Synopsis – Study 15353A

Title of Study

Interventional, open-label, flexible-dose, exploratory study of brexpiprazole as adjunctive treatment of irritability in patients with major depressive disorder and an inadequate response to antidepressant therapy

Investigators

15 investigators at 15 sites in the United States

Signatory investigator – [redacted]

Study Sites

15 centres in the United States

Publications

None (as of the date of this report)

Study Period

First patient first visit – 7 October 2013

Last patient last visit – 30 July 2014

Objectives

- *Exploratory objectives*:
  - to explore the effects of 6 weeks of open-label treatment with a flexible dose of brexpiprazole as adjunctive treatment to SSRI/SNRI antidepressant treatment (ADT) on irritability, anger, and other impulsivity-related symptoms in patients with major depressive disorder and with an inadequate response to ADT
  - to explore these effects in a subgroup of patients with high level of impulsiveness (Barratt Impulsiveness Scale [BIS-11] total score >70)
  - to explore the correlation of treatment-related changes in the irritability, impulsivity, aggressiveness, and anger/hostility symptoms endpoints
  - to explore the re-emergence of impulsivity-driven symptoms after discontinuation of treatment with brexpiprazole but with maintenance of ADT over the 4 weeks of the follow-up period
- *Safety objective*:
  - to evaluate the safety and tolerability of 2 and 3 mg/day brexpiprazole

Methodology

- This was an interventional, multi-site, open-label, flexible-dose, exploratory study.
- The patients were recruited from the study sites' own patient population, by referrals to the study sites, or using advertisement.
- Following a 2-week Lead-in Period where the patients received open-label treatment with their current ADT, the patients who still experienced symptoms of depression and were irritable, and had an inadequate response to ADT at the end of the Lead-in Period were eligible to enter a 6-week open-label Treatment Period with brexpiprazole as adjunctive treatment to their current ADT (non-investigational medicinal products). The patients received 1 mg/day brexpiprazole during Week 1 and 2 mg/day during Week 2 (up-titration) and from Weeks 3 to 6 they received 3 mg/day; depending on tolerability the dose could be reduced to 2 mg/day based on the investigator's judgement.
- A Completion Visit (safety and efficacy follow-up) was scheduled for 4 weeks after completion of the Treatment Period or after withdrawal from the study. The patients continued taking ADT during the Follow-up Period.
- The total study duration per patient from baseline to the end of follow-up was approximately 10 weeks.
- Efficacy and safety data were collected at regular intervals throughout the study.

Number of Patients Planned and Analysed

- 86 patients were planned for screening
- 55 patients were enrolled
- 54 patients were treated and 50 patients completed the study
- 4 patients withdrew – 2 due to adverse events, 1 withdrew consent, and 1 due to protocol violation
- 54 patients were analysed in the all-patients-treated set (APTS)
- 54 patients were analysed in the full-analysis set (FAS)
- 48 patients were analysed in the completer's-analysis set (CAS)

Diagnosis and Main Inclusion Criteria

Outpatients with a primary diagnosis of Major Depressive Disorder (MDD) according to DSM-IV-TR™ criteria, who:

- were between 18 and 65 years of age (extremes included)
- had a reported duration of the current Major Depressive Episode (MDE) of ≥10 weeks
- had an inadequate response to at least one ADT in the current MDE, as documented by self-report as <50% response on the Antidepressant Treatment Response Questionnaire (ATRQ)
- had received prescribed serotonin-specific reuptake inhibitor (SSRI) or serotonin–norepinephrine reuptake inhibitor (SNRI) monotherapy treatment for ≥6 weeks, at the same dosage for ≥2 weeks
- had a Montgomery and Åsberg Depression Rating Scale (MADRS) total score >18 and a Clinical Global Impression – Global Improvement (CGI-I) score ≥3
- had an Inventory of Depressive Symptomatology - Clinician-rated - 30 items (IDS-C30) Item 6 Mood (Irritability) score ≥2 at screening and baseline
- had <25% decrease in MADRS total score during the Lead-in Period
- did not have any current psychiatric disorder or Axis I disorder (DSM-IV-TR™ criteria) established as the principal diagnosis, other than MDD
- did not receive adjunctive treatment with an antipsychotic together with a antidepressant for ≥3 weeks during the current MDE

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

Brexpiprazole – 1, 2, or 3 mg/day; tablets, orally; batch No. 2331228/11L88A001, 2331230/12A73A002, 2331232/12A74A003

Duration of Treatment

6 weeks, followed by a 4-week 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 irritability, impulsivity, aggressivity, hostility and depressive symptoms:
  - Kellner Symptom Questionnaire (KSQ)
  - Sheehan Irritability Scale (SIS)
  - BIS-11
  - Anger Attacks Questionnaire (AAQ)
  - IDS-C30
  - Delay discounting:
    - Monetary Choice Questionnaire (MCQ)
    - Experiential Discounting Tasks (EDT)
  - MADRS
  - Clinical Global Impression – Severity of Illness (CGI-S)
  - CGI-I
- Assessment of cognition:
  - Massachusetts General Hospital Cognitive and Physical Functioning Questionnaire (CPFQ)

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, electrocardiograms (ECGs), and electronic Columbia Suicide Severity Rating Scale (C-SSRS)

Statistical Methodology

- The following analysis sets were used
  - *all-patients-treated set* (APTS) – all patients who took at least one dose of investigational medicinal product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had a baseline assessment and at least one post-baseline efficacy assessment
  - *completer's-analysis set (CAS)* – all patients in the FAS who had at least one efficacy assessment measured at both the End of Treatment and Completion Visits
- All exploratory efficacy analyses for the Treatment Period were conducted on the FAS; exploratory efficacy analyses for the Follow-up Period were conducted on the CAS. All safety analyses were conducted on the APTS.
- *Exploratory efficacy analyses:*
  - The change from baseline to Week 6 in KSQ total and subscale score, SIS total score, BIS-11 total and subscale scores, IDS-C30 total and item 6 score, MCQ score, and MADRS total score measured at all visits was estimated based on a mixed model repeated measures (MMRM) approach, with the site and visit as fixed effects and baseline score-by-visit interaction (FAS, observed cases [OC]). An unstructured variance matrix was used to account for the within-patient errors.
  - The change from baseline to Week 6 in CGI-S, EDT DPDT delay and probability, and EDT DRT was analysed using an analysis of covariance (ANCOVA) with the site as fixed effect and the baseline value as a covariate (FAS, OC).
  - Absolute values for CGI-I was summarised for Week 6.
  - The change from Week 6 to Week 10 was estimated using an ANCOVA with the site as fixed effect and the Week 6 value as a covariate (CAS, OC).

Statistical Methodology (continued)

- Counts and percentages for patients classified as having anger attacks or not based on the AAQ score was presented as shift from baseline to Week 6 (FAS, OC). In addition, the last two questions in AAQ were summarised by visit for the patients classified as having anger attacks.
- Counts and percentages for patients were presented for MADRS remission and response rates (FAS, OC) by visit based on a reduction from baseline ≥50% in MADRS total score (response) and a MADRS total score ≤10 AND a reduction from baseline ≥50% in MADRS total score (remission).

• *Correlation of exploratory endpoints:*

- Pearson and partial correlations were used to evaluate the relationship between the changes in the KSQ anger-hostility subscale score with changes in irritability, impulsivity, aggressivity, hostility symptoms, as assessed by KSQ depression subscale score, BIS-11 total score, SIS total score, IDS-C30 Item 6 Mood (irritable), MCQ score and EDT DPDT and DRT scores.
- The partial correlations were estimated conditional on the baseline values using a multivariate analysis including both endpoints as outcomes in MMRM with an unstructured covariance structure. The MMRM approach uses all available measurements for estimation, therefore, patients where some endpoints had missing values were included in the analysis. Visit, outcome type and the interaction was included as fixed effects, the baseline scores as covariates, and both baseline scores interacting with visit and outcome type.

• *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 were summarised by visit and last assessment for clinical safety laboratory tests, vital signs, and ECG using descriptive statistics. Values outside the reference ranges, as well as potentially clinically significant (PCS) values, were flagged and summarised.
- The C-SSRS data were summarised by treatment and visit both for the raw data and by the Columbia Classification Algorithm for Suicide Assessment categories.

Demography of Study Population

- The ratio of men to women was approximately 1 to 2. The mean age of the patients was 42 years and the majority were white.
- The mean weight at baseline was 90 kg and the mean body mass index was 31 kg/m^2.
- The MADRS total score (mean: 28.5, ranging from 21 to 39) at Baseline indicated that the patients had *moderate* to *severe* MDD and the CGI-S score (mean: 4.1, ranging from 3 to 5) indicated that the patients were *mildly* to *severely* ill. The BIS-11 total score (mean: 73.2, ranging from 53 to 114) indicated that the patients were highly impulsive at Baseline, and the mean IDS-C30 item 6 score (2.2, ranging from 2 to 3) indicated that the patients were irritable ≥50% of the time. Thirty-one percent of the patients had anger attacks during the Screening Period.

Efficacy Results

• The exploratory efficacy results for the Treatment Period are summarised below:

	Baseline (FAS, OC)		Adjusted Change from Baseline to Week 6 (FAS, MMRM)		
	N	mean±SD	N	mean ± SE	95% CI
Patient-rated irritability, hostility, and anger state assessments					
KSQ total score	54	54.9±13.1	50	-24.4±2.9	[-30.3;-18.4]*
KSQ anger-hostility subscale score	54	14.8±4.8	50	-7.7±0.9	[-9.6;-5.9]*
SIS total score	54	44.9±9.8	50	-21.1±2.6	[-26.3;-16.0]*
SIS item 1 score	54	7.1±1.5	50	-3.5±0.4	[-4.2;-2.7]*
Clinician-rated irritable mood state assessment					
IDS-C30 item 6	54	2.2±0.4	50	-1.2±0.1	[-1.5;-1.0]*
Patient-rated impulsivity trait assessments					
BIS-11 total score	54	73.2±12.8	50	-4.9±0.9	[-6.6;-3.1]
MCQ score[a]	54	-3.5±1.5	50	0.0±0.2	[-0.5;0.5]
EDT DPDT delay score[a]	51	-2.8±2.6	47	-0.2±0.3	[-0.9;0.5]
EDT DPDT probability score[a]	51	1.1±1.4	47	-0.3±0.3	[-0.8;0.3]
EDT DRT score	50	31.3±14.8	46	0.7±2.0	[-3.3;4.8]
Clinician-rated depression state assessments					
MADRS total score	54	28.5±4.5	50	-14.2±1.3	[-16.7;-11.6]*
MADRS response		-	50	24 (48%)[b]	-
MADRS remission		-	50	17 (34%)[c]	-
CGI-S score[d]	54	4.1±0.4	54	-1.4±0.2	[-1.8;-1.1]*
CGI-I score		-	50	2.2±1.1[e]	-
IDS-C30 total score	54	37.4±7.5	50	-17.8±1.6	[-21.0;-14.6]*
Patient-rated depression state assessment					
KSQ depression subscale score	54	15.0±4.5	50	-7.7±0.9	[-9.6;-5.8]*
Patient-rated cognitive and function state assessment					
CPFQ total score	54	28.1±5.8	50	7.7±1.0	[-9.7;-5.8]*

* The change is considered to be of statistical importance since the size of the confidence interval is small compared to the overall change observed.

a Natural log-transformed values, adjusted change from Baseline to Week 6 was analysed using FAS, MMRM/ANCOVA

b Response n (%) at Week 6

c Remission n (%) at Week 6

d Adjusted change from Baseline to Week 6 was analysed using FAS, ANCOVA

e CGI-I score at Week 6

Efficacy Results (continued)

• The exploratory efficacy results for the Follow-up Period are summarised below:

	Week 6 (CAS, OC)		Adjusted change from Week 6 to Week 10 (CAS, ANCOVA)		
	N	mean ± SD	N	mean ± SE	95% CI
Patient-rated irritability, hostility, and anger state assessments					
KSQ anger-hostility subscale score	48	8.1±6.6	48	1.2±1.0	[-0.8;3.2]
SIS total score	48	25.4±17.4	48	4.4±2.4	[-0.5;9.4]
SIS item 1 score	48	3.9±2.5	47	0.5±0.4	[-0.3;1.4]
Patient-rated impulsivity trait assessments					
BIS-11 total score	48	69.7±12.3	47	-1.2±0.9	[-3.0;0.6]
MCQ score[a]	48	-3.6±1.9	47	0.4±0.2	[0.0;0.7]
Clinician-rated depression state assessments					
CGI-S score	48	2.7±1.1	48	0.3±0.1	[0.0;0.5]
Patient-rated depression state assessment					
KSQ depression subscale score	48	8.2±6.6	48	2.1±1.0	[0.1;4.2]

a Natural log-transformed values

- The patient-rated scales for irritability, hostility, and anger assessing the state of the patients during the MDE are all indicating an improvement of the irritability and anger-hostility symptoms during the Treatment Period. The mean KSQ total score, KSQ anger-hostility score, SIS total score, and SIS item 1 score decreased (improved) over time from Baseline to Week 6 (FAS, MMRM). The improvement in anger was also supported by the results from the AAQ, which indicated that more patients shifted from having had anger attacks at Baseline to not having anger attacks at Week 6 (15 patients) than from not having had anger attacks at Baseline to having anger attacks at Week 6 (5 patients).
- A similar pattern of improvement was observed with the clinician-rated scale for irritable mood also assessing the state of the patients. The mean IDS-C30 item 6 score decreased (improved) over time from Baseline to Week 6 (FAS, MMRM), indicating an improvement of the irritability symptoms during the Treatment Period.
- A small improvement was observed during the Treatment Period when using the patient-rated scales for impulsivity assessing the personality trait of the patients (BIS-11 total score). The improvement in the BIS-11 total score was likely driven by the changes in the BIS-11 attentional and non-planning subscales (FAS, MMRM).
- No real change was observed over time during the Treatment Period for the mean MCQ and EDT (DPDT delay, DPDT probability, and DRT) scores (FAS, MMRM/ANCOVA).
- The clinician-rated scales for depression assessing the state of the patients indicated an improvement of the depressive symptoms over time during the Treatment Period. The mean MADRS total score, CGI-S score, and IDS-C30 total score decreased (improved) over time from Baseline to Week 6 (FAS, MMRM). In addition, the CGI-I score indicated a global improvement of the symptoms (FAS, OC).
- A similar pattern of improvement over time was observed with the patient-rated scale for depressive symptoms. The mean KSQ depression subscale score decreased (improved) over time from Baseline to Week 6 (FAS, MMRM), indicating an improvement of the depressive symptoms during the Treatment Period.
- The proportion of patients who responded was 48% at Week 6, according to the MADRS criterion and the proportion of patients who were in remission was 34% at Week 6, according to the MADRS criterion.

Efficacy Results (continued)

- A similar improvement was observed from Baseline to Week 6 in the clinician-rated scales for depression (MADRS and CGI-S) for the patients with a BIS-11 total score <70.5 at Baseline as in the patients with a BIS-11 total score ≥70.5 at Baseline (70.5 was the median for BIS-11 at Baseline). In addition, the patients with a BIS-11 total score <70.5 at Baseline showed improvement of the global symptoms (CGI-I) at Week 6 as did the patients with a BIS-11 total score ≥70.5 at Baseline (FAS, OC).
- The patient-rated scale for cognitive and executive dysfunctioning assessing the state of the patients indicated an improvement of the cognition during the Treatment Period. The mean CPFQ total score, decreased (improved) over time from Baseline to Week 6 (FAS, MMRM).
- During the Follow-up Period (after discontinuation of treatment with adjunctive brexpiprazole), the patient-rated scales for irritability, hostility, anger, and depression (state assessments), indicated a re-emergence of the symptoms. The mean KSQ anger-hostility score, SIS total score, SIS item 1 score, and KSQ depression subscale score increased (worsened) from Week 6 to Week 10 (CAS, ANCOVA); the scores did not return to the baseline values during the 4-week Follow-up Period.
- A small continued improvement was observed during the Follow-up Period when using the patient-rated scale for impulsivity assessing the personality trait of the patient (BIS-11 total score [CAS, ANCOVA]).
- No real change was observed during the Follow-up Period for the mean MCQ score (CAS, ANCOVA).
- The correlation of the changes from baseline in the KSQ anger-hostility subscale score with various endpoints was conducted to describe the relationship between the endpoints. The KSQ depression subscale and SIS scale had the highest positive correlation with the KSQ anger-hostility subscale, assessed using both Pearson and partial correlations as they showed the same pattern of improvement during the Treatment Period.

Safety Results

- The adverse event incidence is summarised below:

	Brex + ADT n	(%)
Patients treated	54	
Patients who died	0	(0)
Patients with serious AEs (SAEs)	0	(0)
Patients with AEs leading to withdrawal	2	(3.7)
Patients with treatment-emergent adverse events (TEAEs)	43	(79.6)
Total number of TEAEs	120	

- No deaths or other SAEs occurred during the study.
- Forty-three (80%) of the patients in the APTS had one or more TEAEs during the study.
- A total of 2 patients (3.7%) withdrew from the study due to adverse events (*panic attack*, *somnolence*).
- For the majority of the patients with TEAEs, the events were *mild* or *moderate*. The incidence of *severe* TEAEs was 7.4% (4 events: *insomnia*, *middle insomnia*, *panic attack*, *asthma*).
- The TEAEs with the highest incidences (≥10%) were *akathisia* and *headache*. The TEAEs with an incidence between 5 and 10% were *dry mouth*, *fatigue*, *increased appetite*, *insomnia*, *diarrhoea*, *dizziness*, *fall*, *somnolence*, and *weight increased*.
- Twelve patients (22%) had a total of 14 EPS-related adverse events; the majority of the events were *akathisia* (12 out of 14 events). Three patients were treated for akathisia (two with β-blockers and one with an anticholinergic agent) and no patients withdrew from the study due to *akathisia* or any other EPS-related adverse events.
- The incidence of TEAEs related to sedation was low (7.4%). All the TEAEs related to sedation were considered to be *related* to IMP by the investigator and either *mild* or *moderate* in intensity. One patient withdrew from the study due to *somnolence*.
- Based on the C-SSRS, one patient was classified as *active suicidal activation with some intent to act, without specific plan*, which was also reported as a TEAE.
- There were no patterns in the mean laboratory values, vital signs, or ECG parameter values considered to be of clinical relevance, and the proportion of patients with PCS values were low.

Conclusions

- Symptoms of irritability, hostility, and anger 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 6 is considered to be of clinical relevance.
- A similar improvement of the depressive symptoms was observed both in patients categorised as less irritable and in patients categorised as more irritable.
- Following completion of treatment with adjunctive brexpiprazole, re-emergence of the impulsivity driven symptoms, such as irritability and anger, was observed despite continued treatment with antidepressants.
- There was a positive correlation of the changes from baseline between several of the endpoints providing further evidence that the results are consistent and robust.
- Overall, adjunctive treatment of irritability with brexpiprazole 2 to 3 mg/day was safe and well tolerated in patients with MDD and an inadequate response to their current ADT and no safety issues were raised in this study.

Date of the Report

12 March 2015

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