Neuropsychiatric Disease and Treatment

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SHORT REPORT

Aripiprazole Plasma Concentrations Delivered from Two 2-Month Long-Acting Injectable Formulations: An Indirect Comparison

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Abstract: Aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960) is a novel long-acting injectable (LAI) formulation of aripiprazole monohydrate for administration once every 2 months, developed for the treatment of schizophrenia or maintenance monotherapy treatment of bipolar I disorder in adults (indication will vary by country). Aripiprazole lauroxil 1064 mg (AL 1064) is an LAI formulation of aripiprazole lauroxil, an aripiprazole prodrug, for administration once every 2 months, indicated for the treatment of schizophrenia in adults. This analysis provides an indirect comparison of aripiprazole plasma concentrations following multiple doses of either formulation. Clinical trial data were used to determine average steady-state aripiprazole plasma concentration ($C_{avg,ss}$), maximum aripiprazole plasma concentration (C_{max}), and other pharmacokinetic parameters of either formulation following four administrations (96 patients received Ari 2MRTU 960; 28 patients received AL 1064). All pharmacokinetic parameters were considered in the context of a minimum aripiprazole therapeutic concentration (C_{min}) of ≥95 ng/mL. An exposure–response analysis using data from two Phase III trials of aripiprazole once-monthly (an aripiprazole monohydrate LAI, administered monthly), showed that patients with a C_{min} ≥95 ng/mL are 4.41 times less likely to relapse than patients with a C_{min} <95 ng/mL. A similar analysis has not been performed for AL 1064. However, consensus guidelines for therapeutic drug monitoring recommend a range of 100–350 ng/mL for aripiprazole. Following four administrations, mean (standard deviation [SD]) $C_{avg,ss}$ over the 2-month dosing interval was 263 (133) ng/mL for Ari 2MRTU 960 and 140.7 (57.3) ng/mL for AL 1064. Mean (SD) C_{max} during the fourth dosing interval was 342 (157) ng/mL for Ari 2MRTU 960 and 188.8 (79.8) ng/mL for AL 1064. This indirect comparison showed that, following four administrations, Ari 2MRTU 960 and AL 1064 delivered mean aripiprazole plasma concentrations that remained above the minimum therapeutic concentration of aripiprazole over the 2-month dosing interval.

Keywords: antipsychotic, bipolar I disorder, long-acting injectable, schizophrenia

Introduction

Schizophrenia is a severe, chronic mental illness characterized by positive, negative, and cognitive symptoms.[1] Bipolar I disorder (BP-I) is a recurrent, episodic illness characterized by manic, hypomanic, and depressive episodes, with severe alterations in mood and behavior.[1] Long-term maintenance treatment with antipsychotic medication can help to prevent rehospitalization,[2] and reduce aggressive behaviors[3] and mortality in schizophrenia,[4] and help to prevent mood episodes,[5]

Received: 4 April 2023
Accepted: 24 May 2023
Published: 8 June 2023

and, by extension, cognitive impairment[6] in BP-I. However, non-adherence to antipsychotic treatment is common in schizophrenia and BP-I.[5,7]

Real-world evidence suggests that, compared with oral antipsychotics, long-acting injectable (LAI) formulations are associated with significant improvements in treatment adherence for schizophrenia, as well as BP-I,[8,9] and promote more regular contact between a patient and their healthcare team.[10] In addition, due to the slow release of antipsychotic medication from the LAI formulations,[11] therapeutic plasma drug concentrations are sustained for longer and decrease more slowly than with oral formulations.[12] Patients receiving LAI treatment have reported their preference for LAIs over oral antipsychotics,[13] finding the injections "easier to remember" and stating they have a "more normal life".[14]

Aripiprazole is an atypical antipsychotic used in the treatment of patients diagnosed with schizophrenia or BP-I.[15,16] Aripiprazole can be delivered from two chemically and pharmaceutically distinct LAI formulations that are currently available in the US: aripiprazole once-monthly and aripiprazole lauroxil. Aripiprazole once-monthly (AOM) is an aripiprazole monohydrate formulation available in 400 mg (AOM 400) or 300 mg doses that is indicated in adults for the treatment of schizophrenia or maintenance monotherapy treatment of BP-I.[15] Aripiprazole lauroxil (AL) is a prodrug of aripiprazole that has a higher molecular weight than aripiprazole monohydrate (660.7 g/mol versus 466.4 g/mol)[15,16] and is thought to undergo two steps of hydrolysis for bioconversion to the active drug compound.[16,17] Aripiprazole lauroxil is indicated in adults for the treatment of schizophrenia and is available in 441 mg, 662 mg, 882 mg, and 1064 mg doses, corresponding to 300 mg, 450 mg, 600 mg, and 724 mg of aripiprazole, respectively.[16] The 441 mg and 662 mg doses of AL are intended for administration once-monthly, while the 882 mg dose can be administered once-monthly or once every 6 weeks, and the 1064 mg dose is intended for administration once every 2 months.[16]

The first and only LAI formulation of aripiprazole monohydrate for intramuscular gluteal administration once every two months has been developed: aripiprazole 2-month ready-to-use 960 mg (Ari 2MRTU 960). The aim of this analysis was to indirectly compare the available observed aripiprazole plasma concentrations following the administration of two 2-month LAI formulations – Ari 2MRTU 960 and AL 1064 mg (AL 1064).

Using data from the ASPIRE US[18] and ASPIRE[19] studies (Phase III trials evaluating the efficacy of AOM as a maintenance treatment for the prevention of relapse in patients with schizophrenia), exposure–response analysis has shown that patients diagnosed with schizophrenia and a minimum aripiprazole plasma concentration (C_{min}) of ≥95 ng/mL are 4.41 times less likely to relapse than patients with C_{min} <95 ng/mL.[20] A similar analysis has not been performed for AL 1064. However, consensus guidelines for therapeutic drug monitoring state that the reference range for aripiprazole is 100–350 ng/mL,[21] and 10 mg oral aripiprazole, the lowest daily dose of oral aripiprazole considered effective for the treatment of adults with schizophrenia, has been shown to result in a minimum aripiprazole plasma concentration at steady-state ($C_{min,ss}$) of 94 ng/mL.[22,23] Based on these data, maintaining aripiprazole plasma concentrations of ≥95 ng/mL may be a relevant clinical target, providing meaningful context for the comparison of the two 2-month LAI formulations.

Ari 2MRTU 960 and AL 1064 are LAI formulations with a 2-month dosing interval that deliver a sustained release of aripiprazole via intramuscular gluteal injection – as no head-to-head comparison of plasma concentrations of aripiprazole delivered from Ari 2MRTU 960 and AL 1064 is available, the aim of this analysis was to provide an indirect comparison of the pharmacokinetic (PK) profile of these two 2-month formulations as observed during two separate, but similarly designed, Phase I open-label trials.

Materials and Methods

Data Sources

Data for observed aripiprazole plasma concentrations were sourced from two published Phase I clinical trials that evaluated the pharmacokinetic profiles of Ari 2MRTU 960 and AL 1064.[24–28] Both trials were reviewed and approved by institutional review boards and conducted in accordance with the International Council for Harmonization Good Clinical Practice Guidelines and other applicable laws and regulations, and all patients provided written informed consent. A freedom of information request to the Center for Drug Evaluation and Research provided additional data for AL 1064, in Aristada, NDA 207533, Supplement 004.

The pharmacokinetics of Ari 2MRTU 960 were evaluated in a Phase Ib, open-label, randomized, multiple-dose, parallel-arm, multicenter, pivotal trial that included 266 clinically stable adult patients with schizophrenia or BP-I (ClinicalTrials.gov identifier: NCT04030143).[24] In this trial, patients were randomized 1:1 to receive a gluteal injection of either AOM 400 every 28±2 days (n=134; 8 injections in total) or Ari 2MRTU 960 every 56±2 days (n=132; 4 injections in total) over a 32-week study period. Safety, tolerability, pharmacokinetic, and efficacy measurements were collected throughout the study.[24]

The pharmacokinetics of AL 1064 were evaluated in a Phase I, open-label, multiple-dose, randomized study that included 140 clinically stable adult patients with schizophrenia or schizoaffective disorder (ClinicalTrials.gov identifier: NCT02320032).[27,28] Patients were randomized 1:1:1 to receive a gluteal injection of either AL 441 mg every 4 weeks (n=35; 7 injections scheduled in total), AL 882 mg every 6 weeks (n=35; 5 injections scheduled in total), or AL 1064 mg every 8 weeks (n=35; 4 injections scheduled in total) over a 24-week study period.[27,28] (In addition, 35 patients were randomized to receive AL 1064 mg [S], a formulation with alternative particle size, every 8 weeks; this formulation was not pursued for further development and data for this formulation have not been published.[27,28]) Safety and pharmacokinetic measurements were collected throughout the 24-week treatment period, and during 20 weeks of follow-up.[27,28]

Pharmacokinetic Parameters Presented

Pharmacokinetic parameters evaluated following multiple doses of Ari 2MRTU 960 or AL 1064 included observed average steady-state aripiprazole plasma concentrations ($C_{avg,ss}$), aripiprazole exposure over the dosing intervals (measured as area under concentration-time curve [AUC] from Day 0 to Day 56) and mean maximum (peak) plasma concentration of aripiprazole (C_{max}).

Results

Observed Aripiprazole Plasma Concentrations

Mean aripiprazole plasma concentrations following multiple doses of Ari 2MRTU 960 are shown in Figure 1. Mean aripiprazole plasma concentrations following multiple AL 1064 doses are shown in Figure 2. It is important to note that

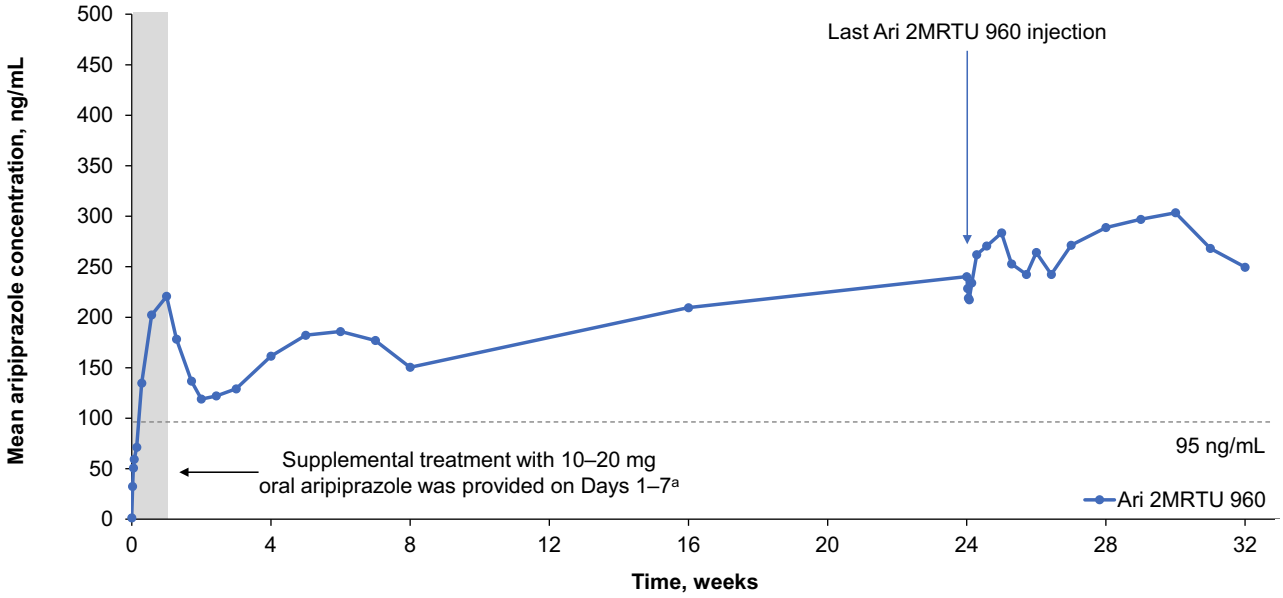

Figure 1 Mean aripiprazole plasma concentrations following multiple doses of Ari 2MRTU 960 in patients with schizophrenia or BP-I.

Notes: All 132 patients randomized to receive Ari 2MRTU 960 received at least one dose, with 113 patients having available data for analysis following the first dose; 104 patients received the fourth (final) dose of Ari 2MRTU 960, with 96 of them having available data for analysis.[24] Dotted line represents the estimated lower efficacy threshold of aripiprazole (95 ng/mL).[20] [a]Patients randomized to receive Ari 2MRTU 960 who were stabilized on an oral antipsychotic received overlapping oral treatment on Days 1–7.[24] For those stabilized on oral aripiprazole, they continued to receive oral aripiprazole (10–15 mg per day).[24] For those stabilized on a non-aripiprazole oral antipsychotic, they either continued to receive their current oral antipsychotic for Days 1–7 or they switched to 10–20 mg oral aripiprazole per day.[24] No overlapping oral antipsychotic treatment was given to patients stabilized on AOM 400.[24]

Abbreviations: Ari 2MRTU 960, aripiprazole 2-month ready-to-use 960 mg; BP-I, bipolar I disorder.

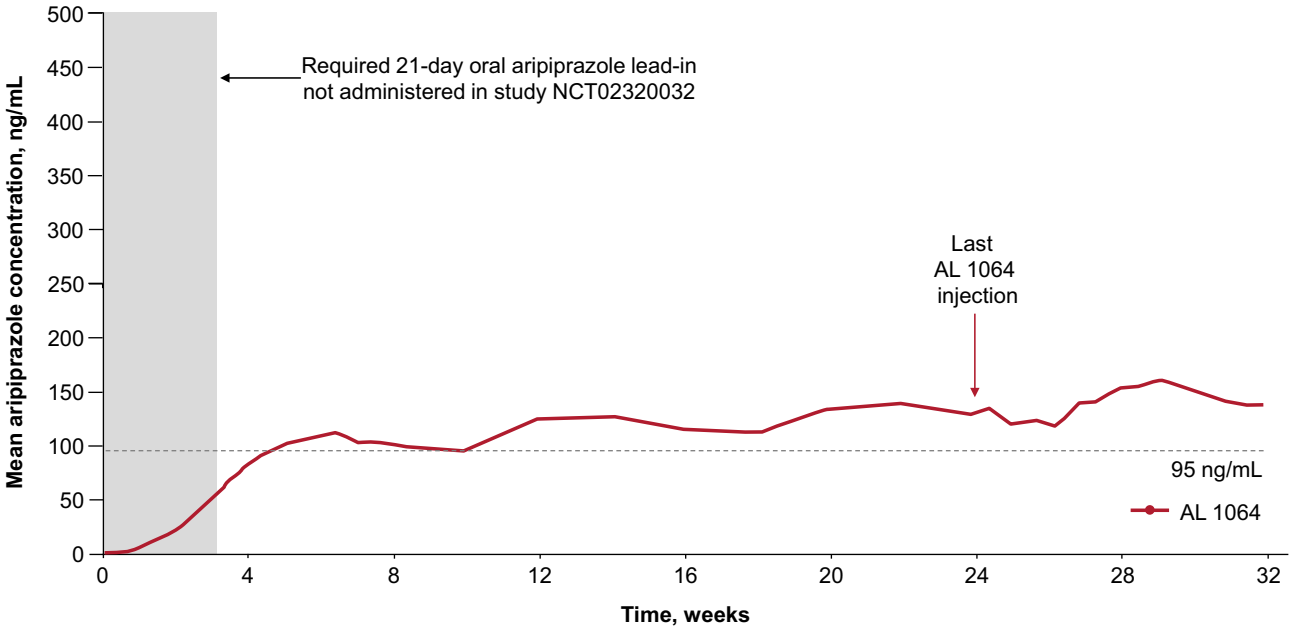

Figure 2 Mean aripiprazole plasma concentrations following multiple doses of AL 1064 in patients with schizophrenia or schizoaffective disorder.
Notes: Figure has been adapted from documents disclosed through a freedom of information request to the Center for Drug Evaluation and Research for Aristada, NDA 207533, Supplement 004, p. 108, and from Figure 1 of Hard ML, Mills RJ, Sadler BM et al. Pharmacokinetic profile of a 2-month dose regimen of aripiprazole lauroxil: a Phase I study and a population pharmacokinetic model. *CNS Drugs*. 2017;31(7):617–624 (distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License; http://creativecommons.org/licenses/by-nc/4.0/).[27] All 35 patients randomized to receive AL 1064 received at least one dose; 28 patients received the fourth (final) dose of AL 1064 and had available data for analysis.[27,28] Dotted line represents the estimated lower efficacy threshold of aripiprazole (95 ng/mL).[20]
Abbreviation: AL 1064, aripiprazole lauroxil 1064 mg.

in the trial evaluating Ari 2MRTU 960, 34.1% (45/132) of patients received oral aripiprazole prior to initiating Ari 2MRTU 960.[24] Furthermore, after the first administration of Ari 2MRTU 960, 35.6% (47/132) of patients received overlapping oral aripiprazole for 7 days (10–20 mg/day).[24] Patients who were stabilized on a non-aripiprazole oral antipsychotic either continued to receive their current oral antipsychotic, or were switched to 10–20 mg oral aripiprazole, for 7 days,[24] although an oral aripiprazole overlap of 14 days is necessary with Ari 2MRTU 960 initiation in the clinic.[29] No overlapping oral antipsychotic treatment was given to patients stabilized on AOM 400.[24] In the trial evaluating AL 1064, any patients who had received oral aripiprazole within 28 days prior to randomization were excluded, and no oral aripiprazole was administered during the initiation of AL 1064, although an oral aripiprazole overlap of 21 days is necessary with AL initiation in the clinic; in the trial, most patients continued on the same maintenance oral antipsychotics.[16,27]

Following four administrations, mean (SD) $C_{avg,ss}$ over the fourth dosing interval was 263 (133) ng/mL for Ari 2MRTU 960[25] and 140.7 (57.3) ng/mL for AL 1064.[27,28] Mean (SD) aripiprazole exposure over the fourth dosing interval ($AUC_{0–56}$) was 14,700 (7,460) ng.day/mL with Ari 2MRTU 960 (Supplementary Table 1)[24] and 7,880 (3,208.7) ng.day/mL with AL 1064 (Supplementary Table 2).[27,28]

Mean (SD) C_{max} following four administrations was 342 (157) ng/mL for Ari 2MRTU 960 (Supplementary Table 1)[24] and 188.8 (79.8) ng/mL for AL 1064 (Supplementary Table 2).[27,28]

Observed Ari 2MRTU 960 pharmacokinetic parameters were consistent with those observed for AOM 400 (see Supplementary Table 1).[24]

Discussion

The present indirect comparison shows that, following four administrations, Ari 2MRTU 960 and AL 1064 provide mean aripiprazole plasma concentrations that remained above a minimum therapeutic concentration of aripiprazole (≥95 ng/mL)[20] over the entire 2-month dosing interval.[24,27] The association between the maintenance of a C_{min} of ≥95 ng/mL and

a 4.41 times lower likelihood of relapse in patients diagnosed with schizophrenia (compared with C_{min} <95 ng/mL)[20] suggests that 95 ng/mL represents a relevant benchmark for the evaluation of aripiprazole plasma concentrations delivered from LAI formulations, and addresses the previously debated issue of whether a $C_{min,ss}$ of 94 ng/mL (delivered by 10 mg oral aripiprazole; the lowest daily dose of oral aripiprazole considered effective for the treatment of schizophrenia[22,23]) can be considered a treatment efficacy threshold rather than a summary pharmacokinetic value.[22,30] The 95 ng/mL threshold is also broadly in line with a previously described aripiprazole therapeutic threshold of 110 ng/mL,[31] the consensus guidelines for therapeutic drug monitoring stating that the reference range for aripiprazole is 100–350 ng/mL,[21] and the results of a recent systematic review and combined analysis of studies with oral and LAI aripiprazole suggesting that the optimal target range for aripiprazole plasma concentrations is 120–270 ng/mL.[32] It is important to note that variability in aripiprazole plasma concentrations may exist among individual patients receiving identical doses of a given aripiprazole formulation due to factors such as sex, concomitant medications, or cytochrome P450 (CYP)2D6 genotype.[33] Dose adjustments may be required to ensure therapeutic aripiprazole plasma concentrations, particularly in patients who are poor CYP2D6 metabolizers or in those receiving concomitant CYP2D6 inhibitors or CYP3A4 inducers.[33]

A single dose of Ari 2MRTU 960 contains 960 mg of aripiprazole, whereas a single dose of AL 1064 corresponds to 724 mg of aripiprazole;[16] thus, Ari 2MRTU 960 would be expected to provide higher sustained aripiprazole plasma concentrations over the 2-month dosing interval (Figure 1) than AL 1064 (Figure 2). Maintaining a therapeutic aripiprazole plasma concentration is more clinically relevant than the actual dose of aripiprazole administered.[34] Although higher aripiprazole plasma concentrations do not imply clinical superiority of one drug over another, they may ensure efficacious aripiprazole plasma concentrations are sustained throughout the dosing interval and reduce the risk of aripiprazole plasma concentrations dropping beneath therapeutic levels.

The aripiprazole plasma concentration profile over the 2-month dosing interval following Ari 2MRTU 960 administration shows peak concentrations comparable to those delivered from AOM 400 administered once-monthly, with a peak-to-trough (PTF) ratio of 1.37 for Ari 2MRTU 960.[24] The reported PTF ratio for aripiprazole lauroxil ranges from 1 to 1.49.[12,35] The PTF ratio of an LAI formulation may have important tolerability implications; low PTF fluctuation has been suggested to offer a reasonable balance between LAI treatment efficacy and tolerability.[12,36]

Introducing a novel LAI formulation with a 2-month dosing interval will help expand treatment options and enhance patient care. In patients diagnosed with schizophrenia, longer duration LAI antipsychotic formulations have been associated with a lower percentage of relapse during active treatment and a longer time to relapse after discontinuing active treatment than shorter-acting formulations.[37]

The present indirect analysis has several limitations. The designs of the Phase I clinical trials of Ari 2MRTU 960 and AL 1064 were not identical. It was, therefore, not possible to carry out a comprehensive like-for-like comparison of all pharmacokinetic parameters for Ari 2MRTU 960 and AL 1064. Importantly, in the clinical trial of Ari 2MRTU 960 (NCT04030143), some patients randomized to receive Ari 2MRTU 960 were previously stabilized on AOM 400 or oral aripiprazole, and others were previously stabilized on a non-aripiprazole antipsychotic and were switched to receive 10–20 mg oral aripiprazole on Days 1–7.[24] In the clinical trial of AL 1064 (NCT02320032), patients randomized to receive AL 1064 did not receive the required 21-day oral aripiprazole lead-in treatment required for AL 1064.[16,27] These differences will have influenced patients' aripiprazole plasma concentration during the first dosing interval in each study only. In addition, patient populations differed between the studies – the clinical trial of Ari 2MRTU 960 (NCT04030143) enrolled patients diagnosed with schizophrenia or BP-I,[24] whereas the clinical trial of AL 1064 (NCT02320032) enrolled patients with schizophrenia or schizoaffective disorder.[27] Lastly, no data are available for the aripiprazole plasma concentration threshold associated with a lower risk of relapse for patients with schizophrenia treated with AL 1064.

Conclusion

Observed aripiprazole plasma concentrations following multiple doses of Ari 2MRTU 960 or AL 1064 suggest that these LAI formulations provide mean aripiprazole plasma concentrations that remained above a minimum therapeutic concentration of aripiprazole over the entire 2-month dosing interval. Knowledge of the pharmacokinetic properties of LAI treatments, such as those reported in the present indirect comparison of observed pharmacokinetic parameters, may

guide clinicians when evaluating the suitability of different formulations for patients diagnosed with schizophrenia or BP-I.

Acknowledgments

Medical writing support was provided by Babette Jamieson, MSc, assisted by her colleagues at Cambridge – a Prime Global Agency (Knutsford, UK). This paper was presented at Psych Congress 2022, New Orleans, LA, USA, 17–20 September 2022 as a poster presentation (poster 56) with interim findings.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA, and H. Lundbeck LLC, Deerfield, IL, USA.

Disclosure

Matthew Harlin, Karimah S. Bell Lynum, Sanjeda R. Chumki, Jessica Madera-McDonough, and Moeen Panni are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc., Princeton, NJ, USA. Craig Chepke has served on advisory boards for AbbVie, Acadia, Alkermes, Axsome, Biogen, Corium, Eisai, Idorsia, Intra-Cellular, Ironshore, Janssen, Jazz, Lundbeck, Karuna, Neurocrine, Noven, Otsuka, Takeda and Teva (his spouse has served on advisory boards for Otsuka); has served as consultant for AbbVie, Acadia, Alkermes, BioXcel, Corium, Eisai, Genomind, Intra-Cellular, Janssen, Jazz, Karuna, Lundbeck, MedinCell, Merck, Neurocrine, Noven, Otsuka, Sage Therapeutics and Sunovion; has received grants or research support from Acadia, Axsome, Biohaven, Harmony, Neurocrine and Teva; is on the Speakers' bureau for AbbVie, Acadia, Alkermes, Corium, Eisai, Genomind, Intra-Cellular, Ironshore, Janssen, Jazz, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sunovion, Takeda and Teva; and has no stocks or ownership interests. Frank Larsen, Pedro Such, and Murat Yildirim are full-time employees of H. Lundbeck A/S, Valby, Denmark. At the time of this analysis, Heather Fitzgerald was a full-time employee of Lundbeck LLC, Deerfield, IL, USA. Stephen R. Saklad is an employee of The University of Texas at Austin College of Pharmacy; has been appointed to the Texas Health and Human Services Commission, San Antonio State Hospital, and the UT Health San Antonio Long School of Medicine; has served as consultant for Alkermes, BioXcel, Genomind, Intra-Cellular, Janssen, Karuna, Lundbeck, and Otsuka; is on the Speakers' bureau for Otsuka PsychU, Neurocrine, Teva and Texas Society of Health-System Pharmacists, and has been an occasional speaker for several professional organizations; is a member of the Business Development Council for the College of Psychiatric and Neurologic Pharmacists; has served as expert witness on both defendant and plaintiff sides; and holds no direct stock ownership in any pharmaceutical corporation. The authors report no other conflict of interest in this work.

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