UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

Alkermes Pharma Ireland Ltd.
and Alkermes, Inc.
Petitioners,

v.

Otsuka Pharmaceutical Co., Ltd.
Patent Owner

Patent No. 9,125,939 B2
Issued: September 8, 2015
Filed: August 2, 2006

Inventors: Tetsuro Kikuchi, Taro Iwamoto, Tsuyoshi Hirose

Title: CARBOSTYRIL DERIVATIVES AND MOOD STABILIZERS FOR TREATING MOOD DISORDERS

Inter Partes Review No. IPR2017-00287

PETITION FOR INTER PARTES REVIEW OF U.S. PATENT NO. 9,125,939

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I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42 *et seq.*, Alkermes Pharma Ireland Limited and Alkermes, Inc. (collectively, "Petitioners") petition for *Inter Partes* Review ("IPR") of claims 2, 6, 7, and 9 of U.S. Patent No. 9,125,939 to Kikuchi *et al.*, titled "Carbostyril Derivatives and Mood Stabilizers for Treating Mood Disorders" ("the '939 patent," Ex. 1001), which is assigned to Otsuka Pharmaceutical Company, Ltd. ("Patent Owner").

II. PRELIMINARY STATEMENT

Claims 2, 6, 7, and 9 of the '939 patent are drawn to methods of treating bipolar disorder using a combination of lithium and aripiprazole. As demonstrated herein, the prior art is replete with references teaching that bipolar disorder could be effectively treated with a combination of lithium and atypical antipsychotics, including aripiprazole, particularly in patients who were partially nonresponsive to lithium monotherapy. Accordingly, the claimed methods were obvious.

In May 2003 (the earliest filing date for an application to which the '939 patent claims priority), lithium was one of most commonly used drugs for the treatment of bipolar disorder. It was also well known prior to May 2003 that patients with severe manic symptoms or patients who did not adequately respond to lithium benefitted from the addition of an antipsychotic in combination with lithium.

Aripiprazole was approved by the FDA in 2002, making it the latest FDA-approved drug belonging to the family of atypical antipsychotics as of May 2003. Studies with aripiprazole showed that it was effective in treating patients with bipolar disorder and had an improved side effect profile as compared to other antipsychotics such as olanzapine. In particular, aripiprazole did not cause weight gain in psychotic patients, which was a characteristic side effect of other atypical antipsychotics, such as olanzapine.

A person ordinarily skilled in the art would have been motivated to use a combination of aripiprazole with a mood stabilizer, *e.g.*, lithium, because it was well known in the art that combinations of antipsychotics, also known as neuroleptics, together with mood stabilizers are more effective than monotherapy. It was also well known that atypical antipsychotics, compared to typical antipsychotics and other neuroleptics, alone or in combination with mood stabilizers, have side effect profiles that are more tolerable to many patients. Based on this understanding, the person of ordinary skill in the art in May 2003 would have readily selected aripiprazole in a combination with lithium to treat bipolar disorder, and would have reasonably expected that such a therapy would treat bipolar disorder in patients partially non-responsive to lithium or valproate monotherapy. Therefore, the evidence produced herein demonstrates that claims 2, 6, 7, and 9 were obvious.

The obviousness of these claims is supported by the attached Declaration of Allen Frances, M.D. (Ex. 1002). Dr. Frances, a psychiatrist with more than 50 years practicing in the field, provides his opinion that combining the newest atypical antipsychotic, aripiprazole, with lithium to treat bipolar patients who did not respond well to lithium monotherapy would have been standard practice in May 2003. Indeed, Dr. Frances discusses the breadth of knowledge regarding combination therapy for patients with bipolar disorder taught in the prior art. Dr. Frances further discusses, *inter alia*, clinical results in patients diagnosed with bipolar disorder with lithium alone, aripiprazole alone, and lithium in combination with atypical antipsychotics such as aripiprazole. Additionally, Dr. Frances discusses clinical results demonstrating that aripiprazole was not only known in May 2003 to be safe, effective, and well-tolerated in treating bipolar disorder patients, but that it could be safely administered in combination with lithium.

Any alleged secondary considerations cannot overcome this overwhelming case of obviousness. Patent Owner, faced with a final rejection of *prima facie* obviousness during prosecution, argued that there was evidence of unexpected "synergy" and supported this assertion with a declaration from inventor Hirose. *See e.g.*, Ex. 1076 at 1160-64. But, contrary to Patent Owner's arguments, the evidence submitted fails to establish that the combination of aripiprazole and lithium produces an unexpected synergy. The data and conclusions drawn in the

Hirose Declaration were based on a mouse model for mania in bipolar disorder (not clinical data, and in spite of the fact that the closest prior art presented clinical data), and, when statistically analyzed, do not show synergy or even superiority when compared to the controls.

In the attached Declaration of Jessie Au, Pharm. D., Ph.D. (Ex. 1004), Dr. Au, who has worked for more than 30 years developing statistically sound methods to analyze drug-drug interactivity and developing drug combinations that produce additive or synergistic antitumor activity, provides her opinions that the results presented in the Hirose Declaration do not show any unexpected results or synergy.

Thus, Petitioners will demonstrate that the challenged claims 2, 6, 7, and 9 of the ’939 patent are invalid as obvious.

III. MANDATORY NOTICES

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

Alkermes Pharma Ireland Limited and Alkermes, Inc. are the real parties-in-interest for the Petitioners. Alkermes plc, the parent company of Alkermes Pharma Ireland Limited and Alkermes, Inc., is also identified as a real party-in-interest out of an abundance of caution.

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

Petitioners are not aware of any reexamination or pending prosecution concerning the ’939 patent. Petitioners are not party to any prior or pending litigation regarding infringement or invalidity of the ’939 patent. Petitioners

identified the following prior litigation regarding infringement or invalidity of the '939 patent: *Otsuka Pharmaceutical Co., LTD. v. Stason Industrial Corp., et al.*, No. 1:16-cv-00557-JBS-KMW (D.N.J.). This case was voluntarily dismissed without prejudice by Otsuka Pharmaceutical Co., LTD.

C. Lead and Back-up Counsel Under 37 C.F.R. § 42.8(b)(3)

Pursuant to 37 C.F.R. §§ 42.8(b)(3) and 42.10(a), Petitioners provide the following designation of counsel.

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

Please direct all correspondence to the lead counsel and back-up counsel at the contact information provided above. Petitioners consent to service by

electronic mail at tkavanaugh@goodwinlaw.com, celmore@elmorepatents.com, and nmitrokostas@goodwinlaw.com.

IV. PAYMENT OF FEES

The Patent Trial and Appeal Board is hereby authorized to charge all fees due in connection with this matter to Attorney Deposit Account 506989.

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

Petitioners hereby certify that the '939 patent is available for IPR and that Petitioners are not barred or estopped from requesting IPR on the grounds identified herein.

VI. THE '939 PATENT

The '939 patent issued on September 8, 2015, from Application No. 10/556,600 ("the '600 application"), which was filed on May 19, 2004. The '600 application claims priority to U.S. Provisional Application No. 60/473,378, filed on May 23, 2003. Therefore, any printed publication by others dated before May 23, 2003 qualifies as prior art under 35 U.S.C. § 102(a), and any printed publication dated before May 23, 2002 qualifies as prior art under 35 U.S.C. § 102(b).

A. Challenged Claims of the '939 Patent

The '939 patent has 10 claims, of which claims 1 and 2 are independent. This Petition challenges claim 2 and claims 6, 7, and 9, each of which is dependent on claim 2. Claim 2 is reproduced below:

2. A method of treating bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy comprising:

administering separately a first amount of aripiprazole, and a second amount of lithium, wherein the amount of lithium is about 0.01 to 500 parts by weight and the amount of aripiprazole is about 1 part by weight,

wherein the bipolar disorder is chosen from bipolar disorder I, polar disorder II, bipolar disorder with or without psychotic features, mania, acute mania, bipolar depression, and mixed episodes.

Claim 6 further requires that the bipolar disorder is bipolar disorder II. Claim 7 further requires that the bipolar disorder is mania with bipolar disorder I. Claim 9 further requires that the bipolar disorder is mixed episode associated with bipolar disorder I.

B. Prosecution History of the '939 Patent

During prosecution of the '939 patent, claims substantially corresponding to claims 2, 6, 7, and 9 were repeatedly rejected as obvious over Kowatch et al. (CNS Spectrum, April 2003, Vol. 8, No. 4, pp. 273-280)("Kowatch," Ex. 1010). *See e.g.*, Ex. 1076 at 944-46, 1030-31, 1085-87, 1128, 1180-81, 1227-29. According to the examiner, although Kowatch did not explicitly teach a composition comprising lithium and aripiprazole, or a method of treating bipolar disorder employing aripiprazole and lithium, it rendered the claims obvious. The examiner

stated that it would have been obvious to a person of ordinary skill in the art at the time of invention to combine the atypical antipsychotic agent aripiprazole with lithium because Kowatch teaches that the combination of olanzapine, an atypical antipsychotic like aripiprazole, with lithium gives better overall response in the method of treating bipolar disorder. *Id*.

Patent Owner initially argued that the claims were not obvious over Kowatch based solely on the prior art. *Id*. at 985-88, 1061-64, 1114-16. According to Patent Owner, Kowatch provided no specific teaching of a combination of lithium and aripiprazole or a specific example of such a combination, nor a teaching, motivation, or suggestion of a patient population which is partially nonresponsive to lithium or valproate monotherapy as recited in the present claims. *See id.* After several cycles of examiner rejections and responsive arguments by Patent Owner, Patent Owner submitted an inventor declaration ("the Hirose Declaration"; *id*. at 1160-64) to support the argument that the combination of lithium and aripiprazole resulted in unexpected, "significantly enhanced" results or synergy.

The Hirose Declaration contained data from a mouse model comparing controls, aripiprazole alone, olanzapine alone, olanzapine in combination with lithium, and aripiprazole in combination with lithium. *See id*. at 1162. The Hirose Declaration further asserted that the animal data demonstrated that aripiprazole in

combination with lithium suppressed locomotion function in mice to a higher degree than any of the other tested substances, and purported to use the data to show a synergistic effect by the claimed combination therapy. *Id*. at 1163. In a series of Office Actions following the Patent Owner's initial submission of the Hirose Declaration, the examiner raised several issues regarding the reliability of the data presented in the Hirose Declaration, and disagreed with the conclusion of synergy. *Id*. at 1184-85, 1229-30. Nonetheless, following successive office action and response cycles, and an interview with the examiner, the Patent Owner presented the same data in a different way (*id*. at 1264), and the examiner finally allowed the claims on the basis of that data. *See* Ex. 1004 at ¶¶ 47-63.

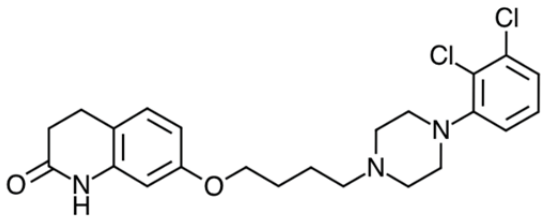
C. Claim Construction

Because the '939 patent has not yet expired and will not expire during the pendency of this proceeding, the challenged claims should be given their "broadest reasonable construction in light of the specification of the patent in which it appears." 42 C.F.R. §42.100(b). *See also Cuozzo Speed Technologies, LLC v. Lee*, 579 U. S. ____ (2016). Applying the broadest reasonable interpretation ("BRI") to the claims of the '939 patent, as Dr. Frances explains, one of ordinary skill in the art would understand the following claim terms to have the following meanings:

- "bipolar disorder," "wherein the bipolar disorder is chosen from bipolar disorder I, polar [*sic*] disorder II, bipolar disorder with or without psychotic features, mania, acute mania, bipolar depression, and mixed episodes" appearing in claims 2, 6, 7, and 9, generally refers to a "mood disorder characterized by the presence (or history) of manic episodes, mixed episodes, or hypomanic episodes, usually accompanied by the presence (or history) of major depressive episodes" and includes at least the following: Bipolar I Disorder, Bipolar II Disorder, Bipolar Disorder with or without psychotic features, mania, acute mania, Bipolar Disorder with Depressive Episodes, and Bipolar Disorder with Mixed Episodes. Ex. 1002 at ¶ 59.
- "a patient partially nonresponsive to lithium or valproic acid, or divalproex sodium or a salt thereof monotherapy," appearing in claim 2, means "a patient that has shown an inadequate response to lithium, valproic acid, or divalproex sodium or salt thereof, as a monotherapy." Ex. 1002 at ¶ 59.
- "administering," appearing in claim 2, means "the oral, intravenous, intradermal, subcutaneous, intraperitoneal or intrarectal administration of a pharmaceutical preparation," as stated in the specification. Ex. 1001, col. 15, lines 15-27. In the case of separate administration of aripiprazole and a mood stabilizer, "each one of aripiprazole and a mood stabilizer are contained individually in a pharmaceutical preparation respectively, and

each one of these preparations may be administered at the same or different times." Ex. 1001, col. 15, lines 28-37; Ex. 1002 at ¶ 59.

- "aripiprazole," appearing in claim 2, means a compound having the following chemical name and structure:



7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]-butyloxy}-3,4-dihydro-2(1H)-quinolinone. Ex. 1022; Ex. 1002 at ¶ 59.

- "lithium," appearing in claim 2, means lithium compounds, also known as lithium salts, primarily used as a psychiatric medication. Ex. 1002 at ¶ 59.
- "parts by weight" appearing in claim 2 means "the weight ratio of the first ingredient to the second ingredient," as stated in the specification. Ex. 1001 at col. 14, ll. 12-13; Ex. 1002 at ¶ 59.

D. Level of Ordinary Skill in the Art

As explained by Dr. Frances in the accompanying declaration, a person of ordinary skill in the art to which the '939 patent pertains would be an M.D. psychiatrist with significant experience in treating patients with psychiatric disorders, including familiarity and personal experience in treating bipolar disorder and mania. Ex. 1002 at ¶ 57.

VII. SCOPE AND CONTENT OF THE PRIOR ART

A. Bipolar Disorder

Bipolar disorder, formerly known as manic depression, is a type of mood disorder where the patient has cycles of both elevated and depressed moods. *See* Ex. 1002 at ¶ 40. In periods of elevated mood, such as mania or hypomania, the patient has an abnormally elevated energy level and can exhibit aggression, agitation, or psychosis. *Id*. at Appendix E, p. 364, 368. The difference between mania and hypomania is only the degree of the manic symptoms. *Id.* at ¶ 42. In periods of depressed mood, the patient will feel sad or empty, or have a loss of interest or pleasure in activities. *Id.* at Appendix E, p. 356.

Bipolar disorder is generally understood to be a term covering at least two subtypes of patients. Patients who have one or more manic or mixed episodes, with or without major depressive episodes are classified as having Bipolar I Disorder. Patients who have recurring, intermittent hypomanic episodes with major depressive episodes are classified as having Bipolar II Disorder. *Id.* at ¶ 41.

B. Treatment of Bipolar Disorder

As of at least May 2002, the combination of antipsychotic medication and mood stabilizer medication had already been the well-established and widely accepted standard of care in the treatment of bipolar disorder for many decades. *Id*. at ¶ 11. As new antipsychotics came on the market over the years, each one was used in the treatment of bipolar disorder in a way equivalent to preceding

antipsychotic drugs. *Id*; *see also*, '939 patent at col. 1, l. 63 – col. 2 l. 2, citing ARCH. GEN. PSYCHIATRY, 2002 January 59:1:62-29 and J. AM. ACAD. CHILD ADOLESC PSYCHIATRY 2002 October; 41(10) 1216-23 ("New therapeutic trials involve proposed combined therapies using an atypical antipsychotic drug, such as olanzepine [sic] or quetiapine, which are agents for treating schizophrenia (anti-psychotic drug), together with mood stabilizing drug such as valproate, lithium or divalproex."). Thus, by May 2003, there was already a very long history in psychiatric medicine of using the combination of a mood stabilizer, such as lithium, with an antipsychotic, such as aripiprazole, to treat bipolar disorder. *Id.*

1. Antipsychotics

The drug chlorpromazine was the first antipsychotic used for the treatment of bipolar disorder, and until lithium, a mood stabilizer, proved to be effective, antipsychotics were the drug of choice among physicians. Ex. 1002 at ¶ 12. By the 1990s, several members of a new class of antipsychotics, termed atypical antipsychotics, were on the market. Ex. 1002 at ¶ 14. While none of the atypical antipsychotics had been proven to have superior efficacy in comparison to each other (or to any first generation antipsychotic), a person of ordinary skill in the art at the time understood that the atypical antipsychotics typically had better side effect profiles than the older agents. Ex. 1002 at ¶ 15.

Antipsychotics were frequently used with patients with bipolar disorder, particularly when the patient had mania or mixed episodes because these patients are extremely impulsive, energetic, and agitated. Ex. 1002 at ¶ 16. Even after the introduction of mood stabilizers, such as lithium, antipsychotics were still highly prescribed, such that any clinician in 2002 would have understood that any new antipsychotic would almost undeniably be useful in the treatment of bipolar disorder. Ex. 1002 at ¶ 11, 17. Indeed, Dr. Frances explains that the use of antipsychotics for the treatment of bipolar disorder is one of the oldest and best-established indications in all of psychiatric medicine, as documented in textbooks, review articles, practice guidelines, surveys and individual papers. *Id.* at ¶ 18.

In 2002, one of the newest atypical antipsychotics on the market was a drug known as aripiprazole. Ex. 1002 at ¶ 14. Aripiprazole was reported to be efficacious in treating bipolar disorder with fewer side effects than other atypical antipsychotics. *Id*. at ¶ 34-35. Indeed, as Dr. Frances explains, at least the following publications reported the benefits of using aripiprazole for the treatment of mood disorders prior to May 2003. *Id*.

a. **Keck (Ex. 1007)**

Aripiprazole versus placebo in acute mania, ("Keck," Ex. 1007) described a randomized placebo-controlled efficacy study comparing aripiprazole to placebo in patients with acute bipolar mania. Ex. 1002 at ¶ 34. The study evaluated the

severity of manic episodes in patients using the Young Mania Rating Scale (Y-MRS), which is a multiple choice diagnostic questionnaire. *Id*. As Dr. Frances explains, Keck reported that aripiprazole improved the response rate in patients with bipolar disorder and provided statistically significant improvements in the Y-MRS total score. *Id*. Keck concluded that aripiprazole was effective and well tolerated in the treatment of acute mania in patients with bipolar disorder. *Id*. Keck also demonstrated a favorable side effect profile, showing that there was no significant changes in patient weights when administered aripiprazole as opposed to placebo. *Id*. Keck is a printed publication that was available to the public at least as early as May 18, 2002, and was presented at the Annual Meeting of the American Psychiatric Association 2002.[1] Therefore, Keck is prior art to the '939 patent under 35 U.S.C. § 102(b).

b. **BMS/Otsuka Press Release (Ex. 1028)**

Data Demonstrate Aripiprazole Significantly Improved Symptoms of Acute Mania in Patients With Bipolar Disorder; New Data Presented Today at American

[1] As Dr. Frances explains, abstracts from Annual Meetings of the American Psychiatric Association were made available in print form to psychiatrists and to the public on or before the first day of the conference. Abstracts from the 2002 Annual Meeting would have been provided to the interested psychiatric public starting on May 18, 2002, if not earlier. Ex. 1002 at ¶ 34.

Psychiatric Association Annual Meeting, ("BMS/Otsuka Press Release," Ex. 1028) is a press release from Bristol-Myers Squibb ("BMS") and Otsuka Pharmaceutical Co., Ltd. ("Otsuka"). The BMS/Otsuka Press Release cited Keck and disclosed that aripiprazole showed significant improvement in symptoms of acute mania. Ex. 1002 at ¶ 35. Keck also showed that aripiprazole had a rapid onset of action, significantly reduced symptoms of acute mania by day four of treatment, and was well tolerated, with discontinuations of therapy due to adverse events similar to placebo. *Id*. Additionally, patients who received aripiprazole did not show significant weight change when compared with placebo patients. *Id*. The BMS/Otsuka Press Release reported that BMS and Otsuka were currently conducting clinical trials with aripiprazole in psychotic illnesses including bipolar disorder. *Id*. BMS/Otsuka Press Release is a printed publication that was available to the public at least as early as May 22, 2002. Therefore, the BMS/Otsuka Press Release is prior art to the '939 patent under 35 U.S.C. § 102(b).

2. Mood Stabilizers

Dr. Frances explains that mood stabilizers have also been important in the treatment of bipolar disorder. Ex. 1002 at ¶ 19. Mood stabilizers typically work to reduce the symptoms of the manic phase of bipolar disorder, but they also can be helpful in reducing relapse and reducing depression as well. Ex. 1002 at ¶ 20.

The mood stabilizer lithium was approved for clinical use in the U.S. in 1970, and currently remains one of the most effective treatments for patients with bipolar disorder. *Id*. Despite being one of the most effective treatments, lithium seems to be under-prescribed due to difficulty in titrating its dose and risks of side effects and complications. *Id*. Additionally, none of the mood stabilizers work quickly enough or consistently enough to control an episode of acute mania or mixed states in bipolar disorder as a monotherapy. *Id*. at 22.

3. Combination Therapy

Since as early as the 1970s, combination therapy in the form of a mood stabilizer and an antipsychotic has been the standard treatment for patients with bipolar disorder. Ex. 1002 at ¶ 23; Appendices A-E. While the use of different antipsychotic and mood stabilizing agents has changed with the popularity of specific drugs over time, the combination of these two categories is, and was in 2002, one of the best-known, well-established aspects of all psychiatric practice. *Id*. at ¶¶ 23-26, Appendix A (textbooks), Appendix B (practice guidelines), Appendix C (surveys), Appendix D (research papers).

According to the literature, combination therapy was particularly important when a patient was not responsive to a mood stabilizer alone. Ex. 1002 at ¶ 25. The following guidelines and publications are relied upon by Dr. Frances to

establish the prevalence of combination therapy using a mood stabilizer and an antipsychotic.

a. **APA Practice Guidelines 2002 (Ex. 1009)**

By 2002, guidelines for the treatment of bipolar disorder recommended the combination of lithium and an antipsychotic as a first line treatment. Ex. 1002 at ¶ 28. *Practice guideline for the treatment of patients with bipolar disorder (revision)* ("APA Practice Guidelines 2002," Ex. 1009), is a guide for psychiatrists on the treatment of bipolar disorder, including treatment of manic or mixed episodes. APA Practice Guidelines 2002 reflects the community standard of care for bipolar patients as of May 2002. Ex. 1002 at ¶ 28. APA Practice Guidelines 2002 advised that "the first-line pharmacological treatment for more severe manic or mixed episodes is the initiation of either lithium plus an antipsychotic or valproate plus an antipsychotic," and that "the *combination* of an antipsychotic with either lithium or valproate may be more effective than any of these agents alone." Ex. 1009 at 4, 9; Ex. 1002 at ¶ 28. APA Practice Guidelines 2002 further states, among other things, that "[c]ontrolled trials of lithium plus an antipsychotic and of valproate plus an antipsychotic suggest greater efficacy or more rapid onset of action with these combinations than with any of these agents alone." Ex. 1009 at 25; Ex. 1002 at ¶ 28. APA Practice Guidelines 2002 also advised that lithium monotherapy may be sufficient for less ill patients, but when such monotherapy

fails, it is recommended to add an antipsychotic or change from one antipsychotic to another. Ex. 1009 at 9; Ex. 1002 at ¶ 28. APA Practice Guidelines 2002 also reported that atypical antipsychotics are preferred over typical antipsychotics because atypical antipsychotics have a more benign side effect profile. Ex. 1009 at 4, 9, 10; Ex. 1002 at ¶ 28. APA Practice Guidelines 2002 is a printed publication that was available to the public as of April, 2002. Therefore, APA Practice Guidelines 2002 is prior art to the '939 patent under 35 U.S.C. § 102(b). *See also* Ex. 1002 at ¶ 31, citing *Management of Bipolar Disorder*, ("American Family Physician," Ex. 1027) (instructing physicians to treat bipolar disorder with antipsychotics as adjunctive treatment for mania with psychosis or psychotic depression).

b. **Expert Consensus (Ex. 1026)**

The Expert Consensus Guideline Series Medication Treatment of Bipolar Disorder 2000, A Postgraduate Medicine Special Report ("Expert Consensus" Ex. 1026) is another set of guidelines for the treatment of bipolar disorder. Ex. 1002 at ¶ 29. Expert Consensus taught that antipsychotics were recommended to treat mania or depression with psychosis, and as potential adjuncts in non-psychotic episodes. Ex. 1026 at 5; Ex. 1002 at ¶ 29. According to Expert Consensus, atypical antipsychotics, such as FDA-approved olanzapine and risperidone, were generally preferred over older antipsychotics, especially for long-term therapy. Ex.

1026 at 5, 10; Ex. 1002 at ¶ 29. Moreover, if a combination of mood stabilizer and antipsychotic was not providing the desired therapeutic result, Expert Consensus recommended substituting another antipsychotic before substituting the mood stabilizer. Ex. 1026 at 19; Ex. 1002 at ¶ 29. As Dr. Frances explains, Expert Consensus reported that the combination of a mood stabilizer with an antipsychotic would be considered either a first or second line treatment for euphoric mania. Ex. 1026 at 7; Ex. 1002 at ¶ 29. Moreover, Expert Consensus disclosed that the combination of a mood stabilizer with an antipsychotic was either the treatment of choice or an alternative treatment for mania with psychosis, dysphoric mania or true mixed mania, and euphoric mania:

Bold italics = treatment of choice

Clinical presentation	**Preferred initial strategies**	**Alternate strategies**
Mania with psychosis	***Mood stabilizer + antipsychotic***	Mood stabilizer + antipsychotic + benzodiazepine
Dysphoric mania or true mixed mania*	***Mood stabilizer alone***	Mood stabilizer + benzodiazepine *or* Mood stabilizer + antipsychotic
Euphoric mania†	***Mood stabilizer alone*** *or* Mood stabilizer + benzodiazepine	Mood stabilizer + antipsychotic
Hypomania	***Mood stabilizer alone***	Mood stabilizer + benzodiazepine

**Dysphoric mania*: patient has a manic episode and also meets 2 to 4 diagnostic criteria for depression, but is below threshold for a current diagnosis of a major depressive episode. *True mixed mania*: patient meets full criteria for both a manic episode and a major depressive episode.

†*Euphoric mania*: patient has a manic episode without features of depression.

Ex. 1026 at 16; Ex. 1002 at ¶ 29. Expert Consensus is a printed publication that was available to the public as of April 2000. Therefore, the Expert Consensus is prior art to the '939 patent under 35 U.S.C. § 102(b).

c. **Tohen (Ex. 1006)**

Efficacy of olanzapine in combination with valproate or lithium in the treatment of mania in patients partially nonresponsive to valproate or lithium monotherapy ("Tohen," Ex. 1006), described a 6-week double blind, randomized, placebo-controlled clinical trial to determine the efficacy of the combination of olanzapine with valproate or lithium when compared with valproate or lithium monotherapy, in the treatment of bipolar disorder. Ex. 1002 at ¶ 36. Tohen reported that olanzapine co-therapy significantly improved patients' Y-MRS total scores and clinical response rates compared with monotherapy. Ex. 1006 at 62; Ex. 1002 at ¶ 36. Dr. Frances notes that Tohen concluded that the addition of olanzapine provided superior efficacy in the treatment of manic and mixed bipolar episodes compared with the use of valproate or lithium alone. Ex. 1006 at 62; Ex. 1002 at ¶ 36. However, Tohen further taught that patients receiving olanzapine had weight gain, a known side effect of olanzapine, and that this weight gain was similar to that reported for olanzapine monotherapy. Ex. 1006 at 68 (right col. ll. 21-22); Ex. 1002 at ¶ 73. Tohen is a printed publication that was available to the public as of January 2002. Therefore, Tohen is prior art to the '939 patent under 35 U.S.C. § 102(b).

d. **Citrome (Ex. 1008)**

Additionally, the prior art specifically described use of aripiprazole with lithium in institutionalized schizophrenic and schizoaffective patients. *Pharmacokinetics and safety of aripiprazole and concomitant mood stabilizers*, ("Citrome," Ex. 1008) described a pharmacokinetic and safety study done on the combination of aripiprazole and lithium or divalproex sodium in chronically institutionalized schizophrenic and schizoaffective patients who required treatment with lithium. Ex. 1002 at ¶ 37. Citrome co-administered aripiprazole with lithium or valproex sodium through concomitant therapy. Ex. 1008; Ex. 1002 at ¶ 37. Citrome reported that aripiprazole can be administered safely with therapeutic doses of lithium or divalproex sodium in patients with schizophrenia or schizoaffective disorder. Ex. 1008; Ex. 1002 at ¶ 37. Citrome is a printed publication that was available to the public at least as early as May 18, 2002, and presented at the Annual Meeting of the American Psychiatric Association 2002.[2] Therefore, Citrome is prior art to the '939 patent under 35 U.S.C. § 102(b).

[2] As explained in footnote 1, above, abstracts from the 2002 Annual Meeting would have been provided to the interested psychiatric public starting on May 18, 2002, if not earlier. Ex. 1002 at ¶ 34.

VIII. GROUNDS FOR PETITION

A petition for *inter partes* review must demonstrate a reasonable likelihood that the petitioner would prevail with respect to at least one of the claims challenged in the petition. 35 U.S.C. § 314(a). This Petition meets this threshold. As explained in detail below, there is a reasonable likelihood that Petitioners will prevail with respect to at least one of the challenged claims and grounds.

Claims 2, 6, 7, and 9 of the '939 patent are unpatentable based on the following grounds:

Ground 1: Claims 2, 6, 7, and 9 are Obvious Based on APA Practice Guidelines 2002, in view of Keck or BMS/Otsuka Press Release

Ground 2: Claims 2, 6, 7, and 9 are Obvious Based on Tohen in view of Keck or BMS/Otsuka Press Release

Ground 3: Claims 2, 6, 7, and 9 are Obvious Based on Expert Consensus in view of Keck or BMS/Otsuka Press Release

Ground 4: Claims 2, 6, 7, and 9 are Obvious Based on APA Practice Guidelines 2002, Keck or the BMS/Otsuka Press Release, and Tohen

Ground 5: Claims 2, 6, 7, and 9 are Obvious Based on Citrome in view of APA Practice Guidelines 2002

Ground 6: Claims 2, 6, 7, and 9 are Obvious Based on Citrome in view of Tohen and/or Keck or BMS/Otsuka Press Release

Petitioners present these grounds as independent and not redundant grounds for cancelling claims 2, 6, 7, and 9 of the '939 patent as obvious pursuant to 35 U.S.C.§ 103.

A. DETAILED EXPLANATION UNDER 37 C.F.R. § 42.104(b)

1. Ground 1: Claims 2, 6, 7, and 9 are Obvious Based on APA Practice Guidelines 2002 (Ex. 1009), in view of Keck (Ex. 1007) or BMS/Otsuka Press Release (Ex. 1028)

A patent claim is invalid for obviousness "if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." 35 U.S.C. § 103. The objective standard for determining obviousness under 35 U.S.C. §103, as set forth in *Graham v. John Deere, Co.*, 383 U.S. 1 (1966), requires a factual determination to ascertain: (1) the scope and content of the prior art; (2) the level of ordinary skill in the art; (3) the differences between the claimed subject matter and the prior art; and (4) objective indicia or "secondary considerations" of nonobviousness. Based on these factual inquiries, it must then be determined, as a matter of law, whether or not the claimed subject matter as a whole would have

been obvious to one of ordinary skill in the art at the time the alleged invention was made. *Id*. at 17.

Here, it would have been obvious for a person of ordinary skill in the art to combine the APA Practice Guidelines 2002 with Keck or BMS/Otsuka Press Release to arrive at the challenged claims. Ex. 1002 at ¶¶ 60-70. APA Practice Guidelines 2002 taught that lithium, valproate, and antipsychotic medications had shown efficacy in the treatment of patients with acute mania and that the *combination* of an antipsychotic with mood stabilizers, such as lithium or valproate, was already viewed as more effective than either agent alone. Ex. 1009 at 9, left col. ll. 26-37; Ex. 1002 at ¶ 61. Specifically, APA Practice Guidelines 2002 taught that bipolar patients with manic or mixed episodes were being treated with lithium or valproate plus an antipsychotic, and preferably an atypical antipsychotic because of its more benign side effect profile. Ex. 1009 at 9, right col. ll. 4-7; Ex. 1002 at ¶ 61. Therefore, prior to May 2003, mood disorders were being commonly treated with polypharmacotherapy, and the combination of antipsychotics with mood stabilizers such as lithium was viewed as providing improved efficacy over either agent alone, especially if the patient did not fully respond to a mood stabilizer monotherapy. *See, e.g.*, Ex. 1002 at ¶ 60; Ex. 1009 at 4, 9; *see generally* Ex. 1002, Appendices A-D. Thus, a person of ordinary skill in the art wanting to treat a patient with bipolar disorder who is partially non-

responsive to lithium/divalproex monotherapy therapy would have looked to use a combination therapy and, specifically, to treat the patient with a combination of lithium and an atypical antipsychotic. Ex. 1002 at ¶ 62.

Keck (Ex. 1007) taught the use of aripiprazole to treat bipolar disorder. Specifically, Keck taught that aripiprazole was effective and well-tolerated in the treatment of acute mania in patients with bipolar disorder. Ex. 1002 at ¶ 63; Ex. 1007. Keck also taught that there was no significant changes in weight for patients taking aripiprazole compared to placebo.[3] Ex. 1002 at ¶ 63; Ex. 1007. BMS/Otsuka Press Release, citing Keck, also taught that aripiprazole was effective and well-tolerated in the treatment of acute mania in patients with bipolar disorder and similarly touted the beneficial side effect profile of aripiprazole of not causing weight gain. Ex. 1002 at ¶ 63; Ex. 1028 at 1.

[3] During prosecution of the '939 patent, Patent Owner argued that "olanzapine and quetiapine has a side effect of increasing the risk of diabetes by body weight increase, so that their clinical use is strictly limited." Ex. 1076 at 987. Thus, as recognized by the Patent Owner's own admission, the ordinarily-skilled artisan would be motivated to replace olanzapine with a further atypical antipsychotic such as aripiprazole, which was known *not* to cause weight gain. *See e.g.*, Ex. 1007; Ex. 1028 at 1.

An ordinarily-skilled artisan would have understood that a combination therapy using atypical antipsychotics in combination with mood stabilizers such as lithium was generally more effective than monotherapy. Ex. 1009; Ex. 1002 at ¶ 64. Thus, an ordinarily-skilled artisan wanting to treat a patient partially non-responsive to lithium or divalproex sodium monotherapy would have been motivated to use a combination therapy of lithium with aripiprazole. Ex. 1002 at ¶ 64. An ordinarily-skilled artisan would have further understood from Keck that aripiprazole, which was new to the market, was safe and effective in treating bipolar disorder and, in fact, showed a beneficial side effect profile that made it more desirable than other atypical antipsychotics available. Ex. 1002 at ¶ 63. Thus, the person of ordinary skill in the art would have had a reasonable expectation that the combination of aripiprazole with lithium would be effective to treat the patient suffering from bipolar disorder and would have been motivated to do so.[4] Ex. 1002 at ¶ 64.

[4] Petitioners note that the '939 patent does not provide any data demonstrating the efficacy of combination of aripiprazole and lithium for treating bipolar disorder in a patient partially nonresponsive to lithium or valproic acid, divalproex sodium or a salt thereof monotherapy. Rather, the '939 patent provides ***prophetic*** Examples 5 and 6 that state "[T]he methods used are generally as described in Tohen et al., (Arch. Gen. Psychiatry, 2002 January; 59(1):62-9)." *See* Ex. 1001 at col. 26, l. 53-

Concerning the claimed range for the ratio of aripiprazole to lithium (*i.e.*, a ratio of about 1 part by weight aripiprazole to about 0.01 to 500 parts by weight lithium), a clinician prescribing aripiprazole and lithium in combination would have tailored the amounts of each drug to suit the needs of the individual patient, rather than relying on a preset ratio. Ex. 1002 at ¶ 65. Moreover, the range of ratios claimed in claim 2 is so broad that it encompasses every reasonable dosage of both lithium and aripiprazole. *Id*. For example, the recommended daily dosage for aripiprazole is 15 mg per day. Ex. 1002 at ¶ 65; Ex. 1055 (Abilify 2002 Labeling) at 23. Based on a 15 mg dosage of aripiprazole, the claimed range of ratios encompasses a daily dosage of 0.15 mg to 7,500 mg for lithium. Ex. 1002 at ¶ 65. Considering that the recommended daily dosage for lithium is about 900 mg,

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col. 27, l. 56, Examples 5 and 6 citing, and quoting from, Tohen (Ex. 1006). Even though the combination of aripiprazole and lithium was not tested, the Patent Owner had a reasonable expectation that the combination would work based on the teachings of Tohen (Ex. 1006). Likewise, Examples 7 and 8 are also prophetic and rely upon a 2002 journal article, describing a therapy combining quetiapine and divalproex (DVP). *See* Ex. 1001 at col. 27, l. 60-col. 28, l. 67, Examples 7 and 8. In these examples, it is stated that "[i]t is hypothesized that DVP in combination with aripiprazole is more effective than DVP alone for treating mania associated with adolescent bipolar disorder." *See, e.g.*, Ex. 1001 at col. 27, l. 67-col. 28, l. 3.

every reasonable dosage of lithium is plainly covered. *Id.*; Ex. 1009 at 20. Thus, a person of ordinary skill in the art prescribing aripiprazole and lithium to treat a bipolar patient would have utilized those drugs in the claimed ratio.

For the foregoing reasons, claim 2 is obvious over APA Practice Guidelines 2002 and Keck or BMS/Otsuka Press Release.

The dependent claims do not impart any patentably distinguishing elements to claim 2, and instead recite features disclosed in the prior art. Claims 6, 7, and 9 depend from claim 2 and further limit bipolar disorder to bipolar disorder II, mania with bipolar disorder I, and mixed episode associated with bipolar disorder I, respectively. For the reasons set forth above with respect to claim 2, an ordinarily skilled artisan would have looked to use aripiprazole in combination with lithium to treat bipolar disorder II, mania, including mania associated with bipolar disorder I, or bipolar disorder I, including mixed episodes associated with bipolar disorder I, with a reasonable expectation of success in doing so. Ex. 1002 at ¶¶ 67-69. Accordingly, claims 6, 7, and 9 do not add any nonobvious elements over claim 2 and are similarly obvious over APA Practice Guidelines 2002 and Keck or BMS/Otsuka Press Release.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are

invalid as obvious over the APA Practice Guidelines 2002 and Keck or BMS/Otsuka Press Release.

2. Ground 2: Claims 2, 6, 7, and 9 are Obvious Based on Tohen (Ex. 1006) in view of Keck (Ex. 1007) or BMS/Otsuka Press Release (Ex. 1028)

It would also have been obvious to a person of ordinary skill in the art to combine Tohen with Keck and/or BMS/Otsuka Press Release to arrive at the challenged claims. Ex. 1002 at ¶¶ 77-79. Tohen taught that, although lithium and valproate are recommended as first-line treatments for bipolar mania, up to 40% of patients respond poorly to monotherapy with either treatment, and that when monotherapy fails, the guidelines recommend combination therapies. *See e.g.*, Ex. 1006 at 62, left col., ll. 1-10, citing the Expert Consensus (Ex. 1026); Ex. 1002 at ¶¶ 73-74.

Tohen taught that patients, characterized as partially nonresponsive to valproate or lithium monotherapy, included in the study were (i) diagnosed as having bipolar disorder, manic or mixed episode, with or without psychotic features; (ii) required to have had a documented trial of treatment, with a therapeutic blood level of lithium (0.6-1.2 mmol/L) or valproate (50-125 ug/mL), for at least 2 weeks immediately prior to visit 1; and (iii) inadequately responsive to lithium or valproate monotherapy. Ex. 1006 at 63, left col. ll. 1-12; Ex. 1002 at ¶¶ 36, 73. Tohen discloses that patients were randomized to receive either

olanzapine or placebo as an add-on to lithium or valproate. Ex. 1006 at 63, left col., ll. 35-38; Ex. 1002 at ¶ 36. According to Tohen, compared with the use of valproate or lithium alone, the addition of olanzapine provided superior efficacy in the treatment of manic and mixed bipolar episodes. Ex. 1006 at 62, Conclusion; Ex. 1002 at ¶ 36. One of ordinary skill in the art would have therefore understood from Tohen that an atypical antipsychotic in combination with lithium was effective in treating bipolar disorder in patients partially non-responsive to lithium or valproate monotherapy. Tohen further taught that patients receiving olanzapine had weight gain, a known side effect of olanzapine, and that such weight gain was similar to that reported for olanzapine monotherapy. Ex. 1006 at p. 68, right col. ll. 21-22; Ex. 1002 at ¶ 73.

Accordingly, an ordinarily skilled artisan seeking to improve upon lithium or divalproex sodium monotherapy for bipolar disorder would have been motivated to vary the combination therapy taught by Tohen (olanzapine and lithium), and substitute aripiprazole, which Keck or BMS/Otsuka Press Release taught was effective for treating bipolar disorder. Ex. 1002 at ¶ 74; Ex. 1007; Ex. 1028, at 1. One skilled in the art would have been further motivated to replace olanzapine with aripiprazole because aripiprazole was known not to cause weight gain associated with other neuroleptics, such as olanzapine. *See e.g.*, Ex. 1006 at 67; Ex. 1007; Ex. 1028, at 1; Ex. 1002 at ¶ 74. Therefore, an ordinarily skilled artisan would have

had a reasonable expectation of success in the combination therapy of aripiprazole and lithium for patients partially non-responsive to a lithium monotherapy. Ex. 1002 at ¶ 74.

As discussed above in Section VIII.A.1 and incorporated herein, the range of ratios of lithium to aripiprazole set forth in claim 2 is so broad that all dosage amounts that reasonably would be used are encompassed by the claimed range of ratios. Accordingly, claim 2 of the '939 patent is invalid for obviousness, as the combination of all the claimed elements in the method of use would have been obvious to a person of ordinary skill in the art in May 2003. Because, as discussed above, claims 6, 7, and 9 merely specify the type of bipolar disorder being treated, they do not add any nonobvious limitations over claim 2 and are likewise obvious.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are invalid as obvious over Tohen and Keck and/or the BMS Otsuka Press Release.

3. Ground 3: Claims 2, 6, 7, and 9 are Obvious Based on Expert Consensus (Ex. 1026) in view of Keck (Ex. 1007) and/or BMS/Otsuka Press Release (Ex. 1028)

It would also have been obvious to a person of ordinary skill in the art to combine Expert Consensus with Keck and/or BMS/Otsuka Press Release to arrive at the challenged claims. Ex. 1002 at ¶¶ 90-94. As discussed above, there was a long history of treating patients suffering from bipolar disorder using combination

therapies. Ex. 1002 at ¶ 90; *see generally* Ex. 1002, Appendices A-D. Expert Consensus taught that when treating bipolar disorder, antipsychotics were recommended to treat mania or depression with psychosis, and as potential adjuncts in non-psychotic episodes. Ex. 1002 at ¶ 90; Ex. 1026 at 5. In 2002, atypical antipsychotics, such as olanzapine and risperidone, were generally preferred over conventional antipsychotics, especially for long-term therapy. Ex. 1002 at ¶ 90; Ex. 1026 at 5, 10. Moreover, if a combination of mood stabilizer and antipsychotic was not giving the desired result, Expert Consensus recommended substituting another antipsychotic before substituting the mood stabilizer. Ex. 1002 at ¶ 90; Ex. 1026 at 19. Expert Consensus reported that the combination of a mood stabilizer with an antipsychotic would be considered either a first or second line treatment for euphoric mania. Ex. 1002 at ¶ 90; Ex. 1026 at 7.

Keck or BMS/Otsuka Press Release taught that aripiprazole was effective and well tolerated in the treatment of acute mania in patients with bipolar disorder. Aripiprazole was also demonstrated to have a beneficial side effect profile compared to other atypical antipsychotics by not causing weight gain in patients. Ex. 1002 at ¶ 91; Ex. 1007; Ex. 1028, at 1. Accordingly, an ordinarily skilled artisan seeking to improve upon lithium or divalproex sodium monotherapy for bipolar disorder would have been motivated to use aripiprazole, as taught by Keck or BMS/Otsuka Press Release, as part of an adjunctive treatment with a mood

stabilizer, as taught by Expert Consensus, with a reasonable expectation of success in doing so. Ex. 1002 at ¶ 92.

As discussed above in Section VIII.A.1 and incorporated herein, the range of ratios of lithium to aripiprazole set forth in claim 2 is so broad that all dosage amounts that reasonably would have been used are encompassed by the claimed range. Accordingly, claim 2 of the '939 patent is invalid for obviousness, because the combination of all the claimed elements in the method of use would have been obvious to a person of ordinary skill in the art in May 2003. Because claims 6, 7, and 9 merely specify the type of bipolar disorder being treated, they do not add any nonobvious limitations over claim 2 and are likewise obvious.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are invalid as obvious over the Expert Consensus and Keck or BMS/Otsuka Press Release.

4. Ground 4: Claims 2, 6, 7, and 9 are Obvious Based on APA Practice Guidelines 2002 (Ex. 1009), Keck (Ex. 1007) or the BMS/Otsuka Press Release (Ex. 1028), and Tohen (Ex. 1006)

It would also have been obvious to a person of ordinary skill in the art to combine APA Practice Guidelines 2002 with Keck and/or BMS/Otsuka Press Release and Tohen to arrive at the challenged claims. Ex. 1002 at ¶¶ 71-76. As discussed above, APA Practice Guidelines 2002 taught that mood disorders were

being commonly treated with polypharmacotherapy and that the combination of antipsychotics with mood stabilizers such as lithium was already being viewed as potentially more effective than either agent alone. Ex. 1002 at ¶ 71; Ex. 1009 at 4, 9. Specifically, APA Practice Guidelines 2002 taught that bipolar patients with manic or mixed episodes were being treated with lithium or valproate plus an antipsychotic, preferably an atypical antipsychotic, because of more benign side effect profiles. Ex. 1002 at ¶ 71; Ex. 1009 at 4, 9, 10. Keck or BMS/Otsuka Press Release taught that aripiprazole was effective and well tolerated in the treatment of acute mania in patients with bipolar disorder. *Id*.

As discussed above, Tohen taught that up to 40% of patients respond poorly to monotherapy with either treatment. Ex. 1006 at 62. Tohen disclosed that patients characterized as partially nonresponsive to valproate or lithium monotherapy improved with the addition of olanzapine in the treatment of manic and mixed bipolar episodes. *See id.*; *supra*, Section VIII.A.2; Ex. 1002 at ¶ 72. One of ordinary skill in the art would have therefore understood from Tohen that atypical antipsychotics, such as olanzapine, in combination with lithium are effective at treating bipolar disorder in patients partially non-responsive to lithium or valproate monotherapy. Tohen further taught that patients receiving olanzapine had weight gain, a known side effect of olanzapine, and that this weight gain was similar to that reported for olanzapine monotherapy. *See supra*, Section VIII.A.2;

Ex. 1002 at ¶ 73; Ex. 1006 at 67. Thus, one skilled in the art would have been motivated to replace olanzapine with aripiprazole because aripiprazole was known *not* to cause weight gain associated with olanzapine and other atypical antipsychotics. *See e.g.*, Ex. 1006 at 67; Ex. 1002 at ¶ 73; Ex. 1007; Ex. 1028, at 1.

Accordingly, an ordinarily skilled artisan seeking to improve upon lithium or divalproex sodium monotherapy for bipolar disorder would have been motivated to vary the combination therapy taught by Tohen (olanzapine and lithium), and substitute aripiprazole, which Keck or BMS/Otsuka Press Release taught was effective for treating bipolar disorder. Moreover, an ordinarily skilled artisan would have had a reasonable expectation of success in the combination therapy of aripiprazole and lithium. Ex. 1002 at ¶ 74.

As discussed above in Section VIII.A.1 and incorporated herein, the range of ratios of lithium to aripiprazole set forth in claim 2 is so broad that all reasonable dosages are encompassed. Accordingly, claim 2 of the ’939 patent is invalid for obviousness, as the combination of all the claimed elements in the method of use would have been obvious. Because, as discussed above, claims 6, 7, and 9 merely specify the type of bipolar disorder being treated, they do not add any nonobvious limitations over claim 2 and are likewise obvious.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are invalid as obvious over the APA Practice Guidelines 2002 with Keck and/or BMS/Otsuka Press Release and Tohen.

5. Ground 5: Claims 2, 6, 7, and 9 are Obvious Based on Citrome (Ex. 1008) in view of APA Practice Guidelines 2002 (Ex. 1009)

It would also have been obvious to a person of ordinary skill in the art to combine Citrome with APA Practice Guidelines 2002 to arrive at the challenged claims. Ex. 1002 at ¶¶ 80-84. As discussed above, APA Practice Guidelines 2002 taught that mood disorders were being commonly treated with polypharmacotherapy and that the combination of antipsychotics with mood stabilizers such as lithium was already being viewed as potentially more effective than either agent alone. Ex. 1009 at 4, 9; Ex. 1002 at ¶ 80. Specifically, APA Practice Guidelines 2002 taught that bipolar patients with manic or mixed episodes were being treated with lithium or valproate plus an antipsychotic, and preferably an atypical antipsychotic because of more benign side effect profiles. Ex. 1009 at 4, 9; Ex. 1002 at ¶ 80. APA Practice Guidelines 2002 also recommended to add an atypical antipsychotic when first line mood stabilizer monotherapy fails. Ex. 1009 at 9; Ex. 1002 at ¶ 80.

As discussed above, Citrome disclosed co-administration of lithium and aripiprazole to patients with schizoaffective disorder and schizophrenia.[5] Ex. 1002 at ¶¶ 37, 81; Ex. 1008. Furthermore, Citrome disclosed that aripiprazole can be safely co-administered with lithium within the range of aripiprazole to lithium claimed in the '939 patent (*i.e.*, 30 mg aripiprazole and 900 mg lithium, or 1 part by weight aripiprazole and 30 parts by weight lithium). Ex. 1002 at ¶ 83; Ex. 1008. An ordinarily skilled artisan would have had a reasonable expectation that the combination of aripiprazole with lithium in the ratio given by Citrome would be safe. Ex. 1002 at ¶¶ 81-82. Accordingly, an ordinarily skilled artisan seeking to improve upon lithium or divalproex sodium monotherapy for mania would have had a reasonable expectation of success in the combination therapy of aripiprazole and lithium taught by Citrome in view of the use of combination therapy taught by APA Practice Guidelines 2002. *Id.*

As discussed above in Section VIII.A.1 and incorporated herein, the range of ratios of lithium to aripiprazole set forth in claim 2 is so broad that it encompasses all reasonable dosages. Accordingly, claim 2 of the '939 patent is invalid for

[5] Although the patient population in Citrome was suffering from schizophrenia and schizoaffective disorder, the teachings of Citrome demonstrate that the ordinarily-skilled artisan had already employed a combination of aripiprazole and lithium to treat mania and that aripiprazole and lithium can be safely administered to patients.

obviousness, as the combination of all the claimed elements in the method of use would have been obvious. Because, as discussed above, claims 6, 7, and 9 merely specify the type of bipolar disorder being treated, they do not add any nonobvious limitations over claim 2 and are likewise obvious.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are invalid as obvious over Citrome and APA Practice Guidelines 2002.

6. Ground 6: Claims 2, 6, 7, and 9 are Obvious Based on Citrome (Ex. 1008) in view of Tohen (Ex. 1006) and/or Keck (Ex. 1007) or BMS/Otsuka Press Release (Ex. 1028)

It would have been obvious to a person of ordinary skill in the art to combine Citrome with Tohen and/or Keck or BMS/Otsuka Press Release to arrive at the challenged claims. Ex. 1002 at ¶¶ 85-89. As discussed above, Tohen taught the superiority of olanzapine together with lithium in the treatment of bipolar disorder in patients partially nonresponsive to lithium or valproate. Ex. 1002 at ¶ 85; Ex. 1006 at 62. Tohen reported that, when compared with lithium or valproate monotherapy, olanzapine cotherapy improved clinical response rates and Y-MRS total scores. Ex. 1002 at ¶ 36, 85; Ex. 1006 at 62. However, as discussed above, Tohen further taught that patients receiving olanzapine had weight gain, a known side effect of olanzapine, and that this weight gain was similar to that reported for olanzapine monotherapy. Ex. 1002 at ¶¶ 73-74, 85; Ex. 1006 at 67.

As discussed above, Keck (Ex. 1007) taught that aripiprazole is effective and well tolerated, with no significant changes in weight compared to placebo, in the treatment of acute mania in patients with bipolar disorder. Ex. 1002 at ¶¶ 63, 85; Ex. 1007. As also discussed above, Citrome (Ex. 1008) taught that aripiprazole was co-administered with lithium or divalproex sodium to treat mania in chronically institutionalized patients with schizophrenia or schizoaffective disorder. Ex. 1002 at ¶¶ 37, 85; Ex. 1008. Citrome concludes that aripiprazole can be administered safely to patients with therapeutic doses of lithium or divalproex sodium. Ex. 1002 at ¶¶ 37, 85; Ex. 1008.

Accordingly, an ordinarily skilled artisan seeking to improve upon lithium or divalproex sodium monotherapy for bipolar disorder would have been motivated to vary the combination therapy taught by Tohen (olanzapine and lithium), and substitute aripiprazole, which Keck taught was effective for treating bipolar disorder and did not cause antipsychotic induced weight gain like olanzapine, and which Citrome taught was safe when given in combination with lithium. Ex. 1002 at ¶ 86-87. Moreover, an ordinarily skilled artisan would have had a reasonable expectation of success in the combination therapy of aripiprazole and lithium. *Id.*

As discussed above in Section VIII.A.1 and incorporated herein, the range of ratios of lithium to aripiprazole set forth in claim 2 is so broad that it encompasses all reasonable dosages. Furthermore, Citrome taught a ratio of lithium to

aripiprazole that falls within the claimed range (*i.e.*, 30 mg aripiprazole and 900 mg lithium, or 1 part by weight aripiprazole and 30 parts by weight lithium). Accordingly, claim 2 of the '939 patent is invalid for obviousness, as the combination of all the claimed elements in the method of use would have been obvious. Because claims 6, 7, and 9 merely specify the type of bipolar disorder being treated, they do not add any nonobvious limitations over claim 2 and are likewise obvious.

As explained in more detail below, there are no secondary considerations that support non-obviousness. Thus, claims 2, 6, 7, and 9 of the '939 patent are invalid as obvious over Citrome with Tohen and/or Keck or BMS/Otsuka Press Release.

7. No Secondary Considerations Support Non-Obviousness

Secondary considerations of non-obviousness, such as commercial success, long-felt but unsolved needs, failure of others, and unexpected results, if present, must also be considered. *Stratoflex, Inc. v. Aeroquip Corp.,* 713 F.2d 1530, 1538-39 (Fed. Cir. 1983). Any comparison needs to be performed against the closest prior art and needs to be commensurate in scope with the claims. *Kao Corp. v. Unilever United States, Inc*., 441 F.3d 963, 970 (Fed. Cir. 2006); *see also In re Huang*, 100 F.3d 135, 139 (Fed. Cir. 1996). These secondary considerations, however, do not control the analysis when there is an otherwise strong case of

obviousness, such as one based upon prior art not considered by the PTO during prosecution. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1372 (Fed. Cir. 2007) (*citing Newell Cos, Inc. v. Kenny Mfg. Co*., 864 F.2d 757, 768-69 (Fed. Cir. 1988)).

Unexpected results, such as an unexpectedly superior property or unexpected synergy resulting from a combination of elements, may be considered as evidence of nonobviousness. However, as the Federal Circuit has stated, "when unexpected results are used as evidence of nonobviousness, the results must be shown to be unexpected compared with the closest prior art." *Kao Corp. v. Unilever U. S., Inc.*, 441 F.3d 963, 970 (Fed. Cir. 2006) (*quoting In re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991)). In general, subject matter arrived at through routine optimization that works for its intended purpose is not patentable, even if it is better or more desirable than the prior art, unless it is unexpectedly superior. *See Pfizer,* 480 F.3d at 1371 ("The fact that amlodipine besylate was the best of the seven acid addition salts *actually tested* proves nothing more than routine optimization that would have been obvious to one of ordinary skill in the art." (emphasis in original)).

In this case, the closest prior art references teach methods of treating patients with bipolar disorder with aripiprazole alone, lithium alone, and lithium in combination with other atypical antipsychotics, such as olanzapine. As Dr. Frances explained, the prior art teaches that combination therapies with lithium and

atypical antipsychotics, such as aripiprazole, would be expected to be superior to monotherapy with lithium alone. For example, Tohen reports that the combination of lithium and olanzapine is more effective than lithium alone in patients partially non-responsive to lithium monotherapy. Thus, the claimed method of treatment, including the effects of such treatment, were obvious to a person of ordinary skill in the art.

As set forth above, during prosecution of the '939 patent, Patent Owner submitted the Hirose Declaration which asserted that, based on data in a mouse model, the combination of aripiprazole and lithium had an unexpected synergistic effect. Ex. 1076 at 1160-64. The Federal Circuit considered an assertion of unexpected results due to alleged synergy in *Merck and Co. v. Biocraft Labs., Inc*., 874 F.2d 804 (Fed. Cir. 1989). The evidence proffered in that case was that two ingredients used in combination, both of which were known to induce sodium excretion, induced more sodium excretion than either agent alone. *Merck*, 874 F.2d at 808. This showing, however, was insufficient to evidence synergy in that case because it was "to be expected that their co-administration would induce more sodium excretion than would either" agent alone. *Id*. In this case, as explained further below and in the Declaration of Dr. Jessie Au (Ex. 1004), the data in the Hirose Declaration does not even reach the threshold that was found to be insufficient in Merck; there is no statistically sound showing that the combination

of aripiprazole and lithium results in a greater effect than either agent alone. As explained by the Federal Circuit in *Merck*, "when an inventor tries to distinguish his claims from the prior art by introducing evidence of unexpected "synergistic" properties, the evidence should at least demonstrate an effect greater than the sum of the several effects taken separately." *Id*. Failing to even show an effect greater than the sum of the effects of aripiprazole and lithium taken separately, the Hirose Declaration is not probative of "unexpected results" and is insufficient to support the nonobviousness of claims 2, 6, 7 and 9. Ex. 1004 at ¶¶ 30-31; *see also* Ex. 1002 at ¶¶ 95-99. *Id*.

a. **The Hirose Data are Unreliable**

As a threshold matter, the data presented in the Hirose Declaration are unreliable. There are many inconsistencies in the data, both between different sets of experiments performed with the same experimental conditions and between the experiments performed and the results expected from the literature. These inconsistencies render the data irreproducible and, therefore, unreliable. Ex. 1004 at ¶¶ 64-89.

As an example of the data's unreliability, Dr. Au points out the wide variation of values for the control experiments. Ex. 1004 at ¶¶ 70-71, 73-74. In the (vehicle 1 + vehicle 2 + methamphetamine) control group, the mean locomotor counts/60 min was 17552.3 in the aripiprazole arm and was 14368.0 in the

olanzapine arm. Ex. 1004 at ¶ 71. This represents an 18.1% difference from the perspective of the aripiprazole arm, and a 22.2% difference from the perspective of the olanzapine arm. *Id.*.

Additionally, Dr. Au explains that the Hirose Declaration reports data that *contradicts the established effect of lithium* on the methamphetamine induced mania experiments. Ex. 1004 at ¶¶ 80-82, Appendix D. As expected, the mean values for the (methamphetamine + lithium) set in the aripiprazole arm had a 13.91% *suppressive* effect compared to the methamphetamine set. Contrary to expected results (as illustrated by multiple studies summarized in Appendix D of Dr. Au's Declaration), however, the mean values for the (methamphetamine + lithium) set in the olanzapine arm had a 5.39% *stimulatory* effect compared to the methamphetamine set. *Id.* at ¶¶ 77, 82. These results, which are *contradictory* to a large body of data consistently reporting that lithium decreased the locomotor count, make the Hirsose data unreliable. *Id*. at ¶¶ 80-82, Appendix D.

In an attempt to dismiss this discrepancy, Patent Owner stated during prosecution that because the values for the (methamphetamine + lithium) sets in the aripiprazole arm and olanzapine arm overlap, the differences in these controls are insignificant. *Id*. at ¶ 75; Ex. 1076 at 1266. Even if overlapping ranges support the conclusion that differences in results from these controls is insignificant (and it does not), this does not address the real concern—that the relative suppression in

the aripiprazole arm control group was positive (*i.e.*, the lithium, as expected, suppressed the methamphetamine induced locomotor counts) whereas the relative suppression in the olanzapine arm control group was negative (*i.e.*, the lithium, contrary to what was expected, increased the methamphetamine induced locomotor counts). *Id.* at ¶ 76. The purpose of a lithium control is to ensure the results seen are reliable. The data from the lithium control demonstrate the complete and total unreliability of the data set.

b. **Hirose's Conclusion is Statistically Unsound**

Another reason the Hirose Declaration fails to demonstrate legally sufficient "unexpected results" is that the Hirose Declaration draws statistically unsound conclusions. *Id*. at ¶¶ 86-89. Specifically, as noted in the legend of Table 1 in the Hirose Declaration, Patent Owner used the "Dunnett's test" to evaluate the differences in the locomotion suppression effects of the different treatment groups. *Id*. at ¶¶ 86-87. A Dunnett's test is a multiple comparison procedure to compare each of several treatments against a single control and does not evaluate the difference among the various experimental treatment groups. *Id*. As Dr. Au explains, in this case, the Dunnett's test can properly yield information regarding (vehicle + methamphetamine + lithium) compared to (vehicle + methamphetamine), and information regarding (methamphetamine + lithium + aripiprazole) compared to (vehicle + methamphetamine); however, the Dunnett's

test cannot give any information regarding (vehicle + methamphetamine + lithium) compared to (methamphetamine + lithium + aripiprazole). *Id*. In other words, Patent Owner compared the test groups to each other, which is not supportable with a Dunnett's test. *Id.*

Additionally, Dr. Au points out that, as opposed to the generally accepted meaning for statistical significance, the Patent Owner defined a statistically significant difference as one for which the ranges of the values do not overlap. However, statistical significance cannot be determined based on whether the ranges for the data in the Hirose Declaration overlap. *Id.* at ¶¶ 89, 103-04, Appendix B. Thus, the Hirose Declaration fails to provide statistically sound results that could be used to draw conclusions about unexpected results.

c. **The Experimental Design Cannot Show Synergy**

Furthermore, based on the designed experiment in the Hirose Declaration, it is not possible to determine whether the combination of aripiprazole and lithium results in any synergy. *Id.* at ¶¶ 93-101. Specifically, the Hirose experiments failed to (i) include a predicted or calculated effect of the combination of aripiprazole and lithium (*id.* at ¶¶ 90-91); (ii) measure the drug effects over correct time points (*id.* at ¶¶ 94-96); (iii) use the same numbers of animals in the aripiprazole and the olanzapine Arms, as is in common practice when the goal is to

compare two treatments (*id.* at ¶ 98); and (iv) establish the "dose response curves" of the single agents as well as their combinations (*id.* at ¶¶ 99-101).

Dr. Au calculated the drug interactions between lithium, aripiprazole and olanzapine, assuming a linear dose response curve (because the Hirose Data presents only one dose for each drug) at the single time point provided. *Id.* at ¶¶ 105-13; Appendix C. Dr. Au determined that the difference between the Additive Effect and Combined Effect of aripiprazole plus lithium lacks statistical significance, using either applicants' definition of statistical significance or recognized statistical methods. *Id.*

In sum, based on the data in the Hirose Declaration, there is no synergy between lithium and aripiprazole or between lithium and olanzapine using scientifically accepted methods, and the combination of aripiprazole and lithium does not achieve an unexpected results. *Id.* at ¶ 114.

d. The Results are Insufficient to Establish Non-Obviousness

Even if one were to assume the results provided in the Hirose Declaration were "unexpected," "unexpected results" do not control the obviousness conclusion where, as here, there is a strong showing of obviousness. *Pfizer,* 480 F.3d at 1372.

The closest prior art includes methods of treating *human* patients with bipolar disorder with effective amounts of aripiprazole alone, lithium alone and

lithium in combination with atypical antipsychotics, such as olanzapine. The closest prior art establishes that the combination of olanzapine and lithium is superior to monotherapy with lithium alone in patients partially non-responsive to lithium monotherapy. Thus, the prior art *human* testing establishes that the expected result of a combination therapy, including lithium and an atypical antipsychotic, is an improvement over monotherapy. A comparison of the locomotor effects in a *mouse* model, which purports that the combination of olanzapine and lithium is not statistically significantly superior to lithium monotherapy, clearly does not compare the closest prior art.

The prior art and expert evidence establishes a strong case of obviousness. The only purported indicia of secondary considerations submitted by Patent Owner during prosecution in support of nonobviousness (the alleged "unexpected results") was limited to a single mouse model, which presented data that Dr. Au explains is unreliable and scientifically unsound. Petitioner is not aware of any other secondary considerations, such as commercial success, that would support a finding of non-obviousness. Although secondary considerations must be taken into account, they do not control the analysis where, as here, there is a strong *prima facie* case of obviousness. *Pfizer*, 480 F.3d at 1372.

IX. CONCLUSION

For the foregoing reasons, claim 2, 6, 7, and 9 of U.S. Patent No. 9,125,939 are unpatentable as obvious. Petitioners have established a reasonable likelihood of prevailing on each ground, and respectfully requests that the Board grant this petition, institute *Inter Partes* Review, and find claims 2, 6, 7, and 9 of the '939 patent to be unpatentable and cancelled.

Respectfully submitted,

/Theresa C. Kavanaugh/ November 17, 2016

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CERTIFICATION OF WORD COUNT

The undersigned certifies that the attached Petition for *Inter Partes* Review of U.S. Patent No. 9,125,939 B2 contains 10,946 words (as calculated by the word processing system used to prepare this Petition), excluding the parts of the Petition exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE ON PATENT OWNER

UNDER 37 CFR §42.105(a)

Pursuant to 38 CFR §§ 42.8(e) and 42.105(b), the undersigned certifies that on the 17th day of November, 2016, a complete and entire copy of this Petition for *Inter Partes* Review, the incorporated exhibit list, and all supporting exhibits were provided via FedEx International Priority (for Otsuka Pharmaceutical Co., Ltd.) and FedEx Priority Overnight (for Sughrue Mion, PLLC), to the Patent Owner by serving the correspondence address of record for the '939 patent:

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