OTSUKA (PHILIPPINES) PHARMACEUTICAL, INC.

# BREXPIPRAZOLE (REXULTI™)
## PROTOCOL

# Brexpiprazole (Rexulti™) Safety and Efficacy Among Filipino Patients (RAISE) - A Post Marketing Surveillance Program

**Protocol No.: 331-414-00243**

Version 1.4

CONFIDENTIAL – PROPRIETARY INFORMATION

| | |
|---|---|
| Clinical Phase: | IV |
| Sponsor: | Otsuka (Philippines) Pharmaceutical, Inc.<br>3F, King's Court II Building,<br>2129 Chino Roces Avenue,<br>Makati City, Philippines |
| Medical Director | Rodney Felimon De Peralta Dalisay, MD, DPBP, FPPA, FPCPsych<br>Otsuka (Philippines) Pharmaceutical, Inc. |
| Immediately Reportable Adverse Event | Marinette O. Magbitang<br>Otsuka (Philippines) Pharmaceutical, Inc. |
| Protocol Version and Date | Version 1.4 – November 12, 2020 |

## LOCAL MEDICAL/SAFETY MONITORS

**Otsuka (Philippines) Pharmaceutical, Inc**.:

Ms. Marinette O. Magbitang
Local Safety Manager
Pharmacovigilance/Clinical Research Associate
Email: oppi-pv@otsuka.com.ph

Ms. Fatima Chelsea P. Perey
Clinical Research Associate/ Post Marketing Surveillance Lead
Email: oppi-pv@otsuka.com.ph

Rodney D. Dalisay, MD, DPBP, FPPA, FPCPsych
Medical Director
Email: oppi-pv@otsuka.com.ph

Otsuka (Philippines) Pharmaceutical, Inc.
3F King's Court II Building, 2129 Chino Roces Ave., corner Dela Rosa St., 1231 Makati City
Tel: (632) 8888 6774
Fax: (632) 8811.2279
Email: oppi-pv@otsuka.com.ph

# TABLE OF CONTENTS

**PROTOCOL SYNOPSIS**

<table>
<tr><td>Name of Sponsor</td><td colspan="3">Otsuka (Philippines) Pharmaceutical, Inc</td><td rowspan="2">Protocol No: 331-414-00243</td></tr>
<tr><td>Name of Product</td><td colspan="3">Brexpiprazole (Rexulti™) Film-coated Tablet as Antipsychotic Agent</td></tr>
<tr><td>Protocol Title</td><td colspan="4">Brexpiprazole (Rexulti™) Safety and Efficacy Among Filipino Patients (RAISE) - A Post Marketing Surveillance Program</td></tr>
<tr><td>Clinical Phase</td><td colspan="4">Phase IV</td></tr>
<tr><td>Treatment Indication(s)</td><td colspan="4">• For the treatment of schizophrenia.<br>• Adjunctive therapy to antidepressants for the treatment of major depressive disorder (MDD)</td></tr>
<tr><td>Objective(s)</td><td colspan="4">To provide post marketing surveillance data on the safety and efficacy of Brexpiprazole (Rexulti™) Film-coated Tablet for schizophrenia and adjunctive therapy of major depressive disorder (MDD) in the Philippines.</td></tr>
<tr><td colspan="5">Study Design</td></tr>
<tr><td>Center</td><td colspan="4">Multi-center</td></tr>
<tr><td>Blinding</td><td colspan="4">Open</td></tr>
<tr><td>Control</td><td colspan="4">Active</td></tr>
<tr><td>Design</td><td colspan="4">Single Group</td></tr>
<tr><td colspan="5">Subject Population</td></tr>
<tr><td>Planned # of subject</td><td colspan="4">A total of 300 subjects will be included in the trial.</td></tr>
<tr><td>Gender</td><td colspan="4">Male and Female</td></tr>
<tr><td>Age range</td><td colspan="4">Adults (18 years old and above)</td></tr>
<tr><td>Healthy subjects or treatment condition</td><td colspan="4">Treatment condition</td></tr>
<tr><td colspan="5">Test Product, Dose, Mode of Administration</td></tr>
<tr><td>Brand name (API)</td><td>Rexulti™</td><td>Administration route</td><td colspan="2">Per Orem (PO)</td></tr>
<tr><td>Dosage form</td><td>Film-coated Tablet</td><td>Dose, regimen</td><td colspan="2">Once a day</td></tr>
<tr><td colspan="5">Criteria for Evaluation</td></tr>
<tr><td>Primary Outcome Variables</td><td colspan="4">Safety Assessment: Safety of Brexpiprazole (Rexulti™) Film-coated Tablet will be evaluated based on the reported AE's per assessment.</td></tr>
<tr><td>Secondary Outcome Variables</td><td colspan="4">Efficacy Assessment: Efficacy of Brexpiprazole (Rexulti™) Film-coated Tablet will be evaluated using the Clinical Global Impression (CGI) Scale:<br>CGI – Severity<br>- Numbers and proportions of responders (defined as patients with CGI severity (CGI-S) score of 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill patients)<br>CGI – Improvement<br>- Numbers and proportions of responders (defined as patients with CGI improvement (CGI-I) score of 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), 7 (very much worse)</td></tr>
<tr><td colspan="5">Study Duration</td></tr>
<tr><td>Treatment duration</td><td colspan="4">8 weeks</td></tr>
<tr><td colspan="5">Further Study Details</td></tr>
<tr><td colspan="5">Assessments will be done upon initiation, (Baseline visit), 4 weeks later (Visit 2), until completion of the study week 8 (Study Completion). Demographic information and vital signs will be collected.</td></tr>
</table>

# INTRODUCTION

Schizophrenia is a serious mental disorder in which people interpret reality abnormally. Schizophrenia may result in some combination of hallucinations, delusions, and extremely disordered thinking and behavior that impairs daily functioning, and can be disabling. Depression is a mood disorder that causes a persistent feeling of sadness and loss of interest. It is also called as major depressive disorder or clinical depression which affects how you feel, think and behave and can lead to a variety of emotional and physical problems.[1]

Brexpiprazole (Rexulti™) is used to treat the symptoms of schizophrenia. It is also used with an antidepressant to treat depression when symptoms cannot be controlled by an antidepressant alone. Brexpiprazole (Rexulti™) is an atypical antipsychotics or second generation antipsychotics. It works by changing the activity of certain natural substances in the brain.

Brexpiprazole (Rexulti™) has partial agonist activity at serotonergic 5-$HT_{1A}$ and dopaminergic $D_2$ receptors, as well as antagonist activity at serotonergic 5-$HT_{2A}$ receptors. The drug also has activity at noradrenergic receptors. It is available as tablets in the following strengths: 0.25, 0.5, 1, 2, 3, and 4 mg under the brand name Rexulti™.

For schizophrenia, the proposed starting dose is 1 mg once daily for 4 days, increasing to 2 mg for 3 days, and then 4 mg once daily (after Day 7) based on clinical response and tolerability. For adjunctive treatment of major depressive disorder (MDD), the proposed starting dose is 0.5 or 1 mg once daily, increasing to a target dose of 2 mg once daily based on clinical response and tolerability.

The main objective of developing this post marketing surveillance is to monitor the safety and efficacy of the drug in the treatment of schizophrenia and major depressive disorder. Another objective is to enhance their chance for early recovery, eventual reintegration to the society and improved quality of life.

## Efficacy and tolerability of Brexpiprazole (Rexulti™) Film Coated Tablet

***For the treatment of Schizophrenia***

The efficacy of Brexpiprazole (Rexulti™) in the treatment of adults with schizophrenia was demonstrated in two 6-week, randomized, double-blind, placebo-controlled, fixed-dose clinical trials in patients who met DSM-IV-TR criteria for schizophrenia.

In both studies, Study 231 (hereafter “Study 3”) and Study 230 (hereafter “Study 4”), patients were randomized to Brexpiprazole (Rexulti™) 2 or 4 mg once per day or placebo. Patients in the Brexpiprazole (Rexulti™) groups initiated treatment at 1 mg once daily on Days 1 to 4. The

Brexpiprazole (Rexulti™) dosage 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 the 5 remaining weeks.

The primary efficacy endpoint of both trials was the change from baseline to Week 6 in the Positive and Negative Syndrome Scale (PANSS) total score. The PANSS is a 30-item scale that measures positive symptoms of schizophrenia (7 items), negative symptoms of schizophrenia (7 items), and general psychopathology (16 items), each rated on a scale of 1 (absent) to 7 (extreme); the total PANSS scores range from 30 (best) to 210 (worst).

In Study 3, Brexpiprazole (Rexulti™) at both 2 mg/day and 4 mg/day was superior to placebo on the PANSS total score. In Study 4, Brexpiprazole (Rexulti™) 4 mg/day was superior to placebo on the PANSS total score (Table 12). Figure 5 shows the time course of response based on the primary efficacy measure (change from baseline in PANSS total score) in Study 3.

Examination of population subgroups based on age, gender and race did not suggest differential responsiveness.

**Table 12: Summary of Efficacy Results for Studies in Schizophrenia**

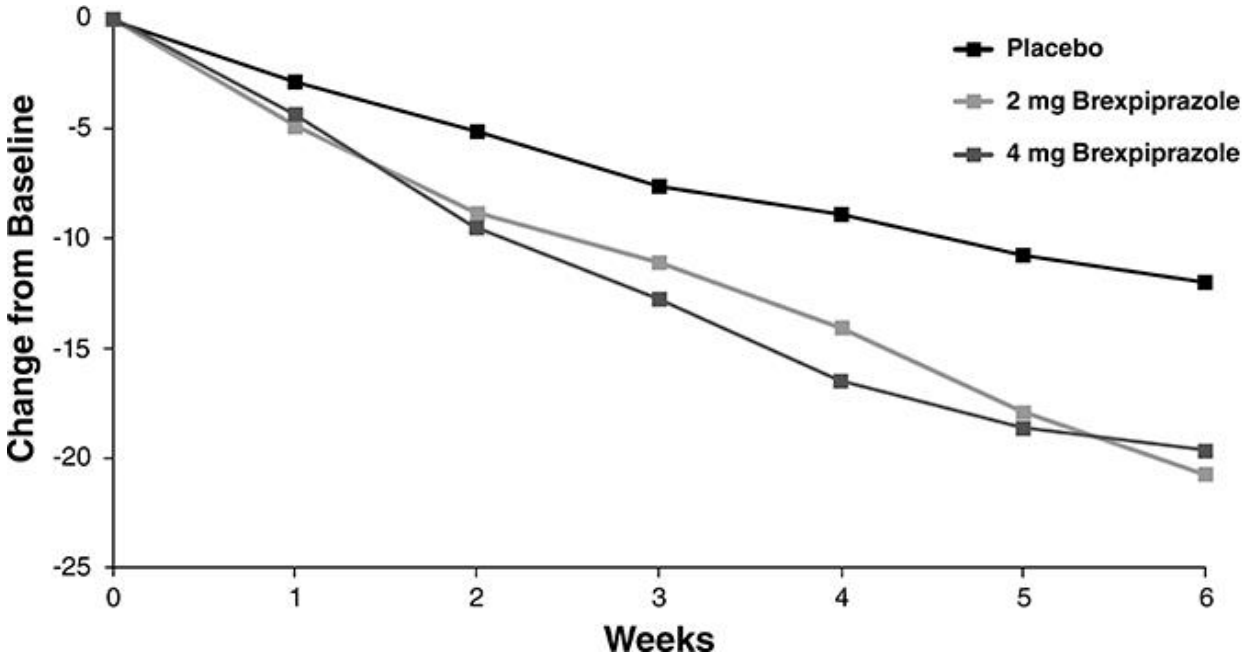
| Study | Treatment Group | N | Primary Efficacy Measure: PANSS | | |
|---|---|---|---|---|---|
| | | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
| 3 | REXULTI (2 mg/day)* | 180 | 95.9 (13.8) | -20.7 (1.5) | -8.7 (-13.1, -4.4) |
| | REXULTI (4 mg/day)* | 178 | 94.7 (12.1) | -19.7 (1.5) | -7.6 (-12.0, -3.1) |
| | Placebo | 178 | 95.7 (11.5) | -12.0 (1.6) | -- |
| 4 | REXULTI (2 mg/day) | 179 | 96.3 (12.9) | -16.6 (1.5) | -3.1 (-7.2, 1.1) |
| | REXULTI (4 mg/day)* | 181 | 95.0 (12.4) | -20.0 (1.5) | -6.5 (-10.6, -2.4) |
| | Placebo | 180 | 94.6 (12.8) | -13.5 (1.5) | -- |

SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

* Dosages statistically significantly superior to placebo.

A Difference (drug minus placebo) in least-squares mean change from baseline.

**Figure 5: Change from Baseline in PANSS Total Score by Study Visit (Week) in Patients with Schizophrenia in Study 3**



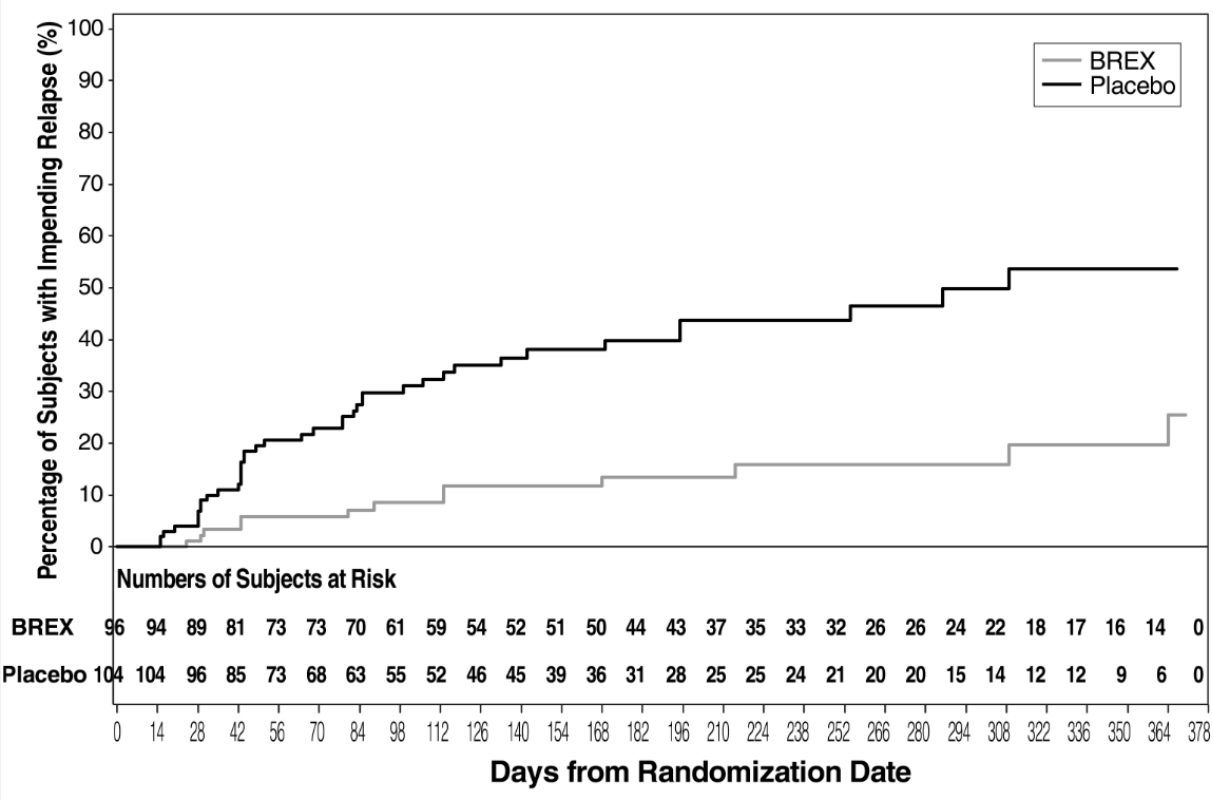

The safety and efficacy of Brexpiprazole (Rexulti™) as maintenance treatment in adults with schizophrenia aged 18 to 65 years were demonstrated in the maintenance phase of a randomized withdrawal trial (Study 331-10-232, hereafter "Study 5"). Patients were stabilized for at least 12 weeks on 1 to 4 mg/day of Brexpiprazole (Rexulti™) (N=202). They were then randomized in the double-blind treatment phase to either continue Brexpiprazole (Rexulti™) at their achieved stable dose (N=97), or to switch to placebo (N=105).

The primary endpoint in Study 5 was time from randomization to impending relapse during the double-blind phase, defined as: 1) CGI-Improvement score of ≥5 (minimally worse) and an increase to a score > 4 on PANSS conceptual disorganization, hallucinatory behavior, suspiciousness, or unusual thought content items, with either a ≥2 increase on a specific item or ≥4 point increase on the combined four PANSS items, 2) hospitalization due to worsening of psychotic symptoms, 3) current suicidal behavior, or 4) violent/aggressive behavior.

A pre-specified interim analysis demonstrated a statistically significantly longer time to relapse in patients randomized to the Brexpiprazole (Rexulti™) group compared to placebo-treated patients. The trial was subsequently terminated early because maintenance of efficacy had been demonstrated. The Kaplan-Meier curves of the cumulative proportion of patients with relapse during the double-blind treatment phase for Brexpiprazole (Rexulti™) and placebo groups are shown in Figure 6. The key secondary endpoint, the proportion of subjects who met the criteria for impending relapse, was

statistically significantly lower in Brexpiprazole (Rexulti™) treated patients compared with placebo group.

**Figure 6: Kaplan Meier Estimation of Percent Impending Relapse in Study 5**




Note: A total of 202 subjects were randomized. Among them, one placebo subject did not take investigational medicinal product and one Brexpiprazole (Rexulti™) subject did not have post-randomization efficacy evaluations. These two subjects were excluded from the efficacy analysis.

***As Adjunctive Treatment of Major Depressive Disorder***

The efficacy of Brexpiprazole (Rexulti™) in the adjunctive treatment of major depressive disorder (MDD) was evaluated in two 6-week, double-blind, placebo-controlled, fixed-dose trials of adult patients meeting DSM-IV-TR criteria for MDD, with or without symptoms of anxiety, who had an inadequate response to prior antidepressant therapy (1 to 3 courses) in the current episode and who had also demonstrated an inadequate response throughout the 8 weeks of prospective antidepressant treatment (with escitalopram, fluoxetine, paroxetine controlled-release, sertraline, duloxetine delayed release, or venlafaxine extended-release). Inadequate response during the prospective antidepressant treatment phase was defined as having persistent symptoms without substantial improvement throughout the course of treatment.

Patients in Study 228 (hereafter “Study 1”) were randomized to Brexpiprazole (Rexulti™) 2 mg once a day or placebo. Patients in Study 227 (hereafter “Study 2”) were randomized to Brexpiprazole

(Rexulti™) 1 or 3 mg once a day or placebo. For patients randomized to Brexpiprazole (Rexulti™), all patients initiated treatment at 0.5 mg once daily during Week 1. At Week 2, the Brexpiprazole (Rexulti™) dosage was increased to 1 mg in all treatment groups, and either maintained at 1 mg or increased to 2 mg or 3 mg once daily, based on treatment assignment, from Week 3 onwards. The dosages were then maintained for the 4 remaining weeks.

The primary endpoint was change from baseline to Week 6 in the Montgomery-Asberg Depression Rating Scale (MADRS), a 10-item clinician-related scale used to assess the degree of depressive symptomatology, with 0 representing no symptoms, and 60 representing worst symptoms.
At randomization, the mean MADRS total score was 27. In Studies 1 and 2, Brexpiprazole (Rexulti™) [+ antidepressant (ADT)] 2 mg/day and 3 mg/day were superior to placebo + ADT in reducing mean MADRS total scores. Results from the primary efficacy parameters for both fixed dose trials are shown below in Table 11. Figure 4 below shows the time course of response based on the primary efficacy measure (MADRS) in Study 1.

**Table 11: Summary of Efficacy Results for Studies 1 and 2 for the Adjunctive Treatment of MDD**

| Study | Treatment Group | N | Primary Efficacy Measure: MADRS | | |
|---|---|---|---|---|---|
| | | | Mean Baseline Score (SD) | LS Mean Change from Baseline (SE) | Placebo-subtracted Difference[a] (95% CI) |
| 1 | REXULTI (2 mg/day) +ADT* | 175 | 26.9 (5.7) | -8.4 (0.6) | -3.2 (-4.9, -1.5) |
| | Placebo +ADT | 178 | 27.3 (5.6) | -5.2 (0.6) | -- |
| 2 | REXULTI (1 mg/day) +ADT | 211 | 26.5 (5.6) | -7.6 (0.5) | -1.3 (-2.7, 0.1) |
| | REXULTI (3 mg/day) +ADT | 213 | 26.5 (5.3) | -8.3 (0.5) | -2.0 (-3.4, -0.5) |
| | Placebo +ADT | 203 | 26.5 (5.2) | -6.3 (0.5) | -- |

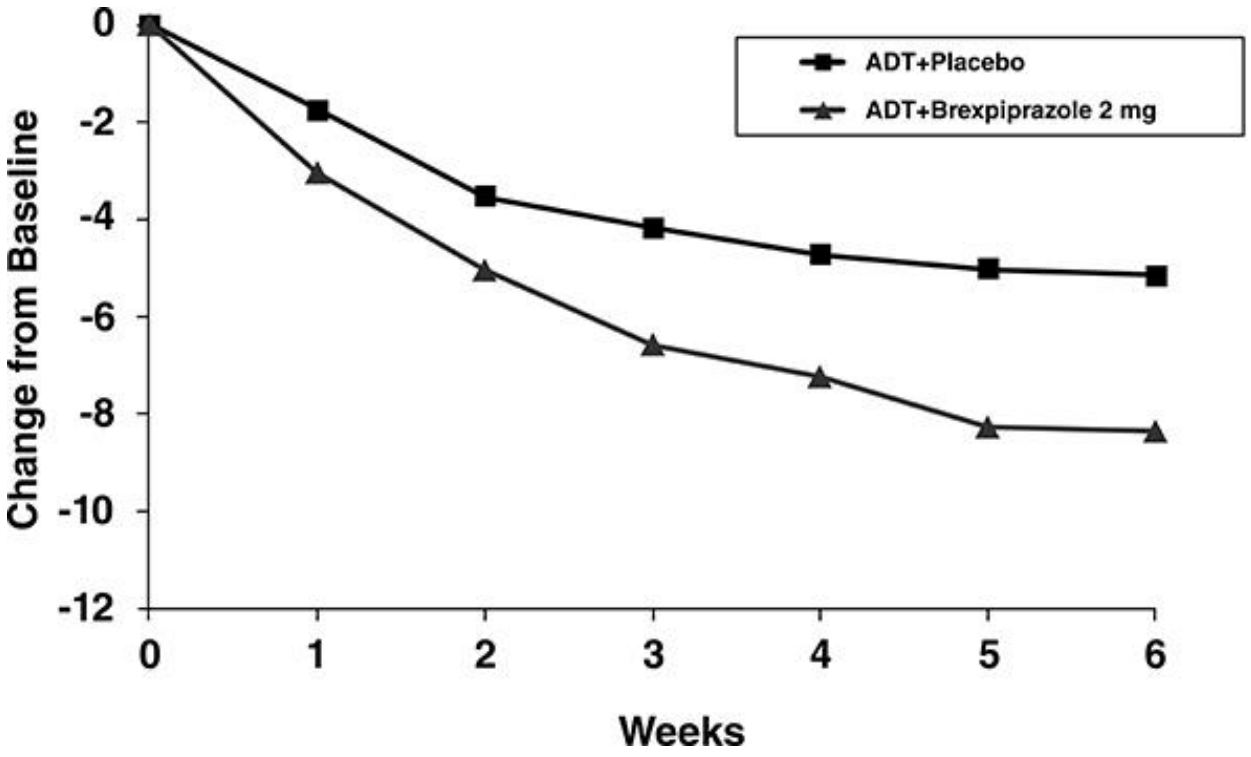
SD: standard deviation; SE: standard error; LS Mean: least-squares mean; CI: unadjusted confidence interval.

* Dosages statistically significantly superior to placebo.

[a] Difference (drug minus placebo) in least-squares mean change from baseline.

An examination of population subgroups did not suggest differential response based on age, gender, race or choice of prospective antidepressant.

**Figure 4: Change from Baseline in MADRS Total Score by Study Visit (Week) in Patients with MDD in Study 1**




**Dosage of Brexpiprazole (Rexulti™) Film-coated Tablet**

For the treatment of schizophrenia, the recommended starting dosage for Brexpiprazole (Rexulti™) is 1 mg once daily on Days 1 to 4, taken orally with or without food. The recommended target Brexpiprazole (Rexulti™) dosage is 2 mg to 4 mg once daily. Titrate to 2 mg once daily on Day 5 through Day 7, then to 4 mg on Day 8 based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 4 mg.

The recommended starting dosage for Brexpiprazole (Rexulti™) as adjunctive therapy for MDD is 0.5 mg or 1 mg once daily, taken orally with or without food. Titrate to 1 mg once daily, then up to the target dosage of 2 mg once daily. Dosage increases should occur at weekly intervals based on the patient's clinical response and tolerability. The maximum recommended daily dosage is 3 mg. It must be periodically reassess to determine the continued need and appropriate dosage for treatment.

For patients with moderate to severe hepatic impairment (Child-Pugh score ≥7), the maximum recommended dosage is 2 mg once daily for patients with MDD, and 3 mg once daily for patients with schizophrenia.

For patients with moderate, severe or end-stage renal impairment (creatinine clearance CLcr<60 mL/minute), the maximum recommended dosage is 2 mg once daily for patients with MDD and 3 mg once daily for patients with schizophrenia.

Dosage adjustments are recommended in patients who are known cytochrome P450 (CYP) 2D6 poor metabolizers and in patients taking concomitant CYP3A4 inhibitors or CYP2D6 inhibitors or strong CYP3A4 inducers. If the coadministered drug is discontinued, adjust the Brexpiprazole (Rexulti™) dosage to its original level. If the coadministered CYP3A4 inducer is discontinued, reduce the Brexpiprazole (Rexulti™) dosage to the original level over 1 to 2 weeks.

## Pharmacology of Brexpiprazole (Rexulti™) Film-coated Tablet

The mechanism of action of Brexpiprazole (Rexulti™) in the treatment of schizophrenia or adjuctive therapy of MDD is unknown. However, the efficacy of Brexpiprazole (Rexulti™) may be mediated through a combination of partial agonist activity at serotonin 5-$HT_{1A}$ and dopamine $D_2$ receptors, and antagonist activity at serotonin 5-$HT_{2A}$ receptors.

Brexpiprazole (Rexulti™) has affinity (expressed as $K_i$) for multiple monoaminergic receptors including serotonin 5-$HT_{1A}$ (0.12 nM), 5-$HT_{2A}$ (0.47 nM), 5-$HT_{2B}$ (1.9 nM), 5-$HT_7$ (3.7 nM), dopamine $D_2$ (0.30 nM), $D_3$ (1.1 nM), and noradrenergic $\alpha_{1A}$ (3.8 nM), $\alpha_{1B}$ (0.17 nM), $\alpha_{1D}$ (2.6 nM), and $\alpha_{2C}$ (0.59 nM) receptors. Brexpiprazole (Rexulti™) acts as a partial agonist at the 5-$HT_{1A}$, $D_2$, and $D_3$ receptors and as an antagonist at 5-$HT_{2A}$, 5-$HT_{2B}$, 5-$HT_7$, $\alpha_{1A}$, $\alpha_{1B}$, $\alpha_{1D}$, and $\alpha_{2C}$ receptors. Brexpiprazole (Rexulti™) also exhibits affinity for histamine $H_1$ receptor (19 nM) and for muscarinic $M_1$ receptor (67% inhibition at 10 μM).

### Cardiac Electrophysiology

At 3-times the maximum recommended human dose (MRHD) for the treatment of schizophrenia and 4-times the MRHD for adjunctive therapy to antidepressants for the treatment of MDD, Brexpiprazole (Rexulti™) does not prolong the QTc interval to any clinically relevant extent.

Absorption

After a single dose administration of Brexpiprazole (Rexulti™) tablets, the peak plasma Brexpiprazole (Rexulti™) concentrations occurred within 4 hours after administration; and the absolute oral bioavailability was 95%. Brexpiprazole (Rexulti™) steady-state concentrations were attained within 10-12 days of dosing. Brexpiprazole (Rexulti™) can be administered with or without food. Administration of a 4 mg Brexpiprazole (Rexulti™) tablet with a standard high fat meal did not significantly affect the maximum concentration ($C_{max}$) or Area under the curve (AUC) of Brexpiprazole (Rexulti™). After single and multiple once daily dose administration, Brexpiprazole (Rexulti™) exposure ($C_{max}$ and AUC) increased in proportion to the dose administered. *In vitro*

studies of Brexpiprazole (Rexulti™) did not indicate that Brexpiprazole (Rexulti™) is a substrate of efflux transporters such as multidrug resistance MDR1 (P-gp) and breast cancer resistance protein (BCRP).

Distribution

The volume of distribution of Brexpiprazole (Rexulti™) following intravenous administration is high (1.56±0.42 L/kg), indicating extravascular distribution. Brexpiprazole (Rexulti™) is highly protein bound in plasma (greater than 99%) to serum albumin and α1-acid glycoprotein, and its protein binding is not affected by renal or hepatic impairment. Based on results of *in vitro* studies, Brexpiprazole (Rexulti™) protein binding is not affected by warfarin, diazepam, or digitoxin.

Elimination

Metabolism

Based on *in vitro* metabolism studies of Brexpiprazole (Rexulti™) using recombinant human cytochrome P450 (CYP1A1, 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4), the metabolism of Brexpiprazole (Rexulti™) was shown to be mainly mediated by CYP3A4 and CYP2D6. *In vivo* Brexpiprazole (Rexulti™) is metabolized primarily by CYP3A4 and CYP2D6 enzymes. After single- and multiple-dose administrations, Brexpiprazole (Rexulti™) and its major metabolite, DM-3411, were the predominant drug moieties in the systemic circulation. At steady-state, DM-3411 represented 23% to 48% of Brexpiprazole (Rexulti™) exposure (AUC) in plasma. DM-3411 is considered not to contribute to the therapeutic effects of Brexpiprazole (Rexulti™). Based on *in vitro* data, Brexpiprazole (Rexulti™) showed little to no inhibition of CYP450 isozymes.

Excretion

Following a single oral dose of [$^{14}$C]-labeled Brexpiprazole (Rexulti™), approximately 25% and 46% of the administered radioactivity was recovered in the urine and feces, respectively. Less than 1% of unchanged Brexpiprazole (Rexulti™) was excreted in the urine and approximately 14% of the oral dose was recovered unchanged in the feces. Apparent oral clearance of a Brexpiprazole (Rexulti™) oral tablet after once daily administration is 19.8 (±11.4) mL/h/kg. After multiple once daily administration of Brexpiprazole (Rexulti™), the terminal elimination half-lives of Brexpiprazole (Rexulti™) and its major metabolite, DM-3411, were 91 hours and 86 hours, respectively.

## 1. OBJECTIVE

The objective of this post marketing surveillance is to further gather local data on the safety and efficacy of Brexpiprazole (Rexulti™) Film-coated Tablet in the treatment of schizophrenia and adjunctive therapy of MDD.

## 2. METHODS

### 2.1. DESIGN OF THE PMS

This is a post marketing surveillance of 8 weeks duration, on 300 male or female patients diagnosed to have schizophrenia and MDD in the Philippines.

### 2.2. PROCEDURES

Based on his clinical decision, the attending physician will enroll patients with schizophrenia and MDD to the program. The attending physician will explain to the patient or his legal guardian the purpose of the PMS and will obtain the patient or legal guardian's consent that Brexpiprazole (Rexulti™) Film-coated Tablet will be administered.

Data on the safety aspects of Brexpiprazole (Rexulti™) Film-coated Tablet will be collected in terms of adverse events. Efficacy will be measured using the Clinical Global Impression (CGI) Scale:

*CGI-Severity*

- Numbers and proportions of responders (defined as patients with CGI severity (CGI-S) score of 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill patients)

*CGI-Improvement*

- Numbers and proportions of responders (defined as patients with CGI improvement (CGI-I) score of 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), 7 (very much worse) after the first and last Brexpiprazole (Rexulti™) Film-coated Tablet dose. Assessments will be done upon initiation, (Baseline visit), and 4 weeks later (Visit 2), until completion of the study week 8 (Study completion). Demographic information and vital signs will be collected.

## 3. MANAGEMENT AND REPORTING OF SAFETY INFORMATION

### 3.1. DEFINITION OF TERMS

| | |
|---|---|
| Safety information | Information from any source containing one or more of the following concepts:<br>▪ Adverse Events<br>▪ Special Situations<br>▪ Off label use<br>▪ Device Vigilance Information |
| Adverse Event (AE) | Any untoward medicinal occurrence in a patient or |

| | |
|---|---|
| | clinical study subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment (see Annex IV, ICH-E2A guideline).<br>An adverse event can therefore be any unfavorable and unintended sign (e.g. abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not it is considered causally related to the medicinal product. |
| Special Situations | Situations related to the use of an Otsuka product which may or may not be associated with an adverse event:<br>- Maternal (pregnancy and breastfeeding) or paternal (via semen) exposure;<br>- Exposure during breastfeeding;<br>- Overdose/Incorrect dosage, misuse, abuse (e.g. patient sharing products);<br>- Medication errors (e.g. patient took wrong dose);<br>- Lack of therapeutic efficacy (e.g. the product doesn't work);<br>- Occupational exposure (e.g.: nurse administering the product is exposed);<br>- Cases of suspected transmission of infectious agents;<br>- Use of suspected or confirmed falsified product(s) or quality defect of the product(s);<br>- Withdrawal reactions;<br>- Accidental exposure (e.g.: child takes parent's product);<br>- Drug-drug/drug-food interactions;<br>- Unintentional use of product in a non-approved population (e.g.: pediatric or geriatric population);<br>- Disease progression/exacerbation of existing disease |
| Off-label Use | Refers to situations where a product is intentionally used for a medical purpose not in accordance with the authorized product information. Off-label use also includes the intentional use in non-authorized population categories not indicated in the label |
| Device Vigilance Information | is a death or serious injury that was or may have been attributed to a medical device component of an Otsuka product, or that a medical device component was or may have been a factor in a death or serious injury, including events occurring as a result of:<br>- Failure,<br>- Malfunction,<br>- Improper or inadequate design,<br>- Manufacture,<br>- Labeling or instructions for use, or |

| | |
|---|---|
| | - User error |
| Serious Adverse Event (SAE) | Any adverse drug experience/event occurring at any dose which<br>・ results in death,<br>・ is life-threatening,<br>・ requires inpatient hospitalization or prolonged of existing hospitalization<br>・ results in persistent or significant disability or incapacity,<br>・ is a congenital anomaly/birth defect,<br>・ is medically significant<br><br>Life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe.<br><br>A medically significant event is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based on appropriate medical and scientific judgment, may jeopardize the patient/subject or may require intervention (e.g. medical, surgical) to prevent one of the other outcomes listed in the definition above) might be considered serious as well, examples of such include, but not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias; or convulsions that do not result in hospitalization; or development of drug dependency of drug abuse. |
| Non-Serious Adverse Event | All AEs that do not meet the definition of a serious Adverse Event (SAE) are considered non-serious AEs. |
| Unexpected Adverse Event/Adverse Drug Reaction | An AE/ADR, the nature, severity, or outcome of which is not consistent with the current Investigator's Brochure (IB) or the approved labeling of the (I)MP. Class-related reactions which are mentioned in the IB, or the approved labeling but which are not specifically described as occurring under the (I)MP are also considered 'unexpected'.<br>For the determination of expectedness, an AE/ADR is considered unexpected only if it is not mentioned in the Adverse Reactions or Undesirable Effects section of the CCDS/SmPC (for MPs) or if it is not clearly described as an expected AE/ADR in section 6 of the IB (for IMPs). Exceptions are reactions related to overdose (considered unexpected if not mentioned in section Overdose) and/or interactions (considered unexpected if not mentioned in section Interaction).<br>The determination of unexpectedness is used for the purpose of expedited reporting and periodic reporting. |
| Date of First Receipt (DFR) | The date when an Otsuka colleague, its Alliance Company/Collaborating Company or External Service |

| | |
|---|---|
| | Provider, any third party providing services (e.g. a CRO), to or on behalf of Otsuka first becomes aware of a case/event. Email and fax headers usually record the date of receipt of communication, and it should be considered as the date of first receipt (calendar day 0). |

## 3.2. COLLECTION AND REPORTING OF SAFETY INFORMATION

All safety information that occur *during* (defined as occurring after patient enrollment until the study completion, or within 30 days of the final dose of Brexpiprazole (Rexulti™) Film-coated Tablet) the study will be documented by the physician. At each visit, the patient will be asked about any symptoms or unexpected occurrences since the last visit. All safety information, regardless of severity or relationship to the Brexpiprazole (Rexulti™) Film-coated Tablet will be reported by the physician to the OPPI using the AE Form (Otsuka Global PV Safety Information Reporting Form in Annex III) immediately or within 24 hours.

## 3.3. RECONCILIATION OF SAFETY INFORMATION

Reconciliation of Adverse Event between the Safety Database and the study database (or safety database if study database is not obtainable) will be performed annually every 10th business day of December and at the end of the study.

## 3.4. SAFETY CONTACT INFORMATION

| | | |
|---|---|---|
| Otsuka (Philippines) Pharmaceutical, Inc. | 3F King's Court II Building, 2129 Chino Roces Ave., corner Dela Rosa St., 1231 Makati City, Philippines | Tel: (632) 888 6774<br>Fax: (632) 811.2279<br>Email: oppi-pv@otsuka.com.ph |
| Marinette O. Magbitang | Local Safety Manager Pharmacovigilance/Clinical Research Associate | |
| Fatima Chelsea P. Perey | Clinical Research Associate/ Post Marketing Surveillance Lead | |
| Rodney D. Dalisay, MD, DPBP, FPPA, FPCPsych | Medical Director | |

# 4. EVALUATION CRITERIA

The Clinical Global Impression Scale (see *Annex I*) will be used to provide a rating of illness severity, improvement and response to treatment.

### 4.1. SAFETY ASSESSMENT

Safety of Brexpiprazole (Rexulti™) Film-coated Tablet will be evaluated based on the reported AEs per assessment.

### 4.2. EFFICACY ASSESSMENT

Efficacy of Brexpiprazole (Rexulti™) Film-coated Tablet will be evaluated using:

1. Clinical Global Impression-Severity (CGI-S) Scale:
   - Numbers and proportions of responders (defined as patients with CGI severity (CGI-S) score of 1 (normal, not at all ill), 2 (borderline mentally ill), 3 (mildly ill), 4 (moderately ill), 5 (markedly ill), 6 (severely ill), 7 (among the most extremely ill patients)

2. Efficacy will be evaluated using Clinical Global Impression-Improvement (CGI-I) Scale:
   - Numbers and proportions of responders (defined as patients with CGI improvement (CGI-I) score of 1 (very much improved), 2 (much improved), 3 (minimally improved), 4 (no change), 5 (minimally worse), 6 (much worse), 7 (very much worse)

## 5. STATISTICAL ANALYSIS

Analysis of data will be limited to descriptive statistics only. Safety will be evaluated based on the reported AEs per assessment. Efficacy will be evaluated using the Clinical Global Impression-Severity (CGI-S) and Clinical Global Impression-Improvement (CGI-I) Scales to monitor severity and improvement from mean baseline score (before initial dose) up to the last assessment (Week 8 – Study Completion).

## 6. PMS MILESTONES

All timelines and milestones written below might be subject to change based on the movement and situation during the study. End of data collection shall not be more than 1 week after the date of the last patient last visit (LPLV). The final Clinical Study Report shall be completed within one year of the end of data collection.

| ACTIVITY | ESTIMATED TIMELINE |
|---|---|
| GSL Approval | April 2019 |
| GPORT Approval | June 2019 |
| PFDA Approval | August 2019 |
| Start of Study | November 2019 |
| First Patient Visit | December 2019 |
| Start of Data Collection | February 2020 |
| Interim Statistical Report | Q2 2022 |
| Last Patient Visit | Q1 2023 |
| End of Data Collection | Q1 2023 |
| Final Clinical Study Report | Q1 2024 |

## 7. AMENDMENTS AND UPDATES

All significant changes and updates to this protocol shall be documented in *Annex V*.

## 8. HANDLING OF CASE REPORT FORMS

For instructions on filling out, editing, and transit of the CRFs, see *Annex II.*

## 9. REFERENCES


1. https://www.mayoclinic.org/diseases-conditions/schizophrenia/symptoms-causes/syc-20354443[1]
2. https://www.mayoclinic.org/diseases-conditions/depression/symptoms-causes/syc-20356007[1]
3. Brexpiprazole (Rexulti™) Film-coated Tablet package insert

## ANNEX I

## ASSESSMENT CRITERIA

### i. Safety

- All adverse events will be collected on Visit 1 and Study Completion. See Annex III for other safety information.

### ii. Efficacy

***Baseline visit (Day 0):***

| Clinical Global Impression - Severity of Illness | |
|---|---|
| **[1]** Normal, not at all ill | **[5]** Markedly ill |
| **[2]** Borderline mentally ill | **[6]** Severely ill |
| **[3]** Mildly ill | **[7]** Among the most extremely ill patients |
| **[4]** Moderately ill | |

***Visit 1 (after 4 weeks) and Study Completion (after 8 weeks):***

| Clinical Global Impression - Severity of Illness | |
|---|---|
| **[1]** Normal, not at all ill | **[5]** Markedly ill |
| **[2]** Borderline mentally ill | **[6]** Severely ill |
| **[3]** Mildly ill | **[7]** Among the most extremely ill patients |
| **[4]** Moderately ill | |
| **Clinical Global Impression - Improvement** | |
| **[1]**Very much improved | **[5]** Minimally worse |
| **[2]** Much improved | **[6]** Much worse |
| **[3]** Minimally improved | **[7]** Very much worse |
| **[4]** No change | |

**ANNEX II**

**GENERAL INSTRUCTIONS ON ACCOMPLISHING THE CASE REPORT FORMS**

1. Consent shall be obtained from the patient prior to enrollment in this program (see Informed consent form)
2. Data privacy is present to uphold the rights of individual and the patient involved in the study
3. Enter all required data on the CRFs specifically designed for this PMS. Each physician is ultimately responsible for ensuring that data on the CRFs are complete, accurate and legible.
4. Complete the CRFs using a black ballpoint pen. Make sure that all entries are legible.
5. Enter/write, check/tick, or encircle the appropriate response/s in the required fields. All text must be written in English using uppercase letters and Arabic numerals.
6. Dates should be entered as MM/DD/YY i.e. January 17, 2012 should be written as 01/17/12
7. Avoid using symbols and abbreviations
8. Recording missing data:
    - For fields with tick boxes, please write ND for "no data"
    - For fields with fill-out boxes, please mark the empty box with a dash
9. Making corrections:
    - Cross-out errors with a single horizontal line. Clearly enter the new information next to the error (anywhere below or above or adjacent to the crossed-out entry). Write your initials and date next to the correct entry.
    - Do not erase nor use opaque/white out correction fluids in making corrections.

**SPECIFIC INSTRUCTIONS ON ACCOMPLISHING THE CASE REPORT FORMS**

| | CRF PARTS | INSTRUCTIONS |
|---|---|---|
| **DEMOGRAPHY / SUMMARY** | CRF Number | • To be provided by the Sponsor/Company |
| | Patient Initials | • Three characters in the following order (First Name, Middle Name, Last Name)<br>o *Example:*<br>*Juan Gomez Cruz is written as JGC*<br>*Juan Gomez dela Cruz is written as "JGC"*<br>*Juan del Gomez Cruz is written as "JGC"* |
| | Date of birth | • Patient birth in MM/DD/YY format |
| | Age | • Patient age |
| | Weight | • Indicate the unit of the patient's weight (must be in kg) |
| | Height | • Indicate the unit of the patient's height (must be in cm) |
| | Sex | • Tick/check appropriate box |
| | Indication/Diagnosis | • Tick/check appropriate box |
| | Concomitant medications | • Tick/check appropriate box<br>• If yes, indicate the generic name, brand name, dose and frequency on page 2 |
| | Treatment completion | • Tick/check appropriate box |
| | Date of the baseline, visit 2 and study completion | • In MM/DD/YY format |

| | | |
|---|---|---|
| | Dose administered during baseline, visit 2 and study completion | • Indicate the dose |
| | CGI-S score before the initial dose | • To write the corresponding scale |
| | CGI-I and CGI-S score of Illness 4 weeks after initial dosing (Baseline) | • To write the corresponding scale |
| | CGI-I and CGI-S score of Illness 8 weeks after initial dosing (Baseline) | • To write the corresponding scale |
| | Discontinuation section | • Tick/check appropriate box |
| | Investigator name, signature and date | • To be signed by the Investigator/ Physician |
| **BASELINE** | Vital signs | • Weight of the patient (in kg)<br>• Patient's blood pressure (BP)<br>• Patient's heart rate (HR)<br>• Patient's respiratory rate (RR)<br>• Patient's temperature (in Celsius) |
| | Psychotropic medications | • Tick/check appropriate box |
| | CGI-S score before the initial dose | • To write the corresponding scale |
| **VISIT 2 & STUDY COMPLETION** | Adverse Events | • Tick/check appropriate box<br>• List all AE and indicate severity of event by putting a tick on the appropriate box. |
| | CGI-I and CGI-S score of illness 8 weeks after initial dosing (Baseline) | • Please encircle the corresponding score |

## HANDLING AND CARE OF THE COMPLETED CRFs

Once the patient has completed the PMS or has been prematurely discontinued from the PMS, the physician can submit the CRFs of these patients to the PSR. The PSR checks the CRF for completeness and legibility and submits the CRF to Medical Affairs (MA). MA collates the CRF and submits clear copies to Data Management for encoding and analysis.

To minimize delay in encoding and analysis, the PSR should carefully check the completed CRF before submitting MA. Queries from the Data Management should be forwarded to MA who will check the CRFs. All the copies of the CRFs will be collected back in the event that an entry on the CRF needs to be edited.

# ANNEX III

# STUDY RESEARCH SAFETY REPORTING FORM

**Otsuka Global**
**Study Research Safety Reporting Form**

**ADVERSE EVENTS/SAFETY INFORMATION MUST BE REPORTED WITHIN 24 HOURS OF AWARENESS DATE**
**LOCAL PV REPRESENTATIVE CONTACT INFORMATION:**
**Phone: Fax: Email:**

| | | |
|---|---|---|
| **Date of Report (DDMmmYYYY):** | **Date of First Awareness (DDMmmYYYY):** | |
| **A. GSL Study ID:** | | |
| **B. Reporter Information** (Applicable data protection laws shall be followed)**:** | | |
| Name: | Relationship to Patient: | |
| Degree: ☐ MD ☐ DO ☐ Pharm.D ☐ R.Ph ☐ Ph.D ☐ R.N ☐ PA ☐ Other: *(Check one as applicable)* | | |
| Institution/Office: | | |
| Mailing Address: | | Country: |
| City: | State: | Zip Code: |
| Telephone Number (including Area Code): | | Fax Number (optional): |
| Reporter consents to be contacted for follow-up information: ☐ Yes ☐ No | | |
| **C. Contact information of the Prescriber:** (In case reporter is not the prescribing physician) (Applicable data protection laws shall be followed) | | |
| Prescriber's Name or Initials: | | |
| Institution/Office: | | |
| Mailing Address: | | Country: |
| City: | State: | Zip Code: |
| Telephone Number (including Area Code): | | Fax Number (optional): |
| **D. Patient Information:** (Applicable data protection laws shall be followed) | | |
| Patient's Name or Initials: | Patient's Unique ID#: | Age (Age Group) or date of birth: |
| Gender: ☐ Male ☐ Female | | |
| Mailing Address: | | Country: |
| City: | State: | Zip Code: |
| Telephone Number (including Area Code): | | |
| **E. Product information (For multiple products, please complete the supplemental form):** | | |
| Product Name: | Lot/Batch/Serial#: | |
| Indication: | | |
| Start Date: | Stop date: ☐ Ongoing: | |
| Route of administration: | Dosing details: | |
| **F. Safety Information details (For multiple events, please complete the supplemental form):** | | |
| Reported Safety Information: | | |
| Start date: | Stop date: | |
| **Seriousness provided by the reporter** (select all that applies) ☐ Fatal ☐ Life-threatening ☐ Hospitalization or its prolongation ☐ Persistent or significant disability or incapacity ☐ Congenital anomaly or birth defect ☐ Serious ☐ Not serious **Outcome provided by the reporter**: ☐ Fatal ☐ Resolved with sequelae ☐ Resolved ☐ Not resolved ☐ Resolving ☐ Unknown | | |
| **Adverse Event/Safety Information description as reported:** | | |
| Research/Study/Program Lead's or Designee's Name: | Phone Number/Extension: | |

**Reporting time frame for safety information**

All safety information should be reported by the physician to Otsuka (Philippines) Pharmaceutical, Inc. (OPPI) immediately or not later than 24 hours.

**Safety Contact Information**

| | | |
|---|---|---|
| Otsuka (Philippines) Pharmaceutical, Inc. | 3F King's Court II Building, 2129 Chino Roces Ave., corner Dela Rosa St., 1231 Makati City | Tel: (632) 8888 6774<br>Fax: (632) 8811.2279<br>Email: oppi-pv@otsuka.com.ph |
| Marinette O. Magbitang | Local Safety Manager Pharmacovigilance/Clinical Research Associate | |
| Rodney D. Dalisay, MD, DPBP, FPPA, FPCPsych | Medical Director | |
| Fatima Chelsea P. Perey | Clinical Research Associate/ Post Marketing Surveillance Lead | |

**Annex IV**

**PROTOCOL AMENDMENT HISTORY**

| Old Version Number | New Version Number | Description of Amendment | Justification | Reference Section | Date of Amendment |
|---|---|---|---|---|---|
| 1.0 | 1.1 | Update of Safety Reporting Form | To follow Global SOP (PV-3000-TMP-003) | PV-3000-TMP-003 | July 3, 2019 |
| 1.1 | 1.2 | Doctor's evaluation of patients improvement | Specified evaluation of doctors for patients with schizophrenia | Case Report Form: Assessment after 4 weeks, Visit 2 (page 4) and Assessment after 8 weeks, Study completion (page 5) | March 8, 2020 |
| 1.2 | 1.3 | Update of Safety Reporting Form<br><br>Update in Definition of Terms | To follow Global SOP (PV-3000-TMP-003 v2.0)<br><br>To follow Global SOP | PV-3000-TMP-003 v2.0<br><br>Global SOP | August 6, 2020 |
| 1.3 | 1.4 | Update in Reconciliation of Safety Information | To specify the frequency of reconciliation within the scope of CO-7000-WP-001 | CO-7000-WP-001 | November 12, 2020 |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |
| | | | | | |