Synopsis – Study 16160A

Study Title Interventional, open-label, flexible-dose, long-term study to evaluate the safety and tolerability of brexpiprazole as adjunctive treatment in elderly patients with major depressive disorder with an inadequate response to antidepressant treatment
Investigator *Signatory investigator* – [redacted]
Study Sites 34 sites – 4 in Estonia, 4 in Finland, 7 in Germany, 6 in Poland, and 13 in the United States
Publications None (as of the date of this report)
Study Period *First patient first visit* – 16 March 2015 (the date when the first *Informed Consent Form* (ICF) was signed) *Last patient last visit* – 1 June 2016 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the long-term safety and tolerability of brexpiprazole (1 to 3 mg/day) as adjunct treatment to antidepressive treatment (ADT) in elderly patients with major depressive disorder (MDD) • *Exploratory objectives*: – to evaluate the therapeutic effect of flexible dose (1 to 3 mg/day) brexpiprazole as adjunct treatment to ADT on: • depressive symptoms • clinical global impression • health-related quality of life and social functioning – to evaluate the pharmacoeconomics of flexible dose (1 to 3 mg/day) brexpiprazole as adjunct treatment to ADT
Study Methodology • This was an interventional, multi-national, multi-site, open-label, flexible-dose, long-term study. • The study consisted of a: – Screening Period (could last from 3 to 28 days) – where the patients continued treatment with the same commercially available ADT they were taking prior to screening – Treatment Period – 26-week treatment period including a 4-week uptitration. The patients started receiving brexpiprazole 0.5 mg/day and were up-titrated in weekly steps to 2 mg/day (1 mg/day from end of Week 1 onwards and 2 mg/day from end of Week 2 onwards). From end of Week 4 onwards, the dose could be increased based on clinical judgement and tolerability to a maximum dose of 3 mg/day. In case tolerability did not allow a dose increase, the brexpiprazole dose was to be kept at the same dose level or reduced to 1 mg/day at any time in the study. The dose and type of ADT was to remain stable for the duration of the study. – Safety Follow-up Period – 30-day period after completion of the study or after withdrawal from the study • Efficacy and safety data were collected at 1 to 6-week intervals throughout the study.
Number of Patients Planned 130 elderly patients were planned for enrolment.

Diagnosis and Main Selection Criterion

Outpatients with a primary diagnosis of MDD according to DSM-IV-TR™ criteria (confirmed using the Mini International Neuropsychiatric Interview [MINI]), who:

- had a Montgomery Åsberg Depression Rating Scale (MADRS) total score >18 at the Screening Visit and at the Baseline Visit
- had a Clinical Global Impression - Severity of Illness (CGI-S) score ≥3 at the Screening Visit and at the Baseline Visit
- had had the current Major Depressive Episode (MDE) for ≥8 weeks
- had an insufficient response to at least one adequate ADT for the current MDE; the most recent as documented by a self-report of <50% response on the Antidepressant Treatment Response Questionnaire (ATRQ)
- was treated with one of the allowed ADTs as non-investigational medicinal products (NIMPs) (specified below) for ≥6 weeks prior to screening at the minimal dose specified in the ATRQ (elderly version)
- were ≥65 years of age

Investigational Medicinal Product (IMP), Doses, Mode of Administration, and Bacth Numbers

Brexpiprazole – 0.5, 1, 2, or 3 mg/day; tablets, orally

- *Brexpiprazole 0.5 mg* – batch No. 13A94A0050, 14D70A0050B, 14D70A0050B
- *Brexpiprazole 1 mg* – batch No. 13A97A001, 14D71A001C, 14D71A001C
- *Brexpiprazole 2 mg* – batch No. 13A98A002, 14D72A002C, 14D72A002C, 13E92A002
- *Brexpiprazole 3 mg* – batch No. 13A99A003, 14D73A003B, 14D73A003B

Non-investigational Medicinal Products and Doses

Citalopram – 10 to 40 mg/day
Escitalopram – 5 to 20 mg/day
Fluoxetine – 10 to 40 mg/day
Sertraline – 25 to 150 mg/day
Paroxetine IR – 10 to 40 mg/day
Paroxetine CR – 12.5 to 50 mg/day
Venlafaxine IR – 75 to 225 mg/day
Venlafaxine XR – 75 to 225 mg/day
Desvenlafaxine – 50 to 100 mg/day
Duloxetine – 30 to 90 mg/day
Mirtazapine – 7.5 to 45 mg/day
Agomelatine – 25 to 50 mg/day
Bupropion – 150 to 300 mg/day

Duration of Treatment

Brexpiprazole as adjunct treatment to ADT for 26 weeks (including 4 weeks uptitration)

Efficacy Assessments

- MADRS
- CGI-S and Clinical Global Impression – Global Improvement (CGI-I)
- Social Adaptation Self-Evaluation Scale (SASS)
- Quality of Life Enjoyment and Satisfaction Questionnaire – Short Form (Q-LES-Q [SF])
- EuroQoL 5 Dimensions 5 Level version (EQ-5D-5L)

Pharmacoeconomic Assessments

- Health Economic Assessment (HEA)

Safety Assessments

- Adverse events, clinical safety laboratory tests, vital signs, weight/body mass index (BMI), waist circumference, electrocardiograms (ECGs), and physical examinations (PEs)
- Columbia Suicide Severity Rating Scale (C-SSRS™)
- Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS), and Modified Simpson Angus Scale (mSAS)
- Mini Mental State Examination (MMSE)

Endpoints

- *Primary endpoint*:
  - description of the safety parameters, see safety endpoints below
- Exploratory *efficacy endpoints*:
  - depressive symptoms:
    - MADRS total score change from baseline at Week 26
    - MADRS total score Response: ≥50% decrease from baseline
    - MADRS total score Remission: MADRS total score ≤10 and a ≥50% decrease from baseline
  - global clinical impression:
    - CGI-S score change from baseline at Week 26
    - CGI-I score absolute value at Week 26
  - health-related quality of life and social functioning:
    - Q-LES-Q (SF) total score change from baseline at Week 26
    - Q-LES-Q (SF) item scores change from baseline for medication and overall life satisfaction at Week 26
    - SASS total score change from baseline at Week 26
    - EQ-5D-5L health state score (VAS), utility index score and individual items absolute values at Week 26
  - pharmacoeconomics:
    - resource utilisation during the study using the HEA
- *Safety endpoints*:
  - adverse events
  - absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight/BMI, waist circumference and ECG parameters
  - potentially clinically significant clinical safety laboratory test values, vital signs, weight changes, and ECG parameter values
  - C-SSRS
  - absolute values and changes from baseline in BARS, AIMS, and mSAS scores
  - absolute values and changes from screening in MMSE total score

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a baseline assessment and at least one post-baseline assessment of the MADRS total score
- Unless otherwise indicated, efficacy analyses are based on the FAS, and the safety analyses are based on the APTS.
- The exploratory efficacy analyses:
  - Absolute values and changes from baseline of exploratory efficacy endpoints including MADRS total score, CGI-S score, Q-LES-Q (SF) total score and its last two item scores (medication and overall life satisfaction), and SASS total score are summarized descriptively by visit, based on both observed cases (OC) and last observation carried forward (LOCF) imputation. EQ-5D-5L VAS score, utility index score and individual item scores are summarized for Completers (patients completing the study) and last assessments, based on OC. Absolute values of CGI-I score are summarized descriptively by visit, based on OC and LOCF.
  - The mixed-effect model repeated measures (MMRM) model for changes from baseline in MADRS total score, CGI-S score, Q-LES-Q (SF) total score, and SASS total score includes pooled site and visit as fixed effects and baseline score-by-visit interaction. An unstructured variance structure is used to model the within-patient errors. Least-squares means of changes at post-baseline visits will be estimated when the baseline covariates are set to their observed mean values. If the model does not converge, pooled site is substituted by country. If the model still does not converge, the following variance structures are tested, and based on Akaike's information criteria the best fitting model is chosen. The variance models considered for the within-patient variation in case of non-convergence are: Ante-dependence, Toeplitz, Heterogeneous AR(1) and Compound symmetry. The Kenward-Roger approximation is used to estimate denominator degrees of freedom. Absolute value of CGI-I score is modelled and CGI-S score at baseline is used as the baseline covariate.
  - In addition, continuous efficacy endpoints at last assessment are analyzed using an analysis of covariance (ANCOVA) model including pooled site as a fixed factor and baseline score as a covariate.
  - Change from baseline in EQ-5D-5L VAS score and utility index score are analyzed with an ANCOVA model basing on OC and LOCF for completers and last assessments separately, including pooled site as fixed effect and baseline score as a covariate.
  - For MADRS response and remission rates, counts and percentages are presented by visit for OC and LOCF.
- Safety endpoints will be summarized descriptively. The long-term safety and tolerability of brexpiprazole in elderly patients will be assessed based on the joint evaluation of the results seen for the safety endpoints.

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Brexpiprazole	
	n	(%)
Patients enrolled	132	
Patients treated (all-patients-treated set [APTS])	132	
Patients completed	88	66.7
Patients withdrawn	44	33.3
Primary reason for withdrawal:		
Adverse event(s)	24	18.2
Lack of efficacy	9	6.8
Withdrawal of consent	7	5.3
Adminstrative or other reason(s)	3	2.3
Non-compliance with IMP	1	0.8
Analysis sets:		
APTS	132	
Full-analysis set (FAS)	132	

Demography and Baseline Characteristics of the Study Population

- The mean age of the patients was 71 years and 26% were ≥75 years; approximately 80% of patients were women and the majority of patients were White (98%).
- The mean and median MADRS total score of 27 points, ranging from 19 to 40, and the mean and median CGI-S score of 4 points (ranging from 3 to 6), indicated that patients were *moderately* to *severely* ill at baseline.
- The mean weight, BMI and waist circumferences were 75 kg, 28 kg/m^2, and 95 cm, respectively.

Efficacy Results

The exploratory efficacy variables results are summarized below:

- The mean change from baseline in MADRS total score was -14.5 points at Week 26 (FAS, MMRM), indicating an improvement of the depressive symptoms after adjunctive treatment with brexpiprazole. The proportion of patients classified as responders was 50% at Week 26 (FAS, LOCF) and the proportion of patients classified as remitters was 43% at Week 26 (FAS, LOCF).
- The mean change from baseline in CGI-S score at Week 26 was -1.8 points (FAS, MMRM), indicating an improvement in CGI-S score. Looking at the distribution of the scores, the majority of patients were considered to be *markedly ill* at baseline and *mildly ill* at Week 26.
- The mean CGI-I score decreased over time during the Treatment Period (FAS, MMRM) and the majority of patients were considered to be *much improved* at Week 26 having a mean score of 2.0 on the CGI-I (FAS, MMRM).
- The mean change from baseline in SASS total score at Week 26 was 3.3 points (FAS, MMRM), indicating an improvement in symptoms related to social adaption after adjunctive treatment with brexpiprazole. Improvement was seen as early as Week 4 (first assessment) and was maintained to Week 26.
- The mean change from baseline in Q-LES-Q (SF) total score at Week 26 was 4.6 points (FAS, MMRM), indicating improvement in quality of life, enjoyment and satisfaction after adjunctive treatment with brexpiprazole; improvement was seen as early as Week 4 (first assessment) and was maintained to Week 26.
- The mean change from baseline in EQ-5D-5L health state score by last assessment was 7.0 points (FAS, LOCF, ANCOVA), indicating an improvement in EQ-5D-5L health state after adjunctive treatment with brexpiprazole; however, the EQ-5D-5L utility index was almost unchanged after adjunctive treatment with brexpiprazole (FAS, LOCF, ANCOVA).

Pharmacoeconomic Results

- The health economics assessment screening evaluation showed that the majority (86%) of patients visited their general practitioner or other resource in the 26 weeks preceding baseline. Within the Treatment Period to last assessment, 49% of patients visited their general practitioner or other resource. Relatively more patients (49%) visited a psychiatrist in the 26 weeks preceding baseline than during the Treatment Period to last assessment (4%; note that study visits were not included).

Safety Results

The adverse event incidences are summarized below:

	Brexpiprazole	
	n	(%)
Patients treated	132	
Patients who died	1	0.8
Patients with treatment-emergent serious adverse events (SAEs)	6	4.5
Patients with treatment-emergent adverse events (TEAEs)	102	77.3
Total number of SAEs	11	
Total number of TEAEs	317	

- Approximately 77% of the patients had one or more TEAEs. The TEAEs with the highest incidences were *fatigue* (15%), *restlessness* (13%) and *increased appetite* (10%) followed by *akathisia*, *weight increased*, *anxiety* and *dizziness* (all approximately 8%). The majority of the patients with TEAEs had TEAEs that were either *mild* or *moderate*. The overall incidence of patients with *severe* TEAEs was 8%.
- One patient died during the study; the patient died in the Safety Follow-up Period due to *acute myocardial infarction* and *myocardial rupture*; both events were considered *not related* by the investigator. The patient had been treated with brexpiprazole for 180 days.
- A total of 6 patients (4.5%) had 11 SAEs; 2 patients had in total 5 SAEs that were considered *related* to brexpiprazole by the investigator: One patient had *hypotension* and worsening of *depression* and the other patient had *fall*, *facial bones fracture*, and *eye contusion*.
- A total of 25 patients (19%) were withdrawn from the study due to TEAEs. The most common TEAE leading to withdrawal was *fatigue* (3.0% of patients).
- Based on the C-SSRS data, no patient had suicidal ideation with an intent or plan, nor had any patient suicidal behaviour.
- The proportion of patients with EPS-related TEAEs was 16% (21 patients); the 21 patients had 30 events; most patients had *akathisia* (11 patients) and *tremor* (9 patients).
- An increase in mean prolactin level was seen during the study, predominatly in women; 16% of patients had PCS high plasma level for prolactin. There were no consistent clinically relevant findings seen with other laboratory parameters during the study (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values. A mean increase in weight (0.9 kg) was noted from baseline to Week 26 for those with a Week 26 assessment; a mean increase of 0.8 kg from baseline to last assessment was noted.
- Among patients with post baseline assessment of metabolic syndrome, a total of 18 out of 89 patients fulfilled criteria for metabolic syndrome at last visit.; however, 8 of them fulfilled the criteria already at baseline. 5 patients met criteria at baseline, but not at the last visit, and 66 patients had unchanged status, all suggesting no consistent shift following long-term exposure to brexpiprazole.
- In general, the scores on the SAS, BARS and AIMS safety rating scales were low with minor fluctuations over time.
- Only a minimal change on the MMSE was seen; the mean score changed from 28.7 to 28.5 during the study.

Conclusions

- Adjunct treatment with brexpiprazole was safe and well tolerated in elderly patients with MDD, treated with 1 to 3 mg/day flexible dose.
- Furthermore, improvements were seen in symptoms of depression as well as patient-rated quality of life and social adaptation. Generally, the use of health care resources was lower during study compared to the same period before study start.

Report Date

21 November 2016

This study is being conducted in compliance with the principles of *Good Clinical Practice* (GCP).