Patients With Schizophrenia (July 2006), https://clinicaltrials.gov/ct2/history/NCT00119756?V_10=View#StudyPageTop ("NCT00119756")
1032	ClinicalTrials.gov, A Study to Evaluate the Effectiveness and Safety of 3 Doses of Paliperidone Palmitate in Treating Subjects With Schizophrenia (October 2006), https://clinicaltrials.gov/ct2/history/NCT00210548?V_11=View#StudyPageTop ("NCT00210548")
1033	ClinicalTrials.gov, Safety and Efficacy of an Anti-Psychotic Versus Placebo in Subjects With Schizophrenia (November 2005), https://clinicaltrials.gov/ct2/history/NCT00101634?V_4=View#StudyPageTop ("NCT00101634")
1034	ClinicalTrials.gov, A Study to Compare the Effectiveness and Safety of Flexibly Varied Doses of Paliperidone Palmitate and Risperidone in Treating Patients With Schizophrenia (July 2006), https://clinicaltrials.gov/ct2/history/NCT00210717?V_10=View#StudyPageTop ("NCT00210717")
1035	ClinicalTrials.gov, Intramuscular Injections of Paliperidone Palmitate in the Arm or Buttock of Subjects With Schizophrenia (June 2005), https://clinicaltrials.gov/ct2/history/NCT00073320?V_1=View#StudyPageTop ("NCT00073320")

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1037	Guarino, Richard A. "Clinical research protocols." New Drug Approval Process. CRC Press, 2004, pages 257-61
1038	Bishara, Delia, and David Taylor. "Upcoming agents for the treatment of schizophrenia." Drugs 68.16 (2008): 2269-2292
1039	Kramer, M., et al. "322–Efficacy/tolerability of paliperidone palmitate: 9-week, placebo-controlled study in schizophrenia patients." Schizophrenia Research 98 (2008): 165-166
1040	'906 Patent Specification as Filed
1041	Kramer M, Litman R, Lane R, et al. "908. Efficacy and tolerability of two fixed dosages of paliperidone palmitate in the treatment of schizophrenia: results of a 9-week placebo-controlled trial." Biol Psychiatry 2008;63:1S-319S
1042	Declaration of Laboratory Research Analyst Alys Tryon
1043	Nankivell, Brian J. Creatinine clearance and the assessment of renal function. Australian Prescriber, 2001
1044	Perry, Paul J., ed. Psychotropic drug handbook. Lippincott Williams & Wilkins, 2007, pages 74-77
1045	Traynor, Jamie, et al. How to measure renal function in clinical practice. Bmj 333.7571 (2006): 733-737
1046	Janicak, Philip G., and Elizabeth A. Winans. Paliperidone ER: a review of the clinical trial data. Neuropsychiatric disease and treatment 3.6 (2007):869

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1047	Physicians' Desk Reference (2002), HALDOL® Decanoate

I. INTRODUCTION

Mylan Laboratories Ltd. ("Petitioner") petitions for *Inter Partes* Review, seeking cancellation of Claims 1-21 ("challenged claims") of U.S. Patent No. 9,439,906 ("the '906 patent") (EX1001), assigned to Janssen Pharmaceutica NV ("Patent Owner").

II. OVERVIEW

The challenged claims of the '906 patent are nothing more than the results of routine optimization of dosing amounts of paliperidone palmitate reported in the prior art. For example, Figure 2 of the '906 patent (which falls within the scope of the challenged claims) states that the injectable dosing regimen of paliperidone palmitate is administered on days 1, 8, 36 and 64. The prior art *repeatedly* teaches this identical dosing schedule for paliperidone palmitate. EX1002 ¶¶70-75; EX1004, Table 1; EX1003, PI-75.

Citrome discloses that in Phase III study, intramuscular depot injections of 50, 100 or 150 mg-eq. paliperidone as paliperidone palmitate were administered on days 1, 8, 36 and 64 of therapy. EX1002 ¶¶70-75; EX1004, Table 1; *see also* EX1038, 2286 (discussing "significant improvement" with 50 or 100 mg eq. on Days 1, 8 and 36). Citrome also discloses that in another Phase III study, a range of 25-100 mg-eq. was administered every four weeks (over a 52-week period). EX1002 ¶¶70-75; EX1004, Table 1. In another Phase III study, doses of 25, 50,

100, or 150 mg-eq. were administered. EX1004, Table 1. Additionally, Cleton discloses that a dose of "25-150 mg-eq." was well-tolerated and resulted in low treatment-emergent adverse events. EX1002 ¶¶66-69; EX1003, PI-74. Thus, the combined teachings of the clinical trials in Citrome and Cleton recurrently teach that a range of 25-150 mg-eq. paliperidone as paliperidone palmitate is safe and effective to administer to humans. This dosing range overlaps with the ranges recited in the challenged claims. *DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) ("[A] prima facie case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

In view of the dosages and the dosing schedule disclosed in the prior art, arriving at the claimed invention would have been nothing more than routine experimentation for a person of ordinary skill in the art ("POSA"). *In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003) (explaining that the normal desire of artisans to improve upon what is already generally known provides the motivation to determine optimum amounts). Indeed, this would not have been a challenge for the POSA—the '906 patent freely admits this: "[t]hose of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above." EX1001, 14:13-15; EX1002 ¶97; *One World Technologies Inc. v. The Chamberlain Group Inc.*, IPR2017-00126,

Paper 67 at 14-16 (P.T.A.B. April 4, 2019) ("admissions in a patent may be considered prior art for any purpose, including as evidence of obviousness under 35 U.S.C. §103").

As for determining the dosage on each day, the POSA would have been guided by well-known principles involving injectable depot formulations. EX1002 ¶¶44-50. The initial objective is to administer depots so that the requisite blood level of the medication is reached quickly. EX1002 ¶47; EX1004, 660. This is done by front-loading the dosing with higher amounts of the depot drug known as the "loading dose". EX1002 ¶47; EX1011, 284-85. The "loading dose" can be given in one or more doses. EX1002 ¶48; EX1021, 27; EX1046, 882 (stating that "*[t]he first two paliperidone palmitate injections* will be administered as a loading dose within 7 days of initiation"); EX1044, 76 (haloperidol decanoate may be split into two loading doses administered 3 to 7 days apart); EX1047, 5 (same).

Once the initial requisite blood levels of the medication are reached through the loading dose, the objective becomes to "obtain a sufficiently constant delivery of the drug from the depot, so that the serum level is kept as constant as possible between injections." EX1002 ¶49; EX1009, 61; EX1011, 284-85. This is done by providing smaller "maintenance doses" at regular intervals. EX1002 ¶49; EX1011, 285. By administering maintenance doses following the initial dose, therapeutic steady-state plasma concentrations are achieved more rapidly than if simply giving

doses of equal size and at identical dosage time intervals. EX1002 ¶49; EX1011, 285. Where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges of a result-effective variable through routine experimentation. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368 (Fed. Cir. 2007) ("[D]iscovery of an optimum value of a variable in a known process is usually obvious.").

III. STANDING (37 C.F.R. § 42.104(A); PROCEDURAL STATEMENTS)

Petitioner certifies that (1) the '906 patent is available for IPR; and (2) Petitioner is not barred or estopped from requesting IPR of any claim of the '906 patent on the grounds identified herein. This Petition is filed in accordance with 37 C.F.R. § 42.106(a). Concurrently filed herewith are a Power of Attorney and an Exhibit List pursuant to § 42.10(b) and § 42.63(e), respectively. The required fee is paid through, and the Office is authorized to charge any fee deficiencies and credit overpayments to, Deposit Acct. No. DA501290 (Customer ID No. 27160).

IV. MANDATORY NOTICES (37 C.F.R. § 42.8(a)(1))

A. Each Real Party In Interest (37 C.F.R. § 42.8(b)(1))

The real parties in interest for this petition are Mylan Laboratories Ltd., Mylan Institutional LLC, Mylan Pharmaceuticals Inc., Mylan Inc., and Mylan N.V.

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

1. Judicial Matters:

Petitioner is aware of the following district court actions involving the '906 patent: *Janssen Pharmaceuticals, Inc. et al v. Teva Pharmaceuticals USA, Inc. et al.*, 2-18-cv-00734 (D.N.J.); *Janssen Pharmaceuticals, Inc. et al. v. Mylan Laboratories Ltd.*, 2-19-cv-16484 (D.N.J.); *Janssen Pharmaceuticals, Inc. et al. v. Mylan Laboratories Ltd*., 1-19-cv-00153 (N.D. W. Va.); *Janssen Pharmaceuticals, Inc. et al. v. Mylan Laboratories Ltd.*, 1-19-cv-01488 (D. Del.); *Janssen Pharmaceuticals, Inc. et al. v. Pharmascience Inc. et al.*, Case No. 2-19-cv-21590 (D.N.J.); *Janssen Pharmaceuticals, Inc. et al. v. Pharmascience Inc. et al.*, 1-19-cv-02313 (D. Del.).

2. Administrative Matters:

The Public Patent Application Information Retrieval (PAIR) website indicates that there are no related United States patents or pending applications.

C. Designation of Lead and Back-Up Counsel (37 C.F.R. § 42.8(b)(3)):

Lead Counsel	**Back-Up Counsel**
Jitendra Malik, Ph.D. Reg. No. 55,823 Katten Muchin Rosenman LLP 550 S. Tryon Street, Suite 2900 Charlotte, NC 28202-4213 jitty.malik@katten.com	Guylaine Haché, Ph.D. Reg. No. 76,083 Jillian Schurr (*pro hac vice* to be filed) Katten Muchin Rosenman LLP 525 W. Monroe Street Chicago, IL 60661-3693 guylaine.hache@katten.com jillian.schurr@katten.com

	Alissa M. Pacchioli Reg. No. 74,252 Katten Muchin Rosenman LLP 550 S. Tryon Street, Suite 2900 Charlotte, NC 28202-4213 alissa.pacchioli@katten.com Lance Soderstrom Reg. No. 65,405 Katten Muchin Rosenman LLP 575 Madison Avenue New York, NY 10022-2585 lance.soderstrom@katten.com

Petitioner consents to email service as indicated above.

V. STATEMENT OF THE PRECISE RELIEF REQUESTED AND THE REASONS THEREFOR (37 C.F.R. § 42.22(A))

Petitioner requests IPR and cancellation of Claims 1-21 of the ’906 patent. Petitioner’s full statement of the reasons for the relief requested is set forth in detail below.

VI. OVERVIEW OF THE ’906 PATENT

The ’906 patent issued on September 13, 2016 and purports to claim priority to U.S. Provisional Application Nos. 61/120,276, filed December 5, 2008 (“’276 provisional”), and 61/014,918, filed December 19, 2007 (“’918 provisional”). EX1001, Cover. As shown below, the challenged claims are not entitled to claim the benefit of priority to the ’918 provisional. Accordingly, the effective filing

date of the challenged claims is no earlier than December 5, 2008—the filing date of the ’276 provisional.

A. The Claims

The ’906 patent issued with 21 claims. Claims 1, 4, 8 and 11 are independent. At a high level, independent Claims 1 and 4 recite the preamble “[a] dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment,” while independent Claims 8 and 11 recite the preamble “[a] dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment.” All independent claims generally recite administering three doses of paliperidone palmitate. Claims 1 and 4 recite administering “a first loading dose” of about 150 mg-eq.[1] paliperidone as paliperidone palmitate, “a second loading dose” of about 100 mg-eq. paliperidone as paliperidone palmitate and a “first maintenance dose” of between about 25 to about 150 mg-eq. paliperidone as paliperidone palmitate.

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[1] EX1002 ¶56, n7 (providing an explanation of “mg-eq” in accordance with the specification).

Claims 8 and 11 recite administering "a first loading dose" of from about 75 mg-eq. paliperidone as paliperidone palmitate, "a second loading dose" of from about 75 mg-eq. paliperidone as paliperidone palmitate and "a first maintenance dose" of between about 25 to about 75 mg-eq. (Claim 8) or to about 50 mg-eq. (Claim 11) paliperidone as paliperidone palmitate.

B. The Specification

The '906 patent admits that paliperidone palmitate has been developed as a long-acting, intramuscular injectable aqueous nanosuspension for the treatment of schizophrenia and other diseases that are normally treated with antipsychotic mediations. EX1001, 1:42-45. The '906 patent also admits that a paliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly, and that this formulation is described in U.S. Patent Nos. 6,555,544. *Id.*, 1:58-63; *One World Technologies*, IPR2017-00126 at 14-16.

VII. CLAIM CONSTRUCTION (37 C.F.R. §§ 42.100(B), 42.104(B)(3))

Under applicable guidance, the claims must be given "the meaning that the term would have to a person of ordinary skill in the art in question at the time of

the invention." *See* 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303, 1313 (Fed. Cir. 2005) (*en banc*). Petitioner is unaware of any prior claim construction determination concerning the '906 patent.[2] Thus, for all terms, Petitioner submits that no construction is necessary and the challenged claims should be afforded a meaning "in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent." 37 C.F.R. § 42.100(b).

VIII. THE CHALLENGED CLAIMS ARE NOT ENTITLED TO CLAIM PRIORITY TO DECEMBER 19, 2007

The earliest effective filing date for the challenged claims is December 5, 2008—the filing date of the '276 provisional application. To claim priority to an earlier filed parent application, "the invention claimed must have been disclosed in the parent application in the manner provided by 35 U.S.C. § 112, ¶ 1." *In re*

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[2] In *Janssen Pharmaceuticals, Inc. et al v. Teva Pharmaceuticals USA, Inc. et al.*, the parties filed a Joint Claim Construction Statement identifying a single claim term. EX1028. The parties eventually settled on the plain and ordinary meaning. EX1029.

Lukach, 442 F.2d 967, 968–69 (C.C.P.A. 1971); *Ariad Pharm., Inc. v. Eli Lilly and Co.*, 598 F.3d 1336, 1344–55 (Fed. Cir. 2010) (en banc)).

The written description requirement ensures "that the inventor had possession, as of the filing date of the application relied on, of the specific subject matter later claimed by the inventor." *Arkema Inc. v. Honeywell Int'l, Inc.*, PGR2016-00011, Paper No. 13 at 16 (P.T.A.B. Sept. 2, 2016) (citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1561 (Fed. Cir. 1991)). To satisfy the written description requirement, the inventor must demonstrate possession by "describing the invention, with all its claimed limitations, not simply that which makes it obvious." *Id.*; *Dr. Reddy's Labs. S.A. v. Indivior UK Ltd.*, IPR2019-00329, Paper 21 at 20 (P.T.A.B. June 3, 2019). "[A]ll the limitations must appear in the specification." *PowerOasis, Inc. v. T-Mobile USA, Inc.*, 522 F.3d 1299, 1306 (Fed. Cir. 2008); *Celltrion, Inc. v. Biogen, Inc.*, IPR2017-01095, Paper No. 60 at 16 (P.T.A.B. Oct. 4, 2018).

A. The '918 Provisional Does Not Provide Written Description Support For "A First Maintenance Dose" Administered "A Month (±7 days) After the Second Loading Dose"

Each of the challenged claims requires administering a first maintenance dose "a month (±7 days)" after the second loading dose. *See, e.g.*, Claim 1(3). However, the first provisional application—the '918 provisional—only discloses that the first maintenance dose be administered "on between about the 34th and

about the 38th day of treatment." EX1016, 2:23-26; 3:2-5; 3:13-16; 3:25-28; 4:3-6; 4:15-18; 5:6; 5:7-8; 5:32-33; 6:1. The relevant support for the limitation was first added in the second provisional application—the '276 provisional—filed December 5, 2008. *See* EX1012, 6-8 (underline indicates new matter added to the '276 provisional); EX1017, 7:12-16; 7:19-21; 7:26-28; 8:14-16; 8:23-28.

When determining whether a specification supports "numerical range limitations, the analysis must take into account which ranges one skilled in the art would consider inherently supported by the discussion in the original disclosure." M.P.E.P. 2163.05(III) (citing *In re Wertheim*, 541 F.2d 257 (C.C.P.A. 1976)). For example, in *In re Wertheim*, the Court of Customs and Patent Appeals found that a claimed range of "at least 35%" was not adequately described by a disclosure of "25-60%." 541 F.2d at 262-264; *Grünethal GmbH v. Antecip Bioventures II LLC*, PGR2017-00008, Paper No. 43 at 17 (P.T.A.B. June 22, 2018) (disclosure of "about 50 to about 500 mg" did not provide written description for "about 80 to about 500 mg."); *Reddy's*, IPR2019-00329, Paper 21 at 20; *Eiselstein v. Frank*, 52 F.3d 1035, 1040 (Fed. Cir. 1995).

The '918 provisional provides no indication that the inventors had possession of administering a first maintenance dose a month (±7 days) after the second loading dose. A POSA, reading the specification, would realize that giving a maintenance dose "a month (±7 days)" after a second loading dose on about the

6th day to 10th day of treatment can encompass giving the maintenance dose ***as early as the 29th day of treatment*** (e.g., the second loading dose is given on day 6 and the first maintenance dose is given 23 days—i.e., a 30-day month minus 7 days—later), and ***as late as the 48th day of treatment*** (e.g., the second loading dose is given on day 10 and the first maintenance dose is given 31 days plus 7 days later). In other words, the window for the first maintenance dose based on the '276 provisional is much broader (20 days) than the window disclosed in the '918 provisional (5 days). EX1002 ¶53, n4. The '918 provisional provides no indication that the inventors had possession of such a dosing regimen comprising administering a first maintenance dose outside of "on between about the 34th and about the 38th day of treatment." *Id.*

Critically, the prosecution history supports Petitioner's position that the "month (±7 days)" limitation is not supported by the '918 provisional. During prosecution, applicant amended the claims to replace "on between about the 34th and about the 38th day of treatment" with the "month (±7 days)" limitation:

> (3) administering intramuscularly in the deltoid or gluteal muscle . . . a <u>first</u> maintenance dose . . . of paliperidone as paliperidone palmitate in a sustained release formulation **<u>a month (±7 days) after the second loading dose.</u>** ~~**on about the 34th to about the 38th day of treatment.**~~

EX1018, 2 (bold added). As support for the amendment, applicant pointed to the description in the as-filed specification of the ’906 patent that is *identical to the new matter added to the ’276 provisional*. EX1018, 8 (“Support for this amendment can be found on page 7, lines 23-25 and page 8, lines 18-20” of the as-filed specification.); *compare* EX1040, 7:23-25, 8:18-20 *with* EX1012, 6:29 – 7:1, 7:25-27 (underline indicates new matter added to the ’276 provisional).

For this reason, the ’918 provisional does not provide written description support for the challenged claims. Thus, the earliest possible effective filing date for the challenged claims is December 5, 2008—the filing date of the ’276 provisional.

IX. PERSON OF ORDINARY SKILL IN THE ART (“POSA”)

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 420 (2007); *Custom Accessories, Inc. v. Jeffrey-Allan Indus., Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986). With respect to the ’906 patent, a POSA would have had (1) several years’ experience in designing and formulating drug delivery systems including parenteral systems based on analyzing pharmacokinetic data such as blood serum or drug plasma levels and clearance rates and familiarity with depot formulations; (2) an advanced degree (Ph.D. and/or M.S.) in pharmaceutical sciences and/or

pharmaceutics or a related degree; and (3) experience with the formulation of therapeutic agents, their dosing, and the literature concerning drug developmental study and design. Furthermore, the POSA may consult with individuals having specialized expertise, for example, a physician with experience in the administration, dosing, and efficacy of drugs, and/or a regulatory affairs specialist. EX1002 ¶¶33-37.

X. IDENTIFICATION OF CHALLENGE (37 C.F.R. § 42.104(b))

Petitioner respectfully requests IPR of Claims 1-21 of the '906 patent on each specific ground of unpatentability outlined below. Per 37 C.F.R. § 42.6(d), copies of the references are filed herewith. In support of the proposed grounds, this Petition includes the declaration of a technical expert, Dr. Mansoor Amiji (EX1002), explaining what the art would have conveyed to a POSA, and relies on other Exhibits set forth in the enclosed Listing of Exhibits. Dr. Amiji is an expert in the relevant field. EX1002, ¶¶33-37.

Ground	References	Basis[3]	Claims Challenged
1	Citrome, Cleton and the '544 patent	§ 103	1-7, 15 and 17-21
2	Citrome, Cleton, the Paliperidone	§ 103	8-14 and 16

[3] All references herein are to pre-AIA 35 U.S.C. § 100 *et. seq.*

	Formulary and the ’544 patent		
3	Citrome and the ’544 patent	§ 103	1-7, 15 and 17-21
4	Citrome, the Paliperidone Formulary and the ’544 patent	§ 103	8-14 and 16

XI. INVALIDITY ANALYSIS

A. The Law of Obviousness

The inquiry for obviousness was established in *Graham v. John Deere Co. of Kansas City*, 383 U.S. 1 (1966). The *Graham* factors require an examination of: (1) the scope and content of the prior art; (2) differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art; and (4) secondary considerations of nonobviousness. The obviousness analysis looks to the state of the art that existed at the time the invention was made. *In re Wesslau*, 353 F.2d 238, 241 (C.C.P.A. 1965).

“Obviousness does not require absolute predictability of success”; rather, “[a]ll that is required is a reasonable expectation of success” in making the invention via the combination. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006) (citation omitted); *see also Duramed Pharm., Inc. v. Watson Labs., Inc.*, 413 F. App’x. 289, 294 (Fed. Cir. 2011) (“there is no requirement that a teaching in the prior art be scientifically tested or even guarantee success before providing a reason to combine. Rather, it is sufficient that one of ordinary skill in the art would perceive from the prior art a reasonable likelihood of success.”). The Federal Circuit “has long rejected a requirement of ‘[c]onclusive proof of efficacy’

for obviousness." *Acorda Therapeutics, Inc. v. Roxane Labs., Inc.*, 903 F.3d 1310, 1333 (Fed. Cir. 2018).

B. The Level of Ordinary Skill in the Pertinent Art

The level of ordinary skill in the art has been described above.

C. The Scope And Content of the Prior Art

1. Depot Antipsychotic Treatments in Schizophrenia

Depot antipsychotic medications were developed in the 1960s for the long-term treatment of schizophrenia. EX1009, Abstract; EX1002 ¶44. Depot drugs such as paliperidone palmitate provide a therapeutic concentration that can last for days with a single dose. EX1005, 2:38-43 (disclosing an "efficient, well-tolerated, sustained or delayed release (depot) formulation of [paliperidone palmitate] which is therapeutically effective for at least three weeks or more, in particular about one month."); EX1002 ¶44. As Kane explained, "non-compliance is very common among patients with schizophrenia and is a frequent cause of relapse" and that a major advantage of depot antipsychotics over oral medication is facilitation of compliance. EX1009, Abstract. Indeed, "any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs." *Id*.; EX1002 ¶78.

Chemically, depot antipsychotics are prepared by esterification of the antipsychotic agent with a long chain fatty acid. EX1009, 61; *see also* EX1005, 3:60-64. As the ester is released from the formulation, the ester is hydrolyzed to its

active form. EX1005, 2:45-46 (active ingredient "liberated by hydrolysis from the alkanoic acid ester"); EX1002 ¶50. As Citrome explained, "[t]he depot intramuscular preparation of paliperidone holds greater promise if it can be demonstrated . . . that there is little lag time prior to the development of adequate blood levels." EX1004, 660. Thus, in depot preparations, the initial objective is to administer the drug such that the requisite blood levels of the medication are reached in a short duration. *Id*. The long term objective, however, "is obtain a sufficiently constant delivery of the drug from the depot, so that the serum level is kept as constant as possible between injections"—in other words, to maintain steady state conditions. EX1009, 61; EX1002 ¶46.

"At steady state, the amount of drug eliminated from the body over each dosing time interval is equal to the amount that was absorbed into the body compartment following administration of the previous dose." EX1011, 280; EX1002 ¶43. At steady state, with constant dosing intervals and the same dose, a patient's blood concentrations will stay between consistent C_{max} (MEC) and C_{min}

(MSC) values.[4] EX1011, Figure 19.4. In general, dosing regimens are designed so that at steady state, the trough (minimum) concentrations present at the end of the dosing interval, immediately before administration of the next dose, are above the minimum effective concentration, and the peak (maximum) concentrations attained after dosing are below the maximum safe plasma concentration. *Id*., 279-280; EX1002 ¶43.

2. Pharmacokinetics Of Depot Drugs

a. Induction or Loading Dose Regimens

Depot antipsychotic esters have longer accumulation half-lives than their oral counterparts. EX1010, 433. Because of this, they require more time to reach stable steady state. *Id*. To reach steady state, an induction regimen or loading dose regimen was proposed to accumulate a rapid therapeutic concentration of the drugs with the patient. "A loading dose . . . is designed to 'load up' the body." EX1022, 36-37; EX1002 ¶¶47-48.

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[4] As Aulton explains, MEC and MSC means "minimum effective plasma concentration" and "maximum safe plasma concentration." EX1011, Figure 19.4.

Aulton discloses that an induction regimen can be beneficial "[t]o reduce the time required for onset of the full therapeutic effect." EX1011, 284. An induction regimen achieves this goal by producing drug concentrations associated with optimal therapeutic benefit much more quickly than if only lower treatment doses are administered. EX1002 ¶19. As Goodman & Gilman explains: "[a] loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (four elimination half-lives) is long relative to the temporal demands of the condition being treated." EX1021, 27; EX1011, 284-85 ("a large single dose of the drug may be administered initially in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug."); EX1002 ¶47.

Moreover, the loading dose is not required to be given in a single dose—it can be split into multiple doses. EX1021, 27 ("The 'loading dose' is one or a series of doses that may be given at the onset of therapy"). For example, the loading dose for haloperidol decanoate may be split into two doses: "[a] 300-mg total loading dose would be administered as 100 mg with the 200-mg dose administered 3 to 7 days later." EX1044, 76; EX1047, 5; EX1002 ¶48.

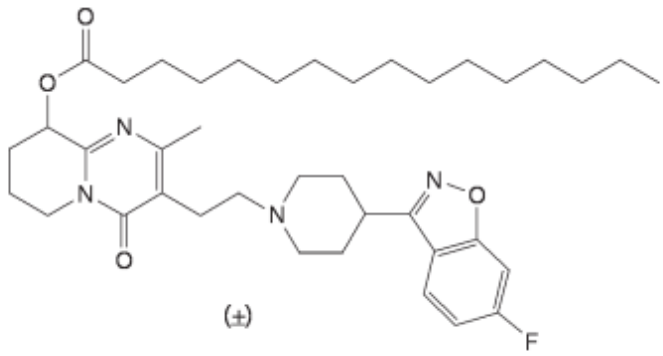
b. Maintenance Doses

After the induction phase, maintenance doses are administered. These are generally smaller doses at suitable intervals "so as to maintain the plasma

concentrations of drug at the . . . levels that provide the patient with the full therapeutic effect." EX1011, 284-85; EX1009, 61; EX1002 ¶49. Maintenance doses following the induction dose allow for a therapeutic steady-state plasma concentration to be achieved more rapidly than if administering doses of equal size at the same dosage time intervals. EX1011, 285; EX1014, 7:54-8:3. ("Usually, the amount of loading dose(s) administered exceeds the amount of the maintenance dose(s) administered and/or the loading dose(s) are administered more frequently than the maintenance dose(s), so as to achieve the desired steady-state concentration of the therapeutic agent earlier than can be achieved with the maintenance dose(s)."); EX1023, 11:62-64; EX1002 ¶49.

3. Paliperidone

Paliperidone, the 9-hydroxy metabolite of risperidone, is a second-generation antipsychotic that was approved on December 20, 2006, by the US Food and Drug Administration (FDA) for the treatment of schizophrenia. EX1004, 653. The relevant paliperidone derivative in this matter is paliperidone palmitate which is depicted below and used in injectable depot formulations:



EX1030; EX1038, 2285; EX1005; 3:11-41, 3:60-64. Paliperidone is primarily excreted renally, i.e., renal clearance. EX1004, 654. This is in contrast to prodrug risperidone, which is metabolized to paliperidone by the liver, i.e., hepatic clearance. *Id.*; EX1002 ¶51.

4. The ’544 Patent

The ’544 patent issued on April 29, 2003, and thus is prior art to the ’906 patent under § 102(b). EX1005, Cover. The ’544 patent discloses an “efficient, well-tolerated, sustained or delayed release (depot) formulation of [paliperidone palmitate] which is therapeutically effective for at least three weeks or more, in particular about one month.” EX1005, 2:38-43; EX1002 ¶63. The composition contains an aqueous nanoparticle dispersion containing paliperidone palmitate at 0.5% to 30 wt%, preferably 7%. *Id.*, 5:52-60. The composition may contain buffering agents; preservatives; isotonizing agents; and suspending agents such as polyethylene glycols. *Id.*, 6:61-7:45. The ’544 patent discloses that “[t]he ester having a C_{15} (pentadecyl) chain and the active ingredient corresponding thereto

being the 9-hydroxyriseridone palmitate ester was found to be the superior ester from a pharmacokinetic, as well as from a tolerance point of view." *Id.*, 3:60-64; EX1002 ¶¶64-65.

5. Cleton

Cleton published in March 2008. EX1003, Cover. Cleton is prior art under 35 U.S.C. § 102(a) because it was published "by another" before the earliest priority date of the '906 patent.[5,6] Cleton is "by another" because it has a different

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[5] As explained above, the earliest priority date of the '906 patent is December 5, 2008.

[6] Under the "totality of the evidence" standard, the printed publications contained herein contain conventional markers signaling that they were published when they claim. *Hulu, LLC v. Sound View Innovations, LLC,* IPR2018-01039 at 17-19 (P.T.A.B. Dec. 20, 2019) (Precedential). In addition, Petitioner submits the Declaration of Alys Tryon (EX1042) discussing, *inter alia*, copyright, ISBN and printing dates; information from the US Copyright Website about the date of first publication; the widespread dissemination of the printed publications relied upon

inventive entity from that of the '906 patent.[7] *Watson Labs., Inc. v. United Therapeutics Corp.*, IPR2017-01621, Paper 33 at 4 (P.T.A.B. Mar. 26, 2018).

Cleton discloses a multiple-dose, open-label, parallel-group study of patients with schizophrenia to investigate the pharmacokinetics profile of 100 mg-eq. paliperidone palmitate. EX1003, PI-75[8]; EX1002 ¶67. Patients with schizophrenia received four injections into either the deltoid or gluteal muscle on days 1, 8, 36, and 64. *Id*. The study found that the median C_{max} was higher in deltoid after the second and fourth injections. *Id.* ("The median C_{max} was higher in deltoid vs. gluteal muscle after the 2nd (31.3 vs. 24.1 ng/mL) and 4th (23.7 vs. 22.3 ng/mL)

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by Petitioner, and the established nature of the publishers of the printed publications. *Hulu*, IPR2018-01039 at 19-20.

[7] As used herein, "Cleton" refers to both PI-74 and PI-75 in EX1003. The inventive entities of PI-74 and PI-75 are different from that of the '906 patent.

[8] Petitioner notes that PI-75 of Cleton appears almost verbatim in the '906 patent as Example 2.

injections."); *see also id.*, PI-74[9] ("Overall, deltoid injection was associated with a higher C_{max} . . . and slightly earlier t_{max} vs gluteal injection."). Further, the median concentration-time profile was higher following deltoid injection. *Id*., PI-75. After four injections, median AUC_{∞} was similar for both injection sites, but C_{max} and AUC for paliperidone were 30% and 20% higher respectively in deltoid vs. gluteal muscle. *Id*. Increased median predose plasma concentrations on days 8, 36, and 64 suggested subjects were not completely at steady state after four injections. *Id*.; EX1002 ¶¶68-69.

6. Citrome

Citrome published in April 2007. EX1004, 653 (bottom left). Citrome is prior art to all claims of the '906 patent under 35 U.S.C. § 102(b). Citrome published information about ongoing clinical trials of paliperidone. *Id.*, Table 1. Of the twenty-two studies registered, eighteen were with patients with schizophrenia, one with schizoaffective disorder, and three in bipolar, manic or mixed episodes. *Id.*; EX1002 ¶71.

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[9] Petitioner notes that PI-74 of Cleton appears almost verbatim in the '906 patent as Example 3.

Fifteen studies investigated the oral extended release formulation of paliperidone and seven investigated the depot intramuscular formulation. *Id*. For example, Citrome states that Phase III clinical study NCT00210548 evaluated intramuscular injections of 50, 100 or 150 mg-eq. paliperidone formulated as a depot preparation vs. placebo, on days 1, 8, 36 and 64 of therapy. *Id*.; *see also* EX1032, 3. Another Phase III study, NCT00210717, evaluated intramuscular injections of 25-100 mg-eq. every four weeks versus risperidone depot 25–50 mg every two weeks. EX1004, Table 1; *see also* EX1034, 3. Citrome also discloses Phase III study NCT00119756, which evaluated the safety and tolerability of paliperidone depot injections in shoulder versus buttock muscles. EX1004, Table 1; *see also* EX1031, 3. Another Phase III study, NCT00101634, evaluating doses of 25, 50 or 100 mg-eq. vs. placebo. EX1004, Table 1; *see also* EX1033[10]; EX1002 ¶¶72-75.

[10] *In re Montgomery*, 677 F.3d at 1378-80 (published protocol for ongoing phase III study considered prior art).

7. Paliperidone Formulary

The Paliperidone Formulary published in July 2007. EX1006, Cover. As such, the Paliperidone Formulary is prior art to all claims of the '906 patent under 35 U.S.C. § 102(b). According to the Formulary, "The dose of paliperidone should be reduced in patients with moderate or severe renal function impairment. Elimination of paliperidone is reduced with declining creatinine clearance (CrCl). Total paliperidone clearance was reduced 32% in patients with mild renal function impairment (CrCl 50 to 79 mL/min), 64% in patients with moderate renal function impairment (CrCl 30 to 49 mL/min), and 71% in patients with severe renal function impairment (CrCl 10 to 29 mL/min), corresponding to an average increase in AUC of 1.5-, 2.6-, and 4.8-fold, respectively." EX1006, 638; EX1002 ¶¶145-47.

D. Ground 1: Claims 1-7, 15 and 17-21 Would Have Been Obvious over Citrome, Cleton and the '544 patent

1. Claims 1 and 4

a. Preamble: A dosing regimen for administering paliperidone palmitate to a psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder (claim 1) or psychotic disorder (claim 4) comprising

As an initial matter, Petitioner notes that the preamble of each challenged claim merely recites a dosing regimen. There is no claim element in the challenged claims that requires the recited steps of administering paliperidone

palmitate achieve a particular result because they impose no "efficacy requirement." *In re Montgomery*, 677 F.3d 1375, 1380 (Fed. Cir. 2012).

Regardless, even if they did, Citrome discloses that "paliperidone is a second-generation antipsychotic" and is approved for the treatment of schizophrenia. EX1004, 653; *see also* EX1005, 1:25-29, 7:59-67, 8:1-15, Claim 7 (disclosing paliperidone palmitate for the treatment of psychosis, schizophrenia, and schizoaffective disorders). With depot formulations, Citrome discloses that paliperidone is administered as paliperidone palmitate. EX1004, at Table 1 ("PD, palmitate depot"), 660. Citrome reports the dosing regimen for Phase III clinical trials NCT00210548, NCT00210717 and NCT00101634. *Id.* ("PD 50, 100 or 150 mg-eq. vs. placebo, 4 injections on days 1, 8, 36 and 64"); *id.* ("PD 25-100 mg eq every 4 weeks"); *id.* ("PD 25, 50 or 100 mg eq vs. placebo"); *see also* EX1032, 3 ("[f]our injections of paliperidone palmitate 50, 100, or 150 milligrams equivalent administered in the gluteal muscle . . . given on Days 1, 8, 36, and 64); EX1002 ¶¶76-77.

The POSA would have been motivated to develop depot formulations of paliperidone palmitate. "In keeping with the flexible nature of the obviousness inquiry, the requisite motivation can come from any number of sources." *Eisai Co. Ltd. v. Dr. Reddy's Labs., Ltd.*, 533 F.3d 1353, 1357 (Fed. Cir. 2008); *Dystar Textilfarben GmbH v. C.H. Patrick Co.*, 464 F.3d 1356, 1361 (Fed. Cir. 2006).

The POSA would have known that "non-compliance is very common among patients with schizophrenia and is a frequent cause of relapse." EX1002 ¶78; EX1009, Abstract. A major advantage of depot antipsychotics over oral medication is facilitation of compliance. *Id*. Indeed, "any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs." *Id*. Moreover, as discussed by Dr. Amiji, a POSA would have focused on developing acceptable blood/serum levels of the medication through a series of loading doses, followed by maintaining suitable blood levels of the medication through a series of maintenance doses. EX1002 ¶¶78-80.

As to combining the teachings of Citrome, Cleton and the '544 patent, Citrome and Cleton both provide information on clinical trials about injectable depot formulations of paliperidone palmitate but provide no information about how to make such a formulation. When a reference is silent as to certain information, the POSA would have been motivated to look to another reference to provide the missing information. *Pharmacosmos A/S v. Luitpold Pharms., Inc*., IPR2015-01490, Paper 54 at 46 (P.T.A.B. Jan. 4, 2017); *KSR*, 550 U.S. at 420 ("[A]ny need or problem"). As explained above, the '544 patent discloses an "efficient, well-tolerated, sustained or delayed release (depot) formulation of [paliperidone palmitate]." EX1005, 2:38-43; EX1002 ¶63. Indeed, the specification of the '906

patent itself admits that "[s]uitable aqueous nano particle depot formulations are described in U.S. Pat. No. 6,555,544." EX1001, 7:42-44.

b. <u>Element (1)</u>: administering intramuscularly in the deltoid of a patient in need of treatment a first loading dose of about 150 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment

By their very nature, the depot formulations of Citrome are sustained release formulations. EX1009, Abstract, 61; *see also* EX1005, 2:38-43 (disclosing paliperidone palmitate depot extended release formulation; 3:60-64; EX1002 ¶81.

Based on Citrome and Cleton reporting actual dosing regimen Phase III clinical trials, the POSA would have considered a dose of paliperidone as paliperidone palmitate ranging between 25 mg-eq. to 150 mg-eq. to be a safe and effective dose.[11] EX1004, Table 1 (reporting dosing regimens between 25 mg-eq.

[11] While the claims impose no "efficacy requirement," the POSA would have reasonably expected a dose ranging from 25 mg-eq. to 150 mg-eq. to be effective since paliperidone was already FDA approved for the treatment of schizophrenia. EX1002 ¶76; EX1004, Summary. Moreover, the POSA would have relied on the teachings of the '544 patent disclosing paliperidone palmitate

to 150 mg-eq. Phase III clinical trials NCT00210548, NCT00210717 and NCT00101634); EX1003, PI-74; EX1002 ¶85.

The amount of paliperidone as paliperidone palmitate claimed ("*about 150mg-eq.*") overlaps with the range disclosed in Citrome and Cleton, *i.e.*, between 25 mg-eq. to 150 mg-eq. *In re Peterson*, 315 F.3d at 1329 ("even a slight overlap in range establishes a *prima facie* case of obviousness."); *DuPont*, 904 F.3d at 1006; *Warner Chilcott Co., LLC v. Teva Pharmaceuticals USA, Inc.*, 642 F. App'x 996 (Fed. Cir. 2016) (finding a dose of 100 mg obvious where the prior art discloses a range of 20-175 mg).

Independent of the fact that the overlapping ranges in the prior art render this limitation obvious, a POSA would have been motivated to select 150 mg-eq. as the loading dose in order to rapidly achieve a therapeutic plasma concentration of paliperidone. EX1002 ¶85. As Citrome teaches, "[t]he depot intramuscular preparation of paliperidone holds greater promise if it can be demonstrated . . . that there is little lag time prior to the development of adequate blood levels." EX1004,

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depot extended release formulations that are effective over a period of time. EX1005, 2:38-43; *see also id.* 3:60-64; EX1002 ¶90.

660. In other words, the initial objective is to administer depot drugs such that adequate blood levels are reached quickly. *Id.* As discussed above, at the time of the alleged invention, the POSA would have known this could be done by using a large loading dose "to achieve a peak plasma concentration that lies within the therapeutic range of the drug . . ." EX1002 ¶85.

Cleton, however, teaches that subjects had **not** reached steady state concentrations of paliperidone after four 100 mg-eq. injections on days 1, 8, 36, and 64. EX1003, PI-75; EX1002 ¶86. That observation in Cleton would have motivated the POSA to select a larger dose in order to more rapidly achieve a steady-state plasma level of paliperidone in the patient. EX1002 ¶86. The largest dose disclosed in Citrome is 150 mg-eq. and because this dose had actually been administered to humans in Phase III clinical trials, the POSA would have considered it safe. *See also* EX1003, PI-74 (150 mg dose considered safe). Thus, the POSA would have been motivated to select this dose. Given that Citrome and Cleton both deal with depot formulations of paliperidone palmitate, the POSA would have been motivated to combine their teachings. EX1002 ¶¶86-90.

Finally, the POSA would have been motivated to select the deltoid as the injection site because Cleton teaches that loading dose injections into the deltoid compared to the gluteal muscle provides better results. EX1003, PI-75 ("The

median C_{max} was higher in deltoid vs. gluteal muscle after the 2nd (31.3 vs. 24.1 ng/mL."); EX1002 ¶91.

Therefore, this limitation would have been obvious.

(i) Reasonable Expectation of Success

"An obviousness determination requires that a skilled artisan would have perceived a reasonable expectation of success in making the invention in light of the prior art." *Amgen Inc. v. F. Hoffman-La Roche, Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). Paliperidone/paliperidone palmitate had been established for the treatment of schizophrenia and its related diseases and the '544 patent discloses an aqueous paliperidone palmitate nanoparticle suspension. EX1004, 653; EX1005, 1:25-29, 7:59-67, 8:1-15, Claim 7, 2:38-43, 8:44-9:44; 3:9-45; EX1001, 7:42-44. EX1002 ¶51.

Citrome showed that between 25-150 mg-eq. was determined safe to administer to humans. For example, Citrome reported *multiple* paliperidone palmitate depot **Phase III** clinical trials. EX1004, Table 1 (NCT00119756, NCT00210548, NCT00210717, NCT00111189, NCT00101634 and NCT00147173). Had a clinical study reached a **Phase III** trial then "tolerance and safety balanced with efficacy" had already been established in the Phase II trial to the satisfaction of the clinical investigators justifying a larger Phase III "reconfirm[ation]" study. EX1002 ¶90; EX1037 at 260 (describing Phase II as

"probably the most important phase in clinical research development."); *Soft Gel Technologies, Inc. v. Jarrow Formulas, Inc*., 864 F.3d 1334, 1342 (Fed. Cir. 2017) ("An incentive to conduct a confirmatory study frequently exists even when one has every reason to expect success."); *Acorda Therapeutics*, 903 F.3d at 1334 (finding clinical trials support reasonable expectation of success).

Likewise, Cleton discloses "[d]ata indicat[ing] AUC_{∞} increased proportionally with increasing paliperidone palmitate dose (25-150mg. eq.)." EX1003, PI-74; *see also* EX1038, 2286 (discussing "significant improvement" with injectable paliperidone palmitate 50 or 100 mg eq. on Days 1, 8 and 36); EX1039, Abstract 322 ("Paliperidone palmitate (50 and 100 mg eq. doses) was effective and well tolerated in acute symptomatic schizophrenia."); EX1041 (same); EX1005 at 2:38-50 (disclosing "an efficient, well-tolerated, sustained or delayed release (depot) formulation of [paliperidone palmitate] which is therapeutically effective for at least three weeks or more, in particular about 1 month" and further noting that "plasma level of [paliperidone] should be above approximately 10 ng/ml [and] remain at all times below a threshold value of approximately 100 ng/ml in order for one to call the formulation 'efficient.'"); 3:60-64 ("9-hydroxyriseridone palmitate ester was found to be the superior ester from a pharmacokinetic, as well as from a tolerance point of view."); EX1002 ¶90.

All that was left for a POSA was determining the dosing amounts on each administration day which, as Dr. Amiji explains, would have been nothing more than routine experimentation. EX1002 ¶90. Indeed, Patent Owner can hardly dispute otherwise since the '906 patent admits it would not be a challenge: "[t]hose of skill in the treatment of diseases could easily determine the effective amount of paliperidone to administer for the treatment of the diseases listed above." EX1001, 14:13-15. Thus, the POSA would have had a reasonable expectation of success in arriving at the claimed invention. EX1002 ¶90.

c. <u>Element (2)</u>: administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of about 100 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment

As noted above, Citrome and Cleton teach administering intramuscularly paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 8th day of treatment, i.e., on the 6th to about 10th day of treatment. The POSA would have known that the 8th day of treatment was "a second loading dose" given (1) its close proximity to the Day 1 dose, and (2) the fact that the loading dose can be broken into two "loading" doses. EX1021 at 27 ("The 'loading dose' is one or a series of doses. . . ."); EX1022, 36 ("A loading dose is a high initial or first dose which . . . is designed to 'load up' the body."); EX1044, 76 ("[a] 300-mg total loading dose would be administered as 100 mg

with the 200-mg dose administered 3 to 7 days later."); EX1047, 5 (loading dose may "be administered in two injections, i.e., a maximum of 100 mg initially followed by the balance in 3 to 7 days."); EX1046, 882 (discussing that in the Phase III trials, "[t]he first two paliperidone palmitate injections will be administered as a loading dose within 7 days of initiation."); EX1002 ¶¶94-95. Moreover, the aggregate teachings of the clinical trials in Citrome and Cleton would have informed the POSA that a dose of 25-150 mg-eq. was safe and effective. EX1002 ¶90. Overlapping ranges establish a *prima facie* case of obviousness. *Applied Materials, Inc.*, 692 F.3d at 1295; *DuPont*, 904 F.3d at 1006.

Separately, it would have been obvious for the POSA to select a dose less than 150 mg-eq. (e.g., 100 mg-eq.) as the second loading dose. When, as here, "there are a finite number of identified, predictable solutions," the claimed dosage would have been at a minimum, obvious to try." *KSR*, 550 U.S. at 421. As discussed above, the prior art discloses a finite number of possible doses (*i.e.*, 25, 50, 100, and 150 mg-eq.) for the POSA to try. It would have been obvious to try a dose of 100 mg-eq. as the second dose within an initial series, as Citrome and Cleton teach doses of 150, *100*, or 50 at days 1, 8, 36, and 64. EX1002 ¶96; *In re Cyclobenzaprine Hydrochloride*, 676 F.3d 1063, 1070 (Fed. Cir. 2012) ("Where a skilled artisan merely pursues 'known options' from 'a finite number of identified, predictable solutions,' the resulting invention is obvious under Section 103.").

Patent Owner may argue that there is no indication that the dose amounts in Citrome or Cleton were changed and that the patients were given the same dose on a given dosing day, e.g., in the case of NCT548 the same dose on days 1, 8, 36 and 64. However, based on the state of the art as discussed above, the POSA would have known that a large loading dose may need to be administered in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug followed by smaller subsequent doses at suitable intervals in order to reach steady state. EX1011, 284-85; EX1002 ¶98. "A person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle." *KSR*, 550 U.S. at 402; *id*. at 421 ("Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under our case law nor consistent with it."). Therefore, the skilled artisan would have been motivated to select the dosing amounts at each dosing day disclosed in Citrome as consistent with well-known depot formulation principles. *Peterson*, 315 F.3d at 1330. The POSA would have done so with a reasonable expectation of success. EX1002 ¶¶97-99.

As to the injection site, the POSA would have been motivated to select the deltoid because Cleton teaches that injection into the deltoid compared to the gluteal muscle provides better results. EX1003, PI-75; EX1002 ¶100.

Therefore this limitation would have been obvious.

d. <u>Element (3)</u>: administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 150 mg-eq. of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose

Citrome discloses administering intramuscularly "a first maintenance dose" of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 36th day of treatment, i.e., a month (±7 days) after the second dose, whether "a month" is 28 days, 30 days, or 31 days. EX1004, Table 1. From Citrome, the POSA would have known that the dose ranges of between 25 mg-eq. to 150 mg-eq. would have been safe and effective since they were actually used in clinical studies. EX1002 ¶¶102-03. The POSA would have known that the Day 36 dose would represent a maintenance dose given the longer lag time between the Days 1 and 8 loading doses. EX1002 ¶104; EX1004, Table 1 (NCT00210548); *id*. (NCT00210717 evaluating four week depot dosing regimens of 25-100 mg-eq.); EX1005, 8:17-20; EX1046, 882 (discussing that in the Phase III trials, "[t]he first two paliperidone palmitate injections will be administered as a loading dose within 7 days of initiation. Thereafter, injections will be given monthly."); EX1001, 1:58-61 ("[p]aliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly."); *One World Technologies*, IPR2017-00126 at 14.

Therefore, this limitation would have been obvious.

2. Dependent Claims

a. Claims 2 and 15

Claims 2 and 15 recite the dosing regimen of Claim 1 or 4 "wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals." EX1001, 32:31-36; 34:4-9.

As noted above, Citrome discloses administering intramuscularly 25 mg-eq. to 150 mg-eq. paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 64th day of treatment, i.e., a month (±7 days) after the 36th day of treatment, whether "a month" is 28 days, 30 days, or 31 days. EX1004, Table 1; EX1002 ¶107. From the clinical trials of Citrome, the POSA would have known that the dose ranges of between 25 mg-eq. to 150 mg-eq. would have been safe and effective since this is the range of doses that were disclosed in the clinical trials including Phase III trials. EX1002 ¶108; *Applied Materials, Inc.*, 692 F.3d at 1295; *DuPont*, 904 F.3d at 1006.

To the extent Patent Owner argues that Claims 2 and 15 require continued treatment at monthly intervals; the claims still would have been obvious. Kane taught that "any patient for whom long-term antipsychotic treatment is indicated should be considered for depot drugs." EX1009, Abstract. As explained by Dr.

Amiji, "long-term" would be considered longer than 64 days. EX1002 ¶¶110-11. Along those lines, the '544 patent teaches that depot paliperidone palmitate may be "administered approximately every three weeks or *even at longer intervals where possible*." EX1005, 8:17-20; EX1002 ¶113. Additionally, Citrome discloses clinical trial NCT717 which provides ongoing a depot dosing regimen of 25-100 mg-eq. every four weeks **for 52 weeks**. EX1004, Table 1; EX1002 ¶112. Furthermore, the '906 patent admits in the "Background of the Invention" that "[p]aliperidone palmitate injection has been developed to provide sustained plasma concentrations of paliperidone when administered once monthly." EX1001, 1:58-61. *One World Technologies*, IPR2017-00126 at 14. Therefore, even if Claims 2 and 15 were to require continued treatment at monthly intervals, the claims still would have been obvious.

b. Claims 3 and 5

Claims 3 and 5 recite the dosing regimen of Claim 1 or 4 wherein the sustained release formulation is an aqueous nanoparticle suspension. EX1001, 32:37-39; 32:58-59. The '544 patent discloses an aqueous nanoparticle suspension. EX1005, 2:38-43, 8:44-9:44; 3:9-45. Additionally, the '906 patent admits that "[s]uitable aqueous nano particle depot formulations are described in U.S. Patent No. 6,555,544." EX1001, 7:42-44. Accordingly, Claims 3 and 5 would have been obvious. EX1002 ¶¶118-20.

c. Claims 6 and 7

Claims 6 and 7 recite the dosing regimen of Claim 4 wherein the psychiatric patient is in need of treatment for psychotic disorder wherein the psychotic disorder is schizophrenia (Claim 6) or a schizoaffective disorder (Claim 7). EX1001, 32:60-65. Citrome teaches the use of paliperidone for the treatment of schizophrenia. EX1004, 653; EX1005, 1:25-29, 7:59-67, 8:1-15, Claim 7. Therefore, Claims 6 and 7 would have been obvious. EX1002 ¶¶121-22.

d. Claim 17

Claim 17 depends from Claims 1, 4, 8, or 11. As shown in the claim chart, the limitations of Claim 17 would have been obvious in light of the formulation information provided in '544 patent:

Claim Element	**'544 Patent's Disclosure**
17. The dosing regimen of claim 1, 4, 8 or 11 wherein the formulation is an aqueous nanoparticle suspension comprises	"The nanoparticles of the present invention . . ." EX1005, 3:65. Title of the '544 patent "**Aqueous suspensions** of submicron 9-hydroxyrisperidone fatty acid esters" EX1005, Title.
(a) from 3 to 20% (w/v) of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm	The '544 patent discloses aqueous nanoparticle dispersions of paliperidone palmitate containing preferably 0.5 to 30 wt%, preferably 7 wt%, paliperidone palmitate. EX1005, 5:52-60. "Most preferably, essentially all of the [paliperidone palmitate] particles have a

	size of less than 2000 nm." *Id.*, 5:24-25. The '544 patent discloses formulations having average particle sizes (d50) of 1.38, 0.74, and 0.52 gm, corresponding to 1380, 740, and 520 nm, which falls within the claimed range. *Id.*, 9:25-31, 9:45-64.
(b) from 0.5 to 3% (w/v) of a wetting agent wherein the wetting agent is polysorbate 20	The '544 patent discloses that the aqueous nanoparticle dispersions may contain polysorbate 20 at 1.1% (w/v). EX1005, 8:60-9:7.
(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5)	The '544 patent discloses that the formulation can include "suitable buffering agents . . . used in an amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5) . . . ." *Id.*, 7:9-12.
(d) from 0.5 to 3% (w/v) of a suspending agent wherein the suspending agent is polyethylene glycol 4000	The '544 patent discloses using a suspending agent in an amount of 0.5% to 2%, most preferably 1%, w/v including "polyethylene glycols." *Id.* EX1005, 6:61-7:2. The use of polyethylene glycol 4000 as a suspending agent in parenteral aqueous suspension was known. *See, e.g.*, EX1008 ('534 patent) at Example D (disclosing a parenteral aqueous suspension of an active agent containing 3% (w/w) polyethylene glycol 4000).
(e) up to 2% (w/v) preservatives	The '544 patent discloses that the aqueous suspension may contain up to 2% w/v preservatives. EX1005, 7:17-25.
(f) water q.s. ad 100%	The '544 patent discloses that water is added "q.s. ad 100%." EX1005, 9:6.

EX1002 ¶¶123-29.

e. Claim 18

Claim 18 recites the dosage regimen of Claim 17 wherein the concentration of paliperidone palmitate is 156 mg/ml in the aqueous nanoparticle suspension. EX1001, 34:29-31. The '544 patent discloses that the concentration of paliperidone palmitate can be between 0.5% and 30% w/v. EX1005, 5:52-60. As Dr. Amiji explains, a dose of 156 mg/ml corresponds to 15.6% w/v. Thus, Claim 18 would have been obvious. EX1002 ¶¶130-33.

f. Claims 19-21

As shown in the claim charts below, the limitations of Claims 19-21 are disclosed in the '544 patent.

Claim 19	
19. The dosing regimen of claims 1, 4, 8 or 11 wherein the sustained release depot formulation is an aqueous nanoparticle suspension consists essentially of[12]	"The nanoparticles of the present invention . . ." EX1005, 3:65. Title of the '544 patent "**Aqueous suspensions** of submicron 9-

[12] As Dr. Amiji explains, "consists essentially of" would not save the validity of the claims. For example, to the extent Patent Owner argues that the '544 patent requires the presence of a preservative—which as Dr. Amiji explains is not necessarily the case—the further inclusion of a preservative would not impact

	hydroxyrisperidone fatty acid esters" EX1005, Title.
(a) 156 mg/ml of the paliperidone palmitate having an average particle size (d50) of from about 1600 nm to about 900 nm;	The '544 patent discloses that the concentration of paliperidone palmitate can be between 0.5% and 30% w/v. EX1005, 5:52-60. 156 mg/ml would be a concentration of 15.6% w/v, approximately in the middle of that range. Additionally, the '544 patent states that "[m]ost preferably, essentially all of the [paliperidone palmitate] particles have a size of less than 2000 nm." EX1005, 5:24-25. The '544 patent further discloses formulations having average particle sizes (d50) of 1.38, 0.74, and 0.52 gm, corresponding to 1380, 740, and 520 nm, which falls within the claimed range. *Id.*, 9:25-31, 9:45-64.
(b) 12 mg/ml of polysorbate 20;	The '544 patent discloses an aqueous nanoparticle dispersion containing 1.1% polysorbate 20 (i.e., 11 mg/ml), and that this concentration may vary between 0.5% and 2% w/v. EX1005, 7:2-8.
(c) one or more buffering agents sufficient to render the composition neutral to very slightly basic (pH 8.5);	The '544 patent further discloses that the formulation can include "suitable buffering agents . . . used in an amount sufficient to render the dispersion neutral to very slightly basic (up to pH

any alleged novel and basic characteristics of the other components. EX1002 ¶¶135-39.

	8.5) . . . .” *Id.*, 7:9-12.
(d) 30 mg/ml of a suspending agent wherein the suspending agent is polyethylene glycol 4000; and	The ’544 patent discloses using a suspending agent in an amount of 0.5% to 2% (e.g., 5-20 mg/ml), 0.5% to 3% (5-30 mg/ml), 0.5% to 2% (0.5-20 mg/ml). EX1005, 6:61-7:8. Appropriate suspending agents include “polyethylene glycols.” EX1005, 6:61-7:8. The use of polyethylene glycol 4000 as a suspending agent in parenteral aqueous suspension was known. *See, e.g.*, EX1008 (’534 patent) at Example D (disclosing a parenteral aqueous suspension of an active agent containing 3% (w/w) polyethylene glycol 4000).
(f) water q.s. ad 100%.	The ’544 patent discloses that water is added “q.s. ad 100%.” EX1005, 9:6.
Claim 20	
20. The dosage regimen of claim 19 wherein in the buffering agents contained in the aqueous nanoparticle suspension are citric acid monohydrate, disodium hydrogen phosphate anhydrous, **sodium dihydrogen phosphate monohydrate**, sodium hydroxide.	The ’544 patent discloses using sodium dihydrogen phosphate anhydrous and monohydrate as buffering agents. EX1005, 8:60-9:7; 7:9-16.
Claim 21	
21. The dosage regimen of claim 19 wherein in the pH of the aqueous nanoparticle suspension is in the range of pH 7 to 7.5.	The ’544 patent discloses that the formulation can include “suitable buffering agents . . . used in an amount sufficient to render the dispersion neutral to very slightly basic (up to pH 8.5), preferably in the pH range of 7 to 7.5.” EX1005, 7:9-12.

EX1002 ¶¶134-40.

E. Ground 2: Claims 8-14, and 16 Would Have Been Obvious Over Citrome, Cleton, the Paliperidone Formulary and the '544 patent

1. Claims 8 and 11

a. <u>Preamble</u>: A dosing regimen for administering paliperidone palmitate to a renally impaired psychiatric patient in need of treatment for schizophrenia, schizoaffective disorder, or schizophreniform disorder (claim 8) or psychotic disorder (claim 11) comprising

Citrome teaches paliperidone palmitate depot formulations for treating schizophrenia and reports a dosing regimen of 25-150 mg-eq. with injections given on days 1, 8, 36 and 64. EX1004, Table 1, 660. The POSA would have been aware that Paliperidone Formulary discusses the monograph for Invega® (a tablet containing paliperidone). EX1006, 637. According to the Paliperidone Formulary, paliperidone may be administered to renally impaired patients. *Id.* at 638. The POSA would have been motivated to combine the teachings of Citrome with the Paliperidone Formulary. EX1002 ¶148.

b. Element (a): administering intramuscularly in the deltoid of a renally impaired psychiatric patient in need of treatment a first loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the first day of treatment)

As explained by Dr. Amiji, the plain and ordinary meaning of "from about 75 mg-eq." recited in the claim imposes only a lower limit on the claim, not an upper limit. EX1002 ¶150. Therefore, a depot dose of 25 mg-eq. to 150 mg-eq. of

paliperidone as paliperidone palmitate on day 1 in Citrome/Cleton overlaps with the claimed range. Because overlapping ranges establish a prima facie case of obviousness, administering a first dose of "from about 75 mg-eq. of paliperidone as paliperidone palmitate" would have been obvious. *DuPont*, 904 F.3d at 1006; *In re Peterson*, 315 F.3d at 1329.

Independently, the Paliperidone Formulary teaches that "[t]he dose of paliperidone should be reduced in patients with moderate or severe renal function impairment." EX1006, 638. The claims are not limited by the degree of severity of renal impairment and thus would include mild, moderate or severe renal function impairment. *American Bioscience, Inc. v. Baker Norton Pharm., Inc.*, 2002 WL 54627 at *2 (C.D. Cal. 2002). Thus, in light of the Paliperidone Formulary, the POSA would have been motivated to titrate down the dose taught in the prior art for renally impaired patients. EX1002 ¶¶151-53.

As Dr. Amiji explains, the POSA would have been aware that the prior art provides information of paliperidone clearance rate as it relates to renal function, e.g., "Elimination of paliperidone is reduced with declining creatinine clearance (CrCl). Total paliperidone clearance was reduced 32% in patients with mild renal function impairment (CrCl 50 to 79 mL/min), 64% in patients with moderate renal function impairment (CrCl 30 to 49 mL/min), and 71% in patients with severe

renal function impairment (CrCl 10 to 29 mL/min)." EX1006, 638, EX1002 ¶152-53.

The POSA would have known that "[s]erum creatinine and calculated creatinine clearance yield a reasonable estimation of renal function with minimal cost and inconvenience." EX1043, 15. As explained by Traynor "[c]reatinine is the closest to an ideal endogenous substance for measuring glomerular filtration rate." EX1045, 733. Furthermore, "[m]easuring the creatinine clearance using serum creatinine level and a timed urine collection gives an estimate of glomerular filtration rate." *Id.* Therefore, the POSA would have looked to the creatinine clearance information in the Paliperidone Formulary to determine how much to reduce the doses of paliperidone palmitate as a function of renal activity. EX1002 ¶152.

As Dr. Amiji explains, looking at the dosing range in Citrome (i.e., 25 mg-eq. to 150 mg-eq.), the POSA would have been motivated to decrease the dose of paliperidone palmitate based on a patient's renal function (as determined by creatinine clearance rate), i.e., by 32% in patients with mild renal impairment, by 64% in patients with moderate renal impairment, and by 71% in patients with severe renal impairment. EX1002 ¶153. A 32% reduction in the dose disclosed in Citrome would result in a dosing range of 17 mg-eq. to 102 mg-eq., a 64% reduction in the dose would result in a dosing range of 9 mg-eq to 54 mg eq., and a

71% reduction would result in a dosing range of 7.25 mg-eq. to 43.5 mg-eq. Therefore, for all patients with renal function impairment, ***irrespective of severity, as claimed***, the range would be **7.25 mg-eq. to 102 mg-eq.**[13] EX1002 ¶153. The

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[13] Petitioner notes that the specification only discloses administering paliperidone palmitate to patients with *mild* renal impairment. EX1001, 5:59-61; 6:14-15. If Patent Owner argues that the Formulary teaches away when it states "[t]he dose of paliperidone should be reduced in patients with moderate or severe renal function impairment" implying that no dose reduction is needed in patients with mild renal impairment, the Formulary also states elsewhere that "[d]osage adjustments are necessary in patients with renal function impairment." EX1006 at 643. In any event, assuming, *arguendo*, that no dose reduction is needed then as explained above, the prior art teaches 25 mg-eq. to 150 mg-eq., which would remain unchanged thus overlapping with the claimed ranges. EX1002 ¶153. **Therefore, any teaching away argument would not get Patent Owner anywhere since the unchanged ranges would still overlap with the claimed ranges.** *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006.

calculated range overlaps with the claimed range. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006.

Furthermore, the '906 patent plainly admits that adjusting the dosage based on an individual's renal function would have been well within the skill set of an ordinary artisan. EX1001, 14:13-15, 5:48-52 ("Those of ordinary skill in the art will understand that the maintenance dose may be titrated up or down in view of the patients [sic] condition (response to the medication and **renal function)**") (emphasis added).[14] Moreover, given the POSA would have based his or her analysis on prior art paliperidone clearance data reported as a function of renal activity (i.e., creatinine clearance), the POSA would have had a reasonable expectation of success. EX1002 ¶154.

Finally, the POSA would have been motivated with a reasonable expectation of success to select the deltoid as the injection site because Cleton teaches that

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[14] Indeed, Petitioner notes that the '906 patent discusses renal impairment in the context of creatinine clearance rates. EX1001, 6:5-15. As explained by Traylor, the Cockcroft and Gault equation "was one of the earliest prediction formulas and is still widely used." EX1045, 735.

injection of paliperidone palmitate depot formulations into the deltoid compared to the gluteal muscle provides better results. EX1003, PI-75; EX1002 ¶155.

c. Element (b): administering intramuscularly in the deltoid muscle of the patient in need of treatment a second loading dose of from about 75 mg-eq. of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 6th to about 10th day of treatment

As noted above, Citrome discloses administering intramuscularly a depot dose of paliperidone as paliperidone palmitate on the 8th day of treatment, i.e., on the 6th to about 10th day of treatment. EX1002 ¶157. The claimed dose of "*from about 75 mg-eq.*" overlaps with the range disclosed in Citrome (i.e., 25 to 150 mg-eq.), establishing a prima facie case of obviousness. *DuPont*, 904 F.3d at 1006; *In re Peterson*, 315 F.3d at 1329.

Independently, the Paliperidone Formulary discloses that the dose of paliperidone should be reduced in patients with renal impairment. EX1006, 638. The relevant calculation against the ranges in Citrome for patients with renal function impairment is presented above, i.e., **7.25 mg-eq. to 102 mg-eq**. EX1002 ¶¶153, 159. The calculated range overlaps with the claimed range. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006. Moreover, adjusting the dosage based on an individual's renal function would have been well within the skill set of an ordinary artisan and would have resulted in an overlap with the claimed range

giving a reasonable expectation of success. EX1002 ¶160; *see also* EX1001, 5:48-52; *Applied Materials, Inc.*, 692 F.3d at 1295.

Finally, the POSA would have been motivated to use the deltoid as the injection site because Cleton teaches that injection of paliperidone palmitate depot formulations into the deltoid compared to the gluteal muscle provides better results. EX1003, PI-75; EX1002 ¶161.

d. Element (c): administering intramuscularly in the deltoid or gluteal muscle of the patient in need of treatment a first maintenance dose of about 25 mg-eq. to about 75 mg-eq. (claim 8) or of about 25 mg-eq. to about 50 mg-eq. (claim 11) of paliperidone as paliperidone palmitate in a sustained release formulation a month (±7 days) after the second loading dose

Citrome discloses administering intramuscularly a dose of paliperidone as paliperidone palmitate on the 36th day of treatment, i.e., a month (±7 days) after the second dose, whether "a month" is 28 days, 30 days, or 31 days. The ranges recited by the claims, a dose of "about 25 mg-eq. to about 75 mg-eq." (Claim 8) or "of about 25 mg-eq. to about 50 mg-eq." (Claim 11), overlap with the range disclosed in Citrome (i.e., 25 to 150 mg-eq.), establishing a prima facie case of obviousness. *DuPont*, 904 F.3d at 1006; *In re Peterson*, 315 F.3d at 1329.

Independently, the Paliperidone Formulary discloses that the dose of paliperidone should be reduced in patients with renal impairment. EX1006, 638. The relevant calculation against the ranges in Citrome for patients with renal

function impairment is presented above, i.e., **7.25 mg-eq. to 102 mg-eq**. EX1002 ¶¶153, 165. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006. The POSA would also know that following the induction phase, smaller doses at suitable intervals are administered. EX1011, 284-85 EX1002 ¶166.

Therefore, these claims would have been obvious.

2. Dependent Claims

a. Claims 9 and 16

Claims 9 and 16 recite dosing regimens of Claim 8 or 11 wherein after administration of the first maintenance dose, subsequent maintenance doses of from about 25 mg-eq. to 150 mg-eq. are administered in the deltoid or gluteal muscle of the psychiatric patient in need of treatment at monthly (±7 days) intervals. EX1001, 33:21-25; 34:9-14.

As noted above, Citrome discloses administering intramuscularly paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 64th day of treatment, i.e., a month (±7 days) after the second dose, whether "a month" is 28 days, 30 days, or 31 days. EX1004, Table 1. From the Phase III clinical trials of Citrome, the POSA would have known that dose ranges of between 25 mg-eq. to 150 mg-eq. would have been safe and effective since this is the range of doses disclosed in the clinical trials, including Phase III trials. *Id*.; *see also* EX1003, PI-74; EX1002 ¶169. Overlapping ranges establish a

prima facie case of obviousness. *Applied Materials, Inc.*, 692 F.3d at 1295; *DuPont*, 904 F.3d at 1006.

As explained with respect to Claims 2 and 15, to the extent Patent Owner argues the claims require continued treatment at monthly interval, the claims still would have been obvious. EX1005, 8:17-20 ("administered approximately every three weeks or *even at longer intervals where possible*."); Citrome (NCT00210717); EX1002 ¶170. Finally, the POSA would be motivated to combine the teachings of Citrome with the '544 patent because the '544 patent explains how to make a depot formulation of paliperidone palmitate. EX1005, 2:38-43; *Pharmacosmos A/S*, IPR2015-01490 at 46; *KSR*, 550 U.S. at 420. Furthermore, the same teachings would have given the POSA a reasonable expectation of success. EX1001, 7:42-44. Accordingly, Claims 9 and 16 would have been obvious. EX1002 ¶¶168-72.

b. Claims 10 and 12

Claims 10 and 12 recite the dosing regimen of Claim 8 or 11 wherein the sustained release formulation is an aqueous nanoparticle suspension. EX1001, 33:26-27; 33:48-49. The '544 patent discloses an aqueous nanoparticle suspension. EX1005, 8:44-9:44; 3:9-45. The '906 patent also admits that "[s]uitable aqueous nano particle depot formulations are described in U.S. Patent

No. 6,555,544." EX1001 at 7:42-44. Accordingly, Claims 10 and 12 would have been obvious. EX1002 ¶¶173-75.

c. Claims 13 and 14

Claims 13 and 14 recite the dosing regimen of Claim 8 or 11 wherein the psychiatric patient is in need of treatment for psychotic disorder wherein the psychotic disorder is schizophrenia (Claim 13) or a schizoaffective disorder (Claim 14). EX1001, 33:50-53; 34:1-3. Citrome and the '544 patent disclose the use of paliperidone for schizophrenia and schizoaffective disorders. EX1004, 653; EX1005, 1:25-29, 7:59-67, 8:1-15, Claim 7; EX1002 ¶176-77.

F. Ground 3: Claims 1-7, 15 and 17-21 Would Have Been Obvious over Citrome and the '544 patent

1. Claims 1 and 4

a. Preamble

As explained above (Section XI.D.1.a.), Citrome discloses a depot dosing regimen comprising administering paliperidone as paliperidone palmitate to schizophrenia patients on days 1, 8, 36, and 64 of treatment. EX1004; EX1005, 1:25-29, 7:59-67, 8:1-15, Claim 7; EX1002 ¶180.

b. Element (1)

As noted above, Citrome discloses sustained release formulations that administer intramuscularly a first loading dose of paliperidone as paliperidone palmitate on the first day of treatment. Citrome discloses dose ranges of 25 mg-eq.

to 150 mg-eq. EX1002 ¶182. "[E]ven a slight overlap in range establishes a *prima facie* case of obviousness." *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006; *Applied Materials, Inc.*, 692 F.3d at 1295; *Warner Chilcott Co.*, 642 F. App'x at 996.

Independently, a POSA would have been motivated to select 150 mg-eq. as the loading dose. Citrome discloses a need for achieving adequate blood levels of paliperidone early on during treatment with depot, sustained release formulations. *See, e.g.*, EX1004, 660. The POSA would thus have had a reason to seek to achieve therapeutic plasma concentration of paliperidone early during treatment. EX1002 ¶183.

At the time of the alleged invention, the POSA would have known that a loading dose or doses is used in order to achieve a peak plasma concentration that lies within the therapeutic range of the drug. EX1011, 284-85; EX1002 ¶184; *see also* EX1005, 2:60-3:1. The POSA would have been motivated to select the largest dose of paliperidone disclosed in Citrome as a loading dose i.e., 150 mg-eq. EX1002 ¶184. Furthermore, Citrome showed that 150 mg-eq. was determined to be safe and effective to administer to humans including being used in Phase III

trials. *Id.* Thus, the POSA would have had a reasonable expectation of success for the reasons stated in Ground 1.[15] EX1002 ¶185; *Amgen Inc.*, 580 F.3d at 1362.

Finally, Citrome discloses three sites of injections: shoulder, arm, and buttock muscles. The deltoid muscle would have been, at the very least, obvious to try. *Cyclobenzaprine Hydrochloride*, 676 F.3d at 1071. The POSA would further have been motivated to select the deltoid as the injection site. At the time of the alleged invention, the POSA would have known that the deltoid muscle was

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[15] Grounds 3 and 4 do not rely on Cleton. Even without Cleton, from the teachings of Citrome and the '544 patent, the POSA would still have had a reasonable expectation of success. EX1002 ¶ 186. Citrome and the '544 patent teach injectable depot formulations of paliperidone palmitate for the use of schizoaffective related disorders. EX1004, Table 1 (disclosing phase III clinical trials for the treatment of Schizophrenia using paliperidone "palmitate depot"); EX1005 at 2:38-43. Because Citrome discloses phase III clinical trials, the POSA would have known that the Phase II studies had shown the necessary safety and efficacy. And for the reasons explained above in Ground 1 it would not have been a challenge for the POSA to determine dosage amounts. EX1002 ¶185.

preferred due to the greater perfusion of the muscle. *See, e.g.*, EX1007, 26. Therefore, this limitation would have been obvious. EX1002 ¶186.

c. Element (2)

As noted above, Citrome discloses sustained release formulations that administer intramuscularly paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 8th day of treatment, i.e., on the 6th to about 10th day of treatment. As explained above in Ground 1, Element (2), given its close proximity to the Day 1 dose, the POSA would have known that the Day 8 dose was "a second loading dose" and the teachings of the clinical trials in Citrome would have informed the POSA that dose ranges of 25 mg-eq. to 150 mg-eq. were safe for humans. *Id.*; EX1002 ¶188. Overlapping ranges establish a *prima facie* case of obviousness. *Applied Materials, Inc.*, 692 F.3d at 1295; *DuPont*, 904 F.3d at 1006.

Independently, it would have been obvious for the POSA to select 100 mg-eq. as the second dose. EX1002 ¶189. As discussed above, the prior art discloses a finite number of dosages (*i.e.*, 25, 50, 100, and 150) for the POSA to try. *Cyclobenzaprine Hydrochloride*, 676 F.3d at 1071. It would have been obvious to try a dose of 100 mg-eq. as the second dose within an initial series as Citrome teaches doses of 150, *100*, or 50 at days 1, 8, 36, and 64. *KSR*, 550 U.S. at 421.

Furthermore, the POSA would have been motivated to select the deltoid as the injection site. At the time of the alleged invention, the POSA would have known that the deltoid muscle was preferred due to the greater perfusion of the muscle. *See, e.g.*, EX1007, 26. Moreover, Citrome discloses three sites of injections: shoulder, arm, and buttock muscles. The deltoid muscle would have been, at the very least, obvious to try. *Cyclobenzaprine Hydrochloride*, 676 F.3d at 1071. Therefore, this limitation would have been obvious. EX1002 ¶190.

d. Element (3)

As discussed above, Citrome discloses administering intramuscularly a dose of paliperidone as paliperidone palmitate in a sustained release formulationon the 36th day of treatment, *i.e.*, a month (±7 days) after the second dose, whether "a month" is 28 days, 30 days, or 31 days. Section XI.D.1.d. Citrome discloses dose ranges of 25 mg-eq. to 150 mg-eq. *Id.* From the clinical trials of Citrome, the POSA would have known that the dose ranges of between 25 mg-eq. to 150 mg-eq. would have been safe and effective since this is the range of doses that were disclosed in the clinical trials including Phase III trials. *Id*.; *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006. Therefore, this limitation would have been obvious. EX1002 ¶192.

2. Dependent Claims

None of the dependent claims add anything inventive to the independent claims.[16] They recite routine modifications to pharmaceutical dosages or obvious variants of the independent claims. EX1002 ¶194.

Claims 2 and 15	For the same reasons in Ground 1, Claims 2 and 15 are obvious.
Claims 3 and 5	For the same reasons in Ground 1, Claims 3 and 5 are obvious.
Claims 6 and 7	For the same reasons in Ground 1, Claims 6 and 7 are obvious.
Claim 17	For the same reasons in Ground 1, Claim 17 is obvious.
Claim 18	For the same reasons in Ground 1, Claim 18 is obvious.
Claim 19	For the same reasons in Ground 1, Claim 19 is obvious.
Claim 20	For the same reasons in Ground 1, Claim 20 is obvious.

[16] Grounds 3 and 4 do not rely on Cleton. The absence of Cleton in Grounds 3 and 4 does not change anything because the related dependent claim analysis in Grounds 1 or 2 did not rely on Cleton.

Claim 21	For the same reasons in Ground 1, Claim 21 is obvious.

G. Ground 4: Claims 8-14, and 16 Would Have Been Obvious Over Citrome, the Paliperidone Formulary and the '544 patent

1. Claims 8 and 11

a. Preamble

As discussed above, Citrome discloses a depot dosing regimen comprising sustained release formulation that administer paliperidone as paliperidone palmitate to schizophrenia patients on days 1, 8, 36, and 64 of treatment. EX1004, Table 1. Furthermore, the Paliperidone Formulary teaches that paliperidone may be administered to renally impaired patients. EX1006, 638. Therefore, this limitation would have been obvious. EX1002 ¶198.

b. Element (a)

As noted above, Citrome discloses sustained release formulation that administer intramuscularly a depot dose range of 25 mg-eq. to 150 mg-eq. of paliperidone as paliperidone palmitate. Citrome discloses administering the dose on the first day of treatment. Therefore, a dose ranging from 25 mg-eq. to 150 mg-eq. of paliperidone as paliperidone palmitate overlaps with the claimed range establishing a prima facie case of obviousness. *DuPont*, 904 F.3d at 1006.

Further, the Paliperidone Formulary teaches that "[t]he dose of paliperidone should be reduced in patients with moderate or severe renal function impairment."

EX1006, 638. The relevant calculation against the ranges in Citrome for patients with renal function impairment is presented above, i.e., **7.25 mg-eq. to 102 mg-eq**. EX1002 ¶¶153, 203. The calculated range overlaps with the claimed range. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006.

Furthermore, the '906 patent admits that adjusting the dosage based on an individual's renal function would have been well within the skill set of POSA. EX1001, 14:13-15, 5:48-52. Moreover, given the POSA based his or her analysis on paliperidone clearance data based on renal function, the POSA would have had a reasonable expectation of success. EX1002 ¶203.

As to the injection site, the POSA would have been motivated to select the deltoid. EX1007, 26; EX1002 ¶204.

c. Element (b)

As noted above, Citrome discloses administering a depot dose of paliperidone as paliperidone palmitate formulated in a sustained release formulation on the 8th day of treatment, i.e., on the 6th to about 10th day of treatment. Citrome discloses dose ranges of 25 mg-eq. to 150 mg-eq. Therefore, the doses disclosed in Citrome overlaps with the claimed range establishing a prima facie case of obviousness. *DuPont*, 904 F.3d at 1006; *In re Peterson*, 315 F.3d at 1329.

Furthermore, the Paliperidone Formulary teaches that "[t]he dose of paliperidone should be reduced in patients with moderate or severe renal function impairment." EX1006, 638. The relevant calculation against the ranges in Citrome for patients with renal function impairment is presented above, i.e., **7.25 mg-eq. to 102 mg-eq**. EX1002 ¶¶153, 208. The calculated range overlaps with the claimed range. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006.

Further, the '906 patent plainly admits that adjusting the dosage based on an individual's renal function would have been well within the skill set of an ordinary artisan. EX1001, 14:13-15, 5:48-52. Moreover, given the POSA based his or her analysis on actual paliperidone clearance data based on renal function, the POSA would have had a reasonable expectation of success. EX1002 ¶208.

As to the injection site, the POSA would have been motivated to select the deltoid. EX1007, 26; EX1002, ¶209.

d. Element (c)

As noted above, Citrome discloses administering intramuscularly a depot dose of paliperidone as paliperidone palmitate on the 36th day of treatment, i.e., a month (±7 days) after the second dose, whether "a month" is 28 days, 30 days, or 31 days. Citrome would have taught the POSA doses ranging between 25 mg-eq. to 150 mg-eq., would be considered safe for humans. A dose of 25 mg-eq. to 150

mg-eq. overlaps with the claimed ranges. *DuPont*, 904 F.3d at 1006; *In re Peterson*, 315 F.3d at 1329.

Separately, the Paliperidone Formulary discloses that the dose of paliperidone should be reduced in patients with renal impairment. EX1006, 638. The relevant calculation against the ranges in Citrome for patients with renal function impairment is presented above, i.e., **7.25 mg-eq. to 102 mg-eq**. EX1002 ¶¶153, 212. The calculated range overlaps with the claimed range. *Peterson*, 315 F.3d at 1329; *DuPont*, 904 F.3d at 1006. Furthermore, the POSA would know that the maintenance doses would be smaller than the loading doses. EX1011, 285; EX1002 ¶213; *Applied Materials, Inc.*, 692 F.3d at 1295.

2. Dependent Claims

None of the dependent claims add anything inventive to the independent claims. They recite routine modifications to pharmaceutical dosages or obvious variants of the independent claims. EX1002 ¶215.

Claims 9 and 16	For the same reasons in Ground 2, Claims 9 and 16 are obvious.
Claims 10 and 12	For the same reasons in Ground 2, Claims 10 and 12 are obvious.
Claims 13 and 14	For the same reasons in Ground 2, Claims 13 and 14 are obvious.

H. No Secondary Considerations of Nonobviousness

While secondary considerations of nonobviousness must be taken into account in an obviousness determination, they do not necessarily control. *Newell Cos., Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). A strong case of obviousness cannot be overcome by secondary considerations of nonobviousness. *Pfizer*, 480 F.3d at 1372. To the extent Patent Owner does assert any secondary considerations, including alleged unexpected results, detailed consideration of Patent Owner's evidence should not be undertaken until Petitioner has had an opportunity to respond to it. *Amneal Pharmaceuticals, LLC v. Supernus Pharmaceuticals, Inc.*, IPR2013-00368, Paper 8 at 12-13 (P.T.A.B. Dec. 2013); *Koios Pharms. LLC v. medac Gesellschaft für klinische Spezialpräparate mbH*, IPR2016-01370, Paper 13 at 35 (P.T.A.B. Feb. 8, 2017); *Quanergy Systems, Inc. v. Velodyne Lidar, Inc.*, IPR2018-00256, Paper 14 at 11 (P.T.A.B. May 25, 2018).

No objective indicia of obviousness was presented or discussed during prosecution. To the extent the specification contends there are alleged unexpected results, such evidence is flawed. Indeed, the specification of the '906 patent itself admits that "[t]hose of skill in the treatment of diseases could **easily** determine the effective amount of paliperidone to administer for the treatment of the diseases listed above." EX1001, 14:13-15 (emphasis added).

XII. THE BOARD SHOULD INSTITUTE TRIAL BASED ON MYLAN'S PETITION (35 U.S.C. § 325(D) OR § 314(A))

The Board should not exercise its discretion pursuant to 35 U.S.C. § 325(d) to deny institution of Mylan's Petition. The Examiner raised no prior art rejections during prosecution. EX1019. Thus, the arguments presented in this Petition are necessarily different from those addressed during prosecution and are not cumulative of the prior art evaluated during examination. *Becton, Dickinson and Company v. B. Braun Melsungen AG*, IPR2017-01586, slip op. at 17-18 (P.T.A.B. Dec. 15, 2017) (Paper 8) (precedential) (factors (a), (b), and (d)). Moreover, even if one or more of the references cited in this Petition were disclosed to the Examiner,[17] "the Board has consistently declined exercising its discretion under Section 325(d) when the only fact a Patent Owner can point to is that a reference was disclosed to the Examiner during the prosecution." *Amgen Inc. v. Alexion*

[17] While the Examiner discussed the '544 patent in a notice of allowance, the Examiner never considered the combined teachings of the '544 patent with the other referenced material relied on in this Petition. *HyperBranch Medical Technology, Inc. v. Confluent Surgical, Inc.*, IPR2018-01099, Paper 14 at 17 (P.T.A.B. Nov. 27, 2018).

Pharmaceuticals Inc., IPR2019-00740, Paper 15 at 65 (P.T.A.B. Aug. 20, 2019) (citing cases). Therefore, Petitioner respectfully asks the Board to decline using its discretion under Section 325(d). *Id.*

Turning to Section 314(a), to the best of Petitioner's knowledge, this is the first IPR directed to the '906 patent. *Valve Corp. v. Elec. Scripting Prods., Inc.*, IPR2019-00062, -00063, -00084, Paper 11 (P.T.A.B. Apr. 2, 2019) (precedential); *Mylan Pharmaceuticals Inc. v. Sanofi-Aventis Deutschland GMBH*, IPR2018-01680, Paper 22 at 17 (P.T.A.B. Apr. 3, 2019). Furthermore, the corresponding district court proceeding between Petitioner and Patent Owner is in its infancy. Thus, Petitioner has not gained any advantage by making the Patent Owner substantively participate in the underlying district court litigation only then to use such information to the detriment of Patent Owner. *NHK Spring Co., Ltd. v. Intri-Plex Techs., Inc.*, Case IPR2018-00752, Paper 8 at 19-20 (P.T.A.B. Sept. 12, 2018) (precedential).[18]

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[18] Even if some information has been exchanged, the inquiry under Section 314(a) is whether the parties remain on equal footing. *Kashiv Biosciences, LLC v. Amgen Inc.*, IPR2019-00791, Paper 15 at 32 (P.T.A.B. Sept. 11, 2019).

XIII. CONCLUSION

Petitioner has demonstrated by a preponderance of the evidence that Claims 1-21 of the ’906 patent are unpatentable as obvious.

Respectfully submitted,

Katten Muchin Rosenman LLP

Date: February 7, 2020

/ Jitendra Malik /
Jitendra Malik, Ph.D. (Reg. No. 55823)
Lead Counsel for Petitioner

Furthermore, activities that occur after filing of a petition have no bearing on Section 314(a). *Id.*; *Apotex Inc. v. UCB Biopharma SPRL*, IPR2019-00400, Paper 17 at 34 (P.T.A.B. July 15, 2019).

CERTIFICATION OF WORD COUNT

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that the argument section of this Petition (Sections I-III and V-XIII) has a total of 13,690 words, according to the word count tool in Microsoft Word™.

CERTIFICATION OF SERVICE ON PATENT OWNER

Pursuant to 37 C.F.R. §§ 42.6(e), 42.8(b)(4), and 42.105, the undersigned certifies that on February 7, 2020, a complete copy of the foregoing Petition for *Inter Partes* Review of U.S. Patent No. 9,439,906, Power of Attorney, Exhibit List, and all supporting exhibits were served via Express Mail to the Patent Owner by serving the correspondence address of record for the '906 patent:

Joseph F. Shirtz
Johnson & Johnson
One Johnson & Johnson Plaza
New Brunswick, NJ 08933-7003

Courtesy copies of the foregoing Petition, Power of Attorney, Exhibit List, and all supporting exhibits were also served via Express Mail to the following:

Barbara L Mullin
Patterson Belknap Webb & Tyler
1133 Avenue of the Americas
New York, NY 10036

Keith J. Miller
Robinson Miller LLC
Ironside Newark
110 Edison Place
Suite 302
Newark, NJ 07102

Respectfully submitted,

Katten Muchin Rosenman LLP

By: / Jitendra Malik /
Jitendra Malik, Ph.D.
Reg. No. 55,823