Synopsis – Study 14644B

Study Title Interventional, open-label, flexible-dose extension study of brexpiprazole in patients with schizophrenia
Investigators 49 principal investigators at 48 sites in 8 countries *Signatory investigator* – [redacted]
Study Sites 48 sites – 2 in Estonia, 3 in Poland, 6 in Romania, 7 in Russian Federation, 4 in Serbia, 1 in Slovakia, 8 in Ukraine, and 17 in United States
Publication None (as of the date of this report)
Study Period *First patient first visit* – 12 July 2013 (the date when the first *Informed Consent Form* was signed) *Last patient last visit* – 30 Dec 2015 (the date of the last protocol-specified contact with any patient)
Objectives • *Primary objective*: – to evaluate the long-term safety and tolerability of flexible doses of brexpiprazole (1 to 4 mg/day) during the 52-week treatment period • *Secondary objectives*: – to evaluate the therapeutic effect of flexible doses of brexpiprazole (1 to 4 mg/day) over a period of 52 weeks in patients with schizophrenia on: • psychotic symptoms • global clinical impression • response rate • personal and social performance • *Pharmacoeconomic objective:* – to evaluate the effects on resource utilisation of flexible doses of brexpiprazole (1 to 4 mg/day) over a period of 52 weeks in patients with schizophrenia
Study Methodology • This was an interventional, multi-national, multi-site, open-label, flexible-dose, long-term (52-week) safety extension study in patients with schizophrenia who completed lead-in Study 14644A. • The Baseline Visit was the same as the Visit 9 (Completion Visit, end of Week 6) in Study 14644A. At the Baseline Visit, the patients received the last current dose of IMPs in Study 14644A (brexpiprazole, quetiapine extended release, or placebo). • The study consisted of a: – Treatment Period – 52-week treatment period with brexpiprazole. Patients received 2 mg/day on Day 1. If a patient could not tolerate the 2 mg dose on Day 1, the dose was decreased to 1 mg/day at Day 2. Patients received 1 or 2 mg/day from Days 2 to 7, 1, 2, or 3 mg/day from Days 8 to 14, and 1, 2, 3, or 4 mg/day from Day 15 to completion of the Treatment Period, based on the patient's response and tolerability. The dose was not allowed to be increased above 4 mg/day or decreased below 1 mg/day. – Safety Follow-up Period – 30-day period after completion or withdrawal from the Treatment Period. • Efficacy and safety data were collected at 2- to 6-week intervals throughout the study.

Number of Patients Planned 140 patients in one treatment group of brexpiprazole 1 to 4 mg/day over a 52-week treatment period
Diagnosis and Main Selection Criterion Patients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria confirmed using the Mini International Neuropsychiatric Interview [MINI]) at screening for lead-in Study 14644A who: • had completed treatment in lead-in Study 14644A • were ≥18 and ≤65 years of age at screening for lead-in Study 14644A
Investigational Medicinal Product, Dose, and Mode of Administration, Batch Number *Brexpiprazole* – 1, 2, 3, or 4 mg; tablets, orally • *Brexpiprazole 1 mg* – batch Nos. 11L88A001, 13A97A001 • *Brexpiprazole 2 mg* – batch Nos. 12A73A002, 13A98A002 • *Brexpiprazole 3 mg* – batch Nos. 12A74A003, 13A99A003 • *Brexpiprazole 4 mg* – batch Nos. 12A75A004, 13A00A004
Duration of Treatment 52 weeks
Efficacy Assessments • Positive and Negative Syndrome Scale (PANSS) • Clinical Global Impression – Severity of Illness (CGI-S) • Clinical Global Impression – Global Improvement (CGI-I) • Personal and Social Performance Scale (PSP)
Pharmacoeconomic Assessments • Resource Utilisation Form (RUF)
Safety Assessments • Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI), waist circumference, electrocardiograms (ECGs), and physical examinations • modified Simpson Angus Scale (mSAS) • Barnes Akathisia Rating Scale (BARS) • Abnormal Involuntary Movement Scale (AIMS) • Columbia Suicide Severity Rating Scale (C-SSRS)

Endpoints

- *Primary endpoint*:
  - description of the safety parameters, see safety endpoints below
- *Exploratory Efficacy endpoints*:
  - Psychotic symptoms:
    - change from baseline in PANSS total score
    - change from baseline in PANSS Positive subscale score
    - change from baseline in PANSS Negative subscale score
    - change from baseline in PANSS General Psychopathology score
    - change from baseline in PANSS Excited Component score
    - change from baseline in PANSS Marder Factor scores: Negative Symptoms
    - change from baseline in PANSS Marder Factor scores: Positive Symptoms
    - change from baseline in PANSS Marder Factor scores: Disorganized thought
    - change from baseline in PANSS Marder Factor scores: Uncontrolled hostility / excitement
    - change from baseline in PANSS Marder Factor scores: Anxiety / depression
  - Global Clinical Impression:
    - CGI-I score
    - change from baseline in CGI-S score
  - Response:
    - reduction of ≥30% from baseline in PANSS total score OR CGI-I score of 1 or 2
  - Personal and Social Performance (PSP):
    - change from baseline in PSP total score
- *Pharmacoeconomic endpoint*
  - resource utilisation during the study using the RUF
- *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
  - absolute values and changes from baseline in mSAS, BARS, and AIMS total scores
  - C-SSRS scores will be summarised

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of open-label brexpiprazole
  - *full-analysis set* (FAS) – all patients in the APTS who had a baseline assessment and at least one post-baseline assessment of the PANSS total score
- Unless otherwise indicated, exploratory efficacy analyses and pharmacoeconomic analyses were based on the FAS, and the safety analyses were based on the APTS.
- *Exploratory efficacy analyses*
  - The continuous efficacy endpoints were analysed using a restricted maximum likelihood (REML)-based mixed model for repeated measures (MMRM) approach. The model includes pooled site and visit (Week 1, 2, 4, 8, 14, 20, 26, 32, 38, 44, 52) as fixed effects, baseline as a covariate, and baseline score-by-visit interaction.
  - For all analyses involving CGI-I, the CGI-S served as baseline.
  - Descriptive statistics were presented for the response by visit using Observed Cases (OC) and Last Observation Carried Forward (LOCF)
- *Pharmacoeconomic analysis*
  - Descriptive statistics of categorised values of the RUF were presented by visit for the total population.
- *Safety analyses*
  - adverse events, absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight/BMI, waist circumference, and ECG parameters were summarised using descriptive statistics.
  - The changes in mSAS, BARS, and AIMS total scores were summarised descriptively and using a MMRM.
  - C-SSRS scores were summarised

Patient Disposition and Analysis Sets

- Patient disposition is summarised below:

	Brexpiprazole	
	n	(%)
Patients enrolled	210	
Patients treated (all-patients-treated set [APTS])	209	
Patients completed	101	48.3
Patients withdrawn	108	51.7
Primary reason for withdrawal:		
Adverse event(s)	32	15.3
Lack of efficacy	12	5.7
Other	64	30.6
Analysis sets:		
APTS	209	
Full-analysis set (FAS)	204	

Demography and Baseline Characteristics of the Study Population

- The baseline of lead-in Study 14644A is described as "baseline-14644A" and the baseline for this study is described as "baseline" which is also the Completion Visit of Study 14644A
- The prior treatment groups were similar with respect to age, sex, and race distribution: the mean age of the patients was 41 years, there were slightly more women than men (54% *versus* 46%), and over four-fifths of the patients were White.
- The mean height, weight, BMI, and waist circumferences were approximately 170 cm, 80 kg, 27 kg/m^2, and 92 cm, respectively, with no clinically relevant differences between the prior treatment groups.
- Schizophrenia history at baseline was similar across the prior treatment groups. Overall, the mean time (years) since the first diagnosis for schizophrenia was 12.8 years and the mean time (years) since the first antipsychotic treatment was 13.3 years. The majority (>72%) had had the schizophrenia diagnosis for at least 5 years.
- There were no clinically relevant differences in mean baseline efficacy scores between the prior treatment groups. The patients were *moderately ill* at study entry, with a mean overall PANSS total score of 72 and a mean overall CGI-S score of 3.5. The PSP total score was approximately 59, indicating that the patients had *marked* or *severe* difficulties in several areas of functioning.

Efficacy Results

- The exploratory efficacy variable results are summarised below:

Exploratory Efficacy Variable	n[a]	Brexpiprazole
Δ PANSS total score	204	-6.8
Δ CGI-S score	204	-0.4
Δ PSP total score	204	4.2
CGI-I score	204	2.8
Responders[b]	204	34.8%

Δ = change from baseline (MMRM)
[a]number of patients at baseline
[b]defined as a reduction of ≥30% from baseline in PANSS total score OR CGI-I score of 1 (very much improved) or 2 (much improved)

- The patients had a mean PANSS total score decrease (improvement) of -6.8 points in the FAS, MMRM, indicating improvement for patients who continued treatment with brexpiprazole to Week 52. The mean PANSS total score decreased by -2.6 points in the FAS, LOCF, supporting the MMRM analysis.
- The patients had a mean score of 2.8 on the CGI-I at the end of the Treatment Period, corresponding to between *much* and *very much improved*. A decrease (improvement) in the CGI-I scale score was seen at Week 2 and continued throughout the Treatment Period.
- The mean change from baseline on the CGI-S from baseline to Week 52 was -0.4 points (FAS, MMRM), indicating a mean improvement from *mildly* and *moderately ill* at baseline to *mildly ill* at study endpoint after long-term treatment with brexpiprazole.
- The mean change in PSP total score from baseline to endpoint was 4.2 points (FAS, MMRM), illustrating an improvement in personal and social performance from baseline to Week 52.
- The proportion of patients classified as Responders increased from 16 to 48% (FAS, OC) and from 16 to 35% (FAS, last assessment) from Week 1 to Week 52.
- Healthcare resource utilization as assessed by the RUF in the 3 months preceding baseline and during the study was limited: only few patients had contact with healthcare professionals and/or hospitalisation.

Safety Results

- The adverse event incidence is summarised below for the Entire Study Period:

	Brexpiprazole	
	n	(%)
Patients treated	209	
Patients with treatment-emergent serious AEs (SAEs)	31	14.8
Patients with treatment-emergent adverse events (TEAEs)	133	63.6
Total number of SAEs	38	
Total number of TEAEs	337	

- No patient died during the study. A total of 32 patients (15%) had an SAE. A total of 11 SAEs (6 worsening of schizophrenia, 2 worsening of psychotic disorder, 1 panic attack, 1 aggressive behavior, and 1 grand mal convulsion) in 10 patients were considered *possibly* or *probably related* to brexpiprazole.
- Approximately two-thirds of the patients had one or more TEAEs. The TEAEs with an incidence ≥10% were *schizophrenia* (12%) and *weight increased* (11%). The most common TEAEs were *headache* (8.6%) and *insomnia* (8.1%). The incidence of TEAEs was similar in each of the prior treatment groups.
- The most common TEAE leading to withdrawal was *schizophrenia* (9.6%). The incidence was similar across prior treatment groups.
- The majority of the patients with TEAEs had TEAEs that were either *mild* or *moderate*. The overall incidence of *severe* TEAEs was 8% and the incidence was similar between prior treatment groups.
- One patient had a non-fatal *suicide attempt* reported as an SAE. Otherwise, based on the C-SSRS data, no patient had suicidal ideation with an intent or plan, nor had any patient suicidal behaviour involving either a preparatory act, or an aborted or actual attempt.
- The proportion of patients with extrapyramidal symptoms (EPS)-related TEAEs was 8%, and was similar across the prior treatment groups. Akathisia was the only EPS-related TEAE with an incidence ≥2% of patients (4.8%).
- The incidence of somnolence-related TEAEs was low (4%). A total of 6 patients reported 7 events of *somnolence* and a total of 2 patients reported 2 events of *sedation*. None of the patients withdrew due to somnolence-related TEAEs.
- No clinically relevant patterns were seen with respect to the mean changes in clinical safety laboratory test values (including fasting glucose and lipid values), vital signs, weight, or ECG parameter values. Mean increases in weight (2.6 kg), BMI (1.0 kg/m^2), and waist circumference (2.1 cm) were noted from baseline to those with a Week 52 assessment and increased by 1.1 kg, 0.4 kg/m^2, and 1.1 cm, respectively, from baseline to the last assessment.
- In general, the scores on the mSAS, BARS, and AIMS safety rating scales were low with minor fluctuations over time. There were no deterioration of the EPS-related symptoms and no clinically relevant differences between the prior treatment groups.

Conclusions

- This 52-week extension study showed that long-term treatment with brexpiprazole, flexible dose (1 to 4 mg/day), was safe and well tolerated in patients with schizophrenia.
- There were no new safety concerns noted after long-term treatment with brexpiprazole.
- Patients treated with long-term, flexible-dose brexpiprazole had improvements in the PANSS total score and PANSS subscale scores, CGI-S score, CGI-I score, the percentage of responders, and PSP total score.
- The results support a maintained therapeutic effect of brexpiprazole.

Report Date

10 May 2016

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