Synopsis – Study 14571A

Title of Study

Interventional, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study to evaluate the efficacy and safety of brexpiprazole (1 and 3 mg/day) as adjunctive treatment in elderly patients with major depressive disorder with an inadequate response to antidepressant treatment

Investigators

61 investigators at 61 sites in 13 countries

Signatory investigator – [redacted]

Study Sites

61 sites – 1 in Bulgaria, 5 in Germany, 2 in Estonia, 1 in Finland, 1 in United Kingdom, 2 in Lithuania, 5 in Poland, 2 in Romania, 6 in Russia, 5 in Sweden, 1 in Slovakia, 4 in Ukraine, and 27 in the United States

Publications

None (as of the date of this report)

Study Period

First patient first visit – 15 April 2013

Study terminated – 1 April 2014

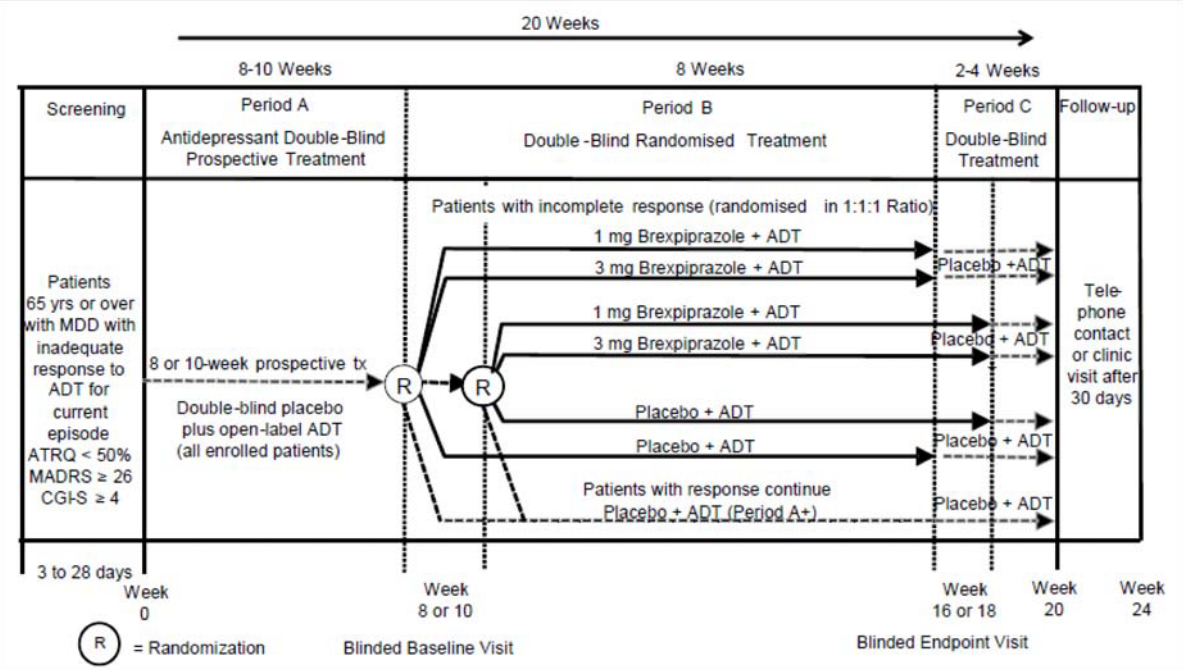
Last patient last visit – 22 May 2014

Objectives

- *Primary objective*:
  - to evaluate the efficacy on depressive symptoms of 1 and 3 mg/day once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants in elderly patients with an inadequate response to antidepressant treatment
- *Key secondary objectives*:
  - to evaluate the efficacy of 1 and 3 mg/day once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants on:
    - global clinical impression
    - functioning
    - social adaptation
- *Other secondary objectives:*
  - to evaluate the efficacy of 1 and 3 mg/day once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants on:
    - cognitive functioning
    - subjective quality of sleep
- *Exploratory objective:*
  - to evaluate the pharmacoeconomics of 1 and 3 mg/day once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants
- *Safety objective:*
  - to evaluate the safety and tolerability of 1 and 3 mg/day once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants in elderly patients

Methodology

- This was an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, fixed-dose study.
- Patients were recruited from the investigator's own patient population, via advertisement (if allowed in the country) or referrals, or via general practitioners.
- The study consisted of a screening period (could last from 3 to 28 days), a blinded treatment period (Weeks 0 to 20), and a safety follow-up period (Weeks 20 to 24) for patients who did not enter the open-label extension Study 14767B.
- The blinded treatment period consisted of Periods A, B, C, and A+:
  - Period A: the patients received 8 or 10 weeks of open-label treatment with one of six antidepressant treatments (ADTs) together with double-blind placebo treatment. The dose of the ADT was increased according to a titration scheme during the first 4 weeks to increase the likelihood of ADT success. The investigator could adjust the ADT dose based on tolerability during the first 4 weeks of treatment; after Week 4, the dose had to remain stable. After 8 weeks of treatment, half of the patients with inadequate response to ADT at every visit in Period A were randomly assigned to Period B; the other half were assigned to Period B two weeks later (at Week 10) if they still had an inadequate response to ADT to blind the time point for when they received add-on placebo or brexpiprazole treatment. Inadequate response was defined as <50% improvement in MADRS total score since the start of Period A, a CGI-S score ≥4 and a CGI-I score ≥3 at every visit in Period A, and a MADRS total score ≥20 at the randomisation visit (Week 8 or 10). The visit at which the patient was randomised was blinded to both the patient and the investigator. The patients who had responded to ADT in Period A continued in Period A+.
  - Period B: the patients received 8 weeks of double-blind treatment with 1 or 3 mg/day brexpiprazole or placebo (1:1:1) in addition to the open-label ADT they received in Period A.
  - Period C: at the end of Period B, the patients received 4 or 2 weeks of double-blind placebo adjunctive to their ADT, depending on whether they were randomised at Week 8 or 10.
  - Period A+: the patients continued with the same treatment they received in Period A and followed the same assessment schedule as the patients in Periods B and C.
- A schematic overview of the study design is presented below:



Methodology (continued)

- Efficacy and safety data were collected at 2-week intervals throughout the study.
- Patients were offered to continue in an open-label extension study after completion of treatment.
- For patients who did not continue in the open-label extension study, a safety follow-up visit was scheduled 4 weeks after completion of/withdrawal from the study.
- The study was terminated early because of recruitment challenges and because the expectations for the randomisation rate were not met. The patients were withdrawn at the next study visit.

Number of Patients Planned

1334 patients were planned for enrolment.

Diagnosis and Main Selection Criteria

Outpatients with a primary diagnosis of recurrent major depressive disorder (MDD) according to DSM-IV-TR™ criteria (current Major Depressive Episode [MDE] confirmed using the Mini International Neuropsychiatric Interview [MINI]), who:

- had at least one previous MDE before the age of 60 years
- had a Montgomery and Åsberg Depression Rating Scale (MADRS) total score ≥26 at screening and at baseline
- had a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 at screening and at baseline
- had had the current MDE for ≥8 weeks
- had an inadequate response to at least one and no more than three adequate ADTs (including the treatment taken during screening) for the current MDE, as documented by a self-report of <50% response on the Antidepressant Treatment Response Questionnaire (ATRQ)
- were ≥65 years of age

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

Brexpiprazole – 0.5 mg (titration only), 1 mg, or 3 mg/day; tablets, orally; batch Nos. 2331226 (0.5 mg), 2355962 (0.5 mg), 2331228 (1 mg), 2355963 (1 mg), 2331232 (3 mg), and 2355965 (3 mg)

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Placebo – tablets; orally; batch Nos. 2331223 and 2355968

Non-investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers

Duloxetine (Cymbalta®) – 60 mg/day; capsules, orally; batch Nos. C072461A (60 mg) and C117981 (60 mg)

Escitalopram (Cipralex® or Lexapro®) – 5 or 10 mg/day; tablets, orally; Cipralex® batch Nos. 2374699 (5 mg), 2337126 (5 mg), 2377406 (10 mg), and 2336308 (10 mg); Lexapro® batch Nos. A270393 (5 mg) and A256961 (10 mg)

Fluoxetine (Prozac®) – 20 or 40 mg/day; capsules, orally; batch Nos. C058468C (20 mg) and 2412D (20 mg)

Paroxetine (Paxil® or *Seroxat®)* – 20, 30, or 40 mg/day; tablets, orally; Paxil® batch Nos. 2ZP1063 (20 mg), 3ZP1779 (30 mg), and 1ZP9197 (30 mg); Seroxat® batch Nos. 640 (20 mg) and 049M (30 mg)

Sertraline (Lustral™ or *Zoloft®)* – 50, 100, or 150 mg/day; tablets, orally; Lustral™ batch Nos. 37202400U (50 mg) and 37202600U (100 mg); Zoloft® batch Nos. C120729 (50 mg) and V122393 (100 mg)

Venlafaxine (Effexor XL® or *Effexor XR®)* – 75, 150, or 225 mg/day; capsules, orally; Effexor XL® batch Nos. G25220 (75 mg) and G37553 (150 mg); Effexor XR® batch Nos. V122024 (75 mg) and V121999 (150 mg)

Duration of Treatment

ADT for 20 weeks; brexpiprazole for 8 weeks

Efficacy Assessments

- MADRS
- CGI-S
- Clinical Global Impression – Global Improvement (CGI-I)
- Sheehan Disability Scale (SDS)
- Social Adaptation Self-evaluation Scale (SASS)
- Cognitive assessments by computerised test battery
  - Simple Reaction Time
  - Digit Vigilance
  - Choice Reaction Time
  - Executive Function Test
  - Picture Recognition
- Pittsburgh Sleep Quality Inventory (PSQI)
- EQ-5D-5L

Pharmacoeconomic Assessments

- Health Economic Assessment (HEA)

Pharmacokinetic Assessments

- Plasma concentrations of brexpiprazole and its major metabolite DM-3411
- Genotyping for CYP2D6

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI) and waist circumference, physical examinations, electrocardiograms (ECGs), electronic Columbia Suicide Severity Rating Scale (eC-SSRS), Simpson-Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS)

Endpoints

- *Primary endpoint*:
  - depressive symptoms:
    - change from randomisation in MADRS total score after 8 weeks of randomised treatment
- *Key secondary endpoints (in hierarchical order)*:
  - global clinical impression:
    - change from randomisation in CGI-S score at the end of randomised treatment
  - functionality:
    - change from randomisation in the SDS total score at the end of randomised treatment
  - social adaptation:
    - change from randomisation in SASS total score at the end of randomised treatment
- Further efficacy endpoints in this study are presented in Addendum I of the study protocol
- *Safety endpoints*:
  - adverse events
  - absolute values and changes from end of Period A 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, BMI, and ECG parameter values
  - C-SSRS categorisation based on the Columbia Classification Algorithm for Suicide Assessment (C-CASA) definitions (1, 2, 3, 4, and 7)
  - change from randomisation in SAS, AIMS, and BARS total scores

Statistical Methodology

- Only safety analyses were performed. The limited number of enrolled patients resulted in insufficient data for any meaningful efficacy or HEA analyses.
- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of Investigational Medicinal Product (IMP) (brexpiprazole or placebo) after randomisation
  - *all-patients-treated Period A set* (APTSPA) – all patients who took at least one dose of ADT and/or placebo
  - *all-patients-treated Period A+ set* (APTSPA+) – all patients who completed Period A but were not randomised in Period B and who had at least one efficacy or safety assessment in Period A+
- Safety data captured during Period C were analysed based on the APTS and reported together with the analysis results for Period B.
- The analyses sets used for the safety analyses in each period were: APTSPA (Period A), APTS (Periods B and C), and APTSPA+ (Period A+).
- Disposition, withdrawals, exposure and compliance (IMP and ADT), demographics, and baseline characteristics (including MDE history and Mini Mental State Examination [MMSE] score) were summarised by treatment group using descriptive statistics.
- Recent and concomitant medication was classified according to the start and stop time of IMP (discontinued prior to first dose; continued after first dose; and started at or after first dose) and summarised by anatomical therapeutic chemical (ATC) code and generic drug name for patients in the APTS.
- The incidences of adverse events (Periods A and A+) and treatment-emergent adverse events (TEAEs) (Period B) were tabulated by primary system organ class (SOC) and preferred term, and for Period B, by intensity and by causality (*probably* and *possibly related* to treatment). All adverse events and adverse events leading to withdrawal were included in the data listings.
- The number and percentages of patients with post-randomisation suicide-related events, based on the eC-SSRS data, were summarised by treatment. In addition, the worst case per evaluation of the eC-SSRS was mapped into the C-CASA categories (Table 1). The number and percentage of patients in the C-CASA categories were summarised for all post-randomisation assessment time points during Period B.
- The absolute value and change from randomisation in AIMS total score, BARS Global Clinical Assessment of Akathisia score (Item 4 of the BARS), and SAS total score were summarised by treatment group for Period B.
- Absolute values and changes from end of Period A to the last assessment in clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameter values were summarised using descriptive techniques. Post-randomisation potentially clinically significant (PCS) values were flagged and tabulated. The PCS criterias for clinical safety laboratory tests, vital signs, weight/BMI, and ECG parameters are presented in Table 2.
- The results of urinalysis were tabulated (dipsticks) and listed (microscopy).

Patients Disposition and Analyses Sets

- The randomisation lists, including patient identifier and treatment assigned, are in Listings 1 and 2.
- Patient disposition by site is summarised in Tables 3 (Period A) and 4 (Period B), and by country in Tables 5 (Period A) and 6 (Period B). The number of patients in the analyses sets are summarised in Table 7.
- Patient disposition in Period A is summarised below (only the ADT is listed; all patients received adjunctive placebo):

	DUL		ESC		FLU		PAR		SER		VXR		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients enrolled													129	
Patients treated in Period A (APTSPA):	36		29		10		11		20		22		128	
Patients completed	7	(19)	7	(24)	2	(20)	2	(18)	5	(25)	4	(18)	27	(21)
Patients withdrawn[a]	29	(81)	22	(76)	8	(80)	9	(82)	15	(75)	18	(82)	101	(79)
Primary reason for withdrawal[a]														
Adverse event(s)	0		2	(7)	1	(10)	0		4	(20)	2	(9)	9	(7)
Administrative or other reason(s)	23	(64)	16	(55)	5	(50)	8	(73)	10	(50)	14	(64)	76	(59)
Withdrawal of consent	2	(6)	1	(3)	2	(20)	0		1	(5)	0		6	(5)
Other	4	(11)	3	(10)	0		1	(9)	0		2	(9)	10	(8)

Cross-references: Tables 7, 8, and 9.
APTSPA = all-patients-treated Period A set; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; PAR = paroxetine; SER = sertraline; VXR = venlafaxine extended release

a During Period A, A+, or B

- Patient disposition in Period B is summarised below:

	Brex 1mg/day + ADT		Brex 3mg/day + ADT		Placebo + ADT	
	n	(%)	n	(%)	n	(%)
Patients randomised in Period B (APRS):	3		6		6	
Patients treated in Period B (APTS):	3		6		6	
Patients completed	1	(33)	1	(17)	1	(17)
Patients withdrawn[a]	2	(67)	5	(83)	5	(83)
Primary reason for withdrawal[a]						
Adverse event(s)	0		1	(17)	0	
Administrative or other reason(s)	2	(67)	4	(67)	5	(83)

Cross-references: Tables 10 and 11.
APRS = all-patients-randomised set; APTS = all-patients-treated set; Brex = brexpiprazole; ADT = antidepressant

a During Period B

Patient disposition by ADT in Period B is summarised in Table 12.

Patients Disposition and Analyses Sets (continued)

- Patient disposition in Period A+ is summarised below (only the ADT is listed; all patients received adjunctive placebo):

	DUL		ESC		FLU		PAR		SER		VXR		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated in Period A+ (APTSPA+):	10		14		5		6		6		6		47	
Patients completed	6	(60)	7	(50)	1	(20)	2	(33)	4	(67)	4	(67)	24	(51)
Patients withdrawn[a]	4	(40)	7	(50)	4	(80)	4	(67)	2	(33)	2	(33)	23	(49)
Primary reason for withdrawal[a]														
Adverse event(s)	0		1	(7)	0		0		0		0		1	(2)
Administrative or other reason(s)	3	(30)	6	(43)	4	(80)	4	(67)	2	(33)	1	(17)	20	(43)
Other	1	(10)	0		0		0		0		1	(17)	2	(4)

Cross-references: Tables 13 and 14.
APTSPA+ = APTSPA = all-patients-treated Period A set; DUL = duloxetine; ESC = escitalopram; FLU = fluoxetine; PAR = paroxetine; SER = sertraline; VXR = venlafaxine extended release

a During Period A+

- The primary reason for withdrawal during the study was administrative or other reason(s), due to the early termination of the study (Table 9). Nine patients withdrew due to adverse events, mainly during Period A (Table 9); 1 patient in the brexpiprazole (3 mg/day) + ADT group withdrew due to adverse events during Period B (Table 11)
- Withdrawals by all reasons are summarised in Tables 15 (withdrawals during Periods A, B, or A+), 16 (withdrawals during Period B), and 17 (withdrawals during Period A+). All withdrawals are in Listing 3.

Exposure

- The median exposure to IMP (Period B) was 55 days (brexpiprazole 1 mg/day + ADT), 20 days (brexpiprazole 3 mg/day + ADT), and 19 days (placebo + ADT) (Table 18). Compliance with IMP in Period B was >80% for >80% of the patients in each treatment group (Table 19). Exposure to and compliance with ADT in Period B are summarised in Tables 20 and 21, respectively.

Demography of Study Population

- The overall mean age of the patients included in Period A was 70 years and >95% of the patients were White. The overall mean baseline weight, height, and BMI were 75 kg, 164 cm, and 28 kg/m^2 and approximately one-quarter were men, with minor variations across treatment groups (Tables 22 and 23).
- The mean age of the patients included in Period B was 71 years and all the patients were White (Table 24). There were more women than men (11 *versus* 4; Table 24). The mean baseline weight, height, and BMI in the three treatment groups were 89 kg, 167 cm, and 31 kg/m^2 (brexpiprazole 1 mg/day), 72 kg, 163 cm, and 27 kg/m^2 (brexpiprazole 3 mg/day), and 81 kg, 168 cm, and 29 kg/m^2 (placebo) (Table 25).
- The overall demography of the patient included in Period A+ was similar to that of the patients included in Period A (Tables 26 and 27).
- The psychiatric history of depression at screening is summarised in Table 28 for patients included in Period A and in Table 29 for patients included in Period B. Patients included in Periods A and B had had approximately 4 to 5 lifetime episodes (range: 2 to 15). The mean duration of the current MDE was approximately 15 months (range: 2 to 362 months) for patients included in Period A and 7 months (range: 3 to 20 months) for patients included in Period B. The duration of the last period of wellness was approximately 44 months (range: 0 to 480 months) for patients included in Period A and 41 months (range: 0 to 110 months) for patients included in Period B.

Demography of Study Population (continued)

- For patients in both Periods A and B, the mean baseline MMSE total score was approximately 29, indicating that the patients did not suffer from dementia (Tables 30 [Period A] and 31 [Period B]).
- The medical, neurological, and psychiatric disorders that were present in patients in Periods A and B are presented in Tables 32 to 35. The concurrent (ongoing at baseline) medical, neurological, and psychiatric disorders that were present in >2 patients in either of the treatment groups in Period B were *vascular disorders*, *gastrointestinal disorders*, and *metabolism and nutrition disorders* (Table 33).
- For patients in Period B, concomitant medication stopped before first dose of randomised IMP, continued after first dose of randomised IMP, and started at or after first dose of randomised IMP are presented in Tables 36, 37, and 38, respectively, and in Listing 4.

Efficacy Results

- The limited number of enrolled patients resulted in insufficient data for any meaningful analyses.

Pharmakokinetic Results

- The limited number of enrolled patients resulted in insufficient data for any meaningful analyses.

Safety Results

- Adverse events are presented for all periods. The focus of this safety presentation is, however, the comparison of brexpiprazole (1 and 3 mg/day) + ADT *versus* placebo + ADT during double-blind treatment in Period B. The adverse event data for Period B are therefore presented first. Furthermore, clinical safety laboratory values, vital signs, weight, and ECGs are only presented for Period B.

Adverse Events

- All adverse events are in Listing 5 and all serious adverse events (SAEs) are in Listing 6. All adverse events leading to withdrawal in Period B are in Listing 7.
- The adverse event incidence during Period B is summarised below:

	Brexpiprazole 1 mg/day		Brexpiprazole 3 mg/day		Placebo	
	n	(%)	n	(%)	n	(%)
Patients treated	3		6		6	
Patients who died	0	(0.0)	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with AEs leading to withdrawal	0	(0.0)	1	(16.7)	0	(0.0)
Patients with AEs	2	(66,7)	2	(33.3)	2	(33.3)
Total number of AEs	5		2		3	

Cross-reference: Table 39

- During Period B, none of the patients died or had SAEs.
- The adverse events during Period B are summarised by system organ class (SOC) and preferred term in Table 40 and by preferred term in Table 41. Four of the five adverse events in the brexpiprazole 1 mg/day + ADT group and both adverse events in the brexpiprazole 3 mg/day + ADT group were *possibly* or *probably related* to treatment (Table 42). Two of the five adverse events in the brexpiprazole 1 mg/day + ADT group were *moderate*; the remaining three were *mild*. In the brexpiprazole 3 mg/day + ADT group, both adverse events were *mild* (Table 43).
- During Period B, one patient in the brexpiprazole 3 mg/day + ADT group withdrew due to an adverse event (*Parkinson's Disease*; *mild*; *possibly related*) (Tables 44 and 45 and Listing 7). None of the patients in the brexpiprazole 1 mg/day + ADT or placebo groups withdrew due to adverse events.

Safety Results (continued)

• The adverse event incidence during Period A is summarised below:

	DUL		ESC		FLU		PAR		SER		VXR	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	36		29		10		11		20		22	
Patients who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	1	(2.8)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with AEs leading to withdrawal	3	(8.3)	2	(6.9)	1	(10.0)	0	(0.0)	4	(20.0)	1	(4.5)
Patients with AEs	20	(55.6)	18	(62.1)	8	(80.0)	5	(45.5)	15	(75.0)	15	(68.2)
Total number of AEs		54		58		18		10		39		32

Cross-reference: Table 46

• During Period A, none of the patients died; 1 patient treated prospectively with duloxetine had an SAE (*diverticulum*; *moderate*; *not related*) (Tables 47 and 48 and Listing 6). The patient recovered and was not withdrawn from the study due to the event.

• The adverse events in Period A are summarised by SOC and preferred term in Table 49 and by preferred term in Table 50. Overall, the SOCs with the highest incidence (>10%) of adverse events were *gastrointestinal disorders* (overall 27%; mainly *nausea*), *nervous system disorders* (19.5%; mainly *headache*), *infections and infestations* (13%; mainly *nasopharyngitis*), and *psychiatric disorders* (13%; mainly *insomnia*).

• During Period A, 11 patients (8.6%) withdrew due to adverse events. The adverse events leading to withdrawal are summarised by SOC and preferred term in Table 51 and by preferred term in Table 52. For 8 of the 11 patients, the adverse events leading to withdrawal were *possibly* or *probably related* to treatment (Listing 5).

• The adverse event incidence during Period A+ is summarised below:

	DUL		ESC		FLU		PAR		SER		VXR	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	10		14		5		6		6		6	
Patients who died	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with AEs leading to withdrawal	0	(0.0)	1	(7.1)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
Patients with AEs	6	(60.0)	6	(42.9)	3	(60.0)	2	(33.3)	3	(50.0)	2	(33.3)
Total number of AEs		13		9		8		6		6		4

Cross-reference: Table 53

• During Period A+, none of the patients died or had SAEs.

• The adverse events in Period A+ are summarised by system organ class (SOC) and preferred term in Table 54 and by preferred term in Table 55. Overall, the SOCs with the highest incidence (>10%) of adverse events were *gastrointestinal disorders* (13%), *nervous system disorders* (13%), *muscoloskeletal and connective tissue disorders* (13%), *infections and infestations* (11%), and *psychiatric disorders* (11%).

• During Period A+, one patient treated with escitalopram withdrew due to an adverse event (*diplopia*; *moderate*; *not related*) (Tables 56 and 57 and Listing 5).

Safety Results (continued)

Extrapyramidal Symptoms Rating Scales (SAS, BARS, and AIMS)

- The SAS total scores and the changes from randomisation in SAS total scores are summarised in Tables 58 and 59, respectively. The BARS global clinical assessment of akathisia scores and the changes from randomisation in BARS global clinical assessment of akathisia scores are summarised in Tables 60 and 61, respectively. The AIMS total scores and the changes from randomisation in AIMS total scores are summarised in Tables 62 and 63, respectively.
- There were no clinically relevant changes in extrapyramidal symptom scores during Period B based on the results of the SAS, BARS, and AIMS ratings.

Prolactin Levels and other Clinical Safety Laboratory Parameters

- The clinical safety laboratory values during Period B are summarised in Tables 64 (cardiac/skeletal muscle), 65 (electrolytes), 66 (endocrine/metabolic), 67 (haematology), 68 (kidney), 69 (lipids), and 70 (liver). The changes from the end of Period A in clinical safety laboratory values are summarised in Tables 71 (cardiac/skeletal muscle), 72 (electrolytes), 73 (endocrine/metabolic), 74 (haematology), 75 (kidney), 76 (lipids), and 77 (liver). An overview of the reference ranges and the PCS criteria is in Table 2. There were no clinically relevant findings.
- The post-randomisation PCS clinical safety laboratory values are summarised in Tables 78 (cardiac/skeletal muscle), 79 (electrolytes), 80 (endocrine/metabolic), 81 (haematology), 82 (kidney), 83 (lipids), and 84 (liver). All PCS clinical safety laboratory values are in Listing 8 and all adverse events in patients with a PCS clinical safety laboratory value are in Listing 9.
- In Period B, PCS high values were seen for creatine kinase (1 patient treated with placebo + ADT), glucose (4 patients, 2 of whom were treated with brexpiprazole + ADT), prolactin (1 patient treated with brexpiprazole + ADT), total cholesterol (3 patients; all treated with brexpiprazole + ADT), low density lipoprotein (LDL) cholesterol (2 patients; both treated with brexpiprazole + ADT), and triglycerides (2 patients; both treated with brexpiprazole + ADT). There were no adverse events associated with any of the PCS high clinical safety laboratory values (Listing 9).
- The urinalysis parameters are summarised in Tables 85 to 88 and the microscopy results are in Listing 10. The majority of the results were *negative* (ketones, protein, and occult blood) or *normal* (glucose).

ECGs

- The ECG parameter values during Period B and the changes from the end of Period A in ECG parameter values are summarised in Tables 89 and 90, respectively. There were no clinically relevant findings. None of the patients in either treatment group had PCS ECG parameter values (Table 91; for an overview of the reference ranges and the PCS criteria, see Table 2).

Vital Signs

- The vital signs during Period B and the changes from randomisation in vital signs are summarised in Tables 92 and 93, respectively. There were no clinically relevant findings. None of the patients in either treatment group had PCS vital signs (Table 94; for an overview of the reference ranges and the PCS criteria, see Table 2).

Weight and Waist Circumference

- The weight and waist circumference during Period B and the changes from the end of Period A in weight and waist circumference are summarised in Tables 95 and 96, respectively. None of the patients in either treatment group had PCS weight changes (defined as a weight change of ≥7% from baseline; Table 97). For an overview of the reference ranges and the PCS criteria, see Table 2.

Safety Results (continued)

C-SSRS (C-CASA)

- During Period B, 2 patients in the brexpiprazole 3 mg/day + ADT group had suicidal ideation (1 *wish to be dead* and 1 *non-specific active suicidal thoughts*) (Tables 98 and 99 and). Both patients had suicidal ideation before entering Period B (Listing 11). None of the events were reported as SAEs and the patients were not withdrawn due to the events (Listing 5).

Conclusions

- Due to the low number of enrolled patients, no firm conclusions can be drawn regarding safety; however, the data indicate that the patients who were treated with brexpiprazole 1 and 3 mg/day adjunctive to a marketed antidepressant tolerated the drug well.
- No conclusions regarding efficacy could be drawn.

Date of the Report

12 February 2015

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