Synopsis

Amended Clinical Report Synopsis for Protocol 331-10-228
EudraCT No. 2011-001350-28

Name of Sponsor: Otsuka Pharmaceutical Development & Commercialization, Inc.

Name of Investigational Medicinal Product: Brexpiprazole (OPC-34712, Lu AF41156)

Protocol Title: A Phase 3, Multicenter, Randomized, Double-blind, Placebo-controlled Trial of the Safety and Efficacy of Fixed-dose OPC-34712 as Adjunctive Therapy in the Treatment of Adults with Major Depressive Disorder, the Pyxis Trial

Principal or Coordinating Investigator and Trial Sites: Michael Thase, MD, University of Pennsylvania, 3535 Market Street, Suite 670, Philadelphia, PA 19104, United States (US)
Multicenter (59 sites); Multinational (Canada, France, Poland, Slovakia, US)

Publications: None to date.

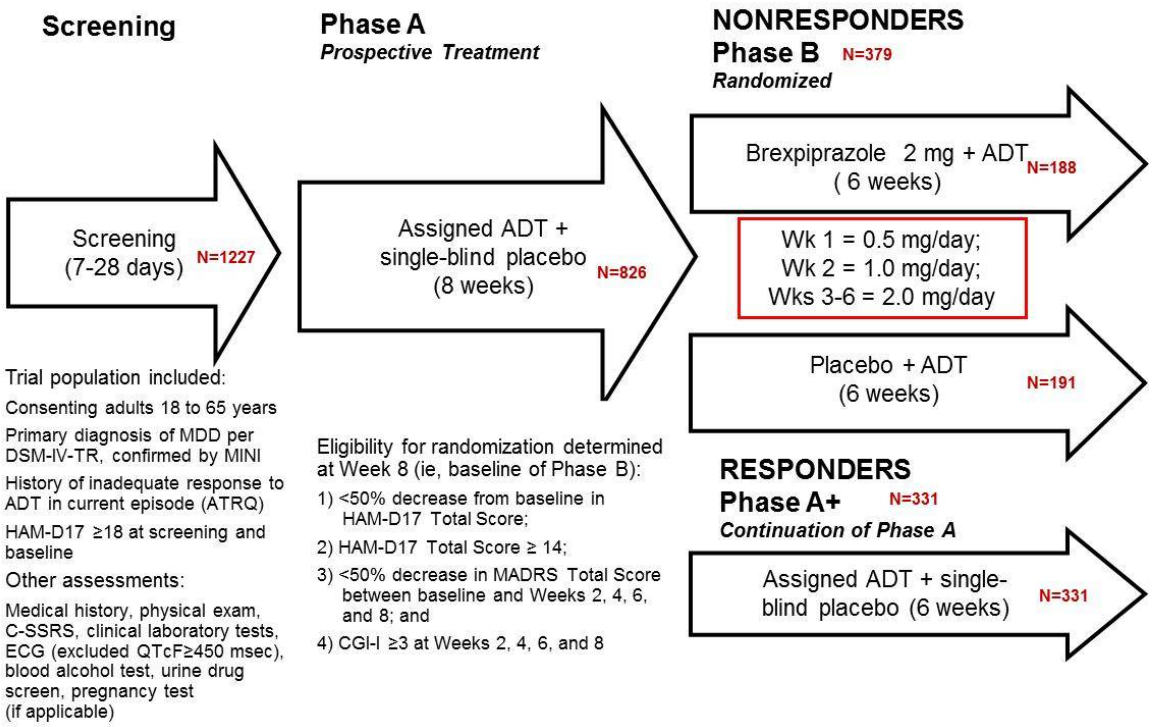
Trial Period:
Date of first signed informed consent: 25 Jul 2011
Date of last trial observation: 02 May 2013

Clinical Phase/Trial Type: 3/Therapeutic use

Objectives:
Primary: To compare the efficacy of brexpiprazole (2 mg/day) with placebo as adjunctive therapy to an assigned open-label antidepressant therapy (ADT) in subjects who demonstrated an incomplete response after 8 weeks of prospective treatment with the same assigned open-label ADT.

Secondary: To evaluate the safety and tolerability of brexpiprazole (2 mg/day) as adjunctive therapy to ADT in the proposed subject population with major depressive disorder (MDD).

Methodology: This was a phase 3, multicenter, randomized, double-blind, placebo-controlled, fixed-dose trial that consisted of the following phases: a screening phase; an 8-week single-blind prospective treatment phase (Phase A); either a 6-week double-blind randomization phase (Phase B) for subjects with incomplete response at the end of Phase A (Week 8 visit) or a 6-week continuation of Phase A treatment (Phase A+); and a follow-up period (see trial design schematic).



ATRQ=Massachusetts General Hospital Antidepressant Treatment Response Questionnaire; CGI-I=Clinical Global Impression - Improvement scale; C-SSRS=Columbia-Suicide Severity Rating Scale; DSM-IV-TR=*Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision; ECG=electrocardiogram; HAM-D17=17-item Hamilton Depression Rating Scale; MADRS=Montgomery Asberg Depression Rating Scale; MINI=Mini International Neuropsychiatric Interview; QTcF=QT interval corrected for heart rate by the Fridericia formula; Wk=week.

Note: Safety was assessed 30 (+2) days after the last dose for subjects not entering the optional open-label rollover trial.

Trial Design Schematic

After the initial screening period, subjects who met entrance criteria at the baseline visit (at the end of the screening period) were enrolled into an 8-week prospective treatment phase (Phase A) and received single-blind placebo plus open-label ADT assigned by the investigator from among the sponsor-provided ADT options. Once assigned to a sponsor-provided ADT, subjects remained on the same ADT for the duration of the trial and attended visits at Weeks 1, 2, 3, 4, 6, and 8 in Phase A.

At the end of Phase A (Week 8 visit), eligible subjects with an incomplete response were randomized in a 1:1 ratio to double-blind treatment with either adjunctive 2 mg/day brexpiprazole-plus-ADT (2 mg/day brexpiprazole+ADT) or continued placebo-plus-ADT (placebo+ADT). Incomplete response was based on prospectively defined efficacy scale criteria as shown in the trial design schematic. Based on the learnings from the phase 2 program and discussions at the End of Phase 2 meeting with the FDA, where the FDA advised that the enrollment criteria should more precisely define the patient population evaluated within the trial, Trial 331-10-227 was amended in Protocol Amendment 3 (dated 23 Mar 2012; date first implemented 24 Apr 2012). It is important to note that the

decision to amend the protocol was entirely based on the phase 2 findings and that the double-blind nature of the phase 3 trials was not affected in any way. Prior to Protocol Amendment 3, these criteria were provided in the body of the trial protocol and investigators, in conjunction with the Medical Surveillance Team (MST) from INC Research (the contract research organization that conducted the trial), confirmed eligibility of subjects for randomization. With Protocol Amendment 3, the randomization criteria were moved from the main protocol to a blinded addendum so that investigators and raters would be blinded to the score-based randomization criteria. The response status for each subject was confirmed through a remote review of scores conducted by the MST and/or through preprogrammed calculations made by the interactive voice response system or interactive web response system. Score-based randomization criteria prior to Amendment 3 were as follows:

- <50% reduction in depressive symptom severity between baseline and the Week 8 visit, as measured by the 17-item Hamilton Depression Rating Scale (HAM-D17) Total Score;
- HAM-D17 Total Score of ≥14 at the Week 8 visit; and
- Clinical Global Impression - Improvement scale (CGI-I) score of ≥3 at the Week 8 visit.

The criteria for incomplete response after implementation of Protocol Amendment 3 were as follows:

- <50% reduction in HAM-D17 Total Score between baseline of Phase A and the Week 8 visit;
- HAM-D17 Total Score ≥14 at the Week 8 visit;
- <50% reduction in Montgomery Asberg Depression Rating Scale (MADRS) Total Score between baseline of Phase A and scheduled visits at Weeks 2, 4, 6, and 8; and
- CGI-I score of ≥3 at scheduled visits at Weeks 2, 4, 6, and 8.

During Phase B, randomized subjects attended weekly visits at Weeks 9, 10, 11, 12, 13, and 14. Subjects who were not randomized into Phase B were either withdrawn or continued single-blind placebo+ADT in Phase A+ and attended visits at Weeks 11 and 14.

Subjects who completed the Week 14 visit either entered an optional open-label rollover trial (Trial 331-10-238) or were followed-up for safety reasons 30 (+2) days after the last dose of investigational medicinal product (IMP). The follow-up contact also applied to early withdrawals.

Number of Subjects: Approximately 925 subjects were planned for enrollment into Phase A (single-blind prospective treatment phase) in order to randomize 370 subjects into Phase B (double-blind randomization phase). A total of 1227 subjects were screened for the trial, 826 enrolled into Phase A and 824 received at least 1 dose of

sponsor-provided ADT. Of these, 114 subjects (13.8%) discontinued during Phase A, 379 subjects (46.0%) were randomized into Phase B (188 in the 2 mg/day brexpiprazole+ADT group and 191 in the placebo+ADT group), and 331 subjects (40.2%) continued treatment with placebo+ADT in Phase A+. Of the 379 randomized subjects, the enrollment distribution across countries was as follows: US (254 subjects, 67.0%), France (43 subjects, 11.3%), Poland (42 subjects, 11.1%), Canada (28 subjects, 7.4%), and Slovakia (12 subjects, 3.2%).

Diagnosis and Main Criteria for Inclusion: The trial population included consenting male and female outpatients between 18 and 65 years of age, inclusive, with a *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision diagnosis of a single or recurrent, nonpsychotic episode of MDD that was at least 8 weeks in duration. Additionally, a 17-item Hamilton Depression Rating Scale (HAM-D17) Total Score ≥18 at screening and baseline was required, as was a treatment history for the current episode of an inadequate response to at least 1 and no more than 3 adequate antidepressant treatments, as measured by the subject's self-report on the Massachusetts General Hospital Antidepressant Treatment Response Questionnaire.

Investigational Medicinal Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): The IMP consisted of brexpiprazole, matching placebo, and commercially marketed ADTs.

Brexpiprazole: Brexpiprazole tablets (0.5-, 1-, and 2-mg) were manufactured by Otsuka Pharmaceutical Co, Ltd. (Japan). Lot numbers were as follows: 10L72A0050 (0.5-mg tablets), 10L73A001 (1-mg tablets), and 10L82A002 (2-mg tablets). Brexpiprazole was dosed orally once daily and was to be taken at the same time each day without regard to meals. The 6-week placebo-controlled treatment period included a 2-week titration period from 0.5 mg/day to 2 mg/day and 4 weeks of treatment at 2 mg/day.

ADT: The ADTs were supplied as bulk drug in the original commercial packaging (ie, bottles) with an ancillary trial-specific label. Subjects remained on the same ADT for the duration of the trial (ie, through Week 14). The ADTs (and allowable daily doses) used in this trial included escitalopram (10 and 20 mg/day, as 10-mg tablets from lots A207012, A209930, and A202698), fluoxetine (20 and 40 mg/day, as 20-mg capsules from lots A741352A, A858742A, and A858742E), paroxetine CR (37.5 and 50 mg/day, as 25-mg tablets from lots 0H004 and 0M001 and 37.5-mg tablets from lots 0M001, OM001, and 3029P08), sertraline (100, 150, and 200 mg/day, as 50-mg tablets from lots C101835, C101628, and C111557), duloxetine (40 and 60 mg/day, as 20-mg capsules from lots A815804A, A861437A, A913011C, and A861475A and 30-mg capsules from lots A856793A, A956879A, A822802A, and A829410A), and venlafaxine XR (75, 150, and 225 mg/day, as 37.5-mg capsules from lot E16891 and 75-mg capsules from lots E78550, E34739, V120822, and F35191).

All doses of ADT were to be administered orally once daily at the same time each day without regard to meals, unless specified otherwise in the product labeling. Investigators were instructed to increase the starting dose of ADT to the maximum tolerated dose in

Phase A to optimize an efficacious response. No change to the dose of ADT was permitted in Phase B.

Reference Product, Dose, Dosage Regimen, Formulation, Mode of Administration, Batch or Lot No(s): Matching brexpiprazole placebo tablets (Lot number: 10L71P005) were manufactured by Otsuka Pharmaceutical Co., Ltd. (Japan). In order to maintain consistency between trial phases, subjects took 1 placebo tablet daily in addition to the assigned open-label ADT in Phase A (all subjects), Phase B (subjects randomized to placebo), and Phase A+ (nonrandomized subjects).

Duration of Treatment: The total duration of treatment was 14 weeks, consisting of 8 weeks of treatment with placebo+ADT in Phase A for all subjects followed by 6 weeks of treatment with either double-blind IMP+ADT (randomized subjects, Phase B) or placebo+ADT (nonrandomized subjects, Phase A+).

Trial Assessments: Trial assessments to determine eligibility for enrollment into Phase A are shown in the trial design schematic.

Efficacy was assessed by completion of the following scales: MADRS (primary efficacy), Sheehan Disability Scale (SDS), Clinical Global Impression - Severity of Illness scale (CGI-S), Inventory of Depressive Symptomatology (Self-Report) scale (IDS-SR), HAM-D17, Hamilton Anxiety Rating Scale (HAM-A), and CGI-I.

Standard safety variables assessed in this trial included adverse events (AEs), physical examinations, vital signs, body weight, body mass index (BMI), waist circumference, clinical laboratory tests (hematology, serum chemistry [including prolactin], urinalysis, and pregnancy tests), and electrocardiograms (ECGs). Other safety variables included the Simpson Angus Scale (SAS), Abnormal Involuntary Movement Scale (AIMS), and Barnes Akathisia Rating Scale (BARS) to assess extrapyramidal symptoms (EPS); the ColumbiaSuicide Severity Rating Scale (C-SSRS) to assess suicidality; and the Massachusetts General Hospital Sexual Functioning Questionnaire (MSFQ) to assess changes in sexual function.

Criteria for Evaluation:

Efficacy: The primary efficacy variable was the change from the end of Phase A (Week 8) to the end of Phase B (Week 14) in the MADRS Total Score. The key secondary efficacy variable was the change from end of Phase A (Week 8) to end of Phase B (Week 14) in SDS Mean Score. Other secondary efficacy variables included change from end of Phase A (Week 8) in MADRS Total Score and SDS Mean Score at Phase B visit weeks other than Week 14, and change from end of Phase A (Week 8) to each Phase B visit (as appropriate to the scale assessment schedule) for CGI-S score, IDS-SR Total Score, HAM-D17 Total Score, HAM-A Total Score, and SDS individual item scores (work/school, family life, and social life). Mean CGI-I score was calculated at each trial week in Phase B. In addition, the proportion of responders during Phase B was determined separately for criteria based on the MADRS (ie, ≥50% reduction in MADRS Total Score from end of Phase A [Week 8]) and CGI-I (ie, score of 1 or 2 [very

much improved or much improved]). MADRS remission, defined as MADRS Total Score ≤10 and ≥50% reduction in MADRS Total Score from the end of Phase A (Week 8), was also evaluated.

Safety: Adverse events were summarized as the frequency and severity of treatment-emergent AEs (TEAEs), deaths, other serious TEAEs, potentially drug-related TEAEs, and TEAEs that led to discontinuation of IMP. Mean change from baseline was calculated for vital signs, body weight, clinical laboratory tests, ECG parameters, waist circumference, and BMI. The incidences of clinically relevant changes were tabulated for vital signs, routine laboratory tests, prolactin, ECG parameters, and body weight. Extrapyramidal symptoms were evaluated by calculating mean change from baseline in SAS, AIMS, and BARS, and by examining TEAEs related to EPS. Sexual dysfunction was evaluated as change from baseline in MSFQ, and the frequencies of overall and treatment-emergent suicidal behavior and ideation were tabulated based on responses to the C-SSRS prompts.

Pharmacokinetic/Pharmacogenomic Methods:
Plasma concentrations of brexpiprazole and its major metabolite DM-3411 were reported and summarized using descriptive statistics. Results of pharmacogenomic testing to assess cytochrome P450 (CYP) 2D6 metabolizer status were also reported. Plasma concentration data will be further analyzed as part of a population PK analysis and will be reported separately.

Statistical Methods:
Subject Samples: Subject samples identified for this trial included the Enrolled Sample (ie, all subjects who signed an informed consent form for the trial and enrolled into Phase A), the ADT Sample (ie, all subjects who took at least 1 dose of sponsor-provided ADT), the Randomized Sample (ie, all subjects who were randomized in Phase B), the Safety Sample (ie, randomized subjects who received at least 1 dose of double-blind IMP), the Efficacy Sample (ie, all subjects in the Safety Sample who had both an end of Phase A [Week 8] value and at least 1 postrandomization efficacy assessment for MADRS Total Score in Phase B), the Efficacy Sample per Amendment 3 Criteria (ie, subjects in the Efficacy Sample who met the revised criteria for incomplete response in Protocol Amendment 3), and the Phase A+ Sample (ie, all nonrandomized subjects who continued on single-blind placebo+ADT beyond Week 8).

Efficacy: The primary analysis used a mixed model repeated measures (MMRM) analysis with trial site, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An “unstructured” covariance was used. The primary MMRM model was repeated using a prespecified efficacy sample consisting of subjects in the Efficacy Sample who met the revised criteria for incomplete response in Protocol Amendment 3 (termed the Efficacy Sample per Amendment 3 Criteria). The key secondary efficacy variable was analyzed using the same MMRM analysis described for the primary analysis. A hierarchical testing procedure was used so that the overall experiment-wise type I error rate was maintained at 0.05. Sensitivity analyses (pattern-mixture model based on multiple imputations, shared parameter model,

and random coefficient pattern mixture model) were performed for the primary and key secondary endpoints to examine the effect of missing data. A hierarchical testing procedure was also applied to SDS individual item scores (work/school, social life, and family life).

For analyses of Phase B data, baseline was the end of Phase A measurement (expected to be at the Week 8 visit), and was defined as the last value before the first dose of double-blind IMP that was obtained at or after the Week 6 visit. Changes from baseline (end of Phase A [Week 8]) for secondary efficacy analyses of the MADRS, SDS, CSI-S, and IDS-SR were evaluated using the same MMRM model described in the primary analysis. Changes from baseline in HAM-D17 Total Score and HAM-A Total Score were evaluated using analysis of covariance (ANCOVA) with baseline (end of Phase A [Week 8]) value as covariate and treatment and, in last-observation-carried-forward (LOCF) analysis, trial site as main effects. Mean CGI-I score was evaluated by the Cochran-Mantel-Haenszel (CMH) Row Mean Score Differ Test controlling, in LOCF analysis, for trial site. Response and remission rates were evaluated by the CMH General Association Test controlling, in LOCF analysis, for trial site. Statistical significance for analysis of the other secondary efficacy variables was evaluated at a nominal 0.05 level (2-sided) without adjustment for multiple comparisons.

The following sensitivity analyses were performed in addition to the sensitivity analyses described above:

- Nonparametric (MI van Elteren and MI robust regression [M-estimator]) and semiparametric methods (generalized estimating equations [GEE] and weighted GEE [WGEE]): These methods for longitudinal data were performed for the Efficacy Sample and Efficacy Sample per Amendment 3 Criteria for mean change from end of Phase A (Week 8) to Week 14 in MADRS Total Score in order to provide a different view on the results seen with analyses that are more robust, and not dependent on distributional assumptions about the data.
- Efficacy Sample post-Amendment 3: Assessment of primary and secondary outcome variables was performed using the Efficacy Sample post-Amendment 3, which included all subjects in the Efficacy Sample who signed informed consent for Protocol Amendment 3 prior to enrolling in Phase A of the trial. Nonparametric and semiparametric analyses performed for the Efficacy Sample and Efficacy Sample per Amendment 3 Criteria were also performed for the Efficacy Sample post-Amendment 3.
- Planned dose (titration scheme): An analysis of the primary Efficacy Sample was performed for the primary endpoint using a model based on the planned doses by week to account for the titration period during the first 2 weeks of the double-blind treatment period. Subjects received 0.5 mg/day for 1 week followed by 1 mg/day for the next week according to the titration scheme. This analysis was repeated for the Efficacy Sample per Amendment 3 Criteria and the Efficacy Sample post-Amendment 3.

Safety: For Phase B, a TEAE was defined as any AE with an onset date on or after the start of double-blind IMP, or if the event was continuous from baseline (end of Phase A [Week 8]) and worsened, became serious, trial-drug related, or resulted in death, discontinuation, interruption or reduction of trial therapy.

Descriptive statistics were used to summarize original values and change from baseline at each scheduled visit and the last visit for clinical laboratory tests, vital signs, and ECGs. Potentially clinically relevant changes in laboratory parameters, ECG findings, vital signs, and weight were identified using prospectively defined criteria and summarized in incidence tables. An ANCOVA model was used for the Phase B evaluation of changes in SAS Total Score, AIMS Total Score, the BARS Global Clinical Assessment, body weight, waist circumference, BMI, and MSFQ scores.

Summary of Results:

Disposition, Demographics, and Baseline Characteristics: The focus of this report is the analysis of data obtained during the double-blind randomization phase (Phase B). The Randomized Sample and Safety Sample consisted of 379 subjects, including 1 randomized subject who was lost to follow-up after the Week 8 visit and for whom exposure to IMP was assumed since no IMP was returned to the site. This subject had no postrandomization value for MADRS Total Score, and thus was excluded from the Efficacy Sample (N=378). A total of 352 subjects (92.9%) in the Randomized Sample completed Phase B (174 [92.6%] in the 2 mg/day brexpiprazole+ADT group, 178 [93.2%] in the placebo+ADT group). Most subjects in the Efficacy Sample (93.4%) fulfilled the revised randomization criteria and were included in the Efficacy Sample per Amendment 3 Criteria. The most common reason for discontinuation was AEs in the 2 mg/day brexpiprazole+ADT group (6 subjects, 3.2%) and withdrawal of consent by the subject in the placebo+ADT group (8 subjects, 4.2%).

The mean age of randomized subjects was 44.6 years; subjects were predominantly female (70.4%) and white (86.8%). Demographic characteristics (eg, weight, BMI, and waist circumference) and psychiatric history were similar between the 2 treatment groups. The majority of randomized subjects (89.2%) experienced recurrent depression, with an average of 3.8 lifetime episodes. The average duration of the current major depressive episode was 13.6 months. Scores for psychiatric scale evaluations were similar between the 2 treatment groups at the Phase B baseline (end of Phase A [Week 8]). The mean MADRS Total Score and CGI-S score at baseline (end of Phase A [Week 8]) were 26.6 and 4.1, respectively, in the 2 mg/day brexpiprazole+ADT group and 27.1 and 4.2, respectively, in the placebo+ADT group. The mean CGI-I score at baseline (end of Phase A [Week 8]) was 3.5 in both treatment groups.

Efficacy Results: Brexpiprazole+ADT was superior to placebo+ADT for the primary endpoint of mean change from baseline (end of Phase A [Week 8]) to Week 14 in MADRS Total Score (see primary efficacy table). The difference between treatment groups ($p<0.05$) was apparent from the first week of double-blind treatment and at each subsequent visit. Brexpiprazole+ADT was superior to placebo+ADT for the key

secondary endpoint of mean change from baseline (end of Phase A [Week 8]) to Week 14 in SDS Mean Score (see secondary efficacy table). The change in the SDS individual item score for family life was also statistically significant in favor of brexpiprazole+ADT using a Hochberg procedure to adjust for multiplicity (Least Squares [LS] mean difference: −0.60 MMRM, p=0.0129).

Results of other secondary efficacy measures (change in CGI-S: LS mean difference: −0.34 MMRM, p=0.0004; change in HAM-D17 Total Score: LS mean difference: −2.34 LOCF, p=0.0001; mean CGI-I score: treatment difference: −0.39 LOCF, p=0.0005) confirmed the effect of adjunctive brexpiprazole on reducing depressive symptoms during randomized treatment. The proportion of subjects who responded to treatment was greater for subjects who received 2 mg/day brexpiprazole+ADT compared with those who received placebo+ADT when assessed using criteria based on 50% reduction in MADRS Total Score (23.5% vs 14.7%, ratio of response rates [RR] for brexpiprazole: placebo=1.63, p=0.0176) and on improvement (ie, score of 1 or 2) on the CGI-I (44.4% vs 27.7%, RR=1.61, p=0.0003). Remission (defined as MADRS Total Score ≤10 and ≥50% reduction from the end of Phase A [Week 8]) occurred for a higher percentage of subjects in the 2 mg/day brexpiprazole+ADT group (14.4%) compared with subjects in the placebo+ADT group (8.38%), and the comparison between treatments showed a trend in favor of adjunctive brexpiprazole (RR=1.68, p=0.0586). As further support for the efficacy demonstrated via clinician-rated scales, improvement was seen between baseline (end of Phase A [Week 8]) and Week 14 on the subject-rated IDS-SR (LS mean difference: −1.96 MMRM, p=0.0435). During the 6-week randomization period, adjunctive brexpiprazole also improved symptoms of anxiety, as measured by the HAM-A (LS mean difference: −1.17 LOCF, p=0.0219).

Analysis using the Efficacy Sample per Amendment 3 Criteria produced a result similar to the analysis of the Efficacy Sample. Adjunctive brexpiprazole 2 mg/day achieved a greater mean change in MADRS Total Score and SDS Mean Score compared with adjunctive placebo at Week 14 (see primary and secondary efficacy tables). Sensitivity analyses of the primary endpoint provided concordant support for the efficacy of adjunctive brexpiprazole 2 mg/day. As a result of the low dropout rate in this trial, sensitivity analyses based on missing not at random (MNAR) showed the same result as the primary analysis. Nonparametric (MI robust regression, MI van Elteren) and semiparametric methods (GEE, WGEE) resulted in treatment differences in favor of adjunctive brexpiprazole 2 mg/day (p<0.0051). As a sensitivity analysis to explore further the impact of Protocol Amendment 3 on Trial 331-10-228 trial conclusions, a posthoc analysis for the primary endpoint was performed using the Efficacy Sample post-Amendment 3 (LS mean difference=−3.14, p=0.0262). Further support of the efficacy of adjunctive brexpiprazole 2 mg/day was provided by the posthoc sensitivity analysis that accounted for the planned dose (titration scheme; LS mean difference at Week 14=−3.12, p=0.0001).

Summary of Primary Efficacy Endpoint		
Variable	**2mg Brex+ADT**	**Placebo+ADT**
MADRS Total Score, MMRM (Efficacy Sample)	N=187	N=191
Mean (SD) End of Phase A	26.61 (5.79)	27.14 (5.60)
LS Mean (SE) Change At Week 14	-8.27 (0.61)	-5.15 (0.60)
LS Mean Difference (95% CI)[a]	-3.12 (-4.70, -1.54)	-
P-value[b]	0.0001	-
MADRS Total Score, MMRM (Efficacy Sample per Amendment 3 Criteria)	N=175	N=178
Mean (SD) End of Phase A	26.87 (5.71)	27.32 (5.64)
LS Mean (SE) Change At Week 14	-8.36 (0.64)	-5.15 (0.63)
LS Mean Difference (95% CI)[a]	-3.21 (-4.87, -1.54)	-
P-value[b]	0.0002	-

Summary of Key Secondary Efficacy Endpoint		
SDS Mean Score, MMRM (Efficacy Sample)	N=179	N=181
Mean (SD) End of Phase A	5.97 (1.95)	6.32 (2.16)
LS Mean (SE) Change At Week 14	-1.35 (0.17)	-0.91 (0.17)
LS Mean Difference (95% CI)[a]	-0.45 (-0.86, -0.03)	-
P-value[b]	0.0372	-
SDS Mean Score, MMRM (Efficacy Sample per Amendment 3 Criteria)	N=167	N=170
Mean (SD) End of Phase A	6.03 (1.94)	6.34 (2.15)
LS Mean (SE) Change At Week 14	-1.35 (0.17)	-0.89 (0.17)
LS Mean Difference (95% CI)[a]	-0.46 (-0.88, -0.03)	-
P-value[b]	0.0349	-

Brex=brexpiprazole; CI=confidence interval; SD=standard deviation; SE=standard error.

[a]LS mean difference=difference in LS mean change.

[b]MMRM, with trial site, treatment group, visit, and treatment group-by-visit interaction as factor and baseline-by-visit interaction as a covariate. An "unstructured" covariance was used.

Pharmacokinetic Results: The observed brexpiprazole and its major metabolite, DM-3411, plasma concentrations were comparable with the previous observed concentrations in subjects with MDD.

Safety Results:

Overall Summary of Adverse Events				
Event	**Phase A**	**Phase B (Safety Sample)**		**Phase A+**
	(ADT Sample) (N=824) n (%)[a]	**2mg Brex+ADT (N=188) n (%)[a]**	**Placebo+ADT (N=191) n (%)[a]**	**(Phase A+ Sample) (N=331) n (%)[a]**
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Serious TEAE	3 (0.4)	2 (1.1)	2 (1.0)	2 (0.6)
Discontinuation due to TEAE	20 (2.4)	6 (3.2)	0 (0.0)	1 (0.3)
Any TEAE	584 (70.9)	111 (59.0)	89 (46.6)	98 (29.6)

[a]Percentages were based on the number of subjects in the designated sample population.

Two subjects in each treatment group experienced a total of 5 serious TEAEs during Phase B (syncope/comminuted fracture and abdominal pain in the 2 mg/day brexpiprazole+ADT group; atrial fibrillation and pneumonia in the placebo+ADT group). The serious TEAEs were assessed by the investigator as unlikely related or not related to IMP except for syncope that was assessed as related to IMP. One subject in the 2 mg/day brexpiprazole+ADT group became pregnant during Phase B and electively terminated the pregnancy after withdrawal from the trial.

Six (3.2%) subjects in the 2 mg/day brexpiprazole+ADT group discontinued IMP in Phase B because of a TEAE (abdominal pain, diarrhea, akathisia, headache, parkinsonism, and anorgasmia). Two of these events (abdominal pain and anorgasmia) began during treatment with placebo+ADT in Phase A and ultimately led to withdrawal during Phase B. None of the subjects in the placebo+ADT group were withdrawn from Phase B due to TEAEs.

The incidence of TEAEs was higher in the 2 mg/day brexpiprazole+ADT group (59.0%) than in the placebo+ADT group (46.6%) group. Most TEAEs were mild to moderate in severity. The TEAEs that occurred with an incidence rate of ≥5% in the 2 mg/day brexpiprazole+ADT group and more than twice placebo were increased weight (8.0% vs 3.1%) and akathisia (7.4% vs 1.0%). Twenty-eight subjects (14.9%) in the 2 mg/day brexpiprazole+ADT group and 6 subjects (3.1%) in the placebo+ADT group experienced EPS-related TEAEs. Akathisia was the most common EPS-related TEAE. Small, but statistically significant, changes in EPS scale scores were observed during Phase B. When present, akathisia was typically mild or moderate.

Brexpiprazole did not result in any consistent, clinically relevant changes in laboratory values, ECG parameters, or vital sign measurements, except body weight, for which a mean increase during Phase B of 1.64 kg was seen in the 2 mg/day brexpiprazole+ADT group compared with a mean increase of 0.37 kg in the placebo+ADT group. Similarly, greater increases in mean BMI (LS mean of 0.58 kg/m^2 vs 0.14 kg/m^2) and in waist circumference (LS mean of 1.33 cm vs 0.17 cm) were observed in the 2 mg/day brexpiprazole+ADT group as compared with the placebo+ADT group at the last Phase B visit. A greater number of subjects in the 2 mg/day brexpiprazole+ADT group demonstrated a potentially clinically relevant increase of ≥7% in body weight between baseline (end of Phase A [Week 8]) and the last visit of Phase B than in the placebo+ADT group (6 subjects, 3.21% vs 1 subject, 0.53%, respectively).

The incidences of potentially clinically relevant laboratory abnormalities were generally similar between the treatment groups. No subjects met the criteria for drug-induced liver injury during the trial. The percentage of subjects who met the criteria for potential metabolic syndrome during Phase B was low and similar between the 2 mg/day brexpiprazole+ADT and placebo+ADT groups (3 subjects, 2.3% and 2 subjects, 1.4%, respectively). No brexpiprazole-treated subject discontinued from Phase B because of a laboratory abnormality.

The C-SSRS showed no suicidal behavior during double-blind treatment, and the incidence of treatment-emergent suicidal ideation during Phase B was lower in the 2 mg/day brexpiprazole+ADT group (9 subjects, 4.8%) than in the placebo+ADT group (12 subjects, 6.3%). There were no TEAE reports of suicide, attempted suicide, or suicidal ideation during the trial. No clinically meaningful differences were seen between the 2 treatment groups with regard to sexual function, as measured by the change in MSFQ item scores.

Conclusions:

- Brexpiprazole 2 mg/day was efficacious as adjunctive therapy to an assigned open-label antidepressant in subjects who demonstrated an incomplete response after 8 weeks of prospective treatment with the same assigned open-label antidepressant, as evidenced by superiority over adjunctive placebo for the primary endpoint (change in MADRS Total Score). The improvement with brexpiprazole compared with placebo, as measured by the MADRS Total Score, was observed after the first week of double-blind treatment and at each subsequent visit. Efficacy was robust, as demonstrated by statistically significant changes not only in MADRS Total Score and SDS Mean Score, but also on multiple clinician-rated and subject-rated scales.
- Brexpiprazole at a dose of 2 mg/day was well tolerated in subjects with MDD when administered as adjunctive therapy to a marketed antidepressant.

Report Date: 18 Sep 2013
Amendment 1: 04 Jun 2014