THE PRIMARY CARE COMPANION FOR CNS DISORDERS

Supplementary Material

Article Title: Effects of Adjunctive Brexpiprazole on Sleep Disturbances in Patients With Major Depressive Disorder: An Open-Label, Flexible-Dose, Exploratory Study

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Disclaimer

This Supplementary Material has been provided by the author(s) as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Appendix 1

1. Full list of protocol specified selection criteria

Inclusion Criteria

1. The patient is a man or woman, age ≥18 years and ≤65 years.

2. The patient is capable of communicating with the site personnel.

3. The patient is able to read and understand the Informed Consent Form.

4. The patient has signed the Informed Consent Form.

5. The patient is willing and able to attend study appointments within the specified time windows.

6. The patient is an outpatient consulting a psychiatrist (the principal investigator may serve as consulting psychiatrist).

7. The patient has a MDE associated to MDD (classification code 296.2x or 296.3x), diagnosed according to DSM-IV-TR. The current MDE should be confirmed using the Mini International Neuropsychiatric Interview (MINI).

8. The patient has had the current MDE for ≥10 weeks.

9. The patient is receiving one adequate SSRI or SNRI as monotherapy antidepressant treatment for ≥6 weeks and at the same dosage for ≥2 weeks.

10. The patient has an inadequate response to ≥1 antidepressant treatment (including the treatment the patient is taking at screening) in the current MDE, documented by self-report of <50% response on the ATRQ.

11. The patient has a MADRS total score >18 at the Screening and Baseline Visit.

12. The patient has a CGI-S score ≥3 at the Screening Visit.

13. The patient has sleep disturbances (difficulty falling asleep and/or difficulty staying asleep and/or problem waking up too early) concurrent to the MDE and confirmed by ISI score ≥8 at the Screening and Baseline Visit.

14. The patient agrees to adhere to the sleep laboratory schedule and rules for sleep time:

• the patient is willing to stay overnight at the sleep laboratory, as requested by the study protocol

• the patient is willing to stay in bed for at least 8 hours each night while at the sleep laboratory

• the patient refrains from smoking during awakenings at night in the sleep laboratory

15. During the PSG visit days and nights, the patient is willing to refrain from alcohol and napping and avoid caffeine after 12:00 pm.

16. The patient is willing to limit caffeine consumption to <5 standard 6-ounce cups of caffeinated beverages a day.

17. The patient has a habitual bedtime between 9:00 pm and midnight and typically spends between 7 and 9 hours in bed per night.

18. The patient, if a woman, must:

• agree not to try to become pregnant during the study, AND

• use adequate, highly effective contraception (defined as those that result in a low failure rate [that is, <1% per year] when used consistently and correctly, for example, implants, injectables, combined oral contraceptives in combination with a double barrier method, some intrauterine devices, sexual abstinence, vasectomised partner),

OR

• have had her last natural menstruation ≥12 months prior to the Screening Visit, OR

• have been surgically sterilised prior to the Screening Visit, OR

• have had a hysterectomy prior to the Screening Visit

19. The patient, if a man, must:

• use two methods of contraception in combination if his female partner is of childbearing potential; this combination of contraceptive methods must be used from the Baseline Visit to ≥1 month after the last dose of IMP, OR

• have been surgically sterilised prior to the Screening Visit

Inclusion Criteria for the Treatment Period (Baseline Visit)

20. The patient has a MADRS total score >18.

21. The patient's improvement in the MADRS total score at the Baseline Visit is <25% compared to the Screening Visit.

22. The patient has a CGI-I (Lead-in Period) score ≥3 and a CGI-S score ≥3.

23. The patient has sleep disturbances (difficulty falling asleep and/or difficulty staying asleep and/or problem waking up too early) confirmed by an ISI score ≥8.

24. The patient has sleep disturbances confirmed by mean latency to persistent sleep (LPS) ≥20 minutes on the 2 nights of 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.

Exclusion Criteria

General

1. The patient has previously been enrolled in this study or any prior brexpiprazole clinical study.

2. The patient has been treated with any IMP within 30 days or 5 half-lives (whichever is longer) prior to the Screening Visit.

3. The patient is a member of the study personnel or of their immediate families, or is a subordinate (or immediate family member of a subordinate) to any of the study personnel.

4. The patient is under forced treatment.

5. The patient has a history of severe drug allergy or hypersensitivity, or known hypersensitivity to the IMP or its excipients.

6. The patient has hereditary problems of fructose intolerance, glucose-galactose malabsorption, or sucrose-isomaltase insufficiency.

7. The patient takes medication that could, in the investigator's opinion, interfere with the assessments of safety, tolerability, or efficacy, or interfere with the conduct or interpretation of the study.

8. The patient is pregnant or breastfeeding.

9. The patient takes or has taken disallowed recent or concomitant medication or it is anticipated that the patient will require treatment with at least one of the disallowed concomitant medications during the study.

10. The patient is treated with hypnotics (benzodiazepine or non-benzodiazepine), select antihypertensives, sedatives, anticonvulsants, opiates, oxybate, modafinil, anti-histamines, amphetamines and amphetamine-like drugs. These drugs could not be stopped within 2 weeks prior the Screening Visit.

11. The patient is, in the investigator's opinion, unlikely to comply with the protocol or is unsuitable for any reason.

Psychiatric

12. The patient has any current psychiatric disorder or Axis I disorder (DSM-IV-TR criteria; including primary insomnia), established as the primary diagnosis, other than MDD, as assessed using the MINI.

13. The patient has a current Axis II (DSM-IV-TR) diagnosis of borderline, antisocial, paranoid, schizoid, schizotypical or histrionic personality disorder.

14. The patient has been diagnosed with insomnia or any sleep disturbances prior to the start of the current MDE and insomnia or any sleep disturbances cannot be determined to be part of current MDE by medical history or patient interview in the opinion of the investigator.

15. The patient has experienced/experiences hallucinations, delusions or any psychotic symptoms in the current MDE.

16. The patient suffers from mental retardation, organic mental disorders, or mental disorders due to a general medical condition (DSM-IV-TR criteria).

17. The patient has a current diagnosis or history of substance abuse or substance dependence (including alcohol, nicotine, caffeine, cannabis, and ecstasy) or pathological gambling within 6 months prior to the Screening Visit (DSM-IV-TR criteria).

18. The patient has reported current use of, or has tested positive for drugs of abuse (amphetamines [including ecstasy], barbiturates, cocaine, cannabinoids, marijuana, methadone, opiates, phencyclidine, and propoxyphene).

19. The patient is, in the opinion of the investigator, at significant risk of suicide, or who

• answered “Yes” on the eC-SSRS suicidal ideation item 4 (active suicidal ideation) within the last 6 months, OR

• answered “Yes” on the eC-SSRS suicidal ideation item 5 (active suicidal ideation with specific plan and intent) within the last 6 months, OR

• answered “Yes” on any of the 5 eC-SSRS suicidal behaviour items (actual attempt, interrupted attempt, aborted attempt, preparatory acts, or behaviour) within the last 2 years

20. The patient has started formal cognitive or behavioural therapy or systematic psychotherapy within 6 weeks prior to screening, or plans to start such therapy during the study. Any ongoing formal psychotherapy initiated more than 6 weeks prior to screening should be continued with the same methodology and at the same frequency and intensity during the study.

21. The patient reports adjunct treatment with an antipsychotic medication together with an antidepressant for ≥3 weeks during the current MDE.

22. The patient has received electroconvulsive therapy <6 months prior to the Screening Visit or at any time during the current MDE (if its duration is longer than 6 months).

23. The patient has had a vagus nerve stimulation or a deep brain stimulation device implanted for the management of depression.

24. The patient has had neuroleptic malignant syndrome.

Medical

25. The patient has met the diagnostic criteria for any sleep or circadian rhythm disorder other than insomnia.

26. The patient has a history of the following conditions or a PSG sleep study in the past 3 months suggesting any of the following conditions: narcolepsy, apnoea, periodic limb movement disorder, or restless leg syndrome.

27. The patient has a history of an underlying pathology of sleep in the past 3 months including: apnoea/hypopnea index (AHI) >10 and periodic limb movements (PLMs) >10 per hour associated with an arousal.

28. The patient has an AHI >10 or PLMs >10 per hour associated with arousal on the baseline PSG.

29. The patient has a history of night-eating syndrome or somnambulism.

30. The patient has a recent history of a circadian rhythm disorder, or who had done shift work or rotating shifts within 30 days prior to the initial Screening Visit.

31. The patient smokes, eats or drinks during the night.

32. The patient has a sleep-wake cycle which includes a sleep period of >1 hour during daytime hours on more than 2 days a week (for example, night shifts, rotation shifts, naps, siesta).

33. The patient has ≥2 nocturnal urinal episodes per night proceeded and followed by sleep.

34. The patient has a history of tardive dyskinesia.

35. The patient has clinically significant extrapyramidal symptoms (EPS) including akathisia.

36. The patient has epilepsy or a history of seizures, except for a single seizure episode (for example, childhood febrile seizure, post traumatic, or alcohol withdrawal).

37. The patient has a history of moderate or severe head trauma or other neurological disorders or systemic medical diseases that are, in the investigator's opinion, likely to affect central nervous system functioning.

38. The patient has chronic, uncontrolled, or unstable clinically relevant medical condition.

39. The patient has a neurodegenerative disorder (for example, Alzheimer's disease, Parkinson's disease, multiple sclerosis, Huntington's disease).

40. The patient has any other disorder for which the treatment takes priority over the treatment of MDD or is likely to interfere with brexpiprazole or impair treatment compliance.

41. The patient has a history of cancer, other than basal cell or Stage 1 squamous cell carcinoma of the skin, that has not been in remission for >5 years prior to the first dose of brexpiprazole.

42. The patient has, at the Screening Visit:

• an abnormal ECG that is, in the investigator's opinion, clinically significant

• a PR interval >250ms

• a QRS interval >130ms

• a QTcF interval >450ms (for men) or >470ms (for women) (based on the Fridericia correction where $QTcF = QT/RR^{0.33}$)

2. Overview of study procedures and assessments

Visit	Screening	Baseline					Treatment			Completion[a]				Follow-up[b]
Visit	**1**	**2**					**3**	**4**	**5**	**6**				**7**
Week	**-2**	**0**					**1**	**2**	**4**	**8**				**12**
Day	**-18**	**-4**	**-3**	**-2**	**-1**	**0**	**7**	**14**	**28**	**53**	**54**	**55**	**56**	**84**
Screening/Baseline Procedures and Assessments														
Signed informed consent	√													
MDE diagnostic	√					√								
MDE Diagnosis (DSM-IV-TR™+MINI)	√													
Depression history	√													
Patient Habits/Sleep History/Sleep Diagnostic Interview	√													
Medical, psychiatric (individual and family), neurological and social history	√													
Demographics (age, sex, race)	√													
Physical and neurological Examination	√													
Height	√													
Drug and alcohol screen[c]	√												√	
Antidepressant history (ATRQ)	√													
Washout of disallowed medication	√													
Smoking and alcohol consumption	√													
Inclusion/exclusion criteria	√	√	√	√	√	√								

Visit	Screening	Baseline					Treatment			Completion[a]				Follow-up[b]
Visit	**1**	**2**					**3**	**4**	**5**	**6**				**7**
Week	**-2**	**0**					**1**	**2**	**4**	**8**				**12**
Day	**-18**	**-4**	**-3**	**-2**	**-1**	**0**	**7**	**14**	**28**	**53**	**54**	**55**	**56**	**84**
Efficacy Assessments														
PSG		√	√							√	√			
PVT (duplicate)[d]			√	√							√	√		
ISI	√					√	√	√	√			√	√	
Consensus Sleep Diary for Morning (CSD-M)[e]	√	√	√	√		√	√	√	√	√	√	√		
Actigraphy[f]		√	√	√		√	√	√	√	√	√	√		
ESS						√	√	√	√			√		
BRIAN						√	√	√	√			√		
BL-VAS-s[g]			√	√								√	√	
CPFQ						√	√	√	√				√	
MADRS, CGI-S	√					√	√	√	√				√	
CGI-I (Lead-in Period)[h]	√					√	√	√	√				√	
CGI-I (Treatment Period)[i]							√	√	√				√	
Cortisol and melatonin blood test[j]					√								√	
Safety Assessments														
Adverse events[k]	√	√	√	√	√	√	√	√	√	√	√	√	√	√[l]
Blood sampling for haematology and clinical chemistry; urinalysis	√								√				√	
Vital signs and Weight	√								√				√	

Visit	Screening	Baseline					Treatment			Completion[a]				Follow-up[b]
Visit	**1**	**2**					**3**	**4**	**5**	**6**				**7**
Week	**-2**	**0**					**1**	**2**	**4**	**8**				**12**
Day	**-18**	**-4**	**-3**	**-2**	**-1**	**0**	**7**	**14**	**28**	**53**	**54**	**55**	**56**	**84**
ECG	√								√				√	
eC-SSRS	√					√	√	√	√				√	
Other Study Procedures														
IMP dispensed						√	√	√	√					
IMP returned and IMP accountability						√	√	√	√				√	
ADT compliance						√	√	√	√				√	
Recent and concomitant medication	√	√	√	√		√	√	√	√	√	√	√	√	
Pregnancy test[m]	√					√			√				√	

a. This visit was to take place as soon as possible after the patient had withdrawn from the study.
b. This visit could be a telephone contact, unless a serious adverse event (SAE) has occurred since the last visit.
c. An unscheduled drug screen could be performed at any time at the discretion of the investigator. Alcohol screen was performed at the Screening Visit only.
d. Two consecutive 10-minute psychomotor vigilance assessments were completed on each day.
e. The patient should have completed the CSD-M from the morning after the screening visit to the morning before the completion visit (from Day -18 to Day 56). Data collected during lead-in period and during the last 2 weeks of treatment with brexpiprazole were to be used for scheduling the PSG assessment at the baseline and endpoints visits.
f. Patient was to wear wristwatch actigraphy while in the study (from Day -4 to Day 55).
g. Patient was to complete the BL-VAS-s on the PSG days at the arrival to the sleep laboratory, 1 hour after awakening and at 12:00 pm of the day a fter.
h. CGI-I (Lead-in Period) assessed the patient's condition at baseline compared to screening.
i. CGI-I (Treatment Period) assessed the patient's condition compared to baseline
j. Cortisol and melatonin blood samples were collected in a subset of patients (approximately 10) on the following day of PSG days. The time of peak cortisol concentration and the timing of DLMO were to be measured. Assessments at the sleep laboratory were to be performed for these patients only from the night of Day -2 to the morning of Day -1, and from the night of Day 55 to the morning of Day 56.
k. Signs and symptoms present at screening and/or baseline (before brexpiprazole intake) were to be recorded on an Adverse Event Form in the eCRF.
l. Only for adverse events ongoing at Completion/Withdrawal and new SAEs.

m. For women of childbearing potential, a pregnancy test at the Screening Visit, Day 28, Completion Visit
(serum βhCG), and at the Baseline Visit (urine βhCG).

3. Protocol details of the screening and study visits, including details of the polysomnographic assessments

Screening Visit

After written informed consent has been obtained, the patient will enter a 2-week screening period. At the initial screening visit on Day -18 prior to baseline visit, the patient will undergo clinical evaluations at the out-patient clinic.

The washout of prohibited concomitant medications (including long-acting sedatives and hypnotics) will begin according to the investigator's judgment and should be finished prior Day -4.

The patient will be asked to complete a Consensus Sleep Diary (CSD-M) within 60 minutes of arising. The diary will be completed every morning starting on Day -17 and continuing through the entire treatment period (up to Day 55).

The patient should be instructed to visit the sleep laboratory on Day -4 and will have to bring back the completed CSD-M.

Baseline Visits

The initial baseline visit should be performed 14 days after the initial Screening Visit.

In exceptional cases, the visit interval between the Screening and Baseline Visits may be extended with consent from the Medical Monitor at Lundbeck, provided the CRO Project Manager accepts the rationale provided for the extension.

Thereafter, all visits during the treatment period are scheduled relative to the Baseline Visit.

The PSG assessments will be doubled at baseline and endpoint to reduce the variability. The patient will then have to stay 2 consecutive nights at the sleep laboratory.

Furthermore, at baseline and endpoint, a third night at the sleep laboratory is scheduled for a sample of patients (approximately 10 patients who have consent to do so). During these two nights, a serial of blood samples will be collected for cortisol and melatonin assessments.

Day -4 (PSG#1)

The patient will have to go to the sleep laboratory and the following procedures will be performed:

- The patient will complete the modified Bond-Lader Visual Analogical Scale – sedation (BL-VAS-s).
- Actigraphy recording will be initiated. Patients will wear an actigraph on their wrist beginning on Day -4 and continuing 24 hours a day through the treatment period.
- PSG leads will be attached to patient and calibration procedures will be carried out.
- The average bedtime will be calculated from the completed CSD-M and the patient will be asked to go to bed within habitual bedtime, at which time PSG recording will commence (PSG #1). The patient will be awakened when 8 hours and PSG recording (960 30-second epochs) have elapsed.

Day -3 (PSG#2)

Upon awaking at the sleep laboratory, the following sleep procedures will be conducted:

- Two 10-min PVTs will be conducted 30 to 60 min. after the light on.
- The patient will thereafter complete the CSD-M and the BL-VAS-s after 10-min PVT session is completed and at lunch time.

Actigraphy recording will continue. In the evening, the patient will come back to the sleep laboratory for the following procedures:

- The patient will complete the BL-VAS-s.
- The patients will go to bed within the calculated mean range of habitual bedtime, at which time PSG recording will commence (PSG #2). Patients will be awakened when 8 hours and PSG recording (960 30-second epochs) have elapsed.
- Actigraphy recording will continue.

Day -2

Upon awaking at the sleep laboratory, if the patient continues to be eligible for the study, the following sleep procedures will be conducted:

- Two 10-min PVTs will be conducted 30 to 60 min. after the light on.
- The patient will thereafter complete the CSD-M and the BL-VAS-s after 10-min PVTsession is completed and at lunch time.
- Actigraphy recording will continue.

The patient, who has accepted to participate to the assessments of cortisol and melatonin, will have to go to the sleep laboratory for the third night.

- During that day, blood samples will be collected every 30 minutes starting at 16.00 until 10.00 the next morning.
- An indwelling catheter will be inserted 2 hours before the first sampling and will remain in place overnight, throughout samples collection.
- Patients are allowed to sleep during the night, while samples are collected.

Day -1

Upon awaking at the sleep laboratory, the patient will complete the CSD-M and actigraphy recording will continue.

Day 0

An external scoring of PSGs is organized to avoid the inter-rater variability for the visual PSG scoring. The PSG scoring data will be sent back to the sleep laboratory and to the site within 48 hours.

The patient will go to the out-patient clinic for clinical evaluations procedures, when the PSG scoring data are available.

If the patient continues to be eligible for the study, the clinical evaluations procedures will be conducted.

The patient should continue to complete the CSD-M within 60 minutes of arising and the actigraphy recording will continue.

Visit 3 (Day 7), Visit 4 (Day 14) and Visit 5 (Day 28)

The patient should continue to complete the CSD-M within 60 minutes of arising and the actigraphy recording will continue.

The patient will go to the out-patient clinic for clinical evaluations procedures.

Completion Visit

Day 53 (PSG #3)

The patient will refer to the sleep laboratory and the following procedures will be performed:

- The patient will thereafter complete the BL-VAS-s.
- The average bedtime will be calculated from the completed CSD-M during the last 2 weeks and the patient will be asked to go to bed within habitual bedtime, at which time PSG recording will commence (PSG #3). Patients will

be awakened when 8 hours and PSG recording (960 30-second epochs) have elapsed.
- Actigraphy recording will continue.

Day 54 (PSG #4)

Upon awaking at the sleep laboratory, the following sleep procedures will be conducted:

- Two 10-min PVTs will be conducted 30 to 60 min. after the light on.
- The patient will thereafter complete a CSD-M and the BL-VAS-s after 10-min PVTsession is completed and at lunch time.
- Actigraphy recording will continue.

In the evening, the patient will come back to the sleep laboratory for the following procedures:

- The patient will thereafter complete the modified BL-VAS-s.
- The patients will go to bed within the calculated mean range of habitual bedtime, at which time PSG recording will commence (PSG #4). Patients will be awakened when 8 hours and PSG recording (960 30-second epochs) have elapsed.
- Actigraphy recording will continue.

Day 55

Upon awaking at the sleep laboratory, the following sleep procedures will be conducted:

- Two 10-min PVTs will be conducted 30 to 60 min. after the light on.
- The patient will thereafter complete the CSD-M and the BL-VAS-s after 10-min PVT session is completed and at lunch time.
- Actigraphy device will be taken off, the data will be downloaded to the computer, and the actigraphy monitoring will be stopped.

Similarly to baseline, the patient, who has accepted to participate to the assessments of cortisol and melatonin, will have to go to the sleep laboratory for the third night in the evening of Day 55.

- During that day, blood samples will be collected every 30 minutes starting at 16.00 until 10.00 the next morning.
- An indwelling catheter will be inserted 2 hours before the first sampling and will remain in place overnight, throughout samples collection.
- Patients are allowed to sleep during the night, while samples are collected.

Day 56

4. The patient will return to the out-patient clinic for clinical evaluations procedures.

Table 1. Multivariate Regression Analyses

Response variable	Regression variable	Estimate (SE)	p-value
Change from baseline in MADRS without item 4	Baseline MADRS without item 4	0.01 (0.36)	0.98
	Baseline ISI	0.93 (0.35)	0.011*
	Change from baseline in ISI	1.07 (0.20)	<0.0001*
	Baseline ESS	-0.24 (0.29)	0.42
	Change from baseline in ESS	-0.36 (0.31)	0.26
Change from baseline in CPFQ	Baseline CPFQ	-0.73 (0.17)	0.0001*
	Baseline MADRS without item 4	0.50 (0.25)	0.051
	Change from baseline MADRS without item 4	0.32 (0.11)	0.006*
	Baseline ISI	-0.11 (0.25)	0.67
	Change from baseline in ISI	0.30 (0.18)	0.09
	Baseline ESS	0.22 (0.19)	0.26
	Change from baseline in ESS	0.12 (0.20)	0.56
Change from baseline in ESS	Baseline ESS	-0.58 (0.13)	<0.0001*
	Baseline MADRS without item 4	-0.33 (0.21)	0.13
	Change from baseline in MADRS without item 4	-0.13 (0.10)	0.21
	Baseline CPFQ	0.086 (0.18)	0.63
	Change from baseline in CPFQ	0.087 (0.15)	0.56
	Baseline ISI	0.57 (0.18)	0.004*
	Change from baseline in ISI	0.39 (0.14)	0.009*
Change from baseline in ESS	Baseline ESS	-0.51 (0.14)	0.001*
	Baseline MADRS without item 4	-0.29 (0.23)	0.20
	Change from baseline in MADRS without item 4	0.02 (0.11)	0.87
	Baseline CPFQ	0.19 (0.20)	0.36
	Change from baseline in CPFQ	0.18 (0.15)	0.25

* Indicates statistical significance

Abbreviations:

CPFQ=Cognitive and Physical Functioning Questionnaire; ESS=Epworth Sleepiness Scale; ISI=insomnia severity index; MADRS=Montgomery Åsberg Depression Rating Scale; SE=standard error

Table 2. Mean Change From Baseline to Last Visit in Fasting Metabolic Parameters (APTS)

Parameter	Baseline		Change from baseline at last visit	
	n	Mean (SD)	n	Mean (SD)
Cholesterol, mg/mL	34	204.6 (42.5)	28	-5.4 (27.0)
HDL cholesterol, mg/mL	34	61.8 (15.4)	28	1.5 (9.3)
LDL cholesterol, mg/mL	34	119.7 (38.6)	28	-7.3 (24.7)
Triglycerides, mg/mL	34	141.6 (106.2)	28	-15.0 (100.0)
Glucose, mg/mL	34	91.9 (7.2)	28	3.8 (10.8)

Abbreviations:

APTS, all-patients-treated set; HDL, high-density lipoprotein; LDL, low-density lipoprotein; SD, standard deviation