# Synopsis – Study 14570A

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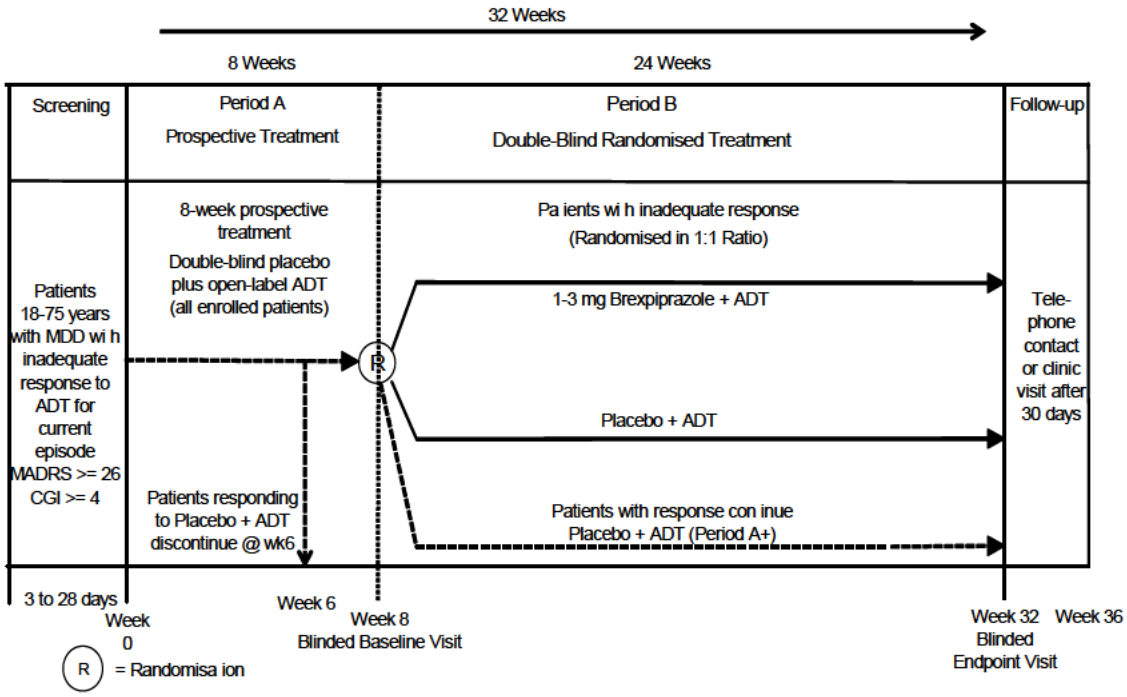
| **Study Title**<br>Interventional, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose long-term study to evaluate the maintenance of efficacy and safety of 1 to 3 mg/day of brexpiprazole as adjunctive treatment in patients with major depressive disorder with an inadequate response to antidepressant treatment |
| **Investigators**<br>114 principal investigators at 112 sites in 16 countries<br>*Signatory investigator* [redacted] |
| **Study Sites**<br>112 sites – 7 in Bulgaria, 5 in Canada, 6 in Estonia, 7 in Finland, 15 in Germany, 5 in Latvia, 5 in Lithuania, 4 in Mexico, 14 in Poland, 2 in Republic of Korea, 4 in Romania, 8 in Russian Federation, 5 in Sweden, 11 in Ukraine, 6 in United Kingdom, and 8 in United States |
| **Publication(s)**<br>None (as of the date of this report) |
| **Study Period**<br>*First patient first visit* – 28 May 2013 (the date when the first *Informed Consent Form* was signed)<br>*Last patient last visit* – 8 June 2016 (the date of the last protocol-specified contact with any patient) |
| **Objectives**<br>• *Primary objective*:<br>– To evaluate the maintenance of efficacy on depressive symptoms during long-term treatment of 1 to 3 mg once daily brexpiprazole *versus* placebo as adjunctive treatment to antidepressants in patients with an inadequate response to antidepressant treatment (ADT)<br>• *Secondary objectives*:<br>– To evaluate the efficacy of 1 to 3 mg once daily brexpiprazole *versus* placebo during long-term adjunctive treatment on:<br>• functionality (key secondary)<br>• clinical global impression (key secondary)<br>• health-related quality of life<br>• *Exploratory objective*:<br>– to evaluate the pharmaco-economics of 1 to 3 mg once daily brexpiprazole *versus* placebo during long-term adjunctive treatment<br>• *Safety objective*:<br>– to evaluate the safety and tolerability of 1 to 3 mg once daily brexpiprazole *versus* placebo during long-term adjunctive treatment |

**Study Methodology**

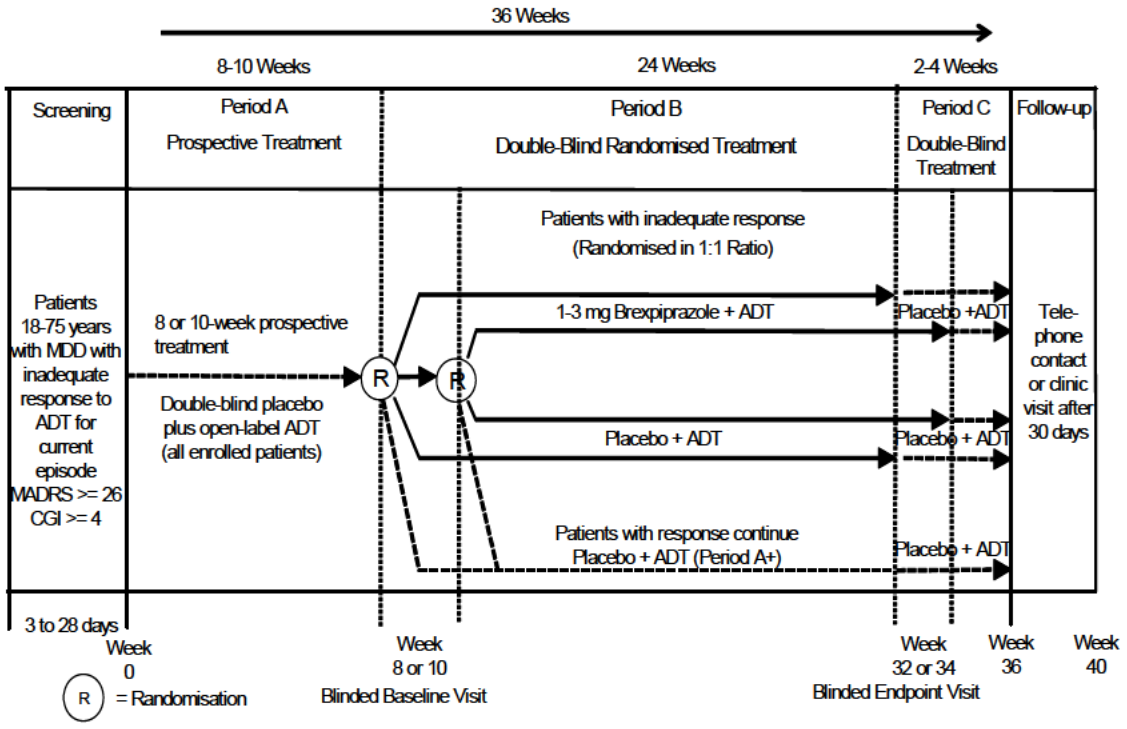
- This was an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, placebo-controlled, flexible-dose study.
- Patients were recruited from the investigator's own patient population, via advertisement (if allowed in the country) or referrals.
- The original protocol (ORG) was amended during the conduct of the study; the major amendment to the protocol was protocol amendment 2 (PA02) and concerned several changes to the study design. The methodology presented below reflects the protocol after implementation of PA02, unless otherwise specified, as the majority of the patients were enrolled/randomised according to PA02.
- The study consisted of a:
  - Screening Period – 3 to 28 days
  - Treatment Period – 32 weeks; consisting of Periods A, B, and A+ (ORG: and Period C). All patients entered the study in Period A. In Period A, all patients were treated open-label with one of six commercially available ADTs (duloxetine, escitalopram, fluoxetine, paroxetine, sertraline, and venlafaxine) + double-blind placebo. The dose of the ADT was increased according to a protocol-specified titration scheme to increase the likelihood of ADT success. Dose adjustments of the ADT were allowed based on tolerability, but was to be kept stable after Week 4. Patients who met the blinded response criteria at the Week 6 Visit, were deemed early responders and were withdrawn from the study, as they are not the target population for adjunct treatment with brexpiprazole (ORG: no early response criteria were applied at Week 6). At Week 8 (ORG: at Week 8 or 10), patients with inadequate response to placebo + ADT, as per the randomisation criteria given below, were randomised to Period B and received double-blind brexpiprazole + ADT or placebo + ADT. The time point and criteria for randomisation was kept blinded for the investigational sites to avoid patient and rater expectation to influence the ratings. Dose adjustments of the adjunct treatment were allowed based on tolerability, but was to be kept stable after 6 weeks of randomised treatment. Non-randomised patients continued in Period A+ and received placebo + ADT until the end of the study.
  - Safety Follow-up Period – 30-day period after completion of the study or after withdrawal from the study .
- Patients were randomised to Period B if they:
  - had completed Period A
  - had a Montomery and Åsberg Depression Rating Scale (MADRS) total score ≥18 at Week 8 (ORG: had a MADRS total score ≥20 at Week 8/10)
  - had an improvement in the MADRS total score of <50% compared to Visit 2 (Baseline) at every visit in Period A
  - had a Clinical Global Impression – Global Improvement (CGI-I) score ≥3 (ORG: and a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4) at every visit in Period A
- The investigators were to follow-up on patients who withdrew after the Week 6 visit, except those who withdrew consent, at the timepoint of the scheduled last visit to obtain the scheduled efficacy assessments and information on concomitant medication.
- Efficacy and safety data were collected at Baseline, at Weeks 1 and 2, and at 2 or 4-week intervals for the remainder of the study.
- All patients received ADT during the entire study; to ease the reading, the treatment groups in Period B (brexpiprazole + ADT and placebo + ADT) are hereafter referred to as the brexpiprazole and placebo groups in the body text.

**Study Methodology (continued)**

• A schematic overview of the study design according to PA02 is presented below:




• For completeness, a schematic overview of the study design according to ORG is presented below:



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| **Number of Patients Planned**<br>2193 patients were planned for enrolment in order to randomise 868 patients: 434 in the brexpiprazole group and 434 in the placebo group (ORG: 1462 patients were planned for enrolment in order to randomise 658 patients: 329 in the brexpiprazole group and 329 in the placebo group). |
| **Diagnosis and Main Selection Criterion**<br>Outpatients with a primary diagnosis of Major Depressive Disorder (MDD) according to DSM-IV-TR™ criteria (current Major Depressive Episode [MDE] confirmed using the Mini International Neuropsychiatric Interview [MINI]), who:<br>• had a MADRS total score ≥26 at the Screening Visit and at the Baseline Visit<br>• had a CGI-S score ≥4 at the Screening Visit and at the Baseline Visit<br>• had had the current MDE for ≥8 weeks<br>• were ≥18 and ≤75 years of age<br>• The patient has an insufficient response to at least one and no more than three adequate antidepressant treatments (including the treatment a patient is taking at screening) for the current MDE; for the most recent antidepressant treatment, this must be documented by self-report as <50% response on the Antidepressant Treatment Response Questionnaire (ATRQ). |
| **Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers**<br>*Brexpiprazole* – 1, 2 or 3 mg/day; tablets, orally; batch Nos. 11L88A001, 13A97A001C, 14D71A001C, 12A73A002, 13A98A002, 14D72A002C, 12A74A003, 13A99A003, and 14D73A003B |
| **Reference Therapy, Dose and Mode of Administration, Batch Number**<br>*Placebo* – tablets, orally; batch Nos. 11L78P005, 13A92P005A, 14C97P005B, and 15D89P005 |
| **Non-investigational Medicinal Products**<br>*Antidepressive Treatment* (ADT) – one of the following: duloxetine, escitalopram, fluoxetine, paroxetine IR, sertraline, venlafaxine XR |
| **Duration of Treatment**<br>Placebo + ADT for 8 weeks (ORG: 8 or 10 weeks) in Period A; brexpiprazole or placebo + ADT for 24 weeks in Period B or placebo + ADT for 24 weeks in Period A+; (ORG: placebo + ADT for 2 or 4 weeks in Period C) |
| **Efficacy Assessments**<br>• MADRS<br>• Sheehan Disability Scale (SDS)<br>• CGI-S<br>• CGI-I<br>• Quality of Life Enjoyment and Satisfaction Questionnaire (Short Form) (Q-LES-Q [SF])<br>• EuroQoL 5 Dimensions 5 Levels version (EQ-5D-5L) |
| **Pharmacoeconomic Assessments**<br>• Health Economic Assessment (HEA) |
| **Pharmacokinetic Assessments**<br>• blood sampling for plasma quantification of brexpiprazole and its major metabolite DM-3411<br>• genotyping for CYP2D6 |
| **Safety Assessments**<br>• Adverse events (AEs), clinical safety laboratory tests, vital signs, weight/body mass index (BMI), waist circumference, electrocardiograms (ECGs), and physical examinations<br>• electronic Columbia Suicide Severity Rating Scale (eC-SSRS™)<br>• modified Simpson Angus Scale (mSAS), Barnes Akathisia Rating Scale (BARS), Abnormal Involuntary Movement Scale (AIMS) |

**Endpoints**

- *Primary endpoint*:
  - full remission (defined as a MADRS total score ≤10 and a ≥50% decrease from randomisation in MADRS total score for at least 8 consecutive weeks during randomised treatment)
- *Key secondary endpoints*:
  - full functional remission (defined as a SDS total score ≤6 and all SDS domain scores ≤2, where the work score may be imputed, for at least 8 consecutive weeks during randomised treatment)
  - full global score remission (defined as a CGI-S score ≤2 for at least 8 consecutive weeks during randomised treatment)
- *Secondary endpoints*:
  - depressive symptoms:
    - change from randomisation in MADRS total score after 6 and 24 weeks of randomised treatment
    - response (defined as a ≥50% decrease in MADRS total score from randomisation) after 6 and 24 weeks of randomised treatment
    - remission (defined as a MADRS total score ≤10 and a ≥50% decrease in MADRS total score from the randomisation visit) after 6 and 24 weeks of randomised treatment
    - total time in remission during randomised treatment
    - time to full remission (defined as the time from randomisation to full remission has been obtained)
    - full sustained remission (defined as being in full remission at completion of the study)
  - clinical global impression
    - change from randomisation in CGI-S score after 6 and 24 weeks of randomised treatment
  - functionality
    - change from randomisation in SDS total score after 6 and 24 weeks of randomised treatment
  - health-related quality of life
    - change from randomisation in Q-LES-Q (SF) total scores after 6 and 24 weeks of randomised treatment
- *Exploratory endpoints*:
  - depressive symptoms:
    - response (defined as a ≥50% decrease in MADRS total score from randomisation) by visit during randomised treatment
    - remission (defined as a MADRS total score ≤10 and a ≥50% decrease in MADRS total score from the randomisation visit) by visit during randomised treatment
    - change from randomisation in MADRS total score and $MADRS_6$ subscale at each visit during randomised treatment
    - time to first remission (defined as time from randomisation to first record of remission)
  - global clinical impression:
    - change from randomisation in CGI-S score at each visit during randomised treatment
    - global score remission at each visit during randomised treatment (defined as a CGI-S score ≤2)
  - functionality
    - change from randomisation in SDS total score and SDS subscale score at each visit during randomised treatment
    - functional remission at each visit during randomised treatment (defined as a SDS total score ≤6 and all SDS subscale scores ≤2, where the work score may be imputed)

**Endpoints (continued)**

- health-related quality of life
  - change from randomisation in Q-LES-Q (SF) total score and Q-LES-Q (SF) domain scores at each visit during randomised treatment
  - EQ-5D-5L health state score (Visual Analogue Scale [VAS]) after 24 weeks of randomised treatment
  - EQ-5D-5L individual domain items after 24 weeks of randomised treatment
  - EQ-5D-5L index score after 24 weeks of randomised treatment
- pharmacoeconomics
  - resource utilisation (based on HEA)

• *Safety endpoints*:

- adverse events
- absolute values and changes from randomisation in clinical safety laboratory tests, vital signs, weight/BMI, waist circumference, and ECG parameters
- potentially clinically significant (PCS) clinical safety laboratory test values, vital signs, weight/BMI changes, waist circumference changes, and electrocardiogram (ECG) parameter values
- eC-SSRS™ categorisation based on Columbia Classification Algorithm of Suicide Assessment (C-CASA) definitions
- absolute values and changes from randomisation in mSAS total, BARS global items, and AIMS total and item scores

**Statistical Methodology**

• The following analysis sets were used:

- *all-patients-treated Period A set* (APTSPA) – all patients who took at least one dose of ADT and/or placebo
- *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of randomised investigational medicinal product (IMP) (brexpiprazole or placebo) in Period B
- *full-analysis set* (FAS) – all patients in the APTS
- *all-patients-treated Period A+ set* (APTSPA+) – all patients who completed Period A, but were not randomised to Period B, and had at least one efficacy or safety assessment in Period A+

• Unless otherwise indicated, the efficacy and safety analyses were based on the FAS and APTS (Period B), APTSPA (Period A), or APTSPA+ (Period A+).

• For all the analyses and the results presentation, the primary comparison was between 1 to 3 mg/day brexpiprazole and placebo. This comparison occurred during double-blind treatment in Period B; therefore, the focus is the randomised and treated population (the FAS and APTS) in Period B.

• *Primary efficacy analysis:*

- The comparison of the proportion of patients in full remission in the brexpiprazole *versus* placebo group was made using a logistic regression (LREG) model including MADRS total score at randomisation as a covariate and treatment group, country, and design factor D as fixed effects. The design factor D reflects the three sets of randomisation criteria that were applied: randomised after 8 weeks using the original criteria (ORG [Week 8]); randomised after 10 weeks using the original criteria (ORG [Week 10]); and randomised after 8 weeks using the amended criteria (AMEND [Week 8]).

**Statistical Methodology (continued)**

- sensitivity analyses were performed using:
  - the robustness of the study conclusions to the type of missing MADRS total scores and thus full remission status was assessed using six multiple imputation (MI) analyses with different assumptions on the missing mechanism.
  - a Cochran-Mantel-Haenszel's test (CMH) was performed to investigate the robustness of results towards analysis method and explanatory factors.
  - the primary logistic regression analysis was repeated with full remission based on data including withdrawal follow-up data to estimate the treatment effect in a more general population.

• *Key secondary efficacy analyses:*

- The key secondary endpoints were analysed using the logistic regression model described for the primary endpoint, but with the MADRS total score replaced with the SDS total score in the analysis of full functional remission, and with the CGI-S score in the analysis of full global score remission.
- For the key secondary endpoints, a CMH test was performed as a sensitivity analysis to test for treatment differences stratified by country.

• *Testing strategy:*

- For the brexpiprazole and placebo groups, the following sequence of hierarchically ordered primary and key secondary endpoints (defined above) was assessed:
  - full remission (primary)
  - full functional remission (key secondary)
  - full global score remission (key secondary)
- The overall significance level was 0.05. Only if the primary endpoint was statistically significant would confirmatory testing continue with the key secondary endpoint.

• *Secondary efficacy analyses:*

- The continuous secondary endpoints were analysed using a mixed model for repeated measurements (MMRM) with treatment and country as fixed effects and the relevant score at randomisation as a covariate. In addition, the design factor D was included as a fixed effect and as interacting with time since randomisation. Interaction between time since randomisation and treatment and interaction between time since randomisation and value at randomisation were included as fixed effects.
- Response and remission were analysed using a logistic regression model with treatment, design factor D, and country as fixed factors and the score at randomisation as a covariate.
- The time to full remission was analysed using a Cox's proportional hazard's model, with treatment and design factor D as fixed factors and the MADRS total score at randomisation as a covariate.
- The total time in remission was analysed using an analysis of covariance (ANCOVA) model with treatment, country, and design factor D as fixed effects and the MADRS total score at randomisation as a covariate.
- Sustained full remission was analysed using the logistic regression model described for the analysis of the primary endpoint.

• *Exploratory efficacy analyses:*

- The change from randomisation in continuous exploratory endpoints (MADRS total score, $MADRS_6$ subscale total score, CGI-S score, SDS total and domain scores, Q-LES-Q total and domain scores, EQ-5D-5L VAS score, EQ-5D-5L index score, and EQ-5D-5L domain scores) were analysed using the same MMRM as for the secondary efficacy analyses.
- Time to first remission was analysed using the same Cox's proportional hazard's model as for the secondary efficacy analyses.

**Statistical Methodology (continued)**

- *Health economic analyses:*
  - All pharmacoeconomic variables (HEA) were summarised by treatment group for the FAS in Period B using descriptive statistics.
- *Safety analyses:*
  - Unless otherwise indicated, the safety analyses were performed for the APTS in Period B, the APTSPA in Period A, and the APTSPA+ in Period A+.
  - The overall incidences of adverse events, serious adverse events (SAEs) and adverse events leading to withdrawal were summarised by primary system organ class (SOC) and preferred term for each treatment group.
  - Absolute values and changes from baseline/randomisation were summarised by visit and last assessment for clinical safety laboratory tests, vital signs, weight (BMI), waist circumference, and ECGs using descriptive statistics. Values outside the reference ranges, as well as PCS values, were flagged and summarised.
  - eC-SSRS™ data were summarised for the APTS in Period B, the APTSPA in Period A, and the APTSPA+ in Period A+. For the APTS in Period B, each rating on the eC-SSRS™ was mapped into C-CASA categories.
  - Descriptive statistics of absolute values and changes from baseline for the SAS total score, BARS item 4 (Global Clinical Assessment of Akathisia) score, and AIMS total score were summarised by visit and treatment group. The single-item scores for BARS items 1, 2, and 3 and AIMS items 8 to 12 were summarised by visit and treatment group for the APTS in Period B. The maximum post-baseline AIMS total score, BARS items 4 score, and mSAS total score were summarised for the APTS and APTSPA.
- *Pharmacokinetic analyses:*
  - Cytochrome P450 (CYP2D6) genotyping results were presented using descriptive statistics for the APTS in Period B. Plasma concentrations of brexpiprazole and DM-3411 were summarised using descriptive statistics for the APTS in Period B.

**Patient Disposition and Analysis Sets**

- A total of 1986 patients were enrolled in the study.
- Patient disposition for the APTSPA in Period A is summarised below:

| | Total | |
|---|---|---|
| | n | (%) |
| **Patients treated in Period A (APTSPA):** | 1982 | |
| Patients completed[a] | 1661 | (83.8) |
| Patients withdrawn[a] | 321 | (16.2) |
| **Primary reason for withdrawal** | | |
| Adverse event(s) | 39 | (2.0) |
| Lack of efficacy | 21 | (1.1) |
| Withdrawal of consent | 70 | (3.5) |
| Early response | 148 | (7.5) |
| Other | 43 | (2.2) |

a Period A

**Patient Disposition and Analysis Sets (continued)**

• Patient disposition for all randomised patients in Period B is summarised below:

| | Placebo + ADT | | Brex + ADT | | Total | |
|---|---|---|---|---|---|---|
| | n | % | n | % | n | % |
| **All Patients Randomised** | 442 | | 444 | | 886 | |
| **All Patients Treated Set** | 441 | | 444 | | 885 | |
| Patients Completed | 380 | (86.2) | 349 | (78.6) | 729 | (82.4) |
| Patients Withdrawn | 61 | (13.8) | 95 | (21.4) | 156 | (17.6) |
| **Primary reason for withdrawal** | | | | | | |
| Adverse event(s) | 13 | (2.9) | 27 | (6.1) | 40 | (4.5) |
| Lack of efficacy | 9 | (2.0) | 11 | (2.5) | 20 | (2.3) |
| Withdrawal of consent | 28 | (6.3) | 35 | (7.9) | 63 | (7.1) |
| Other | 11 | (2.5) | 22 | (5.0) | 33 | (3.7) |
| **Efficacy Data Sets** | | | | | | |
| Full Analysis Set | 441 | | 444 | | 885 | |

• Patients disposition for the APTSPA+ in Period A+ is summarise below:

| | Total | |
|---|---|---|
| | n | (%) |
| **Patients treated in Period A+ (APTSPA+):** | 770 | |
| Patients completed | 653 | (84.8) |
| Patients withdrawn | 117 | (15.2) |
| **Primary reason for withdrawal** | | |
| Adverse event(s) | 16 | (2.1) |
| Lack of efficacy | 6 | (0.8) |
| Withdrawal of consent | 47 | (6.1) |
| Other | 48 | (6.2) |

**Demography and Baseline/Randomisation Characteristics of the Study Population**

- The primary objective of this study was to compare the efficacy 1 to 3 mg/day brexpiprazole with placebo. This comparison occurred during double-blind treatment in Period B; therefore, the focus is the APTS.
- The treatment groups in the APTS were similar with respect to age, sex, and race distribution: the mean age of the patients was 47 years, approximately two-thirds were women, and the majority (96%) of the patients in each treatment group were White.
- The mean baseline height, weight, BMI, and waist circumferences of the patients in the APTS were approximately 168 cm, 78 kg, 27 kg/m2, and 92 cm, respectively, with no clinically relevant differences between the treatment groups.
- The majority (>92%) of the patients in both treatment groups were extensive, intermediate, or ultra metabolizers of CYP2D6.
- Overall, major depression history at baseline for the patients in the APTS was similar in the two treatment groups. The median duration of the current episode was 5 months, the median number of depressive episodes was 3, and the median duration of the last period of wellness was approximately 1 year in both treatment groups.
- There were no clinically relevant differences in mean efficacy scores at baseline or at randomisation between the treatment groups in the APTS. At randomisation, the patients had a mean overall MADRS total score of 26, a mean overall CGI-S score of 4.2, and a mean SDS total score of approximately 17.5.
- Most patients (82%) were randomised according to PA02. Over all, the demographics and other baseline/randomisation characteristics of these patients (AMEND subgroup) were similar to that of the patients who were randomised according to the original protocol (ORG subgroup).

**Efficacy Results**

- This study failed to show a statistically significant difference between brexpiprazole and placebo in the primary efficacy analysis of full remission. Hence, the first hypothesis in the testing strategy could not be rejected, and the testing procedure was stopped at this step.
- The key secondary efficacy analyses also failed to demonstrate an advantage of brexpiprazole over placebo in full functional remission and full global score remission.
- The primary and key secondary efficacy results are summarised below for the APTS in Period B:

| | Patients (n [%]) | | Odds Ratio | p-value |
|---|---|---|---|---|
| | Placebo + ADT | Brex + ADT | | |
| **Primary efficacy analysis** | | | | |
| Full remission | 110 (24.9) | 95 (21.4) | 0.83 | 0.2641 |
| **Key secondary efficacy analyses** | | | | |
| Full functional remission | 73 (16.6) | 68 (15.3) | 0.90 | 0.6250 |
| Full global score remission | 143 (32.4) | 121 (27.3) | 0.77 | 0.1022 |

ADT = antidepressant treatment; Brex = brexpiprazole

- The results of the secondary efficacy analysis were in line with those of the primary and key secondary efficacy analyses.
- In the short-term, after 6 weeks of treatment, there was no difference between brexpiprazole and placebo in mean change from randomisation in MADRS total score.

**Pharmacoeconomic Results**

- The HEA evaluation showed that, overall, the mean number of consultations to health care providers was low in both treatment groups.

**Pharmacokinetic Results**

- In general, the plasma concentrations of brexpiprazole and DM-3411 were in line with those observed in other clinical studies with brexpiprazole.

**Safety Results**

- The adverse event incidence in Periods A, B, and A+ is summarised below:

| | Period A (APTSPA) | | Period B (APTS) Placebo + ADT | | Period B (APTS) Brex + ADT | | Period A+ (APTSPA+) | |
|---|---|---|---|---|---|---|---|---|
| | n | % | n | % | n | % | n | % |
| Number of Patients | 1982 | | 441 | | 444 | | 770 | |
| Patient Years of Exposure | 285 | | 183 | | 177 | | 335 | |
| Patients with AEs | 1185 | (59.8) | 218 | (49.4) | 247 | (55.6) | 436 | (56.6) |
| Patients with SAEs | 24 | (1.2) | 13 | (2.9) | 9 | (2.0) | 24 | (3.1) |
| Patients with AEs leading to Withdrawal | 68 | (3.4) | 15 | (3.4) | 28 | (6.3) | 18 | (2.3) |
| Deaths | 1 | (<0.1) | 0 | | 0 | | 1 | (0.1) |
| Total number of AEs | 2967 | | 550 | | 634 | | 1187 | |
| Total number of AEs leading to Withdrawal | 93 | | 18 | | 31 | | 20 | |
| Total number of SAEs | 26 | | 14 | | 11 | | 31 | |

AEs in Period B are TEAEs
Exposure refers to IMP for Period B and ADT for Periods A and A+

**Safety Results (continued)**

- None of the patients in the APTS (Period B) died; 1 patient died in Period A and 1 patient died in Period A+.
- In the APTS, the incidence of SAEs was 2.0% in the brexpiprazole group and 2.9% in the placebo group. The overall incidence of TEAEs was 56% in the brexpiprazole group and 49% in the placebo group.
- Four SAEs (suicidal ideation; circulatory collapse and loss of consciousness; seizure) in 3 patients (all in the brexpiprazole group) were considered *related* to IMP.
- The incidence of TEAEs leading to withdrawal was 6% in the brexpiprazole group and 3% in the placebo group. Only weight increased (in the brexpiprazole group) led to withdrawal in >2 patients in any treatment group.
- The TEAEs with an incidence ≥2% in the brexpiprazole group (Period B) is summarised below:

| Preferred Term | Placebo + ADT | | Brex + ADT | |
|---|---|---|---|---|
| MedDRA version 19.0 | n | (%) | n | (%) |
| Patients treated | 441 | | 444 | |
| Weight increased | 22 | 5.0 | 42 | 9.5 |
| Headache | 31 | 7.0 | 34 | 7.7 |
| Nasopharyngitis | 34 | 7.7 | 28 | 6.3 |
| Accidental overdose | 25 | 5.7 | 27 | 6.1 |
| Akathisia | 4 | 0.9 | 21 | 4.7 |
| Restlessness | 2 | 0.5 | 18 | 4.1 |
| Fatigue | 6 | 1.4 | 17 | 3.8 |
| Dizziness | 15 | 3.4 | 14 | 3.2 |
| Somnolence | 6 | 1.4 | 13 | 2.9 |
| Tremor | 9 | 2.0 | 13 | 2.9 |
| Back pain | 8 | 1.8 | 10 | 2.3 |
| Waist circumference increased | 2 | 0.5 | 9 | 2.0 |

- The TEAEs with an incidence ≥2% in the brexpiprazole group and for which the incidence was 1 percentage point higher than that in the placebo group, comprised (brexpiprazole *versus* placebo): weight increased (9.5% *versus* 5.0%), akathisia (4.7% *versus* 0.9%), restlessness (4.1% *versus* 0.5%), fatigue (3.8% *versus* 1.4%), somnolence (2.9% *versus* 1.4%), and waist circumference increased (2.0% *versus* 0.5%).
- The majority of the patients in the ATPS with TEAEs had TEAEs that were either *mild* or *moderate*.
- The proportion of patients with EPS-related TEAEs was 9.2% in the brexpiprazole group and 3.6% in the placebo group. In each treatment group, the EPS-related TEAEs with an incidence ≥2% were: akathisia (4.7%) and tremor (2.9%) in the brexpiprazole group and tremor (2.0%) and akathisia (0.9%) in the placebo group.
- Overall, the eC-SSRS data showed no clinically relevant differences between the two treatment groups.
- In general, the scores on the mSAS, BARS, and AIMS 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 brexpiprazole and placebo groups.
- In the brexpiprazole group, the median prolactin value increased from last visit before randomisation (LVBR) to Week 24, especially in women. The median change in prolactin value peaked at Week 4 in both men (37 mIU/L) and women (162 mIU/L) and then decreased towards the end of the study (Week 24) to 32 mIU/L in men and 100 mIU/L in women. In the placebo group, there was almost no change in the median prolactin value from LVBR to Week 24.
- No clinically relevant patterns were seen with respect to the mean changes in other clinical safety laboratory test values, vital signs, or ECG parameter values, and the incidences of PCS values were comparable between the placebo and brexpiprazole groups. The proportion of patients with post-randomisation PCS high glucose values or PCS high or low lipid values in the brexpiprazole group was slightly higher than that in the placebo group.

**Safety Results (continued)**

- Three patients (all in the brexpiprazole group) with PCS high blood glucose had *Type 2 diabetes mellitus* as TEAE. None of them had any relevant medical history of diabetes, however, all 3 patients had increased blood glucose values at screening or baseline. Two of them were considered *related* to IMP by the investigator. None of the patients in the placebo group with PCS high glucose had *Type 2 diabetes mellitus* as TEAE.
- Mean weight gain was 2.1 kg in the brexpiprazole group and 0.8 kg in the placebo group after 24 weeks of treatment, and the increase mainly occurred during the first half of Period B. A larger proportion of patients in the brexpiprazole group (19%) than in the placebo group (8%) had a PCS (≥7%) weight increase from LVBR.
- In both treatment groups, the majority (≥79%) of the patients did not meet the criteria for metabolic syndrome post-randomisation.
- Overall, brexpiprazole was safe and well tolerated.

**Conclusions**

- This study failed to demonstrate a statistically significant difference between brexpiprazole and placebo in the primary efficacy analysis of full remission.
- This study also failed to demonstrate a difference between brexpiprazole and placebo in the key secondary efficacy analyses of full functional remission and full global score remission.
- The results of the secondary efficacy analysis were in line with those of the primary and key secondary efficacy analyses.
- Overall, treatment with brexpiprazole (1 to 3 mg/day) for 24 weeks was safe and well-tolerated in this patient population with MDD.

**Report Date**

22 December 2016

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