Synopsis – Study 15352A

Title of Study Interventional, open-label, flexible-dose, exploratory study of brexpiprazole as adjunctive treatment of sleep disturbances in patients with major depressive disorder
Investigators 12 investigators at 12 sites in the United States *Signatory investigator* – [redacted]
Study Site 12 sites in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 27 September 2013 *Last patient last visit* – 19 August 2014
Objectives • *Exploratory objectives*: – to explore the effect of brexpiprazole as adjunctive treatment to antidepressants on sleep architecture – to explore the effect of brexpiprazole on sleep quality (subjective assessment) – to explore the effect of brexpiprazole on biological rhythm – to explore the effect of brexpiprazole on psychomotor vigilance – to explore the effect of brexpiprazole on intensity of residual sedation following awakening – to explore the correlation of sleep architecture changes with subjective sleep quality changes, biological rhythm shifting, and psychomotor vigilance measures – to explore the effect of brexpiprazole as adjunctive treatment to antidepressants on depressive symptoms • *Safety objective*: – to evaluate the safety and tolerability of brexpiprazole 2 mg/day and 3 mg/day
Methodology • This was an interventional, multi-site, open-label, flexible-dose, exploratory study. • Patients were recruited from the study sites' own patient pool, by referrals to the study sites, or using advertisement. • Following a 2-week Lead-in Period with open-label treatment with current antidepressant treatment (ADT), patients who were still depressed, had sleep disturbances, and were not responding adequately to the ADT at the end of the Lead-in Period (Baseline Visit) were eligible to enter an 8-week open-label Treatment Period with brexpiprazole as adjunct to current ADT. The patients received brexpiprazole 1 mg/day during Week 1 and 2 mg/day during Week 2 (up-titration). From Weeks 3 to 8, patients received brexpiprazole 3 mg/day; depending on tolerability, the dose of brexpiprazole could be reduced to 2 mg/day, based on the investigator's judgement. • A safety follow-up visit was scheduled for 4 weeks after completion of the study or after withdrawal from the study. The ADT could be continued or changed at the discretion of the investigator during this period. • Efficacy and safety data were collected at regular intervals throughout the study.

Number of Patients Planned and Analysed

- 50 patients were planned for enrolment
- 44 patients were enrolled
- 44 patients were treated and 41 patients completed the study
- 3 patients withdrew – 1 due to non-compliance with investigational medicinal product (IMP), 1 due to lost to follow-up, and 1 due to administrative or other reasons
- 44 patients were analysed in the all-patients-treated set
- 44 patients were analysed in the full-analysis set

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of major depressive episode (MDE) associated with major depressive disorder (MDD) according to DSM-IV-TR™ criteria, who:

- were between 18 and 65 years of age (extremes included)
- has had the current MDE for ≥10 weeks
- had an inadequate response to ≥1 ADT in the current MDE
- was receiving one adequate selective serotonin reuptake inhibitor or serotonin-norepinephrine reuptake inhibitor as monotherapy ADT for ≥6 weeks and at the same dosage for ≥2 weeks
- had a MADRS total score >18 and a CGI-S score ≥3 at the Screening and Baseline Visit and a CGI-I score ≥3 at the Baseline Visit
- had <25% decrease in MADRS total score at the Baseline Visit compared to screening
- had sleep disturbances (difficulty falling asleep and/or difficulty staying asleep and/or problem waking up too early) concurrent to the MDE and confirmed by an insomnia severity index (ISI) score ≥8 at the Screening and Baseline Visit
- had sleep disturbances confirmed by mean latency to persistent sleep (LPS) ≥20 minutes on the 2 nights of polysomnography (PSG) monitoring, with an LPS of no less than 15 minutes on either night and an average sleep efficiency <85% on the 2 nights of PSG monitoring

Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Brexpiprazole – 1, 2, or 3 mg/day; tablets, orally; batch No. 2331228/1L88A001, 2331230/12A73A002, and 2331232/12A74A003

Duration of Treatment

8 weeks (2-week up-titration period, 6-week treatment period) followed by a 4-week safety follow-up period

Non-investigational Medicinal Products

ADT – one of the following: citalopram, escitalopram, fluoxetine, fluvoxamine, paroxetine, sertraline, desvenlafaxine, duloxetine, levomilnacipran, venlafaxine

Efficacy Assessments

- Assessment of depressive symptoms:
  - Montgomery Åsberg Depression Rating Scale (MADRS)
  - Clinical Global Impression – Severity of Illness (CGI-S)
  - Clinical Global Impression – Global Improvement (CGI-I)
- Assessment of sleep and sleep-related biological and chronobiological pattern:
  - Polysomnographic recording (PSG)
  - Consensus Sleep Diary for Morning (CSD-M)
  - Actigraphy (ACT)
  - Insomnia Severity Index (ISI)
  - Time of peak cortisol concentration and timing of Dim-Light Melatonin Onset (DLMO)
  - Biological Rhythms Interview of Assessment in Neuropsychiatry (BRIAN)
- Assessment of vigilance, cognition, and functioning:
  - Epworth Sleepiness Scale (ESS)
  - Psychomotor vigilance task (PVT)
  - Bond-Lader Visual Analogue Scale – sedation (BL-VAS-s)
  - Cognitive and Physical Functioning Questionnaire (CPFQ)

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, electrocardiograms (ECGs), and physical examinations, electronic self-reported Columbia Suicide Severity Rating Scale (eC-SSRS™)

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of brexpiprazole
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline efficacy assessment
- All exploratory efficacy analyses were conducted on the FAS. All safety analyses were conducted on the APTS.
- Continuous and ordinal endpoints:
  - The adjusted mean change from baseline was presented with two-sided 95% confidence intervals (CIs)
  - The key sleep parameters assessed were total sleep time [TST], sleep efficiency [SE], wake-time after sleep onset [WASO], number of awakenings [NAW], and sleep onset latency [SOL]. The changes from baseline to Week 8 for these sleep parameters (as assessed by CSD-M and ACT), as well as for ISI total score, ESS total score, CPFQ total score, BRIAN total score, and BRIAN subscale scores, were analysed using a restricted maximum likelihood (REML)-based mixed model repeated measures (MMRM) approach, with the site and week as fixed effects and baseline score-by-week interaction (FAS, observed cases [OC]). In cases where the model using an unstructured variance matrix did not converge, one of the following variance structures were used: Ante-dependence, Toeplitz, heterogeneous autoregressive, and compound symmetry. The change from baseline to Week 8 for depression symptom scores (namely, MADRS total score and CGI-S score) were analysed using the same MMRM model.
  - The CGI-I score at Week 8 was analysed using the same MMRM model including the CGI-S as baseline score
  - The change from baseline to Week 8 in LPS, TST, SE, WASO, NAW, SOL, and latency to rapid eye movement (REM) sleep, the duration and percentage of sleep stages 1, 2, 3, and REM sleep, as assessed by PSG were summarised using descriptive statistics. The change from baseline to Week 8 in response speed (1/RT), PVT number of lapses, BL-VAS-s, time to peak cortisol concentration, and time of DLMO were also summarised using descriptive statistics
- Binary data: response at Week 8 (defined as a ≥50% decrease from baseline in MADRS total score) and remission at Week 8 (defined as a MADRS total score ≤10 and a ≥50% decrease from baseline in MADRS total score) were presented as counts and percentages
- Correlation of Exploratory Endpoints:
  - Pearson and partial correlations were used to evaluate the relationship between the changes in sleep parameters (TST, SE, WASO, NAW, and SOL), as assessed by PSG, with changes in similar sleep parameters, as assessed by ACT and CSD-M. Similarly, Pearson and partial correlations were also used to evaluate the relationship between changes in LPS, as assessed by PSG, with changes in 1/RT, BRIAN total score, ISI total score, and CPFQ total score. Partial correlation was used to adjust for the effects of the corresponding baseline value. The correlation estimates, the two-sided 95% CIs, and the p-values were presented.
- *Safety analyses*:
  - The overall incidences of adverse events, serious adverse events (SAEs) and adverse events leading to withdrawal were summarised
  - Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight/body mass index (BMI), and ECG parameters were summarised by visit and last assessment using descriptive statistics. Values outside the reference ranges, as well as potentially clinically significant (PCS) values, were flagged and tabulated
  - The C-SSRS data were coded and summarised using the Columbia Classification Algorithm for Suicide Assessment (C-CASA) categories

Demography of Study Population

- Sixty-eight percent of the patients were women. The mean age of the patients was approximately 44 years and the majority of patients were either White (55%) or Black/African American (36%).
- The mean baseline weight of all patients was 81 kg and the mean baseline BMI was 29 kg/m^2. For men, the mean weight and BMI was 86 kg and 27 kg/m^2, respectively, and for women, they were 79 kg and 30 kg/m^2, respectively.
- At baseline, the mean MADRS total score (28 points) indicated that patients had *moderate* MDD, and the mean CGI-S score (4.2 points) indicated that patients were *moderately* to *markedly* ill. The mean ESS total score (9 points) indicated indicated that patients had daytime sleepiness and the mean ISI total score (19 points) indicated that patients had clinical insomnia of *moderate* severity. The mean CPFQ total score (27 points) indicated that patients had substantial cognitive and physical function impairment.

Efficacy Results

- In the FAS, MMRM analysis, the mean change from baseline in MADRS total score had decreased by 16 points at Week 8, indicating an improvement of the depressive symptoms after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in MADRS total score (-19.4 to -12.6) did not include zero and the size of the CI was small compared to the overall change observed.
- In the FAS, MMRM analysis, the mean change from baseline in CGI-S score had decreased by 1.8 points at Week 8, indicating an improvement of global symptoms after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in CGI-S score (-2.2 to -1.4) did not include zero and the size of the CI was small compared to the overall change observed.
- The mean CGI-I score was 2.2 points at Week 8. In the FAS, MMRM analysis, the mean CGI-I score was 2.1 points at Week 8, indicating an improvement of global symptoms after adjunctive treatment with brexpiprazole.
- The key sleep parameters, as assessed by PSG, CSD-M, and ACT, are summarised below:

Parameters	Baseline Value/Change from Baseline at Week 8 [Mean (Standard Error)]		
	PSG	CSD-M	ACT
SE (%)	70.46 (1.80)/ 10.44 (1.69)	65.06 (1.75)/ 13.43 (3.17)	82.75 (1.85)/ -1.33* (3.66)
TST (min)	338.22 (8.66)/ 49.02 (8.20)	329.60 (11.19)/ 69.88 (14.62)	367.63 (15.71)/ -9.02 (15.67)
SOL (min)	37.84 (2.58)/ -19.69 (3.78)	64.20 (4.23)/ -37.12* (12.27)	16.69 (3.49)/ -5.49* (3.58)
WASO (min)	88.41 (5.90)/ -26.36 (6.12)	122.70 (13.49)/ -42.90 (29.02)	49.94 (4.71)/ -6.11* (6.51)
NAW	11.84 (0.57)/ 0.06 (0.79)	2.83 (0.30)/ 0.04 (0.46)	14.46 (0.96)/ -1.98 (1.09)

* Partial correlation with PSG with a p-value <0.05
ACT = actigraphy; CSD-M = Consensus Sleep Diary for Morning; NAW = number of awakenings; PSG = polysomnography; SE = sleep efficiency; SOL = sleep onset latency; TST = total sleep time; WASO = wake-time after sleep onset

- Overall, adjunctive treatment with brexpiprazole improved a number of key sleep parameters, as assessed by PSG. In particular, the mean LPS decreased (improved) from 54.5 minutes at baseline to 28.1 minutes at Week 8. In addition, the mean TST increased (improved) from 338 minutes at baseline to 386 minutes at Week 8, while the mean WASO decreased (improved) from 88 minutes at baseline to 68 minutes at Week 8, and the mean SOL decreased (improved) from 38 minutes at baseline to 18 minutes at Week 8. Improvements (increases) in the mean SE were also observed between baseline and Week 8 (70% and 81%, respectively), while no changes were observed in the mean NAW between baseline and Week 8 (12 for both).
- Adjunctive treatment with brexpiprazole was associated with an increase in the duration of Stage N2 sleep (from 196 minutes at baseline to 239 minutes at Week 8) and a reduction in the duration of latency to REM sleep (from 136 minutes at baseline to 125 minutes at Week 8). No substantial changes between baseline and Week 8, however, were observed for the duration of Stages N1, N3, and R, respectively.
- SOL, NAW, and WASO, as assessed by CSD-M, decreased between baseline and Week 8, while the TST and SE increased between baseline and Week 8, indicating improvements in sleep quality and duration after adjunctive treatment with brexpiprazole. When analysed using the FAS, MMRM analysis, the 95% CIs for the changes from baseline in SOL (-58.5 to -26.7), TST (51.7 to 117.3), and SE (9.9 to 20.9) did not include zero and the size of the CIs were small compared to the overall changes observed. The 95% CIs for the changes from baseline in NAW (-1.3 to 0.0) and WASO (-93.7 to -2.4) were relatively wide and the upper bands included zero or were close to zero.

Efficacy Results (continued)

- SOL, as assessed by ACT, decreased from 17 minutes at baseline to 9 minutes at Week 8, after adjunctive treatment with brexpiprazole (FAS, OC). NAW, SE, TST, and WASO appeared comparable between baseline and Week 8. When analysed using the FAS, MMRM analysis, the 95% CI for the change from baseline in SOL (-16.9 to -0.6) was relatively wide and the upper band was close to zero. The 95% CIs for the changes from baseline in NAW (-4.5 to 0.1), SE (-7.6 to 6.7), TST (-41.5 to 40.1), and WASO (-21.5 to 3.5) were relatively wide and included zero.
- There were positive correlations between PSG LPS and BRIAN, CPFQ, and ISI, respectively. There were partial correlations between PSG SE and ACT SE, and between PSG SOL and the SOL for ACT and CSD-M, respectively. There were also partial correlations between PSG WASO and ACT WASO, and between PSG LPS and CPFQ and ISI, respectively.
- The mean ISI total score decreased (improved) from 19 points at baseline to 10 points at Week 8. In the FAS, MMRM analysis, the mean change from baseline in ISI total score had decreased (improved) by 9 points at Week 8, indicating improvements in insomnia after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in ISI total score (-11.4 to -7.0) did not include zero and the size of the CI was small compared to the overall change observed.
- The mean time to peak cortisol concentration decreased from 977 minutes at baseline to 917 minutes at Week 8. The mean time to DLMO increased from 323 minutes at baseline to 372 minutes at Week 8. The phase angle between time of peak cortisol concentration and DMLO decreased from 653 minutes at baseline to 545 minutes at Week 8.
- The mean ESS total score decreased (improved) from 9.1 points at baseline to 6.4 points at Week 8. In the FAS, MMRM analysis, the mean change from baseline in ESS total score was decreased (improved) by 2.1 points at Week 8, indicating improvements in daytime alertness after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in ESS total score (-3.6 to -0.7) was relatively wide and the upper band was close to zero.
- Psychomotor vigilance, as assessed using a PVT device, did not display substantial change after adjunctive treatment with brexpiprazole. The mean response speed changed from 3.4 sec^{-1} at baseline to 3.2 sec^{-1} at Week 8 and the mean number of lapses changed from 9.7 to 10.7, respectively.
- The mean morning BL-VAS-s score in the morning decreased from 50.1 points at baseline to 41.3 points at Week 8, while the mean noon BL-VAS-s score decreased from 43.9 points at baseline to 38.8 points at Week 8, indicating an improvement in alertness during these hours after adjunctive treatment with brexpiprazole. There was no substantial change in the mean evening BL-VAS-s score after adjunctive treatment with brexpiprazole (46.5 and 46.0 points at baseline and Week 8, respectively).
- The mean CPFQ total score decreased (improved) from 27 points at baseline to 19 points at Week 8. In the FAS, MMRM analysis, the mean change from baseline in CPFQ total score had decreased (improved) by 8 points at Week 8, indicating improvements in cognitive and executive function after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in CPFQ total score (-10.5 to -6.2) did not include zero and the size of the CI was small compared to the overall change observed.
- The mean BRIAN total score decreased (improved) from 52 points at baseline to 35 points at Week 8. In the FAS, MMRM analysis, the mean change from baseline in BRIAN total score had decreased (improved) by 17 points at Week 8, indicating less biological rhythm disturbances after adjunctive treatment with brexpiprazole. The 95% CI for the change from baseline in BRIAN total score (-21.0 to -12.7) did not include zero and the size of the CI was small compared to the overall change observed.

Safety Results

- The adverse event incidence is summarised below:

	Brex + ADT	
	n	(%)
Patients treated	44	
Patients who died	0	(0)
Patients with serious AEs (SAEs)	0	(0)
Patients with AEs leading to withdrawal	0	(0)
Patients with treatment-emergent adverse events (TEAEs)	31	(70.5)
Total number of AEs	76	

- No deaths or other SAEs occurred during the study.
- Thirty-one patients (70%) in the APTS had one or more TEAEs during the study.
- No patients withdrew from the study due to adverse events.
- All related TEAEs were either *mild* or *moderate* in intensity, and none were *severe* in intensity.
- The TEAEs with the highest incidence were *nausea* and *sedation* (both 14%). Apart from nausea and sedation, the only other TEAEs with an incidence ≥5% were *headache* (11%), *somnolence* (9%), *upper respiratory tract infection* (9%), *weight increased* (9%), and *fatigue* (7%).
- Three patients (7%) had a total of 4 extrapyramidal symptom (EPS)-related adverse events; the majority of events were *restlessness* (3 out of 4 events) and there was a single event of *akathisia*.
- One in four patients (25%) had sleep-related TEAEs (*insomnia*, *sedation*, or *somnolence*). All sleep-related TEAEs were considered to be *related* to IMP by investigator and either *mild* or *moderate* in intensity. No patients withdrew from the study due to *insomnia*, *sedation*, or *somnolence*.
- Based on the C-SSRS scores, two patients (5%) had *suicidal ideation* during the entire study period. One of the 2 patients with *suicidal ideation* was classified as *wish to be dead* and the other was classified as *non-specific active suicidal thoughts*. None of the other patients had suicide-related TEAEs during the study, and none of them reported suicidal behaviour involving either a preparatory act, or an aborted or actual attempt, based on the C-SSRS.
- No clinically relevant changes over time were seen in the clinical safety laboratory tests, vital signs, or ECG parameters, and the proportion of patients with PCS values was low.

Conclusions

- Symptoms of sleep disturbances as well as overall symptoms of depression improved in patients with MDD and an inadequate response to ADT treated with adjunctive brexpiprazole 2 to 3 mg/day. The improvements from baseline to Week 8 were considered to be of clinical relevance.
- There was a positive correlation in the changes from baseline between several of the PSG-measured sleep parameters and the sleep parameters of other sleep assessment instruments.
- Furthermore, after 8 weeks of adjunctive treatment with brexpiprazole, there was an improvement of daily alertness and functioning associated with a reduction of biological rhythm disturbances and normalisation of circadian rhythm.
- Overall, adjunctive treatment with brexpiprazole 2 to 3 mg/day was safe and well tolerated in patients with MDD with an inadequate response to their current ADT. No safety issues were raised in this study.

Date of the Report

17 February 2015

This study was conducted in compliance with the principles of *Good Clinical Practice*.