

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205422Orig1s000

205422Orig2s000

SUMMARY REVIEW

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

Date	(electronic stamp)
From	Mitchell V. Mathis, MD
Subject	Division Director Summary Review
NDA/BLA #	205422, O-1/O-2
Applicant Name	Otsuka Pharmaceutical Co, Ltd and H. Lundbeck A/S
Date of Submission	July 11, 2014
PDUFA Goal Date	July 11, 2015
Proprietary Name / Established (USAN) Name	Rexulti/ (brexpiprazole)
Dosage Forms / Strength	Tablets/0.25mg, 0.5mg, 1 mg, 2 mg, 3 mg, and 4 mg
Proposed Indication(s)	1. Treatment of Schizophrenia 2. Adjunctive to antidepressants to treat MDD
Action/Recommended Action for NME:	Approval

Material Reviewed/Consulted	Names of discipline reviewers
OND Action Package, including:	
Medical Officer Review	Tiffany Farchione, MD
Statistical Review	Drs. George Kordzakhia (schizophrenia) and Xiang Ling (adjunctive treatment of MDD)
Pharmacology Toxicology Review Supervisory	Violetta Klimek, Ph.D. Linda Fossom, Ph.D.
CMC Review/OBP Review Tertiary Review	Wendy Wilson-Lee, Ph.D. Thomas Wong, Ph.D.
Microbiology Review	-----
Clinical Pharmacology Review and Pharmacometrics	Huixia Zhang, Ph.D. Li Zhang, Ph.D. Praveen Balimane, Ph.D. Kofi Kumi, Ph.D. Jeffrey Kraft, Ph.D. Christian Grimstein, Ph.D. Kevin Krudys, Ph.D. Hao Zhu, Ph.D.
OPDP	Susannah O'Donnell, MPD
OSI	Jen Sellers, MD Susan D. Thompson
OSE/DMEPA	Loretta Holmes, PharmD

OSE/DRISK	Danny Gonzalez, Pharm.D. Kim Lehrfeld, Pharm.D.
Other	
Pediatrics Maternal Health	Carrie, Ceresa, PharmD, MPH Tamara Johnson, M.D.
CSS	Katherine Bonson, PhD

OND=Office of New Drugs
 OSE= Office of Surveillance and Epidemiology
 OPDP=Office of Prescription Drug Promotion
 DMEPA=Division of Medication Error Prevention and Analysis
 DSI=Division of Scientific Investigations
 DDRE= Division of Drug Risk Evaluation
 DRISK=Division of Risk Management
 CSS=Controlled Substances Staff

Background and Summary

Brexpiprazole is a new molecular entity atypical antipsychotic co-developed by Otsuka Pharmaceutical Co, Ltd, and H. Lundbeck A/S. It is a partial agonist at 5-HT1A and D2 neuroreceptors. It also has activity at noradrenergic receptors, although the clinical significance of this is unclear.

The applicant is seeking approval for the treatment of schizophrenia and the adjunctive treatment of major depressive disorder (MDD). Sufficient evidence has been submitted to confirm efficacy for both indications; the safety profile of this NME has been evaluated and characterized adequately so that the drug may be used safely according to negotiated labeling.

I have reviewed the data and received input from the review teams and I agree that the applicant has demonstrated brexpiprazole efficacy for the treatment of schizophrenia and the adjunctive treatment of MDD. The drug has many of the same safety signals as other drugs in the class and will be labeled to provide clinicians with the information they need to safely use the product.

Clinical Summary and Statistics

Efficacy

Dr. Tiffany Farchione conducted the clinical review and Drs. George Kordzakhia (schizophrenia) and Xiang Ling (adjunctive treatment of MDD) conducted the statistical reviews.

Schizophrenia

Drs. Farchione and Kordzakhia have reviewed the development program for schizophrenia and have agreed that substantial evidence has been presented to support the approval of brexpiprazole for the treatment of schizophrenia, and I agree with them.

The applicant submitted two positive Phase 3, multiple-dose, randomized, double-blind, placebo-controlled, multinational studies (Studies 230 and 231). In these studies, brexpiprazole efficacy was demonstrated by mean reduction in the PANSS total score at week 6.

Study 230 Design

Study 230 was a multinational, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of three fixed doses of brexpiprazole (1 mg/day, 2 mg/day, and 4 mg/day) vs. placebo in the treatment of acute schizophrenia in hospitalized adults.

Study 230

Study 230 Endpoints

The primary efficacy endpoint was change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) Total Score using MMRM analysis. The PANSS is made up of 30 symptom constructs scored between 1 and 7 per construct and so the total score range is 30-210. CGI-S was specified as the first secondary to be tested. Multiplicity was addressed per plan by first comparing the difference between the average effect of 2 mg/day and 4 mg/day vs. placebo at an alpha level of 0.05 as a global test of efficacy. If the global test of efficacy was significant, the plan then allowed for each of the two dose groups (2 mg/day and 4 mg/day) vs. placebo at an alpha level 0.05 per dose group group. Secondary endpoints could be tested in order if and only if both comparisons (2 mg/day vs. placebo and 4 mg/day vs. placebo) were significant.

Study 230 Results

The improvement in PANSS Total Score was statistically superior for the brexpiprazole 4 mg/day group compared with the placebo group (LS mean difference = -6.5, $p=0.002$). The brexpiprazole 1 mg/day and 2 mg/day groups did not demonstrate statistical superiority to placebo, although numerical improvement was evident (see below). The secondary endpoint of interest, CGI-S (a seven point scale), was improved in the brexpiprazole 4 mg/day group (LS mean difference = -0.38,

p = 0.002), but the pre-specified testing procedure did not allow statistical consideration of the secondary endpoints. Subgroup analyses based upon gender, race, age, region and country demonstrated results consistent with the full study set analysis.

Study 230 Results

Study 230	Brex. 1 mg	Brex. 2 mg	Brex. 4 mg	Placebo
Number of patients	N=117	N=179	N=181	N=180
Baseline Mean (SD)	93.2 (12.7)	96.3 (12.9)	95.0 (12.4)	94.6 (12.8)
Mean Change at Week 6 (SE)	-16.9 (1.9)	-16.6 (1.5)	-20.0 (1.5)	-13.5 (1.5)
Treatment Difference	-3.4	-3.1	-6.5	-
95% Confidence Interval	(-8.1, 1.3)	(-7.2, 1.1)	(-10.6, -2.3)	-
p-value	0.16	0.15	0.0022	-
Average Effect (2mg & 4mg) versus Placebo	LS Mean Difference=-4.78, p-value=0.0093			

N=number of patients, SD=Standard Deviation, SE=Standard Error

Study 230 by-Visit Mean Change from Baseline in PANSS Total Score (MMRM)



Study 231 Design

Study 321 was a fixed-dose, multinational, randomized, double-blind, placebo-controlled study designed to assess the safety and efficacy of brexpiprazole by dose (0.25 mg/day, 2 mg/day, and 4 mg/day) compared to placebo.

Study 231

Study 231 Endpoints

The primary efficacy endpoint was change from baseline to Week 6 in the PANSS Total Score. The first secondary endpoint of interest was the CGI-S. Multiplicity was addressed per plan by first comparing the difference between the average effect of 2 mg/day and 4 mg/day vs. placebo at an alpha level of 0.05 as a global test of efficacy. If the global test of efficacy was significant, the plan then allowed for each of the two dose groups (2mg/day and 4 mg/day) vs. placebo at an alpha level 0.05 per group. Secondary endpoints could be tested in order if and only if both comparisons (2 mg/day vs. placebo and 4 mg/day vs. placebo) were significant.

Study 231 Results

Brexpiprazole 4mg/day and brexpiprazole 2mg/day were statistically superior to placebo with LS mean treatment differences of -7.64 ($p=0.0006$) and -8.72 ($p<0.0001$), respectively. Improvement in the secondary endpoint of interest, CGI-S (a seven point scale), was also statistically significantly improved for both the 4 mg/day (LS mean difference = -.38, $p = 0.0012$) and 2 mg/day (LS mean difference = -0.33, $p = .0056$) brexpiprazole groups compared to placebo. Subgroup analyses based upon gender, race, age, region and country demonstrated results consistent with the full study set analysis.

Study 231 Results

Study 231	Brex. 0.25 mg	Brex. 2 mg	Brex. 4 mg	Placebo
Number of patients	N=87	N=180	N=178	N=178
Baseline Mean (SD)	93.6 (11.5)	95.9 (13.7)	94.7 (12.1)	95.7 (11.5)
Mean Change at Week 6 (SE)	-14.9 (2.2)	-20.7 (1.5)	-19.7 (1.5)	-12.0 (1.6)
Treatment Difference	-2.9 (2.7)	-8.7 (2.2)	-7.6 (2.2)	-
95% Confidence Interval	(-8.3, 2.5)	(-13.1, -4.4)	(-12.0, -3.3)	
p-value	0.29	<0.0001	0.0006	
Average Effect (2mg & 4mg) versus Placebo	LS Mean Difference=-8.18, p-value<0.0001			

N=number of patients, SD=Standard Deviation, SE=Standard Error

Study 231 by-Visit Mean Change from Baseline in PANSS Total Score (MMRM)



Efficacy Summary—Schizophrenia

From the data presented, brexpiprazole is an effective treatment for schizophrenia. Although there is no clear dose response, doses from 2mg-4 mg are effective and should be labeled as the target dose range with a maximum dose of 4 mg per day. While there was no attempt to control the Type-1 error during the weekly visit analyses, p-values were nominally significant in the 2 mg/day and 4 mg/day groups compared to placebo in study 231 by Week 2. The figure above, or one like it, should be included in labeling to inform the prescriber.

Adjunctive Treatment of MDD

Drs. Farchione and Ling have reviewed the development program for adjunctive treatment of partially-responsive MDD and have agreed that trial 228 (one of two Phase 3 studies) was clearly positive for the 2mg/day dose for both the primary and secondary endpoints.

The protocol for the second trial, 227, was amended (Amendment 3) after the start date to revise the randomization criteria to include only patients who were partially-responsive over the entire evaluation period (entitled Phase A in the protocol, see design below), instead of, as in the original protocol, only at the last visit of Phase A—the efficacy data analyzed per this amendment are positive for the 3 mg dose ($p=.008$), but when analyzed per the original protocol, the difference in drug and placebo was not statistically different ($p=0.0327$, pre-specified threshold of 0.025 per Hochberg for multiplicity correction). There was a fair amount of discussion among the review team members and with the applicant at the Late Cycle Meeting about how the primary analysis set was never changed per protocol Amendment 3 to exclude patients who were not stable partial responders, but it indeed was never changed (see below for more details about the impact of Amendment 3 on the study).

Despite not changing the primary analysis set from the originally defined ITT population, the evidence from trial 228, together with evidence per protocol amendment in trial 227, along with supportive data from Phase 2 (Trial 222 was positive in each of 5 weeks and then missed the endpoint at Week 6) collectively provide substantial evidence of efficacy. After considering all of the data, Dr. Farchione decided that there is substantial evidence of efficacy for brexpiprazole up to 3 mg in the adjunctive treatment of MDD, and I agree with her.

Overview of Trials for Adjunctive Treatment of MDD

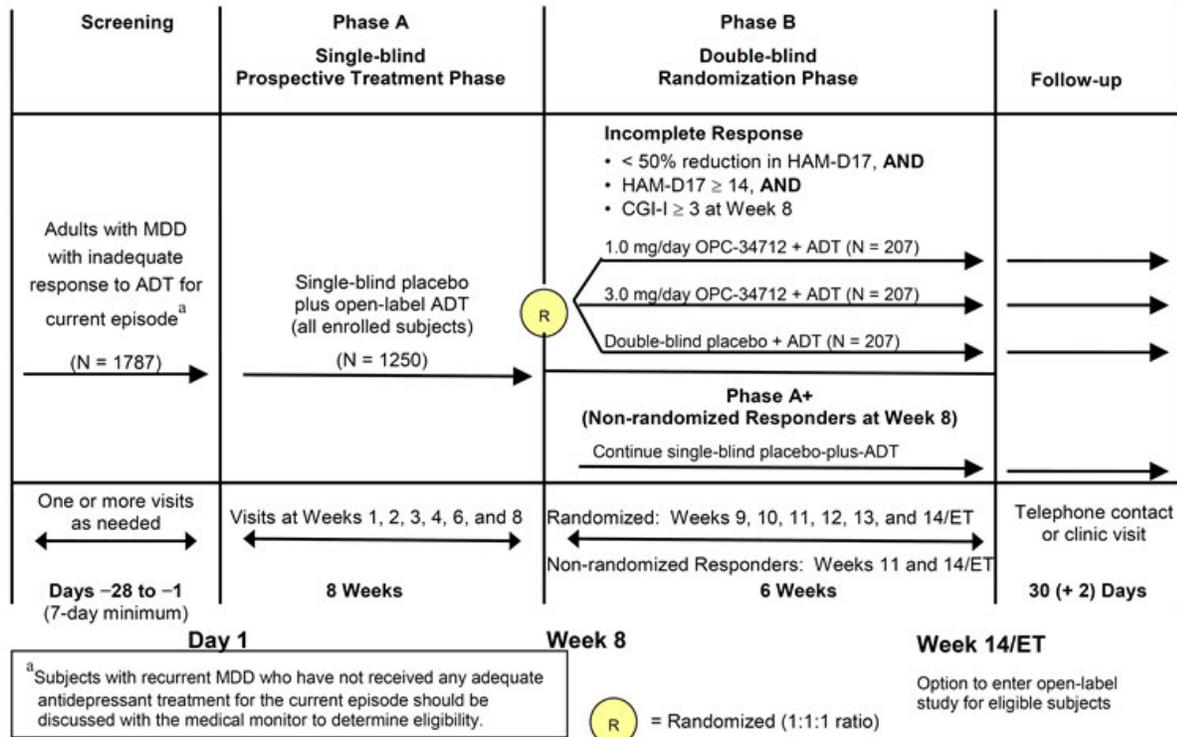
Phase 3 (+ADT)
Randomized
Primary
Key

Study 227 Design

Study 227 was a Phase 3, multinational, randomized, double-blind, placebo-controlled trial designed to assess the safety and efficacy of two fixed doses of brexpiprazole added to an open-label assigned antidepressant (ADT) in depressed patients with inadequate response to prospective treatment with ADT alone (for an adequate duration and at an adequate dose). The study had a

screening phase, a single-blind ADT prospective treatment phase (to define inadequate response), and a double-blind randomization phase to assess efficacy and safety of added brexpiprazole.

Study 227



(source: Study 331-10-227, original clinical trial protocol—April 8, 2011 version, Figure 3.1-1, page 33)

Study 227 Efficacy Endpoints

The primary efficacy outcome variable was change from the end of Phase A (Week 8) to the end of Phase B (Week 14) in the MADRS Total Score (range 0-60). The MADRS is a commonly accepted rating instrument for symptoms of depression. The secondary efficacy variable of interest was change from end of Phase A (Week 8) to end of Phase B (Week 14) in the Sheehan Disability Scale (SDS). The SDS is a self-rated assessment of symptoms on work/school function, social life, and family/home responsibilities (range of 0-30). Hochberg’s procedure was used to adjust for multiple comparisons of the two brexpiprazole groups vs. placebo. The comparison of the key secondary endpoint (SDS) vs. placebo by dose would be tested using another Hochberg procedure at an alpha level of 0.05 (two-sided) only if both null hypotheses for the primary endpoint (MADRS Total Score) were rejected at an alpha level of 0.05 (two-sided).

Study 227 and the Amended Protocol

Study 227 was initiated on 25 Jun 2011 and completed on 12 Sep 2013. While the study was ongoing, the randomization criteria were changed to refine the definition of partial responders to be those patients who did not meet response criteria (see below) over the entire course of Phase A (single-blind placebo plus antidepressant) instead of only at the end of Phase A. The protocol amendment reflecting this change was dated 23 Mar 2012 after 210 patients had been randomized and 42 of these patients were determined to not be stable responders.

We discussed this change with the applicant at the Late Cycle meeting on 2 Apr 15. The applicant explained that they had evidence from Phase 2 that stable partial responders were the patients who benefited from adjunctive treatment with brexpiprazole, and that is why they amended their protocol to include only stable responders over the entire period of Phase A instead of requiring response only at the end of Phase A to be randomized. The discussion at the Late Cycle meeting was informative, and we agreed with the applicant that the patient who was unresponsive to antidepressant alone for the 8 weeks of Phase A (and not just at the end of Phase A) was the appropriate patient to treat clinically with adjunctive treatment, and therefore the patients eligible for randomization per the protocol amendment were the patients of interest for study.

Having made these changes to the protocol (changes the review team agreed with), the Sponsor did not amend the analysis plan. The primary analysis remained all randomized subjects who took at least one dose of trial medication in Phase B (post-randomization) who had both an end of Phase A and at least one post-randomization MADRS Total Score.

Therefore, per the original analysis plan which was never modified, the sponsor just missed statistical significance for the primary endpoint of change in MADRS Total Score from Baseline (End of Phase A) to Week 14 for the ITT population. Per the original plan, the ADT + 3 mg brexpiprazole group had numerical improvement compared to ADT + placebo (LS Mean Diff = -1.52, p = 0.0327), but did not meet the pre-specified, Hochberg method threshold of multiplicity correction (p value less than 0.025).

Study 227 Results

Original Protocol Primary Efficacy Analysis—Mean Change in MADRS Total Score, Study 227

Variable	1mg Brex+ADT	3mg Brex+ADT	Placebo+ADT
MADRS Total Score, MMRM	N=225	N=226	N=218
Mean (SD) End of Phase A	26.69 (5.61)	26.31 (5.24)	26.23 (5.27)
LS Mean (SE) Change At Week 14	-7.65 (0.50)	-7.98 (0.51)	-6.45 (0.51)
LS Mean Difference (95% CI)	-1.19 (-2.58, 0.20)	-1.52 (-2.92, -0.13)	-
P-value	0.0925	0.0327	-

Source: Dr. Farchione's review

Per Protocol Amendment 3 Efficacy Analysis—Mean Change in MADRS Total Score, Study 227

Variable	1mg Brex+ADT	3mg Brex+ADT	Placebo+ADT
MADRS Total Score, MMRM	N=211	N=213	N=203
Mean (SD) End of Phase A	26.85 (5.61)	26.48 (5.29)	26.46 (5.20)
LS Mean (SE) Change At Week 14	-7.64 (0.52)	-8.29 (0.53)	-6.33 (0.53)
LS Mean Difference (95% CI)	-1.30 (-2.73, 0.13)	-1.95 (-3.39, -0.51)	-
P-value	0.0737	0.0079	-

Source: Dr. Farchione's review

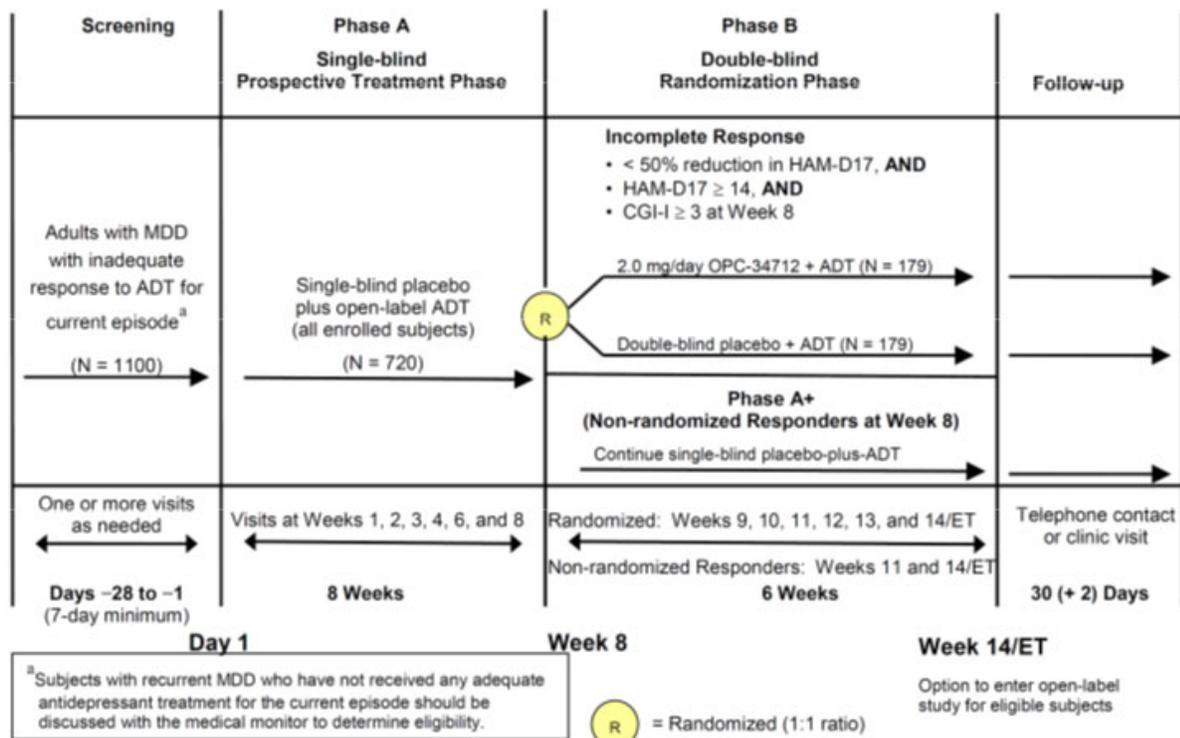
The secondary endpoint of interest, SDS was positive for both doses, but per the original protocol, it was not statistically evaluable because the hierarchical testing procedure terminated after the primary endpoint test.

Dr. Farchione argues that the results of Trial 227 per Protocol Amendment 3, support the clearly positive results of Study 228 (see below), and I agree with her.

Study 228 Design

Study 228 was a Phase 3, multicenter, randomized, double-blind, placebo-controlled fixed-dose study designed to assess the safety and efficacy of 2 mg/day of brexpiprazole as adjunctive treatment to an open-label assigned antidepressant (ADT) in depressed patients with an inadequate response to prospective treatment with ADT alone. The main design difference compared to Study 227 is that this trial compares a single dose, 2 mg, to add-on placebo.

Study 228



(source: Study 331-10-228, original clinical trial protocol—April 8, 2011 version, Figure 3.1-1, page 33)

Study 228 Efficacy Endpoints

The primary comparison of interest is between the 2mg brexpiprazole + ADT vs. placebo + ADT at Week 14 on the MADRS Total Score change from baseline. Brexpiprazole was superior to placebo and the difference is present from week 1 post-randomization (see below). The secondary endpoint of interest was the SDS which was statistically positive, but not replicated due to the protocol amendment problems in Study 227 that prevented analysis of the SDS in that study (see above). Demographic and baseline characteristics were evaluated by the statistical and clinical teams and found to be generally similar across treatment groups.

Study 228 and the Amended Protocol

Although this study has but one dose to compare to placebo, and therefore does not have a requirement to assess for multiple comparisons, the Sponsor provided data using Amendment 3 criteria and the results were unchanged.

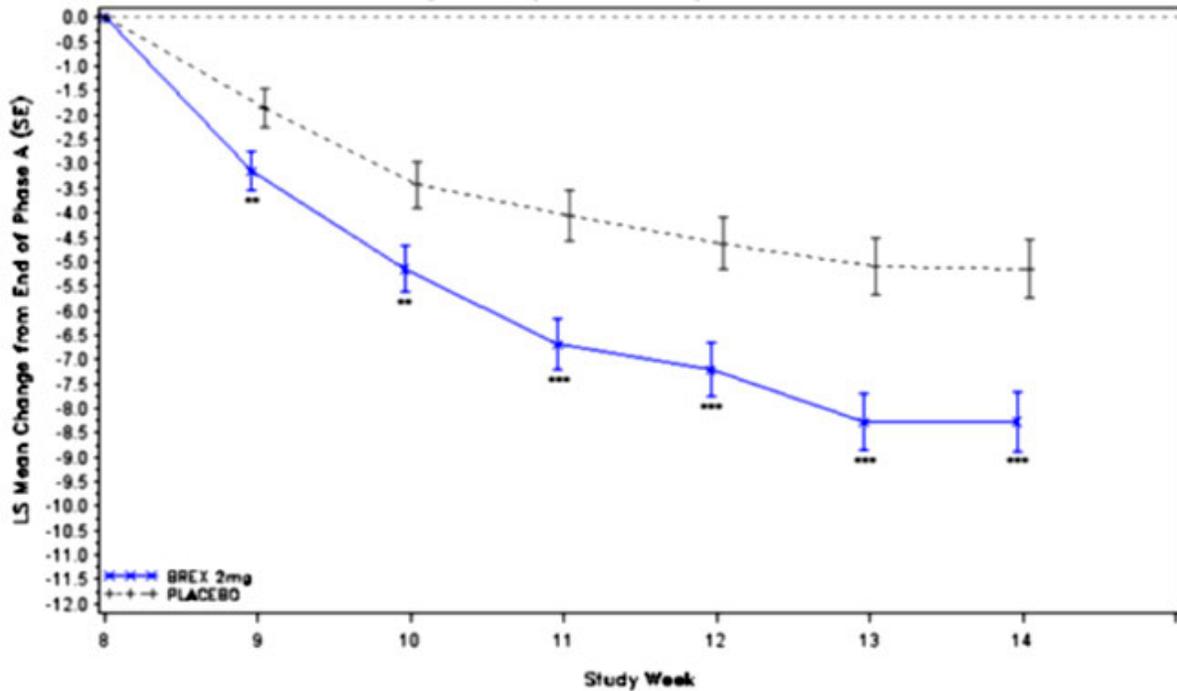
Study 228 Results

Primary Efficacy Analysis—Mean Change in MADRS Total Score, Study 228

Variable	2mg Brex+ADT	Placebo+ADT
MADRS Total Score, MMRM	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)	-3.12 (-4.70, -1.54)	-
P-value	0.0001	-

Source: Dr. Farchione's review

Study 228 by Visit Mean Change from Baseline in MADRS Total Score



* = p-value <0.05, ** = p-value <0.01, *** = p-value <0.001.

Source: Dr. Farchione's review

Efficacy Summary—Adjunctive Treatment of MDD

From the data presented, brexpiprazole is an effective adjunctive antidepressant. Although there is no evidence of a dose response, doses from 2 mg/day-3 mg/day are effective and should be labeled as the target dose range with a maximum dose of 3 mg/day. From the by-visit data presented above, it appears that results are present from week 1 after adding brexpiprazole. The figure above, or one like it, should be included in labeling to inform the prescriber of time course of effect.

Safety Summary

Phase 2/3 data from both development programs were evaluated for the safety review, which was conducted by Dr. Farchione. Safety results were similar in the MDD and schizophrenia development programs and similar to the safety profile of other approved atypical antipsychotics. No unique safety concerns were identified. There were 13 deaths in the clinical development program, 9 in patients taking brexpiprazole. The deaths were from various causes likely unrelated to drug and likely related to disease (e.g., suicide). No obvious pattern of death could be identified. Serious AEs were identified in 5.2% of all brexpiprazole-exposed patients, with 3.6% of patients having AEs within the Psychiatric Disorder SOC. The most common TEAEs were increased weight, headache, akathisia, somnolence, fatigue, anxiety, and increased appetite. Adverse Reactions tables have been constructed (for each indication independently) and included in Section 6 of labeling.

The metabolic profile of brexpiprazole has been evaluated, and the drug causes changes in cholesterol and triglycerides, as well as body weight as would be expected for a drug in this class. These changes are described in labeling and the usual class warning language will apply (5.6 Warnings and Precautions, Metabolic Changes). We identified a prolactin increase signal as is expected for in this class that impact dopamine, and that has been labeled.

Orthostatic hypotension was evident from the placebo-controlled trials, as would be expected for this drug class. In the MDD trial, the brexpiprazole +ADT group compared to placebo for hypotensive-related ARs were: dizziness (2.4% vs 1.5%), orthostatic hypotension (0.1% vs 0%). In the schizophrenia trial, the incidence of orthostatic hypotension on drug vs placebo was 0.4% vs. 0.2%. These rates have been included in the Warnings and Precautions section of labeling (5.8).

Somnolence and sedation are common in this class, and they were present in the placebo-controlled trials for brexpiprazole. In the MDD trial, somnolence was reported in 4.4% of drug-treated patients and 1.4% of patients treated with placebo. These data will be included in the Warnings and Precautions section of labeling (5.12).

We identified a signal for prolactin increase, which is expected for dopamine-blocking drugs in this class, and that has been labeled.

From the fixed-dose studies, it is evident that akathisia, somnolence, and restlessness are dose-related, and these have been prominently labeled. Dr. Farchione was unable to identify any unique safety concerns for brexpiprazole compared to other drugs in the class. I have reviewed her findings and I agree with her assessment of safety.

Clinical/Statistical Conclusion

Sufficient clinical and statistical evidence has been presented to support the safety and efficacy brexpiprazole for the treatment of schizophrenia and for the adjunctive treatment of MDD.

Chemistry Manufacturing and Controls (CMC)

Drs. Wilson-Lee and Wong have recommended approval. Manufacturing and sterility were adequately addressed by the applicant. Adequate information was provided for a satisfactory evaluation of the quality of both the drug substance and the drug product. The expiry was supported to 36 months with storage at controlled room temperature. CMC has provided a

comment for the action letter regarding the amendment of the method for calculating brexpiprazole content in the tablets.

Nonclinical Pharmacology/Toxicology

Drs. Violetta Klimek and Linda Fossom conducted the nonclinical review. They concluded that brexpiprazole was adequately assessed in the nonclinical studies and that there were no findings that would prevent approval of the drug. Standard nonclinical studies were adequately conducted to support chronic use of brexpiprazole.

Toxicities in animals were related to the exaggerated pharmacological activity of brexpiprazole (e.g., hypoactivity, tremors, hypothermia, increased prolactin, decreased blood pressure). The drug was not genotoxic nor teratogenic at doses up to 730 times the maximum recommended human dose.

The final recommendation is approval. The nonclinical team has been involved in labeling negotiations and have modified sections 8.1 (Pregnancy), 12.1 (Mechanism of Action), 12.2 (Pharmacodynamics), and 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility).

Office of Clinical Pharmacology (OCP)

Dr. Huixia Zhang was the primary reviewer for this application. The OCP team has evaluated the pharmacokinetics (PK) of brexpiprazole and its major metabolite (DM-3411) and characterized the effects of intrinsic factors (e.g., hepatic/renal impairment, gender, age) and extrinsic factors (e.g., quinidine, ketoconazole, food) on the PK of brexpiprazole and DM-3411. The findings of the team have been incorporated into labeling and include:

- Brexpiprazole may be taken with or without food.
- No dose adjustment is required based upon age or gender.
- Maximum dose for patients with moderate hepatic or renal impairment is 3 mg/day for patients with schizophrenia and 2 mg/day for patients with MDD.
- Brexpiprazole dose should be halved in patients coadministered a strong CYP3A4 inhibitor or a CYP2D6 inhibitor, or in patients known to be CYP2D6 poor metabolizers.
- Brexpiprazole dose should be quartered in patients coadministered a CYP3A4 AND a strong CYP2D6 inhibitor, or in patients known to be CYP2D6 poor metabolizers concomitantly taking a strong CYP3A4 inhibitor.
- Brexpiprazole dose should be doubled in patients taking a strong CYP3A4 inducer.
- No significant QTc prolongation effect was noted at 12 mg in a QT study.

The OCP team developed an exposure-response model which confirmed, based upon PANSS scores from the pooled schizophrenia population, that the proportion of responders (defined as at least a 30% PANSS reduction) was exposure (AUC)-related. MADRS scores from the pooled MDD population did not demonstrate an exposure-response relationship. OCP was also able to confirm an exposure-safety relationship that matched the dose-safety relationship seen in the clinical trials for akathisia.

Multiple dosing in healthy subjects defined the PK parameters of interest (below), which were found to be very similar in patients with MDD or schizophrenia.

Mean (SD) Pharmacokinetic Parameters for Brexpiprazole and DM3411 after 14 Daily Doses in Health Volunteers

Parameters	0.5 mg (n=11)	1 mg (n=11)	2 mg (n=4)
Brexpiprazole			
C _{max} (ng/mL)	27.9 (14.3)	44.7 (18.8)	69.3 (15.3)
T _{max} (hr)	4 (1-16)	4 (3-8)	4 (4-24)
AUC ₀₋₂₄ (hr.ng/mL)	506 (299)	827 (351)	1377 (365)
Cl/F (L/hr)	1220 (511)	1500 (666)	1548 (489)
T _{1/2} (hr)	84.8 (39.6)	73.6 (20.1)	78.5 (13.3)
DM-3411			
C _{max} (ng/mL)	9.8 (3.3)	19.4(9.3)	29.9 (11.4)
T _{max} (hr)	6 (3-35)	4 (4-8)	5.5 (3-24)
AUC ₀₋₂₄ (hr.ng/mL)	191 (73.2)	395 (207)	631 (244)
T _{1/2} (hr)	76.4 (32)	85 (33.2)	76.2 (15.3)

Source: OCP review

The overall recommendation of the OCP team is for approval.

Office of Scientific Investigation (OSI)

Inspections were conducted by OSI for a total of 4 sites—two from the schizophrenia program and two from the MDD program. Sites for inspection were chosen based upon significant enrollment and not for an *a priori* reason to inspect.

The sites identified for the schizophrenia program (Dr. Segal, North Miami, FL, Study 230 and Dr. Walling, Garden Grove, CA, Study 231) were inspected and no deviations were identified and the data were deemed acceptable by OSI. The sites identified for the adjunctive treatment of MDD program (Dr. Essing, Portland, OR, Study 227 and Dr. Horwitz, Salem, OR, Study 228) identified isolated data discrepancies at both sites that were considered unintentional transcription errors or minor discrepancies that did not materially impact the interpretation of the primary or secondary endpoints data. Overall, the data from both development programs were considered reliable.

Labeling

The team constructed labeling based upon the data from this application using other drugs in the class as models. Comments/suggestions/edits from the team were considered and sent to the applicant multiple times for concurrence. The Office of Prescription Drug Promotion also reviewed the label and their changes were incorporated. The applicant has accepted the labeling changes and a final version will be attached to the letter.

This will be the third drug in the atypical antipsychotic class with an adjunctive treatment of MDD claim, and because of this, it is considered an antidepressant drug in terms of labeling. Antidepressants are labeled with class language that includes a Boxed Warning for suicidal thoughts and behaviors in patients under the age of 24 years, and this label has the Boxed Warning.

Postmarketing Requirements/Commitments

Maintenance efficacy in schizophrenia and MDD should be assessed in Phase 4, per our usual practice we will issue PMCs for this.

Pediatric patients present with schizophrenia and could benefit from this drug. Our practice is to issue a PMR to study schizophrenia in patients 13-17 years old. Pediatric patients with partially responsive depression requiring adjunctive treatment are relatively rare, and treatment guidelines suggest switching medications rather than augmenting a partial response. For these reasons we will not expect pediatric data in MDD for this product.

Conclusions

Sufficient information has been submitted to conclude that brexpiprazole is safe and effective for the treatment of patients with schizophrenia and patients with partially responsive MDD.

The labeling has been negotiated to current Division standards.

The applicant has agreed to the negotiated label; this application should be approved by the PDUFA date.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MITCHELL V Mathis
06/28/2015