

Adjunctive brexpiprazole for elderly patients with major depressive disorder: An open-label, long-term safety and tolerability study

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Objectives: The objective of this study was to evaluate the long-term safety and tolerability of flexible-dose brexpiprazole adjunct to antidepressant treatment (ADT) in elderly patients with major depressive disorder (MDD).

Methods: Elderly patients (≥ 65 years) with MDD and inadequate response to ≥ 1 ADT during the current episode were recruited to a 26-week, interventional, open-label study (NCT02400346) at outpatient centers in the USA and Europe. All patients received brexpiprazole 1 to 3 mg/day adjunct to their current ADT. Safety outcomes included adverse events (AEs), movement disorder scales, and standard safety assessments (vital signs, laboratory safety parameters, physical examination, electrocardiograms). Exploratory efficacy outcomes included the Montgomery-Åsberg Depression Rating Scale (MADRS), Clinical Global Impressions-Severity of Illness (CGI-S), and Social Adaptation Self-Evaluation Scale (SASS).

Results: Of the 132 treated patients, 88 (66.7%) completed the study and 44 (33.3%) withdrew, including 24 who withdrew because of AEs (18.2%). Overall, 102 patients (77.3%) experienced ≥ 1 treatment-emergent AE (TEAE), which were mostly mild or moderate in severity. Treatment-emergent AEs with the highest incidence were fatigue (15.2%) and restlessness (12.9%). The most common TEAE leading to withdrawal was fatigue (3.0%). No consistent clinically relevant findings were seen with regard to movement disorder scales or standard safety assessments. Mean (standard error) efficacy score changes from baseline to week 26 were: MADRS total, -14.5 (0.9); CGI-S, -1.8 (0.1); and SASS, 3.2 (0.5).

Conclusions: Long-term (26-week) treatment with adjunctive brexpiprazole was generally well tolerated in elderly patients with MDD and inadequate response to prior ADT. Improvements were observed in depressive symptoms and social functioning.

KEYWORDS

adjunctive, brexpiprazole, depression, elderly, open-label

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1 | INTRODUCTION

Estimates from the World Health Organization (WHO) show that, in 2015, the global prevalence of depression increased with age, reaching a peak at around 60 years.¹ Beyond 60 years, in the elderly population (65–79 years), the prevalence of depression remained at high levels.¹ Depression in the elderly is associated with considerable burden, by exacerbating other illnesses, and increasing mortality.²

Many older adults with major depressive disorder (MDD) fail to achieve an adequate response to antidepressant treatment (ADT).³ Adjunctive treatment with atypical antipsychotics has been shown to enhance the response to ADT in clinical trials of adults (18–65 years; mean age of approximately 45 years).⁴ However, evidence that adjunctive antipsychotics may enhance antidepressant response in elderly populations (≥ 65 years) is limited. Aripiprazole is the only adjunctive antipsychotic with evidence of efficacy versus placebo in patients aged ≥ 60 years with inadequate response to ADT (and also in patients aged 50–67 years in a post hoc study).^{5,6}

Brexiprazole 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 $\alpha_{1B/2C}$ receptors, all with subnanomolar potency.⁷ The efficacy and safety of brexiprazole as adjunctive treatment to ADT over 6 weeks has been demonstrated in 4 studies in adult patients (aged 18–65 years) with MDD.^{8–11} Brexiprazole is approved in the USA as an adjunctive therapy to antidepressants for the treatment of adults with MDD, and in the USA, Canada, Australia, and Japan as monotherapy for the treatment of adults with schizophrenia.

The use of adjunctive antipsychotic treatment for depression has been limited because of safety concerns in relation to antipsychotics (eg, weight gain, metabolic effects, extrapyramidal symptoms [EPS], sedation, and akathisia).¹² Potential cardiovascular risks are particularly relevant to an elderly population.¹³ The objective of this study (Aquila) was to evaluate the long-term safety and tolerability of flexible-dose brexiprazole as adjunctive treatment to ADT in elderly patients with MDD and an inadequate response to prior ADT.

2 | METHODS

2.1 | Patients

The Aquila study (ClinicalTrials.gov identifier: NCT02400346) was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice Guideline, and with the principles laid out in the Declaration of Helsinki (1964, plus amendments). The study protocol was approved by the relevant institutional review boards and independent ethics committees. All patients provided written informed consent prior to enrolling in the study.

Patients were enrolled at 34 sites in the USA (39.4% of patients), Finland (20.5%), Estonia (15.9%), Poland (12.9%), and Germany (11.4%). The study started on March 16, 2015 and was completed on June 1, 2016.

To be included in the study, patients (male or female) were required to be outpatients, aged ≥ 65 years, with a diagnosis of MDD, as defined by the Diagnostic and Statistical Manual of Mental

Key points

- The use of adjunctive antipsychotics to enhance antidepressant response in depressed elderly populations is hindered by safety concerns and limited evidence of efficacy.
- The present study evaluated the long-term safety of flexibly dosed brexiprazole adjunct to antidepressant treatment in elderly patients with major depressive disorder.
- No new safety or tolerability concerns were noted with adjunctive brexiprazole in the elderly compared to previous studies in adults aged 18–65 years.
- Improvements were observed in depressive symptoms, social functioning, and quality of life, suggesting that brexiprazole may be useful to treat depression in the elderly.

Disorders, Fourth Edition, Text Revision (DSM-IV-TR[®]),¹⁴ and currently experiencing a major depressive episode of duration ≥ 8 weeks. Patients were currently being treated with an ADT selected from the protocol-specified range of ADTs, and must have reported an inadequate response, defined as $< 50\%$ improved on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire (ATRQ)¹⁵ (elderly version), to at least 1 ADT at a therapeutic dose and for an adequate duration (≥ 6 weeks) during the current episode. Patients had a Montgomery–Åsberg Depression Rating Scale (MADRS)¹⁶ total score > 18 and a Clinical Global Impressions–Severity of Illness (CGI-S)¹⁷ score ≥ 3 , at screening and baseline. Patients were excluded if they had previously enrolled in a long-term (> 8 weeks) brexiprazole study; had been treated with any investigational medicinal product within 30 days or 5 half-lives (whichever was longer) prior to screening; were presenting with suicidal ideation or behavior; had a Mini-Mental State Examination (MMSE) score < 24 at screening¹⁸; had a primary diagnosis of a DSM-IV-TR[®] psychiatric or Axis I disorder other than MDD; met criteria for unstable, or newly diagnosed, diabetes mellitus; had unstable cardiovascular disease in the 12 months prior to screening; or had an abnormal electrocardiogram (ECG) reading at screening (a PR interval > 250 milliseconds, a QRS interval > 130 milliseconds, or a Fridericia-corrected QT [QT_{cF}] interval > 450 milliseconds for men or > 470 milliseconds for women).

2.2 | Study design

Aquila was a 26-week, interventional, multicenter, open-label study of the safety and tolerability of flexible-dose brexiprazole (1 to 3 mg/day) as adjunctive therapy in the treatment of elderly patients with MDD who had an inadequate response to prior ADT. Following screening, eligible patients received brexiprazole as adjunctive treatment to their current ADT (the ADT that they were receiving prior to screening) during a 26-week treatment period. Brexiprazole was titrated from 0.5 mg/day to 2 mg/day over the first

4 weeks (first week, 0.5 mg/day; second week, 1 mg/day; third and fourth weeks, 2 mg/day); thereafter, patients received adjunctive brexpiprazole at a dose of 1 to 3 mg/day, depending on clinical judgment and tolerability. Investigators were instructed not to change the dose of ADT during the study.

After study completion or withdrawal, patients entered a 4-week safety follow-up period, during which they stopped brexpiprazole treatment, but continued to receive their same ADT.

2.3 | Outcome measures

The primary objective of this study was to evaluate the long-term safety and tolerability of brexpiprazole 1 to 3 mg/day as adjunct to ADT in elderly patients with MDD. Safety and tolerability outcomes included adverse event (AE) reporting, clinician-rated movement disorder scales (the modified Simpson–Angus Scale [mSAS],^{19,20} the Barnes Akathisia Rating Scale [BARS],²¹ and the Abnormal Involuntary Movement Scale [AIMS]¹⁷), standard safety assessments (vital signs, laboratory safety parameters, physical examination, ECG), cognition (MMSE), and suicidality (Columbia Suicide Severity Rating Scale [C-SSRS]²²). The mSAS is a 10-item scale used to measure drug-induced parkinsonism and EPS; the total score, obtained by taking the mean of the rated items, ranges from 0 (absence) to 4 (most extreme).^{19,20} The BARS Global clinical assessment item measures drug-induced akathisia on a scale from 0 (absent) to 5 (severe akathisia).²¹ The AIMS is a 12-item scale used to assess dyskinetic movements of the face, trunk, and extremities among patients receiving antipsychotic drugs; the total score ranges from 0 (none) to 42 (most severe).¹⁷

Exploratory efficacy outcomes assessed the effect of brexpiprazole 1 to 3 mg/day as adjunct to ADT on depressive symptoms, using the clinician-rated MADRS; global illness severity and change, using the clinician-rated CGI-S and Clinical Global Impressions-Improvement (CGI-I)¹⁷; social functioning, using the Social Adaptation Self-Evaluation Scale (SASS)²³; health-related quality of life, using the Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form (Q-LES-Q-SF)^{24,25}; and well-being, using the EuroQoL 5 Dimensions 5 Levels (EQ-5D-5L) Health state score.²⁶ The SASS is a 21-item, patient-rated scale to assess social functioning in patients with depression; the total score ranges from 0 to 60, with higher scores indicating better functioning.²³ The Q-LES-Q-SF is a 16-item, patient-rated measure of the degree of enjoyment and satisfaction experienced by patients in daily life; the total score of items 1 to 14 ranges from 14 (very poor) to 70 (very good); in addition, 2 global items (“medication” and “life satisfaction and contentment”) are each rated from 1 (very poor) to 5 (very good).^{24,25} The EQ-5D-5L Health state score is obtained from a patient-completed visual analog scale for overall health state, ranging from 0 (worst imaginable health state) to 100 (best imaginable health state).²⁶

Safety and efficacy assessments were conducted at intervals of 1 to 6 weeks throughout the study.

2.4 | Data analysis

No formal sample size calculation was performed for this study. A total of 130 patients were planned to receive adjunctive brexpiprazole

treatment. This sample size was considered to be suitable for observing potential new safety and tolerability signals for adjunctive brexpiprazole in elderly patients.

Safety and tolerability analyses were performed in the safety population, defined as all patients who received ≥ 1 dose of brexpiprazole. Analyses comprised the incidence of treatment-emergent adverse events (TEAEs); the change from screening or baseline in movement disorder scales, standard safety assessments, and MMSE score; and the incidence of suicidality based on the C-SSRS. Descriptive statistics are presented for safety and tolerability outcomes.

Exploratory efficacy analyses were performed in the efficacy population, defined as all patients in the safety population with a valid baseline assessment and ≥ 1 valid postbaseline assessment of the MADRS total score. The baseline value was defined as the latest value obtained from either the screening visit or the baseline visit. Absolute rating scale scores (MADRS, CGI-S, Q-LES-Q-SF, and SASS) were summarized descriptively, based on the observed cases (OC) dataset; changes from baseline (and absolute CGI-I scores) were assessed using a mixed model for repeated measures (MMRM) (except for Q-LES-Q-SF global items, OC). The MMRM included site (sites with < 5 patients were pooled) and visit as fixed effects, and a baseline score-by-visit interaction term. For the MMRM of the CGI-I score, baseline CGI-S score was used as a covariate. EuroQoL 5 Dimensions 5 Levels Health state scores were summarized using an analysis of covariance (ANCOVA) model based on last observation carried forward (LOCF) data, with pooled site as a fixed effect and baseline score as a covariate. Rates of MADRS response (defined as a $\geq 50\%$ reduction from baseline in MADRS total score) and remission (defined as a $\geq 50\%$ reduction from baseline in MADRS total score and a MADRS total score ≤ 10) were calculated for the LOCF dataset.

3 | RESULTS

3.1 | Patients

Patient disposition is presented in Figure 1. A total of 132 patients were enrolled and treated, of whom 88 (66.7%) completed 26 weeks

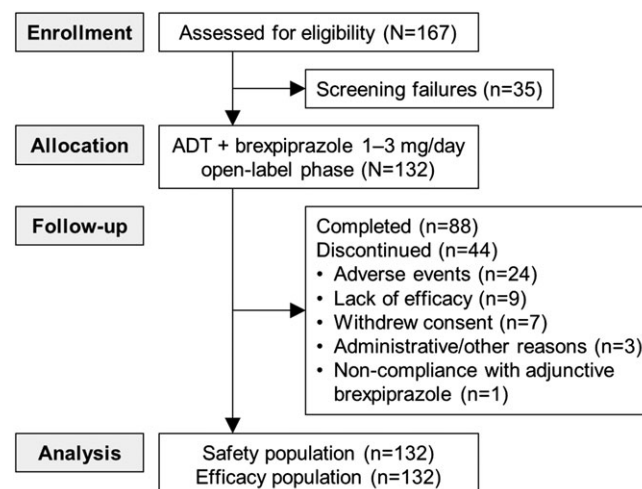


FIGURE 1 Patient disposition. ADT, antidepressant treatment

of treatment and 44 (33.3%) withdrew from the study, including 24 who withdrew because of AEs (18.2%).

Baseline demographic and clinical characteristics of enrolled patients are presented in Table 1. The mean (standard deviation [SD]) age at baseline was 71.4 (5.3) years, and a quarter of patients (26.5%) were aged ≥ 75 years. On average, patients had moderate-to-severe MDD at baseline, with moderately impaired quality of life, well-being, and social functioning. Patients had a low level of deficit in cognitive aspects of mental function.

At baseline, 124 patients (93.9%) had at least 1 concurrent medical, neurological, or psychiatric disorder, most commonly hypertension (51.5%), hypercholesterolemia (22.0%), persisting symptoms of menopause (19.7%), hypothyroidism (18.2%), osteoarthritis (16.7%), or gastroesophageal reflux disease (15.9%).

The distribution of ADTs at baseline, and continued during the study, was as follows: escitalopram, $n = 29$ (22.0%); citalopram, $n = 19$ (14.4%); sertraline, $n = 19$ (14.4%); fluoxetine, $n = 15$ (11.4%); duloxetine, $n = 13$ (9.8%); venlafaxine immediate/extended release (IR/XR), $n = 13$ (9.8%); mirtazapine, $n = 12$ (9.1%); paroxetine immediate/controlled release (IR/CR), $n = 7$ (5.3%); bupropion, $n = 3$ (2.3%); desvenlafaxine, $n = 1$ (0.8%); and vilazodone, $n = 1$ (0.8%).

The mean (SD) of each patient's mean and modal doses of brexpiprazole across the entire study was 1.8 (0.6) mg and 1.9 (0.7) mg, respectively.

3.2 | Safety and tolerability

Overall, 102 patients (77.3%) experienced at least 1 TEAE. Of these patients, 25 (18.9%) had only mild TEAEs, 66 (50.0%) had at least 1 moderate TEAE (but no severe TEAEs), and 11 (8.3%) had at least 1 severe TEAE. Fatigue and restlessness were the 2 most frequently

reported TEAEs, and the only TEAEs with incidence $\geq 10\%$ (Table 2).

Overall, 25 patients (18.9%) discontinued the study because of TEAEs, the most frequent of which were fatigue ($n = 4$; 3.0%), akathisia, tremor (both $n = 3$; 2.3%), anxiety, and depression (both $n = 2$; 1.5%). No patients died during the 26-week open-label treatment period. One death (because of myocardial infarction and myocardial rupture) occurred during the safety follow-up phase, which was considered by the investigator to be unrelated to adjunctive brexpiprazole.

A total of 4 patients (3.0%) experienced a TEAE of fall during treatment with adjunctive brexpiprazole, which was reported as a

TABLE 2 Treatment-emergent adverse events (TEAEs)

	ADT + Brexpiprazole 1 to 3 mg/day (n = 132)
At least 1 TEAE, n (%)	102 (77.3)
Discontinuation because of TEAE, n (%)	25 (18.9)
TEAEs occurring in $\geq 5\%$ of patients, n (%)	
Fatigue	20 (15.2)
Restlessness	17 (12.9)
Increased appetite	13 (9.8)
Akathisia	11 (8.3)
Weight increased	11 (8.3)
Anxiety	10 (7.6)
Dizziness	10 (7.6)
Tremor	9 (6.8)
Insomnia	8 (6.1)
Nasopharyngitis	8 (6.1)
Back pain	7 (5.3)
Headache	7 (5.3)

ADT, antidepressant treatment.

TABLE 1 Baseline demographic and clinical characteristics

	ADT + Brexpiprazole 1 to 3 mg/day (n = 132)
Demographic characteristics	
Age (years), mean (SD)	71.4 (5.3)
≥ 75 years, n (%)	35 (26.5)
≥ 65 to < 75 years, n (%)	97 (73.5)
Female, n (%)	107 (81.1)
White, n (%)	130 (98.5)
BMI (kg/m^2), mean (SD)	28.1 (5.4)
Clinical characteristics	
Time since MDD diagnosis (years), median (range)	18.3 (0.3-56.5)
Number of lifetime depressive episodes, median (range)	4.0 (1.0-22.0)
MADRS total score, mean (SD)	26.9 (4.5)
CGI-S score, mean (SD)	4.3 (0.6)
Q-LES-Q-SF total score, mean (SD)	42.6 (8.3) ^a
EQ-5D-5L Health state score, mean (SD)	60.8 (19.4)
SASS total score, mean (SD)	29.0 (7.0)
MMSE total score, mean (SD)	28.7 (1.4)

ADT, antidepressant treatment; BMI, body mass index; CGI-S, Clinical Global Impressions-Severity of Illness; EQ-5D-5L, EuroQoL 5 Dimensions 5 Levels; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder; MMSE, Mini-Mental State Examination; Q-LES-Q-SF, Quality of Life Enjoyment and Satisfaction Questionnaire, Short Form; SASS, Social Adaptation Self-Evaluation Scale; SD, standard deviation.

^an = 131.

serious adverse event for 1 patient (0.8%). Extrapyramidal symptom-related TEAEs were reported by 21 patients (15.9%), most commonly akathisia ($n = 11$; 8.3%) and tremor ($n = 9$; 6.8%). All other EPS-related TEAEs (muscle spasms, masked facies, parkinsonism, and dyskinesia) occurred in ≤ 2 patients. Mean (standard error [SE]) scores on the movement disorder rating scales showed minor increases from baseline to week 26 (mSAS total score, 0.31 [0.15] points; BARS Global score, 0.08 [0.05] points; AIMS total score, 0.04 [0.04] points; all $n = 96$).

Weight increase was reported as a TEAE in 11 patients (8.3%) (Table 2). One patient (0.8%) who had a history of hypothyroidism experienced a TEAE of increased body weight that resulted in treatment discontinuation. Mean (SD) change in body weight from baseline was 0.9 (3.6) kg at week 26 ($n = 89$). A total of 16 patients (12.3%) had a $\geq 7\%$ weight increase from baseline, whereas 4 patients (3.1%) had a $\geq 7\%$ weight decrease from baseline. Aside from mild increases in mean prolactin level, there were no consistent clinically relevant findings observed with regard to laboratory measurements (including glucose, cholesterol, and triglycerides) (Table 3), or vital signs. The mean change from baseline in QT_c interval on ECG readings was small, and not considered to be clinically relevant.

TABLE 3 Laboratory assessments

Parameter	ADT + Brexpiprazole 1 to 3 mg/day ($n = 132$)
Glucose	
Fasting serum glucose (mg/dL), mean change ^a	4.05 ($n = 69$)
Fasting serum glucose normal to high (<100 mg/dL to ≥ 126 mg/dL), % (n/N) ^b	8.3 (4/48)
Fasting serum glucose impaired to high (≥ 100 and <126 mg/dL to ≥ 126 mg/dL), % (n/N) ^b	18.5 (5/27)
HbA1c (%), mean change ^a	0.04 ($n = 93$)
Lipids (fasting)	
Total cholesterol (mg/dL), mean change ^a	-3.79 ($n = 69$)
HDL cholesterol (mg/dL), mean change ^a	-4.88 ($n = 69$)
LDL cholesterol (mg/dL), mean change ^a	1.81 ($n = 69$)
Triglycerides (mg/dL), mean change ^a	-1.05 ($n = 69$)
Total cholesterol normal to high (<200 mg/dL to ≥ 240 mg/dL), % (n/N) ^b	2.9 (1/35)
HDL cholesterol normal to low (≥ 40 mg/dL to <40 mg/dL), % (n/N) ^b	6.8 (5/74)
LDL cholesterol normal to high (<160 mg/dL to ≥ 160 mg/dL), % (n/N) ^b	7.9 (5/63)
Triglycerides normal to high (<150 mg/dL to ≥ 200 and <500 mg/dL), % (n/N) ^b	12.7 (7/55)
Triglycerides normal/borderline to high (<200 mg/dL to ≥ 200 and <500 mg/dL), % (n/N) ^b	15.9 (10/63)
Prolactin	
Serum prolactin (ng/mL), mean change ^a	
Female	5.3 ($n = 78$)
Male	3.4 ($n = 15$)
Prolactin >2 \times ULN, % (n/N) ^c	
Female	1.0 (1/105)
Male	4.8 (1/21)
Prolactin >3 \times ULN, % (n/N) ^c	
Female	0.0 (0/105)
Male	4.8 (1/21)

ADT, antidepressant treatment; HDL, high-density lipoprotein; LDL, low-density lipoprotein; n/N, number of patients with potentially clinically relevant shift/total number of patients in category; ULN, upper limit of the normal range.

^aFrom baseline to week 26.

^bShift from baseline to any postbaseline visit.

^cAt any postbaseline visit (patients counted in all categories that apply).

The mean (SD) change in MMSE total score from baseline to last postbaseline assessment was -0.2 (1.6) points ($n = 119$).

One patient without suicidal ideation at baseline experienced treatment-emergent suicidal ideation (C-SSRS score of 1). There were no instances of suicidal ideation with intent or a plan (score of 4 or 5), no instances of suicidal behavior (score of 6-10), and no reports of suicide-related TEAEs.

3.3 | Efficacy

On the MADRS total score, patients' depressive symptoms improved on average over 26 weeks of brexpiprazole treatment (Figure 2A). The mean (SE) change from baseline in MADRS total score at week 26 was -14.5 (0.9) points (MMRM; Table 4). Most of the improvement in MADRS total score occurred during the first 14 weeks of adjunctive brexpiprazole treatment, although improvement continued to the end of the 26-week treatment period.

Other exploratory efficacy endpoints for depressive symptoms are presented in Table 4. Patients showed global improvement over 26 weeks, as measured by the CGI-S and CGI-I.

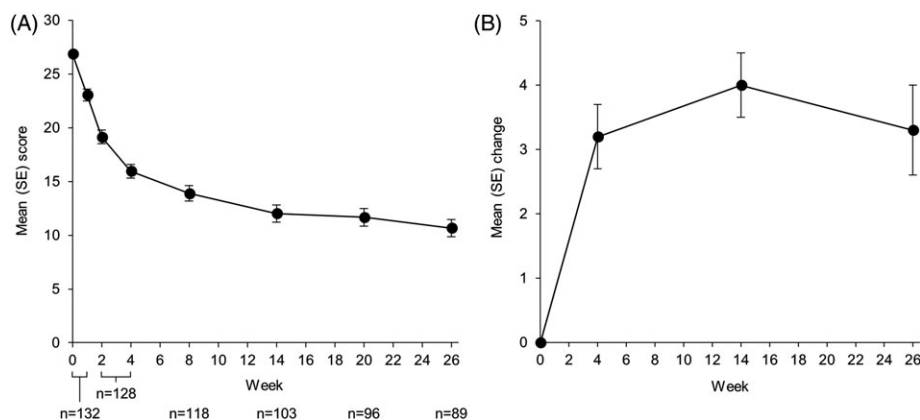


FIGURE 2 Efficacy outcomes over 26 weeks of treatment with adjunctive brexpiprazole 1 to 3 mg/day. A, Mean Montgomery-Åsberg Depression Rating Scale (MADRS) total score (observed cases). B, Mean change from baseline in Social Adaptation Self-Evaluation Scale (SASS) total score (mixed model for repeated measures; $n = 131$). Mean (SD) MADRS total score at baseline: 26.9 (4.5). Mean (SD) SASS total score at baseline: 29.0 (7.0). SD, standard deviation; SE, standard error

TABLE 4 Depressive symptom and global outcomes after 26 weeks of treatment with adjunctive brexpiprazole 1 to 3 mg/day

Variable	ADT + Brexpiprazole 1 to 3 mg/day ($n = 132$)
Mean (SE) change from baseline (MMRM)	
MADRS total score ^a	-14.5 (0.9)
CGI-S score ^b	-1.8 (0.1)
Mean (SE) score (MMRM)	
CGI-I score	2.0 (0.1)
MADRS response and remission (LOCF)	
MADRS response, ^c n (%)	66 (50.0)
MADRS remission, ^d n (%)	57 (43.2)

ADT, antidepressant treatment; CGI-I, Clinical Global Impressions-Improvement; CGI-S, Clinical Global Impressions-Severity of Illness; LOCF, last observation carried forward; MADRS, Montgomery-Åsberg Depression Rating Scale; MMRM, mixed model for repeated measures; SD, standard deviation; SE, standard error.

^aMean (SD) MADRS total score at baseline, 26.9 (4.5).

^bMean (SD) CGI-S score at baseline, 4.3 (0.6).

^cDefined as a $\geq 50\%$ reduction from baseline in MADRS total score.

^dDefined as a $\geq 50\%$ reduction from baseline in MADRS total score and a MADRS total score of ≤ 10 .

The SASS total score increased by a mean (SE) of 3.2 (0.5) points over the first 4 weeks of treatment with adjunctive brexpiprazole (MMRM); this improvement was maintained throughout the duration of the study (Figure 2B). The mean (SE) change from baseline in SASS total score at week 26 was 3.3 (0.7) points (MMRM; $n = 131$). Similarly, the Q-LES-Q-SF total score showed an initial mean (SE) increase of 5.3 (0.6) points after 4 weeks of treatment, which was maintained throughout the study (MMRM; $n = 130$). The mean (SE) change from baseline in Q-LES-Q-SF total score at week 26 was 4.6 (0.9) points (MMRM). Improvements were also observed on the 2 Q-LES-Q-SF global items, which had baseline mean (SD) scores of 3.1 (0.8) for medication ($n = 129$) and 2.8 (0.8) for overall life satisfaction and contentment ($n = 132$). The mean (SE) changes from baseline to week 26 on these global items were 0.5 (0.1) points ($n = 90$) and 0.8 (0.1) points ($n = 93$), respectively (OC).

For the EQ-5D-5L Health state score, the mean (SD) score at baseline was 60.8 (19.4) points ($n = 132$). The mean (SE) change from baseline to last assessment was 7.0 (1.8) points (LOCF; $n = 125$).

4 | DISCUSSION

Adjunctive brexpiprazole 1 to 3 mg/day was generally well tolerated over 26 weeks in elderly patients with moderate-to-severe MDD who had experienced an inadequate response to prior ADT. Fatigue and restlessness were the most commonly reported TEAEs, occurring with an incidence of 15.2% and 12.9%, respectively. Other published studies have considered the antipsychotics quetiapine and aripiprazole in elderly populations with depression. In a randomized, double-blind study of quetiapine XR as monotherapy in 338 elderly patients with MDD (age range 66-89 years), quetiapine was associated with a high incidence of somnolence (33.1% versus 8.1% with placebo) (as well as some fatigue; 7.8% versus 4.1% with placebo).²⁷ Similarly, small, open-label studies of adjunctive quetiapine in elderly patients with inadequate response to ADT have reported high rates of sedating side effects.^{28,29} Considering adjunctive aripiprazole, a 12-week randomized, double-blind study in 181 elderly patients (≥ 60 years) with inadequate response to ADT had a high incidence of akathisia, which was reported by 26.4% of patients receiving aripiprazole, compared with 12.2% in the placebo group.⁵ Thus, in elderly patients with depression, quetiapine shows a propensity for sedating side effects, whereas aripiprazole shows a propensity for activating side effects. In clinical trials of nonelderly adults with MDD and inadequate response to ADT, brexpiprazole has shown favorable numbers needed to harm versus aripiprazole with regard to akathisia (15 versus 5) and restlessness (33 versus 10), and versus quetiapine XR with regard to somnolence (24 versus 5).³⁰

The proportion of patients discontinuing because of TEAEs in the present study was consistent with the findings of previous open-label, long-term studies of brexpiprazole in adult patients (aged 18-65 years) with MDD.³¹ As expected, mild prolactin elevations were observed in the present study, but were not associated with TEAEs. The proportion of patients with prolactin levels $>2\times$ the upper limit of normal was also low and consistent with the previous long-term studies of

brexpiprazole in adult patients (18-65 years) with MDD.³¹ Body weight increased by an average of 0.9 kg over 26 weeks in the present study, with most of the gain occurring in the first 3 months of brexpiprazole treatment. The incidence of $\geq 7\%$ weight increase from baseline was lower than reported in the other long-term brexpiprazole studies (although the previous studies were 52 weeks in duration).³¹ There was no indication that the weight gain observed in the present study was associated with clinically meaningful changes in metabolic parameters, which is consistent with the findings of other studies in the brexpiprazole clinical development program. In the randomized, double-blind study of adjunctive aripiprazole in elderly patients, it is notable that, while modest weight gain was observed over 12 weeks (1.9 kg on average), only about 30% was because of body fat gain.⁵ Thus, it can be hypothesized that modest weight gain in elderly patients, such as that observed with aripiprazole and brexpiprazole, may represent a return to premorbid weight because of the successful treatment of depression.³²

Exploratory efficacy endpoints indicated that patients' depressive symptoms improved while receiving adjunctive brexpiprazole 1 to 3 mg/day. Improvement occurred predominantly during the first 14 weeks of adjunctive brexpiprazole treatment, and continued throughout the remainder of the 26-week treatment period. Early improvements in quality of life and social functioning were observed (at week 4, the first postbaseline assessment) and were sustained for the remainder of the 26-week treatment period. Improvement in social functioning with adjunctive brexpiprazole, as measured by SASS total score, has also been shown in younger patients (18-35 years) with MDD and an inadequate response to prior ADT.³³ Thus, there is evidence that brexpiprazole can improve social functioning in both the young and the elderly.

Although limited by its open-label, noncomparative design, the promising results of the Aquila study suggest that further research is warranted into the use of adjunctive brexpiprazole by elderly patients with MDD.

Overall, long-term (26-week) adjunctive treatment with brexpiprazole 1 to 3 mg/day was well tolerated in elderly patients with MDD who had experienced an inadequate response to prior ADT. Improvements were observed in depressive symptoms, social functioning, and quality of life.

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