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A Long-Term, Open-Label Study to Evaluate the Safety and Tolerability of Brexpiprazole as Adjunctive Therapy in Adults With Major Depressive Disorder

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Abstract:

Background: Long-term treatment is recommended in major depressive disorder (MDD) to prevent relapse and to restore functioning. The aim of this study (Orion; NCT01360866) was to assess the long-term safety, tolerability, and efficacy of open-label treatment with adjunctive brexpiprazole in adult patients with MDD.

Methods: Patients rolled over into this 52-week study (amended to 26 weeks) from 3 randomized, double-blind, placebo-controlled studies. Patients received brexpiprazole 0.5 to 3 mg/d (flexible dose) adjunct to their current antidepressant treatment. The primary outcome variable was the frequency and severity of treatment-emergent adverse events (TEAEs). Efficacy was assessed as a secondary objective using clinical rating scales.

Results: A total of 2944 patients were enrolled (1547 for 52 weeks, 1397 for 26 weeks), of whom 1895 (64.4%) completed the study. The TEAEs with incidence of 5% or greater were weight increase (17.7%), somnolence (8.0%), headache (7.2%), akathisia (6.7%), increased appetite (6.3%), insomnia (6.3%), fatigue (6.1%), viral upper respiratory tract infection (5.4%), and anxiety (5.2%). Most TEAEs were mild or moderate in severity. The mean increase in body weight was 2.7 kg to week 26 and 3.2 kg to week 52; 25.8% of patients had a weight increase of 7% or greater at any postbaseline visit. There were no clinically relevant findings related to extrapyramidal symptoms, prolactin, lipids, or glucose. Patients' symptoms and functioning showed continual improvement.

Conclusions: Adjunctive treatment with open-label brexpiprazole 0.5 to 3 mg/d was generally well tolerated for up to 52 weeks in patients with MDD and was associated with continued improvement in efficacy measures and functional outcomes.

Key Words: brexpiprazole, long-term, major depressive disorder, open-label, safety

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Major depressive disorder (MDD) has a high prevalence and a high burden in terms of patient functioning and societal costs and is a leading cause of disability worldwide.^{1,2} Despite the availability of different classes of antidepressants, approximately 50% of patients with MDD do not achieve an adequate response with antidepressant treatment (ADT).³ For such patients, there is considerable evidence supporting the use of atypical antipsychotics as adjunctive treatment.^{4,5} While demonstrating efficacy in MDD, atypical antipsychotics are associated with akathisia, sedation, and weight gain, which may limit their use in clinical practice.⁶ For patients with inadequate response to ADT, there is a need for an effective, safe, and well-tolerated atypical antipsychotic to help patients gain the most benefit from their treatment.

Brexpiprazole is a serotonin-dopamine activity modulator that acts as a partial agonist at serotonin 5-HT_{1A} and dopamine D₂ receptors and as an antagonist at serotonin 5-HT_{2A} and noradrenaline α_{1B}/α_{2C} receptors, all with subnanomolar potency.⁷ The efficacy and safety of brexpiprazole 2 to 3 mg/d when taken as adjunctive treatment to ADT in patients with inadequate response to ADT have been demonstrated in 4 short-term studies in MDD (Pyxis, Polaris, Sirius, and Delphinus).^{8–11} Brexpiprazole is approved in various countries and regions, including the United States, Canada, Australia, Japan, and the European Union, for the treatment of schizophrenia in adults. Brexpiprazole is also approved in the United States and other countries as an adjunctive therapy to antidepressants for the treatment of MDD in adults.

Long-term treatment is recommended in MDD to prevent relapse, eliminate any residual symptoms, restore the patient's prior level of psychosocial and occupational functioning, and prevent recurrence.¹² Consequently, long-term studies of new agents should be undertaken to monitor safety over an extended period. The aim of the present study (the Orion study) was to assess the long-term safety and tolerability of open-label treatment with adjunctive brexpiprazole (flexible dose 0.5 to 3 mg/d) in adult patients with MDD. Efficacy assessments were also included.

MATERIALS AND METHODS

The Orion study (ClinicalTrials.gov identifier NCT01360866) was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Consolidated Guideline and local regulatory requirements, and the protocol was approved by the governing institutional review board or independent ethics committee for each investigational site or country, as appropriate. All patients provided written informed consent prior to the start of Orion and after procedures and possible adverse effects were explained to them.

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Parent Studies

Patients were rolled over into Orion after completion of 1 of 3 randomized, double-blind, placebo-controlled studies of adjunctive brexpiprazole in MDD: Pyxis, NCT01360645; Polaris, NCT01360632; and Delphinus, NCT01727726. For full details of the parent studies, refer to Thase et al^{8,9} (2015; 2 papers) and Hobart et al¹¹ (2018). In brief, the parent studies enrolled patients with a diagnosis of MDD (*Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria), a current depressive episode of at least 8 weeks' duration, and an inadequate response to between 1 and 3 prior ADTs. In Pyxis and Polaris, eligible patients received prospective ADT + placebo for 8 weeks. Those patients who responded continued on prospective ADT + placebo until the end of the study (week 14), whereas those patients who showed inadequate response were randomized to 6 weeks of adjunctive treatment with brexpiprazole or continued adjunctive placebo. Delphinus had a slightly different design: eligible patients received prospective ADT + placebo for 8 or 10 weeks. Those patients who responded continued on prospective ADT + placebo until the end of the study (week 18), whereas those patients who showed inadequate response were randomized to 6 weeks of adjunctive treatment with brexpiprazole, placebo, or quetiapine extended-release (XR) (active reference), before returning to adjunctive placebo until the end of the study.

Patients

Patients were recruited into Orion at 188 sites across 11 countries in Europe (France, Germany, Hungary, Poland, Romania, Russia, Serbia, Slovakia, Ukraine) and North America (Canada, United States). Patients were eligible for inclusion if they were outpatients (male or female) aged 18 to 65 years who, in the investigator's opinion, could potentially benefit from administration of oral brexpiprazole as adjunctive therapy to their ADT. Patients must have completed the last scheduled visit of Pyxis (week 14), Polaris (week 14), or Delphinus (week 18), regardless of whether they had been randomized in the parent study. Patients from Pyxis or Polaris who were not randomized (ie, who responded to prospective ADT + placebo) could not be in remission at the last scheduled visit, where remission was defined as a Montgomery-Åsberg Depression Rating Scale¹³ total score of 10 points or less. Key exclusion criteria were hospitalization during the parent study, having received electroconvulsive therapy for the current depressive episode, presenting with suicidal ideation or behavior, or meeting *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* criteria for substance abuse or dependence (within the past 180 days) or a specified Axis I disorder other than MDD. In summary, patients in Orion were outpatients who rolled over from the parent studies, who had not remitted on ADT + placebo in the parent studies, and who may or may not have been categorized as responders in the parent studies.

Study Design

Orion was a multicenter, open-label study, conducted from October 7, 2011, to May 18, 2017. Patients were screened for eligibility at the last visit of their respective parent study, which was defined as the baseline visit for Orion. Eligible patients entered a 52-week, open-label treatment phase (visits at weeks 1, 2, 4, 8, 14, 20, 26, 32, 38, 44, and 52, plus unscheduled visits as necessary for dose adjustment). All patients were titrated to oral brexpiprazole (regardless of previous brexpiprazole exposure) as follows: first week, 0.5 mg/d; second week, 1 mg/d; third and fourth weeks, 0.5 to 2 mg/d; fifth week onward, 0.5 to 3 mg/d. From the third

week onward, doses could be adjusted within the specified range for reasons of efficacy or tolerability, according to the investigator's judgment.

Patients remained on the same assigned open-label ADT from their parent study. Allowed ADTs and doses were as follows: escitalopram, 10 and 20 mg/d; fluoxetine, 20 and 40 mg/d; paroxetine controlled-release, 37.5 and 50 mg/d; sertraline, 100, 150, and 200 mg/d; duloxetine, 40 and 60 mg/d; and venlafaxine XR, 75, 150, and 225 mg/d.

Safety follow-up comprised telephone contact or a clinic visit 30 days after the last dose.

The study protocol was amended on April 11, 2014, approximately midway through the study, to reduce the study duration from 52 to 26 weeks. Patients who had already completed their week 26 visit at the time of the amendment were withdrawn from the study at their next scheduled visit. The reason for this amendment was that the safety profile of brexpiprazole was considered to be well established based on the data already collected in this study together with completed double-blind and long-term studies.

Assessments

The primary objective of the study was to assess the long-term safety and tolerability of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD. Safety was assessed by treatment-emergent adverse events (TEAEs; primary outcome), clinical laboratory tests, physical examination, vital signs, body mass index, and electrocardiograms. Extrapyramidal symptoms (EPS) were formally assessed using the Simpson-Angus Scale (SAS),¹⁴ Barnes Akathisia Rating Scale (BARS),¹⁵ and Abnormal Involuntary Movement Scale (AIMS).¹⁶ Suicidality was assessed using the Columbia Suicide Severity Rating Scale.¹⁷ Sexual functioning was assessed using the patient-rated Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ), in which interest in sex, arousal, ability to achieve orgasm, ability to maintain an erection (men only), and overall sexual satisfaction were each scored from 1 (greater than normal) to 6 (totally absent).¹⁸

The secondary objective of the study was to assess the long-term efficacy of oral brexpiprazole as adjunctive therapy in the treatment of adults with MDD. Efficacy was assessed using the Clinical Global Impressions–Severity of Illness (CGI-S) and Improvement (CGI-I) scales,¹⁶ the Sheehan Disability Scale (SDS), and the Inventory of Depressive Symptomatology, Self-report (IDS-SR). The patient-rated SDS is a measure of functional disability with regard to work/studies, social life, and family life; each item, and the mean of all 3 items, is scored from 0 (best functioning) to 10 (worst functioning).^{19–21} The patient-rated IDS-SR measures the severity of depressive symptoms, with lower scores indicating lower severity.²²

Information regarding the extent of medical care sought by patients while participating in the study was collected using a resource utilization form.

Statistical Analyses

The sample size was determined by the number of eligible patients who completed one of the parent studies, rather than by statistical power considerations.

The enrolled population comprised all patients who signed an informed consent form for the study. The safety population comprised all patients who received at least 1 dose of open-label brexpiprazole. The efficacy population comprised all patients in the safety population who had a baseline and at least 1 postbaseline efficacy evaluation on the CGI-S.

The primary outcome variable was the frequency and severity of TEAEs in the open-label treatment phase. All safety variables were summarized using descriptive statistics for the safety population. Mean MSFQ score change from baseline was calculated using observed cases (OC). Mean EPS scale (SAS, BARS, and AIMS) score changes from baseline were reported using OC and also using last observation carried forward (LOCF) to impute missing values. Efficacy variables (mean score change from baseline, plus absolute CGI scores) were summarized with descriptive statistics for the efficacy population, using OC and LOCF approaches. The distribution of CGI-S scores at baseline, week 26, and week 52 was calculated in a post hoc analysis.

RESULTS

Patients

A total of 2944 patients enrolled in the study (Fig. 1). Of these patients, 1547 enrolled for 52 weeks (ie, they enrolled before the amendment that reduced the study duration from 52 to 26 weeks), and 1397 enrolled for 26 weeks (ie, after the amendment). Considering patients' previous treatment before rolling over in to Orion, 1645 patients had responded to prospective ADT + placebo and therefore remained on ADT + placebo in their parent study, whereas 1299 patients had shown inadequate response to prospective ADT + placebo and therefore received ADT + brexpiprazole, ADT + placebo, or ADT + quetiapine XR in their parent study (Fig. 1).

Of the enrolled patients, 64.4% (1895/2944) completed the study: 46.7% (723/1547) who enrolled for 52 weeks and 83.9% (1172/1397) who enrolled for 26 weeks. Overall, 2132 patients had at least 6 months of exposure (72.6%). The most common reasons for discontinuation were withdrawal of consent (11.7%) and

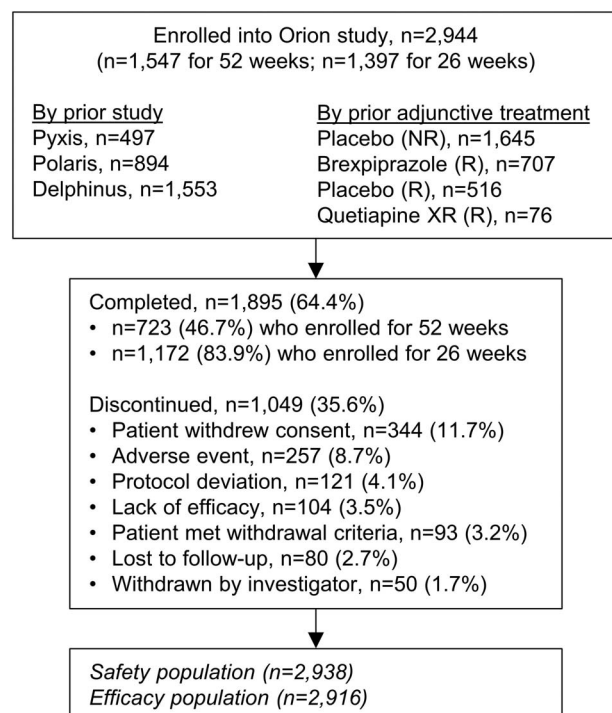


FIGURE 1. Patient disposition and reasons for discontinuation. NR indicates not randomized in parent study (ie, responded to prospective ADT); R, randomized in parent study (ie, inadequate responder to prospective ADT).

TABLE 1. Baseline Demographic and Clinical Characteristics and Assigned ADT

Demographic Characteristics	Enrolled Population (n = 2944)
Age, mean (SD), y	45.0 (12.0)
BMI, mean (SD), kg/m ²	29.0 (7.0) (n = 2942)
Female, n (%)	2005 (68.1)
White, n (%)	2588 (87.9)
Clinical Characteristics, Mean (SD)	Efficacy Population (n = 2916)
CGI-S score	2.8 (1.1)
SDS Mean score	3.6 (2.5) (n = 2912)
Work/studies	3.3 (2.6) (n = 2186)
Social life	3.6 (2.6) (n = 2913)
Family life	3.6 (2.6) (n = 2913)
IDS-SR Total score	23.9 (13.1) (n = 2911)
Assigned ADT, n (%)*	Enrolled Population (n = 2944)
Escitalopram	579 (19.7)
Fluoxetine	367 (12.5)
Paroxetine CR	353 (12.0)
Sertraline	473 (16.1)
Duloxetine	625 (21.2)
Venlafaxine XR	541 (18.4)

*Six patients did not receive a dose of ADT during the study.

BMI indicates body mass index; CR, controlled-release.

TEAEs (8.7%) (Fig. 1). The mean daily dose of brexpiprazole at last visit was 1.5 mg (n = 2938).

Baseline demographic and clinical characteristics are shown in Table 1. On average, the patients were mildly ill at baseline, with a mean CGI-S score of 2.8.

Safety

The proportion of patients who experienced at least 1 TEAE during treatment with open-label ADT + brexpiprazole was 72.3% (Table 2). The TEAEs with an incidence of 5% or greater were weight increase, somnolence, headache, akathisia, increased appetite, insomnia, fatigue, viral upper respiratory tract infection, and anxiety (Table 2); the only TEAE with an incidence of 10% or greater was weight increase (17.7%). Most TEAEs were mild or moderate in severity; 215 patients (7.3%) experienced a severe TEAE. The only TEAE associated with discontinuation in at least 1.0% of patients was weight increase (60 patients; 2.0%).

The mean increase in body weight from baseline to week 26 was 2.7 kg (n = 2068) and from baseline to week 52 was 3.2 kg (n = 771) (Fig. 2). The incidence of an increase in body weight of 7% or greater at any postbaseline visit was 25.8%, and the incidence of a decrease in body weight of 7% or greater at any postbaseline visit was 2.8%.

There were no clinically relevant findings (ie, leading to treatment intervention) for events related to prolactin, lipids, or glucose, including the incidence of shifts to abnormal levels (see Supplementary Table 1, which summarizes additional safety outcomes, Supplemental Digital Content 1, <http://links.lww.com/JCP/A560>). The mean prolactin level changes from baseline to week 26 were 2.4 ng/mL in females (n = 1381) and 1.1 ng/mL in males (n = 656), and those from baseline to week 52 were

TABLE 2. Summary of TEAEs Over 52 Weeks

	Safety Population (n = 2938)
At least 1 TEAE	2123 (72.3)
Discontinuation due to TEAE	253 (8.6)
TEAEs occurring in ≥5% of patients	
Weight increase	519 (17.7)
Somnolence	235 (8.0)
Headache	211 (7.2)
Akathisia	197 (6.7)
Increased appetite	185 (6.3)
Insomnia	184 (6.3)
Fatigue	178 (6.1)
Viral upper respiratory tract infection	160 (5.4)
Anxiety	152 (5.2)
Other relevant TEAEs	
Restlessness	100 (3.4)
Sedation	78 (2.7)
Hypersomnia	19 (0.6)
Hyperprolactinemia	10 (0.3)

All values are n (%).

0.5 ng/mL in females (n = 511) and 0.4 ng/mL in males (n = 237). The mean change in fasting glucose from baseline to week 26 was 3.1 mg/dL (n = 1766), and that from baseline to week 52 was 4.6 mg/dL (n = 678). The proportion of patients meeting the criteria for treatment-emergent metabolic syndrome (ie, ≥3 of central obesity, dyslipidemia, increased blood pressure, and increased fasting serum glucose levels) at any visit was 2.9% (65 of 2276 patients who did not meet the criteria at baseline and who had a postbaseline measurement).

No clinically meaningful changes (ie, leading to treatment intervention) were observed on formal EPS rating scales (see Supplementary Table 2, which provides SAS, BARS, and AIMS score changes, Supplemental Digital Content 2, <http://links.lww.com/JCP/A561>). Overall, 12.1% (355/2938) of patients had an EPS-related TEAE during the open-label

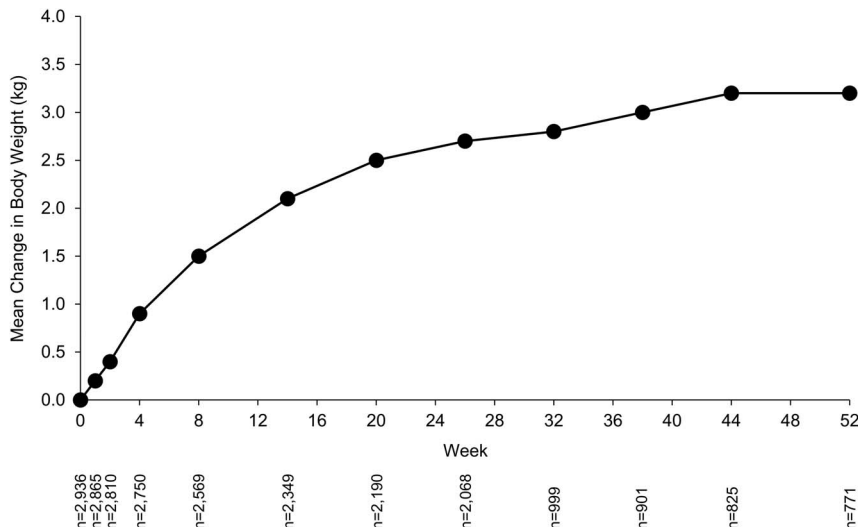


FIGURE 2. Mean change from baseline in body weight. Observed cases. Mean (SD) body weight at baseline: 82.9 (20.6) kg.

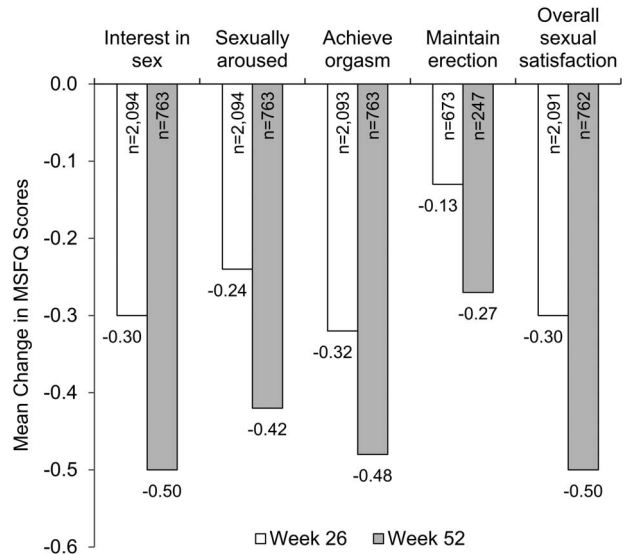


FIGURE 3. Mean change from baseline in MSFQ scores. Observed cases. Mean (SD) scores at baseline: interest in sex, 3.9 (1.5) (n = 2924); sexually aroused, 3.8 (1.5) (n = 2924); achieve orgasm, 4.0 (1.6) (n = 2923); maintain erection (men only), 3.2 (1.3) (n = 935); overall sexual satisfaction, 4.0 (1.5) (n = 2921). A reduction in score indicates improvement.

treatment phase. The most frequently reported EPS-related TEAE was akathisia (6.7%).

During the open-label treatment phase, suicidal ideation emerged in 5.5% of patients, and suicidal behavior emerged in 0.2% of patients. Suicidal ideation as a TEAE occurred in 0.4% of patients. Four patients died during the study, including 2 suicides. One death (suicide) was considered by the investigator to be possibly related to adjunctive brexpiprazole treatment; the other 3 deaths were considered to be unrelated to adjunctive brexpiprazole treatment.

All domains of the MSFQ showed decreases from baseline to week 26 and to week 52, indicating improvement in sexual functioning (Fig. 3).

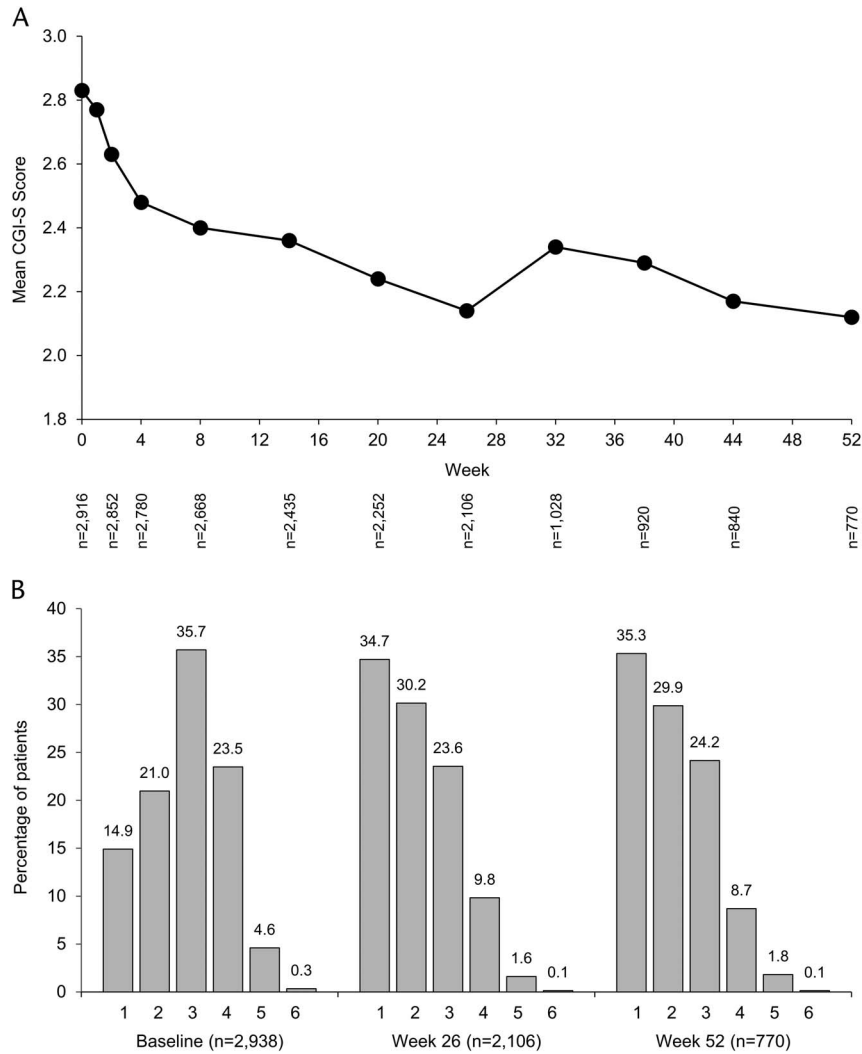


FIGURE 4. Mean CGI-S score over time (A) and distribution of CGI-S scores (B). Observed cases.

Efficacy

Long-term adjunctive brexpiprazole treatment was associated with improvement in all efficacy measures and functional outcomes. The CGI-S scores over 52 weeks of open-label adjunctive brexpiprazole treatment are shown in Figure 4A. The mean (SD) absolute CGI-S score was 2.1 (1.1) at both week 26 (n = 2106, OC) and week 52 (n = 770, OC); with LOCF, the CGI-S score at week 52 was 2.3 (1.2) (n = 2916). The mean (SD) change in CGI-S score from baseline to week 26 was -0.6 (1.0) (n = 2106, OC) and from baseline to week 52 was -1.1 (1.1) with OC (n = 770) and -0.6 (1.1) with LOCF (n = 2916). The modal CGI-S score shifted from 3 (“mildly ill”) at baseline to 1 (“normal, not at all ill”) at weeks 26 and 52 (Fig. 4B). The mean (SD) CGI-I score at week 26 was 2.5 (1.3) (n = 2106, OC) and at week 52 was 2.1 (1.1) with OC (n = 770) and 2.6 (1.4) with LOCF (n = 2879), indicating that, on average, patients were “minimally to much improved” compared with their condition at baseline (the last visit of the parent study).

Mean changes in SDS Mean and item scores at weeks 26 and 52 are shown in Figure 5. The mean (SD) change in SDS Mean score from baseline to week 26 was -0.7 (2.1) (n = 2101, OC),

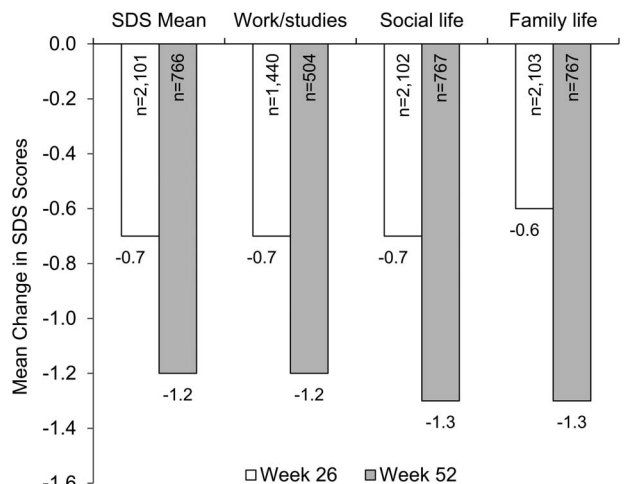


FIGURE 5. Mean change from baseline in SDS Mean and item scores. Observed cases. Mean (SD) scores at baseline: SDS Mean, 3.6 (2.5) (n = 2912); work/studies, 3.3 (2.6) (n = 2186); social life, 3.6 (2.6) (n = 2913); family life, 3.6 (2.6) (n = 2913).

and that from baseline to week 52 was -1.2 (2.3) with OC ($n = 766$) and -0.6 (2.3) with LOCF ($n = 2785$), indicating improved functioning. Improvement was also observed on all 3 items (work/studies, social life, and family life).

The mean (SD) change in IDS-SR total score from baseline to week 26 was -5.2 (10.0) ($n = 2103$, OC), and that from baseline to week 52 was -7.8 (11.0) with OC ($n = 769$) and -4.5 (11.2) with LOCF ($n = 2786$), indicating a reduction of depressive symptoms.

Considering resource utilization, the average yearly use of health resources generally decreased from baseline to week 26 and to week 52 (see Supplementary Table 3, which summarizes resource utilization, Supplemental Digital Content 3, <http://links.lww.com/JCP/A562>).

DISCUSSION

This study showed that treatment with adjunctive brexpiprazole 0.5 to 3 mg/d in MDD was generally safe and well tolerated for up to 52 weeks, consistent with the findings of other short- and long-term studies in the brexpiprazole MDD clinical development program.^{8–11,23} The most common TEAE was weight gain, experienced by 17.7% of patients. Most of this weight gain occurred in the first 6 months (mean change from baseline to week 26, 2.7 kg), with indications that weight increase may plateau over the course of long-term exposure (mean change from baseline to week 52, 3.2 kg). Treatment duration and adherence were minimally affected by weight gain, as reflected by only 2.0% of patients discontinuing due to weight gain, and there was no indication that weight gain was associated with clinically meaningful changes in metabolic parameters. The weight gain observed with adjunctive brexpiprazole is comparable to that reported for adjunctive aripiprazole (4.0 kg over 52 weeks)²⁴ and quetiapine XR monotherapy in MDD (1.6 kg over 16–26 weeks)²⁵ and considerably less than that reported for olanzapine-fluoxetine combination (approximately 7 kg over 52 weeks).²⁶

Other adjunctive atypical antipsychotics in MDD are associated with pronounced adverse effects that may limit their use.⁵ For example, aripiprazole is associated with akathisia, quetiapine with sedation, and olanzapine-fluoxetine combination with abnormal metabolic laboratory results.⁵ Olanzapine is also associated with prolactin increase,²⁷ which is linked to sexual dysfunction.²⁸ In the present study of adjunctive brexpiprazole, akathisia and sedating adverse events had low incidences, and changes in clinical laboratory tests and EPS rating scale scores were small and not considered clinically meaningful, and there was no clinically relevant adverse effect on sexual function. The incidence of akathisia in this study was 6.7%, much lower than that observed in a comparable 52-week open-label study of adjunctive aripiprazole (26.2%).²⁹ Adjunctive brexpiprazole was associated with a low rate of discontinuation due to TEAEs (8.6%). Thus, brexpiprazole is a well-tolerated treatment option in the long-term treatment of MDD.

Regarding completion rates, although the majority of patients who enrolled for 26 weeks completed the study (83.9%), fewer than half of patients who enrolled for 52 weeks completed the study (46.7%). High dropout rates are expected in MDD studies of this duration; in the 52-week adjunctive aripiprazole study, only 32.2% of patients completed 52 weeks of open-label treatment.²⁹

The tolerability of brexpiprazole may be attributed to its pharmacologic profile. Compared with aripiprazole, brexpiprazole has lower intrinsic activity at D_2 receptors, making it less likely to induce D_2 -agonist-mediated adverse effects such as akathisia and nausea.^{7,30,31} Compared with antipsychotics associated with

dopaminergic blockade, brexpiprazole is less likely to induce D_2 -antagonist-mediated adverse effects such as EPS and hyperprolactinemia.^{30,32} Relative to its $D_2/5-HT_{1A}$ receptor affinity, brexpiprazole has a moderate to low affinity for histamine H_1 receptors,⁷ which may limit the risk of diabetes, sedation, and excessive weight gain.³³

The efficacy outcomes of Orion are limited by the open-label design of the study and the lack of a comparator. It should also be noted that 55.9% of enrolled patients had responded to prospective ADT + placebo in the parent studies; the effects of including both responders and nonresponders in Orion are unknown.

On average, CGI-S scores showed continued improvement, by 1.1 points over 52 weeks (OC), on top of any initial improvement in the parent studies. The CGI-I and IDS-SR outcomes were supportive, also indicating continued improvement. With regard to patient functioning, adjunctive brexpiprazole was associated with improvement on the SDS Mean and all 3 SDS domains, including work and studies. In the short-term brexpiprazole studies, a benefit was observed in the domains of social life and family life, but not work and studies,³⁴ thereby supporting the hypothesis that improvement in work functioning may lag behind improvement of mood, particularly among patients with inadequate response to ADT who are at risk of persisting impairment.^{35,36}

In conclusion, although potentially biased by its open-label design, this study showed that adjunctive treatment with brexpiprazole 0.5 to 3 mg/d (flexibly dosed) was generally well tolerated for up to 52 weeks in patients with MDD. No unexpected safety or tolerability issues emerged, and the long-term safety profile was consistent with other brexpiprazole studies in MDD. Furthermore, open-label adjunctive treatment with brexpiprazole 0.5 to 3 mg/d was associated with continued improvement in efficacy measures and functional outcomes in the long term.

AUTHOR DISCLOSURE INFORMATION

M.H., P.Z., A.S., C.B., and R.D.M. are full-time employees of Otsuka Pharmaceutical Development & Commercialization Inc. N.H. is a full-time employee of H. Lundbeck A/S. At the time that this work was conducted, R.S. was an employee of Otsuka Pharmaceutical Development & Commercialization Inc.

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