

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**205422Orig1s000**

**205422Orig2s000**

**OFFICE DIRECTOR MEMO**

## Office of Drug Evaluation-I: Decisional Memo

<b>Date</b>	July 10, 2015
<b>From</b>	Ellis F. Unger, MD, Director Office of Drug Evaluation 1, Office of New Drugs, CDER
<b>Subject</b>	Office Director Decisional Memo
<b>New Drug Application (NDA) #</b>	NDA 205422/Original-1 NDA 205422/Original-2
<b>Applicant Name</b>	Otsuka Pharmaceutical Company, Ltd.
<b>Date of Submission</b>	July 11, 2014
<b>PDUFA Goal Date</b>	July 11, 2015
<b>Proprietary Name/ Established (USAN) Name</b>	REXULTI/ (brexpiprazole)
<b>Dosage Forms/ Strengths</b>	Tablet/ 0.25, 0.5, 1, 2, 3, & 4 mg
<b>Indication (PROPOSED)</b>	1. Treatment of Schizophrenia 2. Adjunctive to antidepressants to treat MDD
<b>Action:</b>	Approval

<b>Material Reviewed/Consulted - Action Package, including:</b>	
Project Manager	Kofi Ansah, PharmD
Medical Officer /Cross-Discipline Team Leader	Tiffany Farchione, MD
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Statistical	Xiang Ling, PhD (Adjunctive MDD) George Kordzakhia, PhD (Schizophrenia) Peiling Yang, PhD, HM James Hung, PhD
Pharmacology Toxicology	Violetta Klimek, PhD, Linda Fossom, PhD
Office of Product Quality	Thomas Wong, PhD, Wendy Wilson-Lee, PhD
Microbiology	John Metcalfe, PhD, Bryan Riley, PhD
Office of Scientific Investigations	Jenn Sellers, MD, PhD, Susan Thompson, MD, MPH
Division of Pediatric and Maternal Health	Carrie Ceresa, PharmD, MPH, Tamara Johnson, MD, MS
Biopharmaceutics	Minerva Hughes, PhD, Angelica Dorantes, PhD
Carcinogenicity Study	Mohammad Atiar Rahman, PhD, Karl Lin, PhD
Division of Medication Error Prevention and Analysis	Loretta Holmes, PharmD, Danielle Harris, PharmD, BCPS
Division of Risk Management	Danny Gonzalez, PharmD, Kim Lehrfeld, PharmD, BCPS
Controlled Substance Staff	Katherine Bonson, PhD, Martin Rusinowitz, MD Silvia Calderon, PhD
Office of Prescription Drugs Promotion	L. Shenee Toombs, PharmD, Susannah O'Donnell, MPH
Division of Medical Policy Programs /Patient Labeling	Sharon Williams, MSN, Melissa Hulett, MSBA, MSN
Director, Division of Psychiatry Products	Mitchell Mathis, MD

## 1. Introduction

Otsuka Pharmaceutical Company, Ltd. is seeking approval of brexpiprazole with a proposed indication statement:

“REXULTI is an atypical antipsychotic indicated for:

- Use as an adjunctive therapy to antidepressants for the treatment of major depressive disorder.
- Treatment of schizophrenia.”

With a number of changes to the label, the review team endorses approval. I agree with their recommendation, and will approve the drug today.

## 2. Background

### Description:

Brexpiprazole (proposed proprietary name “Rexulti”) is a new molecular entity atypical antipsychotic co-developed by Otsuka Pharmaceutical Co, Ltd (Otsuka) and H. Lundbeck A/S (Lundbeck). Brexpiprazole has partial agonist activity at serotonergic 5-HT<sub>1A</sub> and dopaminergic D<sub>2</sub> receptors, as well as antagonist activity at serotonergic 5-HT<sub>2A</sub> receptors. The drug also has activity at noradrenergic receptors; however, the clinical significance of this is unknown.

The drug will be available as tablets in the following strengths: 0.25, 0.5, 1, 2, 3, and 4 mg. For adjunctive treatment of major depressive disorder (MDD), the proposed starting dose is 0.5 or 1 mg qd, increasing to a target dose of 2 mg qd based on clinical response and tolerability. For schizophrenia, the proposed starting dose is 1 mg qd for 4 days, increasing to 2 mg for 3 days, and then 4 mg qd (after Day 7) based on clinical response and tolerability.

### Disease Background:

#### **Adjunctive Treatment of Major Depressive Disorder**

As summarized by Dr. Farchione, depression is a chronic debilitating illness and a leading cause of disability. Depression is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, various problems with sleep, and other emotional and physical symptoms. In severe cases, the disease can lead to suicide. The prevalence of major depression is ~15 million in the U.S., approximately 5 to 8% of the adult population.

Selective serotonin reuptake inhibitors (SSRIs) are the mainstay of treatment for MDD, but partial response is common. In the National Institutes of Health-sponsored Sequenced Treatment Alternatives to Relieve Depression (STAR\*D) trial, only 28% of patients treated with the SSRI citalopram achieved remission (Trivedi MH, et. al. *Am J Psychiatry*. 2006;163:28-40).

To date, only aripiprazole and quetiapine XR (both atypical antipsychotics) have received indications for the adjunctive treatment of MDD.

## Schizophrenia

Schizophrenia is a chronic, disabling mental illness characterized by abnormal behavior and psychosis. Onset is typically in early adulthood, and prevalence is approximately 1%. Symptoms are categorized as positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal and lack of emotion, energy, and motivation). The available medications affect chiefly positive symptoms. A number of drugs are approved for schizophrenia, but individuals typically require trials of several antipsychotic drugs before an effective and reasonably-tolerated treatment is identified. These drugs have significant side effects, which lead to drug non-compliance and abandonment, compounding the problem.

The drugs are broadly divided into the older “typical” and newer “atypical” antipsychotics. As noted by Dr. Farchione, relevant class safety issues for antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias. In general, the atypical antipsychotics tend to have fewer extrapyramidal side effects than the older ‘typical’ antipsychotics, but they cause more weight gain and metabolic effects (hyperglycemia and hyperlipidemia).

In clinical trials, the Positive and Negative Syndrome Scale (PANSS) is frequently used for assessing psychotic symptom severity, capturing both positive and negative symptoms, as well as general psychopathology. The PANSS is an interviewer-rated scale consisting of 30 items: 7 positive, 7 negative, and 16 general, all of which are rated from 1 to 7. Thus, the possible range of scores is 30 (best) to 210 (worst).

## Regulatory History

Brexpiprazole was developed for adjunctive treatment of MDD and schizophrenia under INDs 103,958 and 101,871, respectively. The important regulatory history is well detailed by Dr. Farchione in her review.

### 3. Product Quality

The Office of Product Quality (OPQ) recommends approval from a drug product perspective. Adequate information was provided for a satisfactory evaluation of the quality of both the drug substance and the drug product. Manufacturing and sterility were adequately addressed. A 36-month drug product expiration date has been granted when stored at room temperature. OPQ provided a comment for the action letter regarding the method for calculating brexpiprazole content in tablets.

### 4. Nonclinical Pharmacology/Toxicology:

The Pharmacology/Toxicology review, having determined that the nonclinical studies adequately support chronic use of brexpiprazole, recommended approval. Toxicities observed in rats, mice, and monkeys were deemed to represent exaggerated pharmacological activities of brexpiprazole, and caused hypoactivity, tremors (monkey), hypothermia, increased serum prolactin (rats and mice), decreased blood pressure, and prolonged QT/QTc interval (monkey and dog at 146 and 243 times, respectively, the maximum recommended human dose [MRHD] of 4 mg/day on mg/m<sup>2</sup> basis).

Brexpiprazole was tested in 2-year carcinogenicity studies in rats and mice by oral gavage. Both studies were found to be acceptable by the Executive Carcinogenicity Assessment Committee. In mice, the combined incidences of mammary gland neoplasms in females were increased in all dose groups, and were thought to be related to elevated prolactin levels. No drug-related neoplasms were observed in rats. Brexpiprazole was not teratogenic in rats or rabbits at doses that produced exposures that exceeded the MRHD.

## **5. Clinical Pharmacology**

The Office of Clinical Pharmacology (OCP) review team recommends approval.

The OCP team has evaluated the pharmacokinetics of brexpiprazole and its major metabolite, DM3411, and characterized the effects of intrinsic (i.e., hepatic/renal impairment, gender, age) and extrinsic factors (e.g., quinidine, ketoconazole, food). They also evaluated the applicant's study of pharmacokinetics in the elderly.

The chief findings of the review team have been incorporated into labeling and include:

- The metabolism of brexpiprazole is mainly mediated by CYP3A4 and CYP2D6.
- Brexpiprazole may be taken without regard to food.
- No dose adjustment is required based upon sex or age.
- Brexpiprazole is highly bound to serum proteins.
- For patients with moderate hepatic or renal impairment, the maximum dose recommended is 3 mg/day for schizophrenia and 2 mg/day for MDD.
- The dose should be halved in patients who receive a strong CYP3A4 inhibitor or a CYP2D6 inhibitor, and in patients known to be CYP2D6 poor metabolizers.
- The dose should be quartered in patients who receive a CYP3A4 along with a strong CYP2D6 inhibitor, or in patients known to be CYP2D6 poor metabolizers concomitantly taking a strong CYP3A4 inhibitor.
- The dose should be doubled in patients taking a strong CYP3A4 inducer.

Based on exposure (area under the concentration curve, AUC) and a responder analysis of PANSS scores, OCP developed an exposure-response model from the pooled schizophrenia population that showed that response is exposure-related. For the pooled MDD population, they could not confirm an exposure-response relationship; however, the variability in response was considerable.

Pharmacokinetic parameters were similar in patients with MDD and schizophrenia (Table 1).

**Table 1: Mean (SD) Pharmacokinetic Parameters for Brexpiprazole and DM3411 after 14 Daily Doses**

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

QT Effects:

No significant QTc prolongation was observed at 12 mg in a QT study.

Abuse Potential:

The Controlled Substance Staff reviewed the nonclinical and clinical abuse-related data and concluded that brexpiprazole does not have abuse potential.

**6. Clinical Microbiology**

John Metcalfe, conducted the primary Product Quality Microbiology assessment, and found the microbial limits specification for brexpiprazole to be acceptable. The drug product will be tested for microbial limits annually as part of the post-approval stability protocol.

**7. Clinical/Statistical Efficacy**

Adjunctive Treatment of MDD

Drs. Ling and Farchione performed comprehensive reviews of the clinical data for adjunctive treatment of MDD in adult patients with an inadequate response to an SSRI antidepressant. The MDD efficacy program included 4 trials of similar design (Table 2). There were two phase 2 studies with flexible-dose designs (331-08-211 and 331-09-222). These were followed by 2 fixed-dose phase 3 trials: Study 331-10-227 (hereafter “Study 227”), which compared brexpiprazole 1 and 3 mg/d to placebo; and Study 331-10-228 (hereafter “Study 228”), which compared brexpiprazole 2 mg/d to placebo (Table 2).

All 4 studies enrolled adult patients (age 18 to 65) with a DSM-IV-TR diagnosis of MDD. Depression was ongoing: a single or recurrent, non-psychotic episode, ≥ 8 weeks in duration. Each patient was to have received 1 to 3 courses of an antidepressant with inadequate responses (HAM-D17 Total Score ≥18).

Enrolled subjects were begun in an 8-week single-blind prospective treatment phase (phase A) followed by a 6-week randomization phase (phase B). In phase A, subjects received a protocol-determined SSRI at its labeled dose, along with single-blind placebo. (Possible SSRIs were escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed-release, or venlafaxine extended-release.) In phase B, subjects with an inadequate response in phase A continued their SSRI from phase A (dose unchanged) and were randomized (allocation ratios in Table 2) to receive double-blind adjunctive brexpiprazole or placebo.

**Table 2: Overview of Trials for Adjunctive Treatment of MDD**

Trial	331-10-228	331-10-227	331-08-211	331-09-222
Trial Phase	3		2	
Design	Phase A: Single-blind placebo+ADT Phase B: Double-blind, placebo-controlled+ADT			
Treatment Duration	Phase A: 8 weeks Phase B: 6 weeks			
Dosing Schedule	Fixed		Flexible	
Phase B Treatment Groups (+ADT)	2 mg/day Placebo	1 mg/day 3 mg/day Placebo	0.15 mg/day fixed 0.5±0.25 mg/day 1.5±0.5 mg/day Placebo	1 to 3 mg/day Placebo
Randomization Ratio	1:1	1:1:1	1:2:2:2	1:1

The 1° endpoint was the Montgomery Åsberg Depression Rating Scale (MADRS) Total Score as the change from the phase B baseline to Week 6. The MADRS consists of 10 items, all rated on a 0 to 6 scale. The MADRS Total Score is the sum of ratings for all 10 items; therefore, possible total scores range from 0 to 60. Total scores from 0 to 6 are generally considered “normal,” scores from 7 to 19 are consistent with mild depression, 20 to 34 with moderate depression, and 35 to 60 with severe depression. Though not widely used in clinical practice, the MADRS is commonly used in efficacy studies of antidepressant medications.

The 2° efficacy variable was  $\Delta$  in Sheehan Disability Scale (SDS) Mean Score (the mean of 3 individual item scores). The SDS is a self-rated visual analogue scale used to measure functional impairment in 3 interrelated domains: work/school, social, and family life. Scores range from 0 (not at all) to 10 (extremely). Scores  $\geq 5$  on any of the 3 domains are associated with significant functional impairment. The SDS is commonly used as a 2° measure to assess functional impairment associated with MDD.

The efficacy analyses for the 1° and key 2° endpoint were performed using a mixed model repeated measures (MMRM) analysis, as is typical in such studies.

All on the review team agreed that one of two phase 3 studies, Study 228, was positive at the 2 mg/day dose. There were concerns, however, with respect to the second study, Study 227, which evaluated doses of 1 and 3 mg qd. These concerns are discussed below.

Study 227:

This was a 3-armed study that compared brexpiprazole, 1 and 3 mg qd, to placebo.

The applicant completed analyses of their phase 2 study results while Study 227 was ongoing. The phase 2 data showed that for some 20% of patients who had exhibited a transient response on one or more visits during phase A, a treatment response was more likely in the placebo group in phase B. In other words, patients who were possibly mischaracterized as non-responders in phase A were demonstrating apparent responsiveness to placebo, presumably decreasing the study's ability to detect a treatment effect.

In light of these phase 2 findings, the applicant amended the protocol (amendment 3) to redefine incomplete responders as patients who failed to meet response criteria throughout phase A, rather than failing to meet response criteria only at the end of phase A. At the time this protocol amendment was implemented, some 31% of patients (210 of 677) had been randomized.

The analysis of the 1° endpoint included all patients who had a MADRS score the end-of-phase A, who had at least one score during phase B, and who had received at least one dose of study medication in phase B. Importantly, however, for the analysis of the 1° endpoint, the applicant elected to include all of these subjects. Thus, despite their concerns regarding uncertain responsiveness of 42 of the first 210 subjects randomized, they elected to include all of them in the analysis. As a supportive analysis, they excluded these 42 patients whose response in phase A had been transient, as re-defined in protocol amendment 3.

With 2 active treatment groups, the analyses had to account for multiple comparisons and control the Type-I error. Hochberg's procedure was used to adjust for the multiple comparisons of the two brexpiprazole groups vs. placebo. The comparisons of the key secondary endpoint (SDS Mean Score) would be tested using another Hochberg procedure at an alpha level of 0.05 (two-sided) only if both null hypotheses for the 1° endpoint were rejected at an alpha level of 0.05 (two-sided).

### Results:

A total of 2310 subjects were screened for the trial. There were 1539 patients enrolled into phase A. Of these, ~17% discontinued during phase A, ~44% were randomized to continue in phase B, and ~39% were successfully treated and went into an uncontrolled treatment phase. For the 677 patients randomized and continued in phase B, retention was good, with only 6% discontinuing and 0.3% lost to follow-up.

Demographic and baseline disease characteristics are extremely well summarized by Dr. Farchione (below). Mean age was 46, and two-thirds of patients were female. Representation of Blacks was quite reasonable (13%). About two-thirds of patients were from the U.S.

**Table 3: Study 227 – Demographic and Baseline Disease Characteristics – Dr. Farchione**

		<b>brexpiprazole 1 mg + ADT N = 226</b>	<b>brexpiprazole 3 mg + ADT N = 230</b>	<b>placebo + ADT N = 221</b>
Age	Mean (SD)	45.7 (11.6)	44.5 (11.2)	45.6 (11.0)
Sex	Male (%)	68 (30.1%)	74 (32.2%)	75 (33.9%)
	Female (%)	158 (69.9%)	156 (67.8%)	146 (66.1%)
Race	Caucasian (%)	183 (81%)	201 (87.4%)	188 (85.1%)
	Asian (%)	6 (2.7%)	0 (0%)	2 (0.9%)
	Black/African American (%)	34 (15%)	23 (10%)	29 (13.1%)
	Native American/Alaskan (%)	1 (0.4%)	3 (1.3%)	1 (0.5%)
	Other (%)	2 (0.9%)	3 (1.3%)	1 (0.5%)
Ethnicity	Hispanic or Latino (%)	13 (5.8%)	14 (6.1%)	16 (7.2%)
	Not Hispanic or Latino (%)	213 (94.2%)	214 (93%)	205 (92.8%)
	Unknown (%)	0 (0%)	2 (0.9%)	0 (0%)
Location	US	148 (65.5%)	149 (64.8%)	145 (65.6%)
	Non-US	78 (34.5%)	81 (35.2%)	76 (34.4%)
Weight (kg)	Mean (SD)	80.3 (20.8)	84.8 (20.9)	85.0 (21.5)
Body Mass Index (kg/M <sup>2</sup> )	Mean (SD)	29.4 (6.7)	29.9 (7.0)	29.6 (7.0)
Duration of current episode (mos)	Mean (SD)	18.7 (43.0)	17.4 (33.0)	16.9 (35.0)
# of lifetime episodes	Mean (SD)	3.6 (3.9)	3.5 (2.8)	3.7 (4.9)
Type of episode	single (%)	29 (12.8%)	31 (13.5%)	33 (14.9%)
	recurrent (%)	197 (87.2%)	199 (86.5%)	188 (85.1%)
Antidepressant therapy	escitalopram (%)	53 (23.5%)	41 (17.8%)	41 (18.6%)
	fluoxetine (%)	16 (7.1%)	28 (12.2%)	34 (15.4%)
	paroxetine CR (%)	31 (13.7%)	22 (9.6%)	14 (6.3%)
	sertraline (%)	33 (14.6%)	30 (13%)	29 (13.1%)
	duloxetine (%)	53 (23.5%)	72 (31.3%)	52 (23.5%)
	venlafaxine XR (%)	40 (17.7%)	37 (16.1%)	51 (23.1%)

Efficacy results for the 1° endpoint are summarized in Table 4. Based on the prospectively planned analytical plan, neither dose group was statistically significantly superior to placebo on the MADRS total score. The *p*-value for the brexpiprazole 3-mg group was < 0.05, but was not statistically significant after adjusting for multiplicity using the Hochberg procedure. Moreover, the placebo-subtracted treatment effects for both brexpiprazole dose groups were modest at best (least square mean differences were -1.2 and -1.5 for the 1 and 3 mg groups, respectively, on a scale of 0 to 60). The clinical meaningfulness of a 1.2- to 1.5-point difference from placebo is dubious.

	Brexpiprazole		Placebo
	1 mg n=225	3 mg n=226	n=218
MADRS Total Score			
Mean (SD), end of phase A	26.7 (5.6)	26.3 (5.2)	26.2 (5.3)
LS mean (SE) $\Delta$ at Week 14	-7.6 (0.5)	-8.0 (0.5)	-6.4 (0.5)
LS mean $\Delta$ vs. placebo (95% CI)	<b>-1.2 (-2.6, 0.2)</b>	<b>-1.5 (-2.9, -0.1)</b>	-
p-value	0.0925	0.0327	-

Because the study did not “win” on the 1° endpoint, the pre-specified hierarchical testing procedure was terminated. As it turned out, the 2° endpoints were nominally statistically significantly positive, but with placebo-subtracted effect sizes that were, at best, slightly greater than 1 (on a 0 to 10 visual analog scale).

Two Ways Study 227 Could Have Succeeded:

Sensitivity Analysis on Amendment 3

The supportive analysis excluded 42 patients who did not meet the revised criteria for incomplete response in phase A. The resulting placebo-subtracted estimates of the treatment effect were -1.95 and -1.30, respectively, for the 3 and 1 mg groups, and the nominal *p*-values were 0.008 and 0.074, which, for the higher dose, would have been statistically significant even after correction using the Hochberg method.

Was the Hochberg Method Really Necessary to Control Type-I Error?

The applicant chose to use the Hochberg procedure to control the Type-I error, but other approaches would have been perfectly acceptable, and would have led to a statistically significant result. Specifically, given that the primary goal was to demonstrate efficacy, and given that the higher dose was more likely than the lower dose to show a treatment effect, they could have used sequential testing, whereby they would have tested the 3 mg dose vs. placebo with  $\alpha=0.05$ , and, upon rejecting the null hypothesis, used all of that  $\alpha$  (0.05) to test the lower dose vs. placebo. Alternatively, they could have used the approach used for the schizophrenia studies (see below). The first approach would have led to a statistically significant finding; the second approach might have been successful as well.

Study 228:

This was a 2-armed study that compared brexpiprazole 2 mg qd to placebo. At the time of amendment 3 (see description for Study 227), 153 of the 379 subjects (40%) were already randomized. A total of 1227 subjects were screened for Study 228 and 826 were enrolled into phase A. Of these patients, ~14% discontinued during phase A, ~46% were randomized to continue in phase B, and ~40% were successfully treated and went into an uncontrolled treatment phase. For the 379 patients randomized in phase B, retention was good, with only 7% discontinuing and 0.3% lost to follow-up.

Demographic and baseline disease characteristics are succinctly summarized by Dr. Farchione in her review (Table 5), and are quite similar to those of Study 227. Mean age was 45, and 70% of patients were female. Representation of Blacks was 11%. About two-thirds of patients were from the U.S.

**Table 5: Study 228 – Demographic and Baseline Disease Characteristics – Dr. Farchione**

		<b>brexpiprazole 2 mg + ADT N = 188</b>	<b>placebo + ADT N = 191</b>
Age	Mean (SD)	44.1 (11.6)	45.2 (11.3)
Sex	Male (%)	58 (30.9%)	54 (28.3%)
	Female (%)	130 (69.1%)	137 (71.7%)
Race	Caucasian (%)	163 (86.7%)	166 (86.9%)
	Asian (%)	1 (0.5%)	0 (0%)
	Black/African American (%)	19 (10.1%)	22 (11.5%)
	Native American/Alaskan (%)	1 (0.5%)	0 (0%)
	Other (%)	3 (1.6%)	2 (1%)
	Unknown (%)	1 (0.5%)	1 (0.5%)
	Hispanic or Latino (%)	20 (10.6%)	18 (9.4%)
Ethnicity	Not Hispanic or Latino (%)	162 (86.2%)	168 (88%)
	Unknown (%)	6 (3.2%)	5 (2.6%)
	US	125 (66.5%)	129 (67.5%)
Location	Non-US	63 (33.5%)	62 (32.5%)
	Weight (kg)	Mean (SD)	84.2 (21.2)
Body Mass Index (kg/M <sup>2</sup> )	Mean (SD)	29.9 (6.8)	29.6 (7.1)
Duration of current episode (mos)	Mean (SD)	13.5 (14.2)	13.7 (17.1)
# of lifetime episodes	Mean (SD)	3.8 (3.2)	3.8 (2.9)
Type of episode	single (%)	21 (11.2%)	20 (10.5%)
	recurrent (%)	167 (88.8%)	171 (89.5%)
Antidepressant therapy	escitalopram (%)	41 (21.8%)	39 (20.4%)
	fluoxetine (%)	23 (12.2%)	29 (15.2%)
	paroxetine CR (%)	26 (13.8%)	21 (11%)
	sertraline (%)	28 (14.9%)	26 (13.6%)
	duloxetine (%)	40 (21.3%)	41 (21.5%)
	venlafaxine XR (%)	30 (16%)	35 (18.3%)

**Table 6: Study 228 - 1<sup>o</sup> Endpoint**

	<u>Brexpiprazole 2 mg</u>	<u>Placebo</u>
	n=187	n=191
MADRS Total Score		
Mean (SD), end of phase A	26.6 (5.8)	27.1 (5.6)
LS mean (SE) Δ at Week 14	-8.3 (0.6)	-5.1 (0.6)
LS mean Δ vs. placebo (95% CI)	<b>-3.1 (-4.7, -1.5)</b>	-
p-value	0.0001	-

The results are statistically significant with a placebo-subtracted treatment effect of 3.1 on a 60-point scale, from a baseline score of ~27 (Table 6).

Dr. Ling’s subgroup analyses by sex, race, age, and region are largely consistent, except for some subgroups with small size. The effect size in the US (-4.1) was larger than the effect size outside of the US (-0.7).

Adjunctive treatment of MDD – efficacy summary:

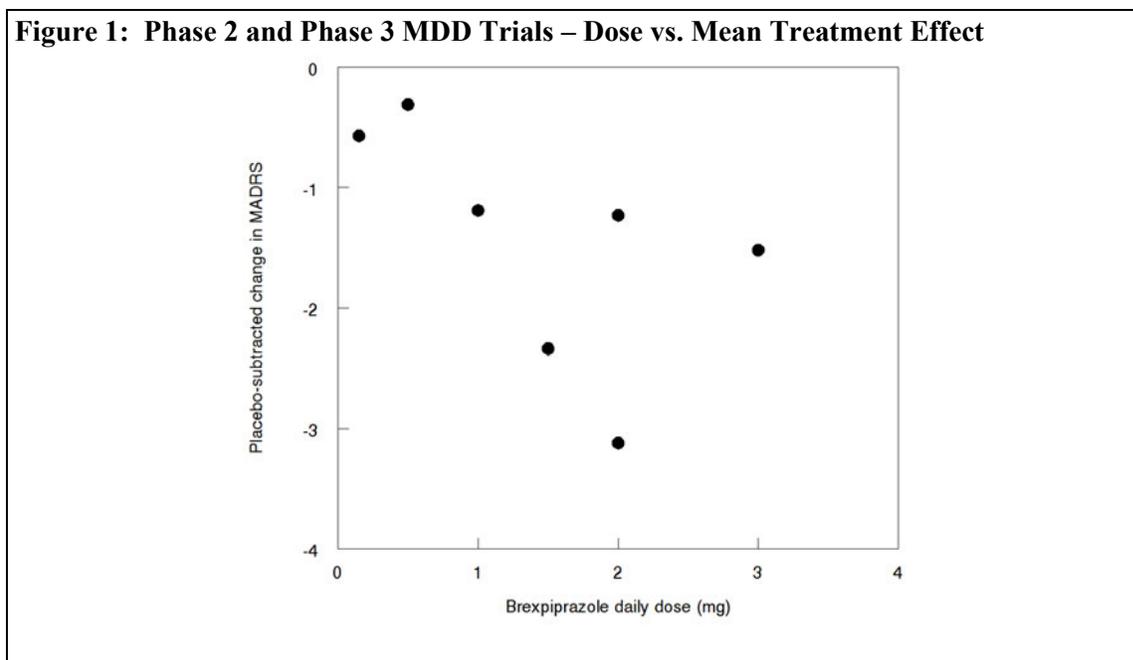
The overall evidence is thoughtfully discussed by Dr. Farchione, and I agree with her logic. The applicant conducted two adequate and well-controlled trials to assess the efficacy of brexpiprazole for the adjunctive treatment of MDD.

- Study 228 was a clearly positive in a population of individuals with a history of having failed multiple antidepressant drugs. Having then had a suboptimal response to another SSRI during phase A of the study, patients were randomized to brexpiprazole 2 mg qd or placebo, and there was a placebo-subtracted treatment effect of 3.1 points on the MADRS. The results were robust to exploration, consistent across the larger subgroups, and positive in US patients.
- As noted by Drs. Ling and Farchione, Study 227 was not a positive study based on its prespecified 1° endpoint. Nevertheless, had the applicant excluded the 42 patients who had partial responses, the study would have been successful. In addition, there are other commonly used procedures that could have been used to control Type-I error, and the study might have succeeded.
- Also, as pointed out by Dr. Farchione, a phase 2 trial, Study 331-08-211, used the same statistical plan and the same pre-amendment 3 inclusion criteria as Study 227. Reanalysis of the data from this trial using amendment 3 criteria yields statistically significant results for the 1.5 ± 0.5 mg/day brexpiprazole treatment group.
- Although the review team did not believe that the data showed a dose-response, I would note that the results across the phase 2 and 3 studies provide a sense of a dose-response, which, if believed, would support the evidence of effectiveness (Table 7).

**Table 7: Results of Phase 2 and Phase 3 Studies for Adjunctive Treatment of MDD**

Study	Brexpiprazole dose (mg/d)	N	placebo-subtracted treatment effect
228	2	187	-3.12
	1	225	-1.19
227	3	226	-1.52
211	0.15	62	-0.57
	0.5 ± 0.25	119	-0.31
	1.5 ± 0.5	118	-2.34
222	1 - 3	184	-1.23

In Figure 1, I have plotted the brexpiprazole daily dose vs. treatment effect for the studies listed in Table 7 (for Study 331-09-222, I considered the dose of 1-3 mg/day to be ~2 mg/day).



In summary, in light of all the considerations above, I agree with Drs. Farchione and Mathis that the strong evidence from Study 228 ( $p$ -value < 0.0001), together with supportive evidence from Studies 227 and 222, collectively provide substantial evidence of efficacy for brexpiprazole for the adjunctive treatment of MDD. The fact that the drug has efficacy in schizophrenia (see below), and the fact that other atypical antipsychotics are effective for adjunctive treatment of MDD, helps the case for approval.

### Schizophrenia

Drs. Farchione, Kordzakhia, and Mathis have reviewed the program for schizophrenia and all have agreed that substantial evidence has been presented to support the approval of brexpiprazole for this indication. I agree with their assessment. The applicant submitted two positive phase 3, fixed-, multiple-dose, randomized, double-blind, placebo-controlled, multinational studies (Studies 230 and 231), 6 weeks in duration. Both studies were positive on the basis of a placebo-subtracted reduction in the PANSS total score.

The enrollment criteria for both studies included total Brief Psychiatric Rating Scale (BPRS) score >40, with a score >4 on 2 or more of the following items: hallucinatory behavior, unusual thought content, conceptual disorganization, or suspiciousness, as well as a score >4 on the Clinical Global Impression - Severity of Illness scale (CGI-S).

In Study 331-10-230 (hereafter "Study 230"), subjects were randomized to brexpiprazole 4, 2, or 1 mg/day, or placebo, at an allocation ratio of 3:3:2:3.

In Study 331-10-231 (hereafter “Study 231”), subjects were randomized to brexpiprazole 4, 2, or 0.25 mg/day, or placebo, in a 2:2:1:2 ratio.

Patients in the 2 mg or 4 mg brexpiprazole groups initiated treatment at 1 mg/day on Days 1 to 4. The dose was increased to 2 mg on Days 5 to 7. The dosage was then either maintained at 2 mg once daily or increased to 4 mg once daily, depending on treatment assignment, for 5 remaining weeks.

The 1° efficacy endpoint was the change from baseline to Week 6 in PANSS Total Score. Multiplicity was addressed by first comparing the difference between the average effect of the 2 and 4 mg/day groups vs. placebo at an alpha level of 0.05 as a global test of efficacy. If the global null hypothesis was rejected, the plan allowed testing of the 2 mg and 4 mg dose groups vs. placebo with alpha = 0.05 for both dose groups. The 2° endpoints could be tested in order if both comparisons (2 mg/day vs. placebo and 4 mg/day vs. placebo) were statistically significant.

The pre-specified key 2° efficacy endpoint was the change from baseline to Week 6 in the CGI-S score. Both 1° and the key 2° endpoints were analyzed using MMRM analyses.

**Results:**

In Study 230, a total of 674 patients were randomized; ~30% of patients discontinued, such that 458 patients completed the double-blind treatment period. In Study 231, a total of 636 patients were randomized; ~35% of patients discontinued, such that 410 subjects (65%) completed the

**Table 8: Study 230 – Baseline Characteristics**

		brexpiprazole 1 mg N = 120	brexpiprazole 2 mg N = 186	brexpiprazole 4 mg N = 184	placebo N = 184
Age	Mean (SD)	39.1 (11.9)	36.9 (10.9)	38.6 (11.0)	39.3 (10.8)
Sex	Male (%)	77 (64.2%)	122 (65.6%)	113 (61.4%)	111 (60.3%)
	Female (%)	43 (35.8%)	64 (34.4%)	71 (38.6%)	73 (39.7%)
Race	Caucasian (%)	75 (62.5%)	118 (63.4%)	104 (56.5%)	110 (59.8%)
	Asian (%)	5 (4.2%)	7 (3.8%)	12 (6.5%)	10 (5.4%)
	Black/African American (%)	26 (21.7%)	41 (22%)	50 (27.2%)	45 (24.5%)
	Native American/Alaskan (%)	5 (4.2%)	8 (4.3%)	6 (3.3%)	5 (2.7%)
	Other (%)	9 (7.5%)	12 (6.5%)	12 (6.5%)	14 (7.6%)
	Hispanic or Latino (%)	27 (22.5%)	31 (16.7%)	32 (17.4%)	31 (16.8%)
Ethnicity	Not Hispanic or Latino (%)	93 (77.5%)	155 (83.3%)	150 (81.5%)	151 (82.1%)
	Unknown (%)	0 (0%)	0 (0%)	2 (1.1%)	2 (1.1%)
Location	US	44 (36.7%)	66 (35.5%)	66 (35.9%)	67 (36.4%)
	Non-US	76 (63.3%)	120 (64.5%)	118 (64.1%)	117 (63.6%)
Weight (kg)	Mean (SD)	80.3 (20.8)	84.8 (20.9)	84.8 (20.9)	85.0 (21.5)
Body Mass Index (kg/M <sup>2</sup> )	Mean (SD)	29.4 (6.7)	29.9 (7.0)	29.9 (7.0)	29.6 (7.0)
Age at first diagnosis (yrs)	Mean (SD)	18.7 (43.0)	17.4 (33.0)	17.4 (33.0)	16.9 (35.0)
Duration of current episode (weeks)	Mean (SD)	3.6 (3.9)	3.5 (2.8)	3.5 (2.8)	3.7 (4.9)
	Total Score	93.3 (12.8)	96.3 (12.8)	95.1 (12.5)	94.8 (13.0)
PANSS [Mean (SD)]	Positive Subscale Score	24.9 (4.3)	24.9 (4.3)	24.9 (4.4)	25 (4.6)
	Negative Subscale Score	23.2 (5.4)	24.1 (5.2)	23.9 (5.0)	24 (5.3)
	CGI-S Score	Mean (SD)	4.9 (0.7)	5 (0.7)	4.9 (0.6)
PSP Score	Mean (SD)	45.5 (10.7)	43.7 (11.4)	44.7 (11.1)	43.7 (10.8)
BPRS Total Score	Mean (SD)	54.4 (8.6)	55.5 (7.5)	55.2 (7.5)	55.1 (8.0)

trial. In both studies the incidence of discontinuations was slightly higher in the placebo group than in the brexpiprazole groups. Baseline characteristics for Study 230 and 231 are summarized in Tables 8 and 9, respectively, from Dr. Farchione.

In both studies, baseline characteristics were reasonably balanced. Mean age was ~40, 60-70% of patients were female, and about a quarter of patients were Black. Baseline total PANSS was ~95.

**Table 9: Study 231 – Baseline Characteristics**

		brexpiprazole 0.25 mg N = 90	brexpiprazole 2 mg N = 182	brexpiprazole 4 mg N = 180	placebo + ADT N = 184
Age	Mean (SD)	40.5 (11.4)	39.6 (10.2)	40.8 (11.0)	39.7 (10.8)
Sex	Male (%)	61 (67.8%)	111 (61%)	111 (61.7%)	118 (64.1%)
	Female (%)	29 (32.2%)	71 (39%)	69 (38.3%)	66 (35.9%)
Race	Caucasian (%)	63 (70%)	120 (65.9%)	119 (66.1%)	121 (65.8%)
	Asian (%)	7 (7.8%)	19 (10.4%)	16 (8.9%)	16 (8.7%)
	Black/African American (%)	20 (22.2%)	43 (23.6%)	42 (23.3%)	45 (24.5%)
	Native American/Alaskan (%)	0 (0%)	0 (0%)	0 (0%)	1 (0.5%)
	Native Hawaiian/Pacific Islander	0 (0%)	0 (0%)	1 (0.6%)	1 (0%)
	Other (%)	0 (0%)	0 (0%)	2 (1.1%)	0 (0%)
Ethnicity	Hispanic or Latino (%)	8 (8.9%)	3 (1.6%)	10 (5.6%)	9 (4.9%)
	Not Hispanic or Latino (%)	82 (91.1%)	179 (98.4%)	170 (94.4%)	175 (95.1%)
Location	US	33 (36.7%)	63 (34.6%)	65 (36.1%)	67 (36.4%)
	Non-US	57 (63.3%)	119 (65.4%)	115 (63.9%)	117 (63.6%)
Weight (kg)	Mean (SD)	78.0 (18.7)	80.0 (19.7)	80.1 (18.3)	77.8 (18.3)
Body Mass Index (kg/M <sup>2</sup> )	Mean (SD)	26.2 (6.3)	27.3 (5.9)	27.1 (5.8)	26.5 (5.4)
Age at first diagnosis (yrs)	Mean (SD)	27.5 (8.9)	26.6 (8.6)	28 (9.6)	27.4 (9.5)
Duration of current episode (weeks)	Mean (SD)	2.6 (1.8)	2.8 (2.3)	2.4 (1.6)	2.7 (2.6)
	Total Score	93.4 (11.7)	95.9 (13.7)	94.9 (12.2)	95.9 (11.5)
PANSS [Mean (SD)]	Positive Subscale Score	24.9 (3.5)	25.6 (4.4)	25 (4.5)	25.2 (4.1)
	Negative Subscale Score	22.7 (4.5)	23.2 (4.60)	23.3 (4.7)	23.5 (4.4)
CGI-S Score	Mean (SD)	4.9 (0.6)	4.9 (0.6)	4.8 (0.6)	4.8 (0.7)
PSP Score	Mean (SD)	44.2 (9.8)	45.4 (10.5)	45.3 (10.9)	45.1 (9.5)
BPRS Total Score	Mean (SD)	55 (7.5)	56.4 (8.6)	55.3 (7.4)	55.7 (7.1)

Results are shown in Table 10:

**Table 10: Least Squares Mean Change from Baseline in PANSS at Week 6 - Studies 230 and 231**

<b>Study 230</b>	<b>Brex. 1 mg</b>	<b>Brex. 2 mg</b>	<b>Brex. 4 mg</b>	<b>Placebo</b>
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			
<b>Study 231</b>	<b>Brex. 0.25 mg</b>	<b>Brex. 2 mg</b>	<b>Brex. 4 mg</b>	<b>Placebo</b>
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			

In Study 230, the improvement in PANSS Total Score was statistically significant for the brexpiprazole 4 mg/day, but not for the brexpiprazole 2 mg/day group. In Study 231, both the 2 and 4 mg/day groups were statistically significantly different than placebo. Results were robust to exploration and generally consistent across subgroups.

Because the comparison of brexpiprazole 2 mg/day versus placebo was not statistically significant in the 1° analysis of Study 230, no additional formal statistical testing was performed for the 2° endpoints. For Study 231, the placebo-subtracted improvement in CGI-S score from baseline to Week 6 was statistically significant for both brexpiprazole groups.

#### Summary of efficacy:

Based on Studies 230 and 231, the applicant has submitted substantial evidence of efficacy for brexpiprazole for the treatment for schizophrenia. As Dr. Mathis points out, there is no clear dose-response, such that doses from 2 mg to 4 mg are effective and will be labeled as the target dose range with a maximum dose of 4 mg per day.

### **9. Advisory Committee Meeting**

We chose not to convene an advisory committee to evaluate this NDA. Although the drug is a new molecular entity, there is nothing novel about the drug, and the applicant provided conventionally-designed studies with typical endpoints. The studies were well executed; the clinical benefit was clear for schizophrenia, and fairly clear for adjunctive treatment of MDD. There were no unique safety issues and no risks of sufficient magnitude to make one seriously question whether the benefit outweighed the risk (see benefit-risk framework table).

## 10. Pediatrics

### MDD

We are waiving the pediatric study requirement for ages 0 to 6 years because of the low prevalence of MDD. We are also waiving the pediatric study requirement for ages 7 to 17 years because brexpiprazole is not likely to yield a meaningful therapeutic benefit over existing therapies for pediatric patients, and it is not likely to be used in a substantial number of patients. For these reasons, the Division will not expect pediatric data in MDD for this product.

### Schizophrenia

We are waiving the pediatric study requirement for ages 0-12 years for children with schizophrenia because onset of schizophrenia prior to 13 years of age is rare.

We are deferring pediatric studies for ages 13 to 17 years because the drug is ready for approval for use in adults and the pediatric studies have not been completed.

## 11. Other Relevant Regulatory Issues

### Site Inspections:

Inspections were conducted by the Office of Scientific Investigations OSI for a total of 4 sites—2 from the schizophrenia program and 2 from the MDD program. Sites for inspection were chosen on the basis of significant enrollment numbers and not for any *a priori* reason. No deviations were identified at the sites from the schizophrenia program, and the data were deemed acceptable. For the MDD program, isolated data discrepancies were identified at both sites, but did not materially impact the interpretation of critical data. Overall, therefore, the data from both development programs were considered reliable.

OSI also inspected the sponsor, Otsuka, because brexpiprazole is a new molecular entity. They inspected the oversight plan, the monitoring reports and correspondence, regulatory documents, work instructions, and Transfers of Regulatory Obligations (TOROs), as well as various study records from 5 sites. No significant regulatory violations were noted and no Form FDA 483 was issued.

Overall, the data submitted by the applicant were deemed reliable.

### Name Review:

The Division of Medication Error Prevention and Analysis concluded that the proposed proprietary name, "Rexulti" is acceptable from both a promotional and safety perspective.

## 13. Post-marketing Commitments

There are post-marketing commitments to demonstrate maintenance of brexpiprazole's efficacy for both indications.

- The applicant has agreed to a conduct a placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients who require adjunctive treatment of MDD.
- The applicant has agreed to a conduct a placebo-controlled, randomized withdrawal maintenance study of brexpiprazole in patients with schizophrenia.

### **Summary/Conclusions**

Having negotiated the labeling with the applicant, brexpiprazole will be approved with agreed upon labeling and the following indication statement:

“REXULTI is indicated for:

- Adjunctive treatment of major depressive disorder (MDD).
- Treatment of schizophrenia.”

The benefit-risk framework that follows is adapted from Dr. Tiffany Farchione’s review.

**Table 11: Benefit-Risk Summary and Assessment—Adjunctive Treatment of MDD**

Brexpiprazole is a NME atypical antipsychotic that was shown to be effective in the adjunctive treatment of MDD, as described under ‘Benefit,’ below. The evidence of efficacy was based on improvement in MADRS, a standard 60-point scale that is typically used in clinical trials of antidepressant drugs. Studies 227 and 228 show that patients with a mean MADRS of ~27 (i.e., moderate depression), despite an adequate course of an SSRI, improved by 5-6 points in the placebo group, vs. some 8 points in the brexpiprazole groups. Compared to placebo, and based on point estimates, brexpiprazole improved the MADRS by 1.3 to 3.2 points. Although a 3-point improvement on top of placebo on a 60-point scale seems meager, psychiatrists have the view that the approved antidepressant drugs, most of which have shown treatment effects on the MADRS in this range, have clinically meaningful effects that are beneficial to patients. All of this suggests that better scales might be developed to assess clinical response in antidepressant trials.

Although the drug label will carry some 12 class warnings, we have little or no data for most of these risks. These drugs cause strokes, but there were none in this development program. The same can be said of neuroleptic malignant syndrome, tardive dyskinesia, and agranulocytosis, among others. When writing the Drug Snapshot, we will want to be able to assess these risks by demographic subgroups, and yet we have no data. This drug is typical of all of the atypical antipsychotic drugs in this regard. The clinical development programs are not large enough to quantify the occurrence of rare events, such as mortality in elderly patients with dementia, suicides, strokes, etc.

The more common adverse reactions found in the development program were similar to those reported for other atypical antipsychotics (e.g., metabolic syndrome, extrapyramidal symptoms, etc.); no unique safety concerns were identified. The most common TEAEs were akathisia, weight gain, headache, somnolence, fatigue, anxiety, and increased appetite.

In order to make an approval/non-approval decision on this drug for adjunctive treatment of MDD, we have solid efficacy data upon which to assess the drug’s benefit, but very little data upon which to assess the specific risk of this drug. We are reassured that with placebo-controlled trials that exposed some 643 patients to brexpiprazole and 411 to placebo (with uncontrolled exposure in additional patients), the safety seems similar to other drugs in the class. (We also have data from the schizophrenia program, below.) In quantifying risk, the problem (fortunately) is that irreversible harm is relatively rare with this class of drugs. Quantitative assessment would require many thousands of patients; if we demanded that, we would shut down psychiatric drug development.

But the good news is that individual patients, and their providers, are able to determine, reasonably well, whether the drug is working for them, determine whether there are important side effects, and make individual benefit-risk decisions.

We are satisfied that for the overall population for whom the drug is labeled, the benefits outweigh the risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	MDD is a debilitating and chronic illness, the leading cause of disability worldwide, and a major contributor to the global burden of disease. It is characterized by low mood, anhedonia, feelings of guilt and worthlessness, low energy, and other emotional and physical symptoms. In severe cases, MDD can result in suicide. Partial response to pharmacologic treatment is common, with fewer than 30% of patients achieving remission during first-	MDD is a potentially fatal condition (i.e., via suicide). Partial response to existing treatment options is common.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	line treatment with a selective serotonin reuptake inhibitor (SSRI).	
Current Treatment Options	Only 2 drugs have received indications for adjunctive treatment of MDD—aripiprazole and quetiapine XR. Like brexpiprazole, these drugs are atypical antipsychotics. Other strategies for patients with inadequate responses include dose increases, changing to a different antidepressant, adding or changing psychotherapy, electroconvulsive therapy, or use of other (off-label) medications.	For patients with inadequate response to antidepressant treatment, options are limited. Brexpiprazole is in the same class as the two drugs approved for use as adjunctive treatment of MDD. It is expected to work in a similar manner, and to have a similar benefit-risk profile.
Benefit	<p>The Sponsor conducted 2 adequate and well-controlled trials to assess brexpiprazole’s efficacy for adjunctive treatment of MDD.</p> <ul style="list-style-type: none"> <li>• Study 228 was a “strongly positive” study—in a population of individuals with a history of multiple failed antidepressant trials and a suboptimal response to an additional SSRI antidepressant, brexpiprazole 2 mg/day, added to the SSRI, improved the MADRS total score by 3.1 points relative to placebo.</li> <li>• Study 227 was not a positive study based on its prespecified 1° endpoint. However, prior to Protocol Amendment 3, the inclusion criteria resulted in what was arguably inappropriate randomization of 42 subjects. Exclusion of these subjects results in a positive study. In addition, the prespecified analyses were very statistically conservative. Use of a number of alternative, yet reasonable, analyses results in statistically significant improvement in the 3 mg/day brexpiprazole treatment group vs. placebo.</li> <li>• An additional trial, Study 211, a phase 2 study, used the same conservative statistical plan and the same pre-Amendment 3 inclusion criteria as Study 227. Reanalysis of the data from this trial either using Amendment 3 criteria or less stringent analyses yields statistically significant results for the 1.5 ± 0.5 mg/day brexpiprazole treatment group.</li> </ul>	<ul style="list-style-type: none"> <li>• The improvement with 2 mg/day brexpiprazole on the MADRS observed in Study 227 was 3.1 points greater than the improvement in placebo—a difference that was highly statistically significant, <math>p=0.0001</math>, and clinically meaningful.</li> <li>• Although both 227 and 211 failed on their prespecified 1° analyses, they are considered supportive.</li> <li>• Moreover, there are relevant prior here: the drug has clear activity in schizophrenia, and 2 other drugs in this class have indications for adjunctive treatment of MDD.</li> <li>• Thus, with one strongly positive trial and supportive evidence from two additional trials, there is adequate evidence of efficacy to approve this product for the adjunctive treatment of MDD.</li> <li>• Although cross-trial comparisons are fraught with uncertainty, compared to the 2 atypical antipsychotic drugs approved for adjunctive treatment of MDD, nothing about brexpiprazole seems unique.</li> </ul>

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk	<p>A number of risks are known for the class of atypical antipsychotic drugs. Labeled risks include: increased mortality in elderly patients with dementia-related psychosis, suicidal thoughts and behaviors, cerebrovascular adverse reactions including stroke, neuroleptic malignant syndrome (NMS), tardive dyskinesia, metabolic changes (weight and lipids), leukopenia, neutropenia, and agranulocytosis, orthostatic hypotension, syncope, seizures, body temperature dysregulation, dysphagia, and cognitive and motor impairment. The drug labeling will include these class warnings.</p> <p>In the development program, the most common TEAEs were weight gain, insomnia, headache, akathisia, somnolence, fatigue, anxiety, and increased appetite. In both MDD and schizophrenia trials, weight gain was more common and greater in the long-term trials. Elevated triglycerides were reported in short- and long-term trials in both populations.</p>	<p>Safety results were similar in the MDD and schizophrenia development programs, and similar to the known safety profile of atypical antipsychotics as a class; no unique safety concerns were identified.</p>
Risk Management	<p>There are several previously approved agents in the atypical antipsychotic class of drugs. The evaluation of the safety data did not reveal particular safety issues that were unexpected for this class. The design of the efficacy trials was similar to that used in trials used to approve other products for this indication. The risks associated with other drugs in this class approved for this indication are adequately managed via the product labeling and medication guide, and we anticipate that the usual measures will be adequate for brexpiprazole.</p>	<p>A medication guide will be included in labeling for this product. No REMS is required.</p>

**Table 12: Benefit-Risk Summary and Assessment—Treatment of Schizophrenia**

Brexpiprazole is a NME atypical antipsychotic that was shown to be effective for treatment of schizophrenia in 2 adequate and well controlled trials.

In Study 231, both the 2 and 4 mg/day dosage groups were statistically significantly better than placebo in improving psychotic symptoms as measured by the Positive and Negative Syndrome Scale (PANSS). In Study 230, however, only the 4 mg/day dosage group was statistically superior to placebo.

Studies 230 and 231 show that patients with a mean PANSS of ~95 (the score's range is 30 – no symptoms; 210 worst symptoms), improved by ~13 points in the placebo group, vs. ~19 points in the brexpiprazole groups. Compared to placebo, and based on point estimates, brexpiprazole improved PANSS by 7 to 8 points. Although an 8-point improvement on top of placebo on a 180-point scale seems meager, psychiatrists have the view that the approved antipsychotic drugs, many of which have shown treatment effects on the PANSS in this range, have clinically meaningful effects that are beneficial to patients. All of this suggests that better scales might be developed to assess clinical response in trials of antipsychotic drugs.

The risks associated with brexpiprazole are thought to be similar to the known safety profile of atypical antipsychotics as a class and are noted below (e.g., metabolic syndrome, extrapyramidal symptoms, etc.); no unique safety concerns were identified.

Although the drug label will carry some 12 class warnings, we have little or no data for most of these risks. These drugs increase mortality in elderly patients with dementia-related psychosis, but in this drug development program we have no deaths in patients with dementia. These drugs cause strokes, but there were none in this development program. The same can be said of neuroleptic malignant syndrome, tardive dyskinesia, and agranulocytosis, among others. When writing the Drug Snapshot, we will want to be able to assess these risks by demographic subgroups, and yet we have no data. This drug is typical of all of the atypical antipsychotic drugs in this regard. The clinical development programs are not large enough to quantify the occurrence of rare events, such as mortality in elderly patients with dementia, suicides, strokes, etc.

In order to make an approval/non-approval decision on this drug for adjunctive treatment of schizophrenia, we have solid efficacy data upon which to assess the drug's benefit, but very little data upon which to assess the specific risk of this drug. We are reassured that with placebo-controlled trials that exposed some 852 patients to brexpiprazole and 368 to placebo (with uncontrolled exposure in additional patients), that the safety seems similar to other drugs in the class. (We also have data from the MDD program, above.) In quantifying risk, the problem (fortunately) is that irreversible harm is relatively rare with this class of drugs. Quantitative assessment would require many thousands of patients; if we demanded that, we would shut down psychiatric drug development.

But the good news is that individual patients, and their providers, are able to determine, reasonably well, whether the drug is working for them, determine whether there are important side effects, and make individual benefit-risk decisions.

We are satisfied that for the overall population for whom the drug is labeled, the benefits outweigh the risks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
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<p><b>Analysis of Condition</b></p>	<p>Schizophrenia is a severe, chronic, disabling mental illness affecting approximately 1% of the population. Onset of illness is typically in early adulthood. The disease is characterized by abnormal behavior and psychosis. Symptoms are categorized as positive (e.g., hallucinations and delusions) and negative (e.g., social withdrawal; lack of emotion, energy, and motivation) domains. Most medications have predominant effects on positive symptoms. Although there are a number of approved treatments for this condition, an individual patient may require several trials with different antipsychotic drugs before an effective and reasonably-tolerated treatment is identified.</p>	<p>Schizophrenia is a severe and debilitating illness. For many patients, existing treatment options are unable to adequately control their symptoms, or may cause intolerable adverse reactions.</p>
<p><b>Current Treatment Options</b></p>	<p>A number of “typical” and “atypical” antipsychotics are currently available for the treatment of schizophrenia. Some of the relevant class safety issues for antipsychotics include extrapyramidal side effects, tardive dyskinesia, neuroleptic malignant syndrome, hyperprolactinemia, orthostatic hypotension, weight gain, metabolic changes, and blood dyscrasias. The atypical antipsychotics have been associated more with weight gain, hyperglycemia and hyperlipidemia side effects compared to the typical antipsychotics.</p>	<p>Although there are a number of approved atypical antipsychotics currently on the market, individual patient response to a given antipsychotic cannot be predicted. For an individual patient, several trials of different drugs are often required before an effective treatment can be identified. Some patients do well for some period of time on a drug, only to develop side effects, requiring a switch to another drug. There are also some patients for whom an effective treatment has yet to be identified, despite multiple trials. Thus, having additional treatment options is valuable.</p>
<p><b>Benefit</b></p>	<p>The Sponsor conducted two adequate and well-controlled studies to assess the efficacy of brexpiprazole in the treatment of schizophrenia.</p> <ul style="list-style-type: none"> <li>In Study 231, both the 2 mg/day (LS mean difference=-8.7, p&lt;0.0001) and 4 mg/day (LS mean difference=-7.6, p=0.0006) dosage groups showed statistically greater improvement on the PANSS.</li> <li>In Study 230, only the 4 mg/day dosage group was statistically superior to placebo (LS mean difference=-6.5, p=0.002). The brexpiprazole 2 mg/day group did not demonstrate superiority to placebo, although it did show a greater numerical improvement.</li> <li>Pooling data across the two pivotal Phase 3 trials supports the concept that the 2 mg/day dosage is effective.</li> </ul>	<p>Although statistical superiority was substantiated for only one dose, there is no specific regulatory requirement that the efficacy of every labeled dosage must be shown with 2 trials. The Dosage and Administration section of labeling will state a “target dose” recommendation that includes both 2 and 4 mg/day. In clinical practice, one should attempt to treat patients with the lowest effective dose and, clearly, for a proportion of subjects in these trials, 2 mg/day was effective.</p>
<p><b>Risk</b></p>	<p>In the overall development program, the most common TEAEs were weight increased, insomnia, headache, akathisia, somnolence, fatigue, anxiety, and increased appetite. With regard to potential risk for metabolic syndrome, in both MDD and schizophrenia trials, weight gain was more common and greater in the long-term trials. Elevated triglycerides were shown even in the short-term trials in both populations.</p>	<p>Safety results were similar in the MDD and schizophrenia development programs, and similar to the known safety profile of atypical antipsychotics as a class; no unique safety concerns were identified.</p>

<b>Risk Management</b>	There are several previously approved agents in the atypical antipsychotic class of drugs. The evaluation of the safety data did not reveal particular safety issues that were unexpected for this class. The risks associated with other drugs in this class approved for this indication have been adequately managed via the product labeling and medication guide.	A medication guide will be included in labeling for this product. No REMS is required.
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