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# Two randomized, double-blind, placebo-controlled trials and one open-label, long-term trial of brexpiprazole for the acute treatment of bipolar mania

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## Abstract

**Background:** Brexpiprazole is a dopamine/serotonin receptor partial agonist (D<sub>2</sub>, 5-HT<sub>1A</sub>) and antagonist (5-HT<sub>2A</sub>) approved for treatment of schizophrenia and major depressive disorder (adjunct to antidepressants).

**Aims:** This study aimed to investigate brexpiprazole as monotherapy in acute mania (bipolar I disorder) in two short-term (ST) studies (study 080 and study 081) and one open-label (OL) extension (study 083).

**Methods:** ST studies were three-week randomized, double-blind, flexible dose (2–4 mg/day), placebo-controlled studies. The primary endpoint was mean change in Young Mania Rating Scale (YMRS) total score from baseline to day 21. The OL study was a 26-week flexible dose (2–4 mg/day) study for patients completing the ST studies.

**Results:** A total of 164 and 158 (study 080) and 170 and 162 (study 081) inpatients with DSM-5 mania with/without mixed features were randomized to placebo or brexpiprazole, respectively. The primary analyses did not show a statistically significant difference between brexpiprazole and placebo: study 080: least squares mean difference (95% confidence limits): 0.14 (–1.74, 2.03),  $p=0.8797$ ; study 081: –1.62 (–3.56, 0.32),  $p=0.1011$ . OL study patients ( $n=381$ ) demonstrated a gradual improvement in YMRS total score. Akathisia was the only adverse event, with an incidence of  $\geq 5\%$  with brexpiprazole and more than placebo in the ST studies, or  $\geq 5\%$  in the OL study. Brexpiprazole was more efficacious in patients with impaired or no insight (predominantly EU patients) than in patients with excellent insight (predominantly US patients).

**Conclusions:** Further studies are necessary to address the potential efficacy of brexpiprazole in acute mania, which should ensure that the study sample is severe enough (especially with regard to insight), and that the dose/titration schedule is not too modest.

## Keywords

Bipolar I disorder, brexpiprazole, dopamine, serotonin receptor partial agonist and antagonist, insight, clinical trial

## Introduction

Bipolar disorder is a lifelong illness characterized by recurrent manic and depressive episodes that may last for weeks or months, interspersed with periods of euthymia (El-Mallakh and El-Mallakh, 2013; Grande et al., 2016).

Global and national guidelines, including the World Federation of Societies of Biological Psychiatry, the British Association for Psychopharmacology, and the Canadian Network for Mood and Anxiety Treatments, support the use of dopamine/serotonin/noradrenaline receptor antagonists/partial agonists (atypical antipsychotics) for the acute and maintenance treatment of bipolar disorder (Goodwin et al., 2016; Grunze et al., 2009, 2018; Yatham et al., 2018). Despite the availability of effective treatments, one study showed that people with bipolar I disorder spent an average of 44% of their time ill over a mean 7.8-year follow-up period (Forte et al., 2015).

In a survey investigating patient preferences relating to medication non-adherence in 469 people with bipolar disorder, individuals identified weight gain and cognitive impairment as the most important factors affecting adherence, even more than most

efficacy attributes (such as severity and frequency of manic episodes; Johnson et al., 2007).

Brexpiprazole is a partial agonist at 5-HT<sub>1A</sub> and dopamine D<sub>2</sub> receptors, and an antagonist at 5-HT<sub>2A</sub> and noradrenaline alpha<sub>1B/2C</sub> receptors, all with subnanomolar affinity (Maeda et al., 2014). Brexpiprazole exhibits a favorable safety and tolerability profile in several psychiatric disorders, including schizophrenia and the adjunctive treatment of major depressive disorder (MDD).

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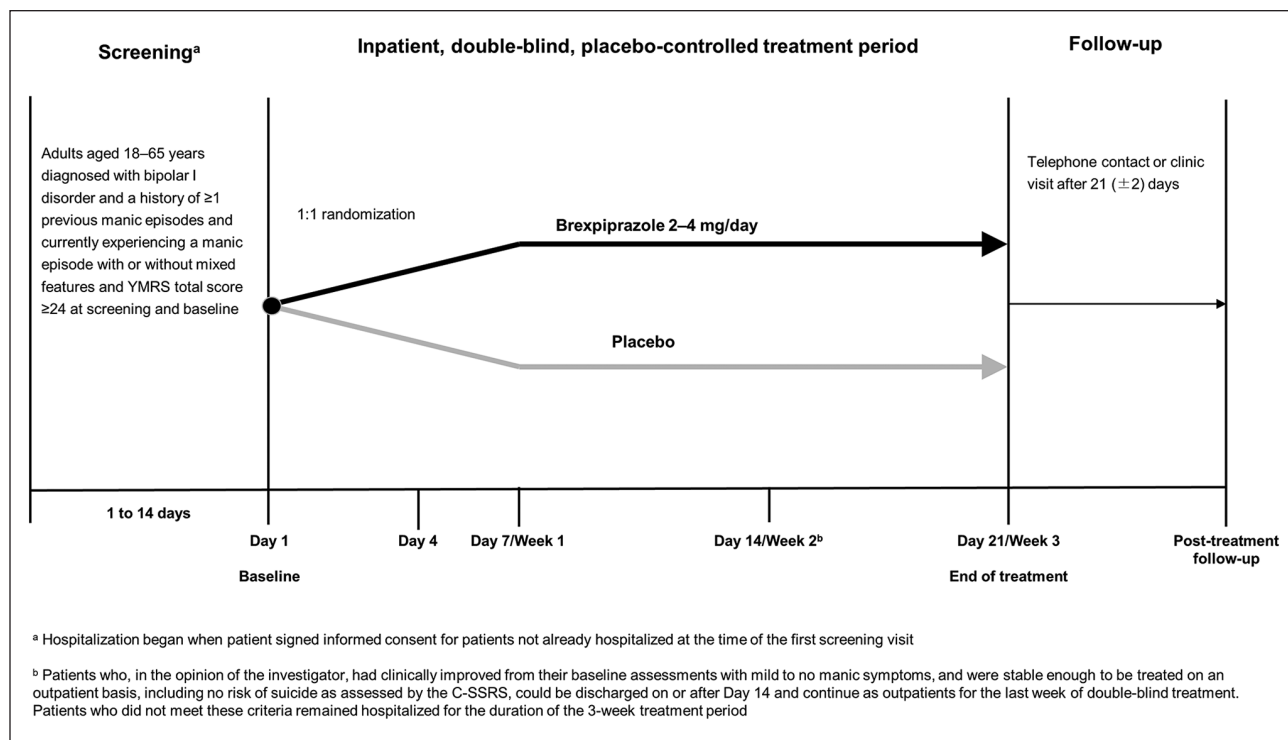
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**Figure 1.** Study design.

C-SSRS: Columbia Suicide Severity Rating Scale; YMRS: Young Mania Rating Scale.

At the recommended doses of brexpiprazole in the pivotal Phase III trials in schizophrenia and MDD, discontinuation rates due to adverse events (AEs) were low (Citrome, 2015; Correll et al., 2015; Hobart et al., 2018; Thase et al., 2015). Brexpiprazole is approved in various countries and regions for the treatment of schizophrenia and as adjunctive therapy to antidepressants for the treatment of MDD.

This paper presents the results from two randomized, double-blind, placebo-controlled, Phase III, short-term studies and one open-label extension study of brexpiprazole as monotherapy in patients diagnosed with mania, with or without mixed features, in the context of bipolar I disorder. These are the first controlled trials of this compound in acute mania.

## Methods

### Study design and patients

The short-term studies (ClinicalTrials.gov identifiers: NCT03259555 (study 080) and NCT03257865 (study 081)) were two three-week multicenter, randomized, double-blind, placebo-controlled studies of brexpiprazole in patients diagnosed with bipolar I disorder (current manic episode with or without mixed features) according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5; American Psychiatric Association, 2013; updated terminology replaces “mixed episodes” per DSM-IV, with the descriptor “with mixed features”).

The extension study (ClinicalTrials.gov identifier: NCT03287869 (study 083)) was a 26-week open-label study for patients completing study 080 or study 081, who, in the opinion of the

investigator, could potentially benefit from treatment with brexpiprazole.

Study 080 was conducted at 42 sites across three countries in EU (Bulgaria, Poland and Serbia) and the USA; study 081 was conducted at 38 sites across two countries in EU (Croatia and Ukraine) and the USA. Study 083 aimed to enroll 384 patients, with 60% coming from the USA and 40% from Europe.

The studies were designed and conducted in accordance with the principles of the Declaration of Helsinki, and the study protocols and amendments were approved by the governing Institutional Review Board or independent ethics committee for each investigational site or country, as appropriate. Eligible patients provided written informed consent before participating. Patients enrolling in the open-label extension study provided written informed consent before any study-related procedures specific to that study were performed.

The total duration of the short-term studies was up to eight weeks and included a screening period, a three-week double-blind treatment period, and, for patients not continuing in the extension study, a  $21 \pm 2$ -day safety follow-up period. The short-term study design is summarized in Figure 1.

During the double-blind treatment phase, patients received a starting dose of 2 mg/day brexpiprazole (or placebo) from days 1 to 3, followed by titration to 3 mg/day brexpiprazole (or placebo) on day 4. Patients could be titrated (or re-titrated) to a higher dose of brexpiprazole (or placebo), up to a maximum of 4 mg/day, based on treatment response and at the investigator’s discretion, from day 7 onwards. Patients who were unable to tolerate their current dose could be titrated down to a minimum of 2 mg/day any time after day 4. Patients enrolling in the extension study

started on 2 mg/day brexpiprazole regardless of previous treatment assignment, with an identical titration schedule as in the short-term studies.

The short-term study samples included men and women aged 18–65 years, with a DSM-5 diagnosis of bipolar I disorder and displaying an acute manic episode with or without mixed features requiring hospitalization. Diagnosis was confirmed by the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) and a history of one or more previous manic episodes (with or without mixed features), with manic symptoms of sufficient severity to require one of the following interventions: hospitalization or treatment with a mood stabilizer, or treatment with an antipsychotic agent. Eligible patients also had to have a Young Mania Rating Scale (YMRS; Young et al., 1978) score of  $\geq 24$  at screening and baseline.

Short-term study exclusion criteria included unwillingness to practice two different methods of birth control or remaining abstinent during the studies and for 30 days after the last dose of study medication; having a history of DSM-5 diagnosis other than bipolar I disorder, including schizophrenia, schizoaffective disorder, MDD, attention-deficit/hyperactivity disorder, delirium, dementia, amnesic, or other cognitive disorders; or a current DSM-5 diagnosis or history of substance or alcohol use disorder, or positive drug screen for cocaine or other drugs of abuse. Other exclusion criteria included having a current manic episode lasting for more than four weeks overall or requiring hospitalization for  $>21$  days for the current acute episode (to prevent patients with persistent manic symptoms from being exposed to placebo); being unresponsive to clozapine or only being responsive to clozapine; being considered resistant or refractory to treatment for manic symptoms by history; having had electroconvulsive treatment within the past two months; clinically significant abnormalities (as determined by laboratory testing); or taking concomitant medications that would interfere with the safety and efficacy assessments. The following medications were prohibited during the trials: all psychotropic agents (including, but not limited to, antipsychotics, anticonvulsants, antidepressants, mood stabilizers (including lithium)], prescription stimulants, and opioid analgesics), hypnotics (including ramelteon and other non-benzodiazepine sleep aids), antihistamines (except loratadine and cetirizine), varenicline, vitamins/nutritional supplements/herbal preparations (unless approved in advance by the medical monitor), investigational agents, and CYP2D6 inhibitors or CYP3A4 inhibitors and inducers. Benzodiazepines were prohibited, except for lorazepam rescue therapy for the short-term management of anxiety, agitation, and insomnia, which must not be administered in the eight hours prior to scheduled efficacy and safety scale assessments.

The extension study consisted of a 26-week open-label treatment period, and a  $21 \pm 2$ -day safety follow-up period. To be eligible for the extension study, patients were required *not* to have severity of bipolar symptoms that, in the opinion of the investigator, would require hospitalization.

### Randomization and masking

Following the screening period, patients were randomized to receive either flexible doses (2–4 mg/day) of brexpiprazole or placebo provided in identical blister cards.

Treatment assignments were based on a fixed-block computer-generated randomization code provided by the Biometrics

Department of Otsuka Pharmaceutical Development and Commercialization, Inc. The randomization was stratified by trial site and designed to allocate patients to a treatment regimen in a 1:1 ratio. Sponsor personnel, including those involved in monitoring, data management, and data analysis, did not have access to the treatment code during the trial.

### Endpoints

Short-term efficacy parameters were assessed at baseline and on days 4, 7, 14, and 21. The primary endpoint in studies 080 and 081 was mean change in YMRS total score from baseline to day 21. The YMRS consists of 11 items that assess the core symptoms of mania: (1) elevated mood, (2) increased motor activity/energy, (3) sexual interest, (4) sleep, (5) irritability, (6) speech (rate and amount), (7) language/thought disorder, (8) content, (9) disruptive/aggressive behavior, (10) appearance, and (11) insight. The severity of four items (items 5, 6, 8, and 9) is graded from 0 (best) to 8 (worst), while the other seven items are graded from 0 (best) to 4 (worst). The YMRS total score is the sum of all the items; possible scores range from 0 (best) to 60 (worst).

The key secondary endpoint in studies 080 and 081 was change from baseline to day 21 in Clinical Global Impression—Bipolar version (CGI-BP; Spearing et al., 1997) severity of illness score in mania, which is scored from 1 (normal, not ill at all) to 7 (very severely ill).

Other secondary endpoints in studies 080 and 081 included change in YMRS total score from baseline for each study visit besides day 21; YMRS response rate, where response was defined as  $\geq 50\%$  reduction in YMRS total score from baseline or YMRS total score  $\leq 12$ ; and YMRS remission rate, where remission was defined as YMRS total score  $\leq 12$ .

Safety was assessed by spontaneous reporting of AEs, clinically significant changes in electrocardiogram (ECG) parameters, vital signs, clinical laboratory tests, changes in body weight, and physical examination. Suicidality was assessed using the Columbia Suicide Severity Rating Scale (C-SSRS; Posner et al., 2011).

In study 083, the primary endpoint was the safety and tolerability of brexpiprazole, as assessed by the frequency and severity of AEs. ECG parameters, vital signs, clinical laboratory tests, changes in body weight, physical examination, and C-SSRS were also assessed. Change from baseline in YMRS total score and CGI-BP severity of illness score in mania were assessed as exploratory efficacy endpoints.

### Statistical methods

The power calculations for studies 080 and 081 were each based on an expected between-group difference versus placebo of  $-4.5$  (standard deviation (*SD*) = 12) in the mean change from baseline to day 21 of the double-blind treatment phase in YMRS total score. The planned sample size of 304 evaluable patients in each short-term study (152 in each treatment arm) would yield at least 90% power to detect the treatment effects at a two-tailed significance level of 0.05.

The sample size of the open-label extension study (study 083) was not based on statistical power considerations, but rather on International Conference on Harmonisation/Good Clinical Practice (ICH/GCP) requirements, aiming to achieve a target completion of approximately 175 patients at six months.

Safety analyses were based on all randomized patients who took at least one dose of study medication in the double-blind treatment phase. Efficacy analyses were based on all randomized patients who took at least one dose of study medication in the double-blind treatment phase and who had both a baseline value and at least one post-randomization YMRS total score evaluation during the double-blind treatment phase.

Each short-term study was analyzed separately, as outlined in their respective protocols. The primary efficacy analysis was performed by fitting a mixed-effect model repeated measure analysis with an unstructured variance covariance structure in which the change from baseline in YMRS total score during the double-blind treatment phase was the dependent variable based on all available data. The model included fixed class effect terms for treatment, trial site, visit week, and an interaction term of treatment by visit week. The model also included the interaction term of baseline YMRS total scores by visit week as covariates. The primary comparison between the brexpiprazole group and the placebo group at day 21 of the double-blind treatment phase was estimated as the difference between least squares (LS) means utilizing the computing software SAS procedure PROC MIXED. The comparison between the brexpiprazole group and placebo group was tested at a significance level of 0.05 (two-sided).

Subgroup analyses were performed, looking at treatment differences in mean change in YMRS total score from baseline to day 21, stratified by sex, age, region, and race.

Long-term data were analyzed using descriptive statistics, with observed cases.

### Post hoc analysis of the effect of insight

Prompted by findings by Welten et al. (2016), a post hoc analysis was performed, assessing whether YMRS item 11 (“insight”) modifies the effect of brexpiprazole compared to placebo on the mean change in YMRS score from baseline to endpoint.

A score of 0 is described as “excellent insight” (patient admits illness, agrees with need for treatment); a score of 1 as “good insight” (patient admits to being possibly ill); a score of 2 as “moderate insight” (patient admits behavior change but denies illness); a score of 3 as “poor insight” (patient admits possible change in behavior but denies illness); and a score of 4 as “no insight” (patient denies any behavior change).

The post hoc analysis was performed on short-term study data, with pooled brexpiprazole and pooled placebo groups. A multilevel mixed effect linear regression analysis with a random intercept for study was performed. Similarly, to assess whether insight modifies the effect of treatment on response and remission rates based on YMRS, two multilevel mixed effect logistic regression analyses were performed with a random intercept for study, using a likelihood ratio test to investigate the interaction of treatment group and level of insight. “Excellent insight” (score 0 on item 11) and placebo arm were used as reference groups. All findings were adjusted for age, body mass index, sex, and illness severity at baseline.

## Results

### Patients

Study 080 was initiated on 14 September 2017 and completed on 2 January 2019, while study 081 was initiated on 19 September 2017 and completed on 23 January 2019. In the

studies, a total of 538 and 537 patients were screened, and 322 and 333 were randomized, respectively. Most patients from the EU in studies 080 and 081 (54.5% and 81.9%, respectively) were hospitalized at screening. Corresponding figures for US patients were 19.3% and 21.8%. In both studies, the most common primary reasons for discontinuation were withdrawal of consent to participate by the patient (10.9% and 12.0%, respectively) and AEs (3.1% and 3.6%, respectively). Overall completion rates for the studies were 80.1% and 79.0%, respectively (Figure 2(a) and (b)).

Baseline demographic and clinical characteristics were similar between the treatment groups in both short-term studies (Table 1).

Study 083 was initiated on 24 October 2017 and completed on 31 July 2019. A total of 381 patients were enrolled in the study (Table 1). Of these, 188 patients had previously received brexpiprazole, and 193 had previously received placebo in either study 080 or study 081. The most frequently reported reasons for discontinuation overall were withdrawal of consent to participate by the patient (20.7%), lost to follow-up (8.4%), and AEs (6.8%). Overall, 53.8% of all enrolled patients completed the study.

The mean daily dose of brexpiprazole was 3.21 mg in study 080, 3.22 mg in study 081, and 3.35 mg in study 083. The titration intensity differed between EU and US sites, with 79.6% and 80% of EU patients in study 080 and study 081, respectively, reaching the 4 mg dose, while the corresponding figures for US patients were 59.6% and 65.8%.

In the short-term studies, lorazepam was the only concomitant psychoactive medication used by  $\geq 10\%$  of patients. For the brexpiprazole and placebo groups, respectively, lorazepam was used by 38.0% and 38.0% of patients in study 080, and by 26.5% and 22.9% of patients in study 081. In study 083, no concomitant medications were used by  $\geq 10\%$  of patients.

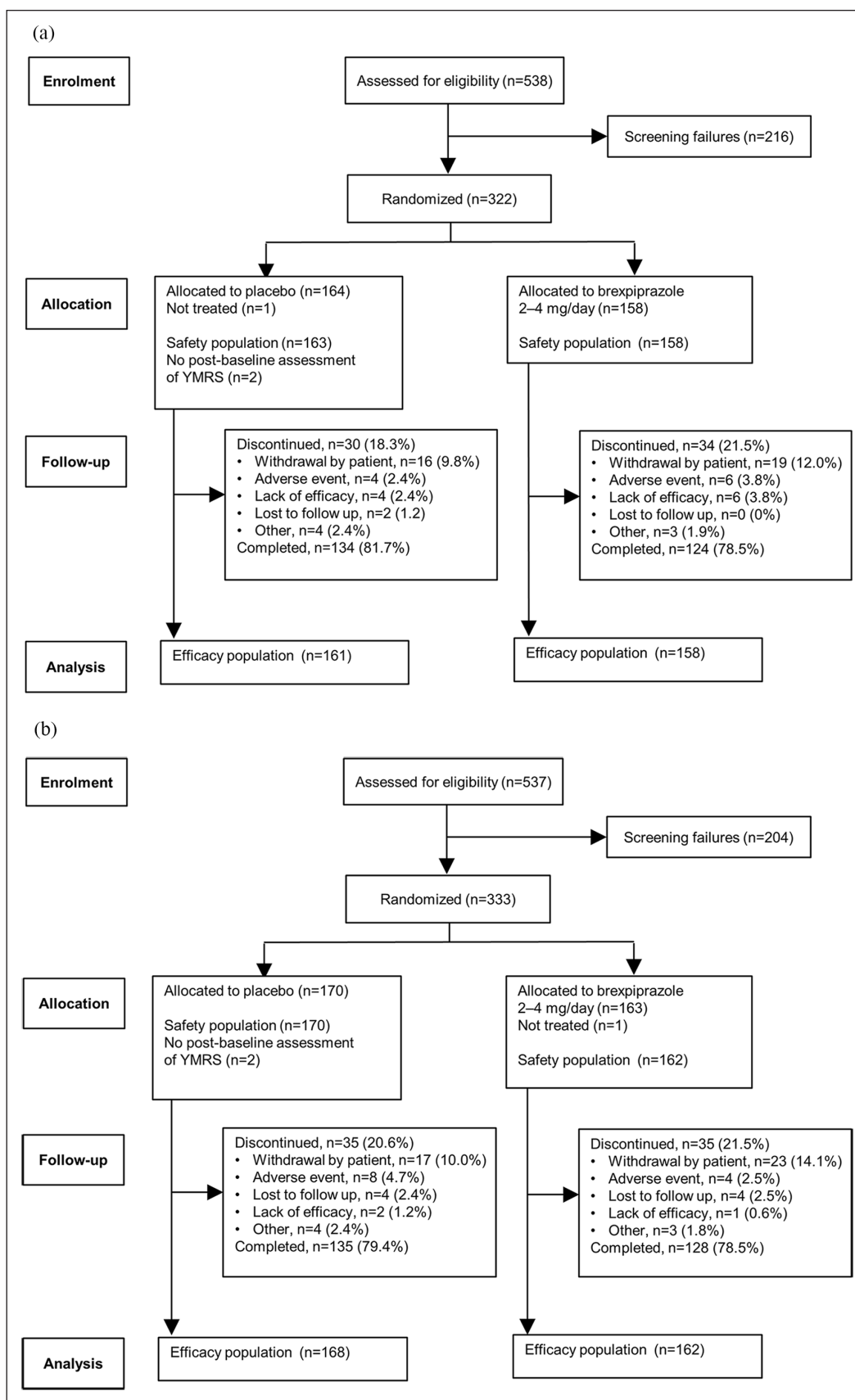
### Short-term efficacy

In study 080 and in study 081, the primary efficacy analysis of change from baseline to day 21 in YMRS total score failed to show a statistically significant difference between brexpiprazole and placebo: study 080—LS mean difference 0.14 (95% confidence limits (CLs)  $-1.74, 2.03$ ),  $p=0.8797$ ; study 081—LS mean difference  $-1.62$  (95% CLs  $-3.56, 0.32$ ),  $p=0.1011$ ; Figure 3(a) and (b)).

The key secondary analysis of change from baseline to day 21 in CGI-BP severity of illness score in mania showed a difference between brexpiprazole and placebo in study 081 (LS mean difference:  $-0.26$  (95% CLs  $-0.51, -0.01$ )) with a nominal  $p$ -value of 0.0441, but not in study 080 (LS mean difference: 0.09 (95% CLs  $-0.14, 0.32$ ); nominal  $p$ -value = 0.4632).

### Effect of region on short-term efficacy

In treatment-by-subgroup (sex, age, region, and race) interaction analyses, none of the subgroup interactions at day 21 were significant at the 0.05 level except for the treatment-by-region interaction term in study 081 ( $p=0.0016$ ). There was a difference between brexpiprazole and placebo in change from baseline to day 21 in YMRS total score in patients from the EU in study 081 (LS mean difference:  $-6.42$  (95% CLs  $-9.79, -3.05$ )), with a nominal  $p$ -value of 0.0003, but not in study 080 (LS mean difference:  $-2.38$  (95% CLs  $-5.10, 0.34$ ); nominal  $p$ -value = 0.0858; Figure 4(a) and (b)).

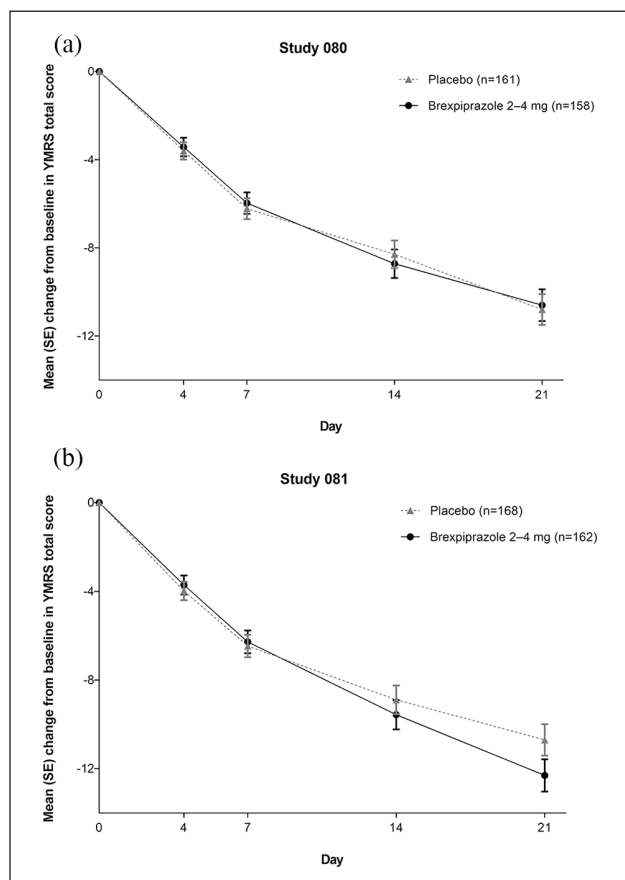


**Figure 2.** Study flow chart: (a) study 080; (b) study 081.  
YMRS: Young Mania Rating Scale.

**Table 1.** Baseline demographic and clinical characteristics.

	Short-term studies				Open-label extension
	080		081		083
	Placebo (N=164)	Brexiprazole 2–4 mg (N=158)	Placebo (N=170)	Brexiprazole 2–4 mg (N=163)	Brexiprazole 2–4 mg (N=381)
<b>Demographic characteristics</b>					
Age (years), <i>M</i> ( <i>SD</i> )	44.5 (11.2)	43.4 (11.7)	44.3 (12.0)	44.6 (10.7)	45.8 (11.2)
Male, <i>n</i> (%)	81 (49.4)	78 (49.4)	88 (51.8)	78 (47.9)	192 (50.4)
Caucasian, <i>n</i> (%)	113 (68.9)	95 (60.1)	102 (60.0)	90 (55.2)	275 (72.2)
BMI (kg/m <sup>2</sup> ), <i>M</i> ( <i>SD</i> )	27.8 (5.6)	28.2 (5.4)	28.9 (5.6)	29.3 (5.4)	28.5 (5.4)
Time since initial diagnosis (months), <i>M</i> ( <i>SD</i> )	166.2 (114.4)	182.4 (113.0)	181.3 (129.5)	160.1 (124.2)	167.7 (117.5)
Time since last manic episode (months), <i>M</i> ( <i>SD</i> )	24.0 (37.4)	25.3 (43.2)	28.3 (51.0)	30.6 (46.3)	31.6 (47.9)
<b>Clinical characteristics</b>					
YMRS total score, <i>M</i> ( <i>SD</i> )	30.5 (4.2)	30.4 (4.7)	30.7 (4.0)	30.7 (4.3)	18.8 (8.8)
CGI-BP severity of illness score in mania, <i>M</i> ( <i>SD</i> )	4.6 (0.6)	4.6 (0.6)	4.6 (0.6)	4.7 (0.6)	3.4 (1.1)
MADRS total score, <i>M</i> ( <i>SD</i> )	10.1 (4.9)	10.9 (5.6)	10.5 (5.1)	10.5 (5.4)	7.0 (5.8)
GAF score, <i>M</i> ( <i>SD</i> )	48.4 (8.6)	49.3 (8.7)	50.8 (10.1)	50.7 (9.2)	62.3 (12.4)

BMI: body mass index; CGI-BP: Clinical Global Impression—Bipolar Version; GAF: Global Assessment of Functioning; M: mean; MADRS: Montgomery-Åsberg Depression Rating Scale; SD: standard deviation; YMRS: Young Mania Rating Scale.



**Figure 3.** Primary efficacy analysis—mean change from baseline to day 21 in YMRS total score: (a) study 080; (b) study 081. SE: standard error; YMRS: Young Mania Rating Scale.

### Effect of baseline level of insight on short-term efficacy

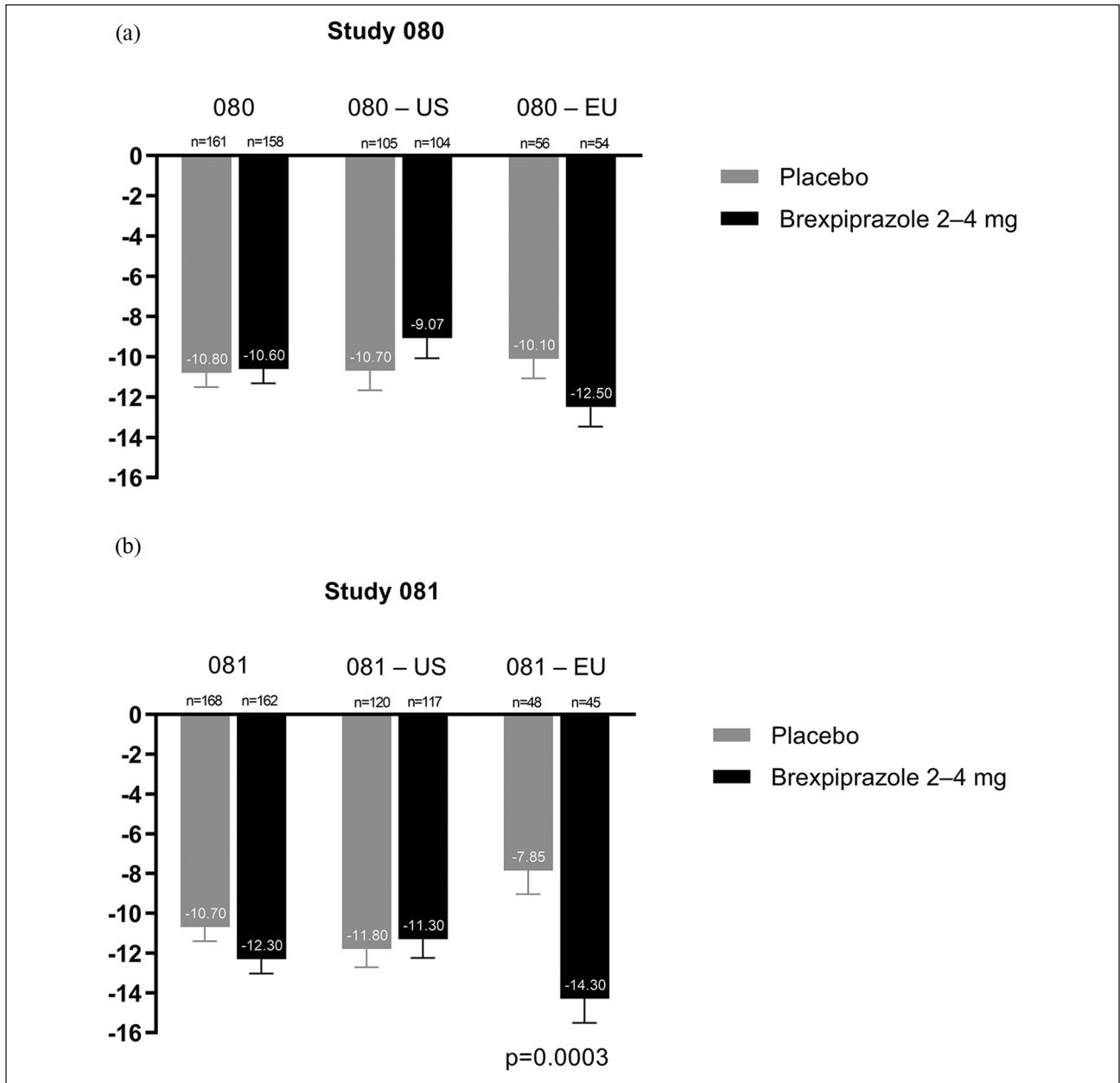
Examination of YMRS line item baseline scores for studies 080 and 081 revealed differences in baseline levels of insight (line item #11) between patients from the US and EU (Table 2).

In both studies, patients from the US had on average “excellent insight” (range 0.45–0.75), while patients from the EU had “good insight” to “moderate insight” (range 1.82–2.04) at baseline. Baseline severity as measured by YMRS total score was not different between regions, but US patients had higher scores on line item #8 (“content”) compared to EU patients.

When pooling the studies and presenting baseline insight scores by region, a total of 282 (63.2%) US patients had “excellent insight,” 101 (22.6%) had “good insight,” 40 (9.0%) had “moderate insight,” 17 (3.8%) had “poor insight,” and six (1.3%) had “no insight.” Thus, insight was impaired or absent (as defined by Welten et al., 2016) in 36.8% of the US patients. In contrast, insight was impaired or absent in 95.1% of the EU patients: 10 (4.9%) EU patients had “excellent insight,” 52 (25.6%) had “good insight,” 90 (44.3%) had “moderate insight,” 44 (21.7%) had “poor insight,” and seven (3.4%) had “no insight.”

The post hoc analysis (as conducted by Welten et al., 2016) of both studies pooled showed that baseline level of insight significantly modified the efficacy of treatment as measured by YMRS mean change score ( $p=0.0013$ ) and response rate ( $p=0.0298$ ), with greater improvement in patients with “impaired” or “no insight” than in patients with “excellent insight.”

Compared to “excellent insight,” the adjusted effect of baseline insight on the effect of treatment on the mean change score was  $-4.412$  (standard error: 1.364; 95% CLs  $-7.091, -1.733$ ) for “impaired” or “no insight.”



**Figure 4.** Mean change from baseline to day 21 in YMRS total score by region: (a) study 080; (b) study 081. YMRS: Young Mania Rating Scale.

Compared to “excellent insight,” the adjusted odds ratio of baseline insight on the effect of treatment on response rate was 2.1789 (95% CLs 1.080, 4.397) for “impaired” or “no insight.”

Remission rate was unaffected by baseline level of insight (odds ratio=2.0651 (95% CLs 0.725, 5.881),  $p=0.1741$ ).

#### Long-term efficacy

The mean (*SD*) change from baseline in YMRS total score demonstrated gradual numeric improvement (mean decrease) to week 26 ( $-14.0$  (8.9)) and last visit ( $-10.9$  (9.8)) following long-term treatment with open-label brexpiprazole (Figure 5).

Similarly, the mean (*SD*) change from baseline in CGI-BP severity of illness score in mania demonstrated numeric improvement (mean decrease) to week 26 ( $-1.8$  (1.2)) and last visit ( $-1.4$  (1.3)) following long-term treatment with open-label brexpiprazole.

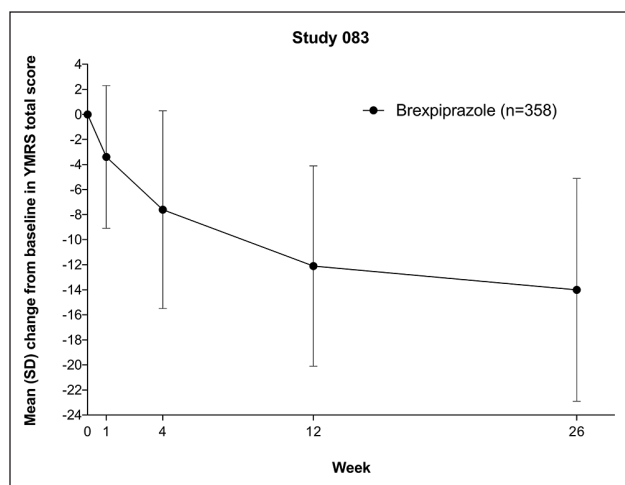
#### Short-term safety and tolerability

AE data from the studies are presented in Table 3, including treatment-emergent AEs (TEAEs) reported by at least 2% of patients in the brexpiprazole group and with an incidence greater than the placebo group in the short-term studies or in at least 2% of

**Table 2.** Baseline YMRS total score and line item scores in studies 080 and 081 by region.

Baseline scores	080		080 (US)		080 (EU)		081		081 (US)		081 (EU)	
	Placebo (N=161)	Brexpipra- zole 2–4 mg (N=158)	Placebo (N=105)	Brexpipra- zole 2–4 mg (N=104)	Placebo (N=56)	Brexpipra- zole 2–4 mg (N=54)	Placebo (N=168)	Brexpipra- zole 2–4 mg (N=162)	Placebo (N=120)	Brexpipra- zole 2–4 mg (N=117)	Placebo (N=48)	Brexpipra- zole 2–4 mg (N=45)
YMRS total score	30.55	30.39	30.41	30.18	30.82	30.80	30.71	30.75	30.44	30.56	31.38	31.24
Elevated mood	2.89	2.92	2.82	2.86	3.04	3.04	2.94	2.93	2.91	2.92	3.02	2.93
Increased motor activity/energy	2.90	2.87	2.90	2.96	2.89	2.70	2.99	2.99	3.03	3.03	2.92	2.87
Sexual interest	1.82	1.89	1.60	1.60	2.23	2.44	1.96	2.12	1.88	2.06	2.17	2.27
Sleep	2.63	2.60	2.56	2.51	2.75	2.78	2.78	2.83	2.73	2.85	2.92	2.80
Irritability	3.95	3.77	4.18	3.93	3.52	3.44	3.83	3.87	3.90	3.91	3.65	3.76
Speech (rate and amount)	4.61	4.53	4.74	4.61	4.38	4.37	4.63	4.65	4.62	4.68	4.65	4.56
Language- thought disorder	2.37	2.42	2.46	2.48	2.20	2.30	2.39	2.38	2.48	2.47	2.15	2.13
Content	4.19	4.28	4.50	4.68	3.59	3.52	3.97	4.10	4.24	4.37	3.29	3.40
Disruptive- aggressive behavior	2.66	2.54	2.78	2.60	2.43	2.44	2.79	2.59	2.88	2.62	2.58	2.51
Appearance	1.48	1.44	1.22	1.21	1.98	1.89	1.51	1.41	1.30	1.19	2.02	1.98
Insight	1.05	1.13	0.64	0.75	1.82	1.87	0.92	0.90	0.48	0.45	2.02	2.04

YMRS: Young Mania Rating Scale.



**Figure 5.** Mean change from baseline to week 26 in YMRS total score. SD: standard deviation; YMRS: Young Mania Rating Scale.

patients in the open-label extension, TEAEs leading to discontinuation, and serious TEAEs.

The incidence of patients who reported at least one TEAE during the studies was similar in both treatment groups in study 080, but slightly higher overall and higher in the brexpiprazole group than in the placebo group in study 081. Akathisia was the only TEAE that occurred with an incidence of  $\geq 5\%$  in the brexpiprazole group and more than placebo in the short-term studies.

There were no deaths reported during the short-term studies.

The incidence of patients discontinuing the study due to TEAEs was similar between the treatment groups in study 080, and lower in the brexpiprazole group compared to the placebo group in study 081.

The incidence of serious TEAEs was higher in the brexpiprazole group compared to the placebo group in study 080, while there were no serious TEAEs reported in the brexpiprazole group in study 081.

Akathisia was the most common type of extrapyramidal symptom (EPS)-related TEAE reported during the short-term studies.

Mean changes from baseline for fasting glucose and lipid parameters were generally small and comparable between the treatment groups (Table 4). None of the changes were considered clinically meaningful. One patient in each treatment group in study 080 met the criteria for metabolic syndrome; no patients met the criteria in study 081. No TEAEs related to metabolic parameters were reported during the studies.

Mean (SD) weight gain from baseline to week 3 was 1.22 (2.45) kg in the brexpiprazole group and 1.10 (3.26) kg in the placebo group in study 080, and 1.88 (5.64) kg in the brexpiprazole group and 1.19 (3.59) kg in the placebo group in study 081. Mean changes in serum prolactin levels (Table 4), chemistry, hematology, and urinalysis were minimal and generally similar within the treatment groups. No meaningful differences between the treatment groups were seen in ECG parameters and vital signs.

No suicidal behavior was reported on the C-SSRS, and the incidence of emergent suicidal ideation was lower in the brexpiprazole groups compared to the placebo groups. No TEAEs related to suicidality were reported.

### Long-term safety and tolerability

Akathisia was the only TEAE that occurred, with an incidence of  $\geq 5\%$  in the open-label extension. No deaths were reported during the study.

Events that led to discontinuation reported in more than one patient were depression (six patients, 1.6%), mania (six patients, 1.6%), and suicidal ideation (two patients, 0.5%).



**Table 3.** Adverse events.

	Short-term studies				Open-label extension
	080		081		083
	Placebo (N=163)	Brexpiprazole 2–4 mg (N=158)	Placebo (N=170)	Brexpiprazole 2–4 mg (N=162)	Brexpiprazole 2–4 mg (N=368)
Patients with at least one TEAE	49 (30.1)	53 (33.5)	65 (38.2)	72 (44.4)	165 (44.8)
Discontinuation due to TEAE	5 (3.1)	5 (3.2)	8 (4.7)	4 (2.5)	26 (7.1)
Serious TEAEs	1 (0.6)	4 (2.5)	3 (1.8)	0	19 (5.2)
TEAEs occurring in at least 2% of patients in the brexpiprazole group and more than the placebo group in either of the short-term studies or in at least 2% of patients in the open-label extension					
Akathisia	2 (1.2)	8 (5.1)	4 (2.4)	13 (8.0)	25 (6.8)
Constipation	6 (3.7)	2 (1.3)	5 (2.9)	6 (3.7)	1 (0.3)
Dizziness	1 (0.6)	4 (2.5)	1 (0.6)	5 (3.1)	6 (1.6)
Insomnia	3 (1.8)	2 (1.3)	2 (1.2)	5 (3.1)	12 (3.3)
Weight increased	1 (0.6)	2 (1.3)	1 (0.6)	4 (2.5)	12 (3.3)
Somnolence	4 (2.5)	3 (1.9)	3 (1.8)	4 (2.5)	6 (1.6)
Diarrhea	4 (2.5)	1 (0.6)	4 (2.4)	4 (2.5)	4 (1.1)
Dry mouth	3 (1.8)	1 (0.6)	1 (0.6)	4 (2.5)	4 (1.1)
Dyspepsia	1 (0.6)	3 (1.9)	0	4 (2.5)	0
Nasopharyngitis	4 (2.5)	3 (1.9)	0	0	8 (2.2)
Headache	11 (6.7)	6 (3.8)	18 (10.6)	10 (6.2)	15 (4.1)
Tremor	1 (0.6)	0	0	2 (1.2)	11 (3.0)
Depression	1 (0.6)	0	0	0	14 (3.8)
Mania	2 (1.2)	2 (1.3)	3 (1.8)	2 (1.2)	9 (2.4)

Values are *n* (%).

TEAE: treatment-emergent adverse event.

Serious TEAEs were reported for 19 (5.2%) patients in the total sample. Serious TEAEs reported in more than one patient were depression (five patients, 1.4%) and mania (six patients, 1.6%). Overall, 26 (7.1%) patients experienced at least one TEAE that led to discontinuation.

Akathisia events (6.8%) were the most common type of EPS-related TEAE reported during the open-label treatment period, followed by tremor (3.0%), dystonia and parkinsonism (each 0.8%), and muscle spasms (0.5%). None of the TEAEs akathisia were considered serious.

Overall, small mean increases from baseline for fasting glucose, low-density lipoprotein cholesterol, and total cholesterol were observed following long-term treatment with open-label brexpiprazole in the total sample (Table 4). None of these changes were considered clinically meaningful.

Four patients (1.9% of the 206 who did not meet the criteria at baseline and who had a post-baseline result; two in each prior treatment group) met the criteria for treatment-emergent metabolic syndrome during the open-label treatment period. None of these four patients experienced a TEAE associated with metabolic syndrome.

Mean (*SD*) changes in body weight from baseline to week 26 and to last visit were 1.7 (4.6) kg and 1.0 (4.8) kg, respectively, in the total sample. Mean changes in serum prolactin levels (Table 4), chemistry, hematology, and urinalysis were small during the 26-week open-label treatment period. Mean changes from baseline to week 26 and to last visit in ECG parameters and vital signs were minimal and not considered clinically meaningful.

As reported on the C-SSRS, the incidence of emergent suicidal ideation was 3.0% in the total sample. TEAEs related to

suicidality (one event of suicidal behavior and three events of suicidal ideation) were reported for four patients. Two of the four events were serious TEAEs (one event of suicidal behavior and one event of suicidal ideation). Both events were considered severe in intensity and not related to study medication. The serious TEAE of suicidal ideation led to discontinuation of study medication.

## Discussion

Based on two short-term studies, brexpiprazole was not efficacious in acute mania at the chosen dosage and titration schedule. In both studies, the primary efficacy analysis of change from baseline to day 21 in YMRS total score failed to show a statistically significant difference between brexpiprazole and placebo. The key secondary analysis of change from baseline to day 21 in CGI-BP severity of illness score in mania showed a difference between brexpiprazole and placebo in study 081, but not in study 080.

Patients enrolling in the open-label extension study 083 demonstrated gradual numeric improvements to week 26 in YMRS total score and CGI-BP severity of illness score in mania.

As in previous studies in other indications, brexpiprazole was well tolerated (Citrome, 2015; Correll et al., 2015; Hobart et al., 2018; Thase et al., 2015).

In general, D<sub>2</sub> blockers are superior to placebo in acute mania (Vieta et al., 2018), but studies fail from time to time—a notable example being a study of two fixed doses of aripiprazole in acutely manic or mixed bipolar I hospitalized patients (El Mallakh et al., 2010). The aripiprazole study displayed a high

**Table 4.** Fasting glucose, lipid parameters and prolactin—changes from baseline to week 3 (short-term studies) and week 26 (open-label extension).

Laboratory assessments	Short-term studies				Open-label extension
	080		081		083
	Placebo	Brexpiprazole 2–4 mg	Placebo	Brexpiprazole 2–4 mg	Brexpiprazole 2–4 mg
Baseline glucose (mg/dL), (N), M (SD)	(N=143), 91.22 (9.75)	(N=144), 90.10 (10.46)	(N=160), 91.42 (10.90)	(N=150), 92.39 (10.63)	(N=328), 96.30 (16.33)
Glucose (mg/dL), (N), mean change (SD)	(N=113), 4.52 (17.56)	(N=104), 7.14 (21.52)	(N=116), 2.72 (15.84)	(N=113), 4.12 (16.11)	(N=177), 2.42 (23.46)
Baseline triglycerides (mg/dL), (N), M (SD)	(N=143), 132.45 (86.74)	(N=144), 126.19 (79.19)	(N=159), 132.52 (89.55)	(N=150), 129.49 (78.51)	(N=333), 139.98 (85.96)
Triglycerides (mg/dL), (M), mean change (SD)	(N=115), 4.43 (74.38)	(N=104), 6.16 (67.75)	(N=118), 1.40 (70.73)	(N=112), 16.79 (75.95)	(N=178), -1.76 (86.81)
Baseline total cholesterol (mg/dL), (N), M (SD)	(N=143), 191.29 (36.05)	(N=144), 186.02 (36.76)	(N=159), 192.60 (43.09)	(N=150), 189.99 (43.04)	(N=333), 191.49 (36.78)
Total cholesterol (mg/dL), (N), mean change (SD)	(N=115), -2.30 (33.36)	(N=104), 3.32 (28.89)	(N=118), -2.40 (36.38)	(N=112), 2.88 (34.95)	(N=178), 2.33 (36.55)
Baseline LDL cholesterol (mg/dL), (N), M (SD)	(N=139), 107.43 (31.43)	(N=143), 104.08 (31.80)	(N=157), 110.49 (38.99)	(N=150), 108.65 (36.86)	(N=328), 109.60 (33.31)
LDL cholesterol (mg/dL), (N), mean change (SD)	(N=110), -0.20 (27.67)	(N=102), 2.80 (26.54)	(N=116), -0.41 (31.30)	(N=108), -0.32 (29.71)	(N=170), 3.74 (31.89)
Baseline HDL cholesterol (mg/dL), (N), M (SD)					
Female	(N=77), 61.42 (16.23)	(N=74), 58.77 (15.76)	(N=77), 57.90 (15.30)	(N=79), 57.08 (16.53)	(N=333), 54.24 (15.74)
Male	(N=66), 54.27 (21.90)	(N=70), 55.14 (18.22)	(N=82), 52.55 (16.43)	(N=71), 53.59 (18.16)	
HDL cholesterol (mg/dL), (N), mean change (SD)					
Female	(N=58), -3.16 (13.88)	(N=52), -0.31 (12.18)	(N=54), -1.31 (11.21)	(N=58), 3.76 (13.69)	(N=178), -0.24 (13.76)
Male	(N=57), -4.09 (20.97)	(N=52), -2.12 (10.65)	(N=64), -2.42 (13.41)	(N=54), -1.50 (14.07)	
Baseline prolactin (ng/mL), (N), mean (median)					
Female	(N=83), 21.63 (10.79)	(N=80), 18.10 (10.14)	(N=82), 13.87 (7.40)	(N=85), 19.49 (9.48)	(N=184), 15.43 (11.24)
Male	(N=80), 8.48 (7.10)	(N=78), 10.63 (7.22)	(N=88), 10.51 (6.45)	(N=77), 10.30 (6.04)	(N=182), 9.92 (8.04)
Prolactin (ng/mL), (N), mean (median) change					
Female	(N=65), -11.19 (-2.29)	(N=65), 0.21 (3.43)	(N=62), -1.92 (0.37)	(N=64), -1.19 (4.94)	(N=99), 3.11 (-0.84)
Male	(N=69), 0.84 (1.22)	(N=58), 0.99 (1.91)	(N=73), -1.44 (-0.49)	(N=62), -0.42 (2.54)	(N=102), -0.40 (-0.29)

HDL: high-density lipoprotein; LDL: low-density lipoprotein; M: mean; SD: standard deviation.

placebo response rate, as in the current short-term studies with brexpiprazole. When excluding patients with less severe baseline symptoms from the analyses, the placebo response became less pronounced (El Mallakh et al., 2010). Yildiz et al. (2011) identified additional factors associated with greater drug–placebo differences, and these included trials with fewer study sites, younger age, male sex, and psychotic features.

Apart from factors that can be associated with a high placebo response, what can we learn from these studies of brexpiprazole in acute mania? Of note is that the titration schedule in the studies was markedly slower than in studies with aripiprazole (Keck et al., 2009) and cariprazine (Calabrese et al., 2015; Durgam et al.,

2015; Sachs et al., 2015), in which the maximum dose was reached after three to four days if not starting on the maximum dose (Keck et al., 2003; Sachs et al., 2006). In the brexpiprazole studies, maximum dose was not reached until day 7.

Furthermore, there was a clear effect of region, with numerical or nominally significant differences in favor of brexpiprazole versus placebo in patients from the EU but not in those from the US. This phenomenon is not new, and has been reported before in acute mania trials (Vieta et al., 2011) and in MDD (Thase et al., 2016). In study 081, the placebo response was greater in patients from the US than in those from the EU which will have contributed to this region effect.

Another factor contributing to these regional differences in efficacy could be differences in the study medication titration intensity between EU and US sites. Approximately 80% of EU patients reached the 4 mg dose, while the corresponding figure for US patients was approximately 65%.

There were also regional differences in whether patients were hospitalized or not at screening (i.e. when signing the informed consent form). Most EU patients in studies 080 and 081 were hospitalized at screening (range 54.5–81.9%). The corresponding figure for US patients was approximately 20% in both studies. The different hospitalization rates between the EU and the US most likely reflect different treatment practices and standards of care (e.g. hospitalization vs. outpatient treatment), but also that slightly different patient samples were recruited in the EU compared to the US.

Indeed, despite no differences in baseline YMRS total scores, baseline YMRS line item analysis revealed apparent differences in YMRS item 11 (“insight”) between patients from the EU and those from the USA. Insight was impaired or absent at baseline in 95.1% of EU patients, but only in 36.8% of US patients. This is potentially an important finding, as baseline insight has been shown to modify the efficacy of dopamine/serotonin/noradrenaline receptor antagonists in acute mania, with treatment being more efficacious in patients with impaired or no insight than in patients with excellent insight (Welten et al., 2016). Similarly to Welten et al., we found that the baseline level of insight significantly modified the efficacy of treatment as measured by YMRS mean change score ( $p=0.0013$ ) and response rate ( $p=0.0298$ ), with greater improvement in patients with impaired or no insight (predominantly EU patients) than in patients with excellent insight (predominantly US patients).

Despite the apparent lack of insight in EU patients, all patients had agreed to participate in the studies. Unfortunately, granular information on who signed the informed consent form (patient, guardian, or legal representative) is not available in the study databases.

Further limitations include a study sample limited by selection criteria, which may limit the generalizability of the results; the lack of an active comparator, meaning that it cannot be ascertained whether the present studies were negative or failed; the intermittent use of lorazepam rescue therapy by 23–38% of patients in the short-term studies, which may have increased the placebo effect; and the post hoc nature of the analyses of the impact of insight on efficacy.

In conclusion, brexpiprazole failed to separate from placebo in these short-term studies. While it is possible that brexpiprazole has no efficacy in acute mania, further studies are necessary to address this point, in which the study sample must be severe enough (especially with regard to insight) and the dose/titration schedule must not be too modest.

## Data availability

To submit inquiries related to Otsuka clinical research, or to request access to individual participant data (IPD) associated with any Otsuka clinical trial, please visit <https://clinical-trials.otsuka.com/>. For all approved IPD access requests, Otsuka will share anonymized IPD on a remotely accessible data sharing platform.

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