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APPLICATION NUMBER:

210655Orig1s000

CLINICAL REVIEW(S)

Clinical Review

Michael C. Davis, MD, PhD and Qi Chen, MD, MPH (Safety Review)

NDA 210655

Perseris (RBP-7000 risperidone-ATRIGEL)

CLINICAL REVIEW

Application Type	Initial 505(b)(2) New Drug Application (NDA)
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Review Completion Date	June 22, 2018
Established/Proper Name	RBP-7000 (risperidone-ATRIGEL)
(Proposed) Trade Name	Perseris
Applicant	Indivior
Dosage Form(s)	Injectable Suspension
Applicant Proposed Dosing Regimen(s)	90 mg or 120 mg subcutaneous injection monthly
Applicant Proposed Indication(s)/Population(s)	Schizophrenia/Adults
Recommendation on Regulatory Action	Approve
Recommended Indication(s)/Population(s) (if applicable)	N/A

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Glossary

AC	advisory committee
AE	adverse event
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
C-CASA	Columbia Classification Algorithm of Suicide Assessment
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia-Suicide Severity Rating Scale
DMC	data monitoring committee
DMEPA	Division of Medication Error Prevention and Analysis
ECG	electrocardiogram
eCTD	electronic common technical document
EPS	extrapyramidal symptoms
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICD	Informed Consent Document
ICH	International Council for Harmonization
IND	Investigational New Drug Application
ISE	integrated summary of effectiveness
ISS	integrated summary of safety

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ITT	intent to treat
IWRS	interactive web-response system
LAI	long acting injectable
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
MMRM	Mixed-Effect Model Repeated Measure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PANSS	Positive and Negative Syndrome Scale
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information or package insert or principal investigator
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PO	per os (by mouth)
PP	per protocol
PPI	patient package insert
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneous
SGE	special government employee
SOC	standard of care
TEAE	treatment emergent adverse event

1. Executive Summary

1.1. Product Introduction

RBP-7000 (proposed trade name: Perseris; used interchangeably in this review) is a combination product (drug/device) supplied as a kit containing one syringe with risperidone powder, one syringe with the ATRIGEL delivery system, and one 18-gauge 5/8-inch sterile safety needle. RBP-7000 single-use kits will be available in 90 mg or 120 mg versions. The Applicant proposes that RBP-7000 should be indicated for the treatment of schizophrenia. The proposed dosing regimen is 90 mg or 120 mg once monthly, administered as a subcutaneous injection to the abdomen by a healthcare professional.

This 505(b)(2) application relies on the FDA's previous findings of safety and effectiveness for risperidone in the treatment of schizophrenia (Risperdal, Janssen Pharmaceuticals, NDA 20272). Risperidone is an atypical antipsychotic that was approved by the FDA in 1993 for the treatment of schizophrenia. Additional indications specified in current Risperdal prescribing information include: treatment of schizophrenia in adolescents (age 13 to 17 years), treatment of irritability associated with autistic disorder in children and adolescents (age 5 to (b) (4) years), and treatment of acute manic or mixed episodes associated with bipolar I disorder in adults (as monotherapy in adults and children and adolescents age 10 to 17 years, and as an adjunct to lithium or valproate in adults).

1.2. Conclusions on the Substantial Evidence of Effectiveness

Substantial evidence of effectiveness is provided by the Agency's previous finding of effectiveness for Risperdal oral tablets (NDA 20272) and the establishment of a pharmacokinetic bridge between oral risperidone and RBP-7000; based on average daily plasma concentrations, RBP-7000 90 mg SC monthly approximates risperidone 3 mg PO daily and 120 mg SC monthly approximates 4 mg PO daily. In addition, the Applicant conducted an adequate and well-controlled trial (Study RB-US-09-0010) that demonstrated efficacy of both RBP-7000 doses by achieving positive results on the primary and key secondary endpoints. Although the magnitudes of change on the primary efficacy measure should not be directly compared between Study RB-US-09-0010 and previous studies of oral risperidone (due to differences in trial design), they appear to be generally similar. Therefore, from a clinical perspective, the Applicant has provided substantial evidence of effectiveness as required by law to support product approval.

1.3. Benefit-Risk Assessment

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Benefit-Risk Integrated Assessment

RBP-7000 (proposed trade name: Perseris) is a combination product (drug/device) supplied as a kit containing one syringe with risperidone powder, one syringe with the ATRIGEL delivery system, and one 18-gauge 5/8-inch sterile safety needle. RBP-7000 single-use kits will be available in 90 mg or 120 mg versions for monthly administration. RBP-7000 is intended to be administered to adults with schizophrenia, and its anticipated benefit to the target population is a reduction in symptoms of schizophrenia, such as delusions and hallucinations. Based on the clinical review and input from the multidisciplinary review team, I recommend that RBP-7000 be approved for marketing.

Schizophrenia is a serious and disabling mental illness characterized by chronic or recurrent psychosis and frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., impaired attention, executive function, working memory, and social cognition). Symptomatic exacerbations of schizophrenia, which are associated with nonadherence to antipsychotic medications, can severely impact patients' functioning and necessitate psychiatric hospitalization. Antipsychotic medications are the first-line pharmacotherapy for schizophrenia and are recommended to be used for the treatment of acute schizophrenia exacerbations as well as on a continuing basis to reduce the risk of relapse. Long-acting injectable antipsychotics maintain therapeutic blood levels of antipsychotics for extended periods and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral antipsychotics.

This New Drug Application relies on the Agency's previous finding of effectiveness for risperidone oral tablets (Risperdal, NDA 20272) and the establishment of a pharmacokinetic bridge between oral risperidone and RBP-7000. In addition, efficacy of RBP-7000 was demonstrated in a Phase 3 randomized controlled inpatient trial (RB-US-09-0010), conducted with 354 subjects who were experiencing an acute exacerbation of schizophrenia. RBP-7000 may provide an incremental practical benefit over the currently-available risperidone long-acting injection product, because it requires less-frequent injections (monthly vs. every two weeks) and requires no overlap period with daily oral antipsychotic treatment during initiation of therapy.

The safety profile of RBP-7000 is generally like other formulations of risperidone; it is associated with increased weight, increased prolactin, sedation/somnolence, and extrapyramidal symptoms. A minority of subjects experienced transient injection site pain and/or erythema or inflammation/swelling at the injection site. Although it did not occur in the development program, there is a theoretical safety risk from improper product administration (i.e., intravenous administration), because RBP-7000 forms a solid mass upon contact with body fluids. It is expected that this risk will be adequately mitigated by product labeling and administration by trained healthcare professionals.

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Overall, I believe that RBP-7000 has a favorable benefit-risk profile to support marketing approval. The serious and disabling condition of schizophrenia suggests that it is reasonable to accept some increased risks from treatment when compared to less-serious conditions. Because the doses of RBP-7000 approximate oral risperidone doses of 3 or 4 mg daily and a significant proportion of schizophrenia patients require higher daily doses, we recommend that the Applicant, as a postmarketing commitment, develop a dose of RBP-7000 to approximate risperidone 6 mg by mouth daily.

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Schizophrenia is a serious mental illness characterized by chronic or recurrent psychosis (e.g., delusions, hallucinations, and thought disorganization). • Schizophrenia is also frequently associated with negative symptoms (e.g., social withdrawal, avolition, blunted affect) and cognitive deficits (e.g., attention, executive function, working memory, and social cognition). • Individuals with schizophrenia experience significant impairments in social and occupational functioning and, on average, have a life expectancy around 15 years less than individuals without schizophrenia. • Approximately 50% of individuals with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after their last episode; most relapses occur in the context of medication nonadherence. • The worldwide prevalence of schizophrenia is approximately 0.5 to 1%, and schizophrenia is one of the leading causes of years lost due to disability worldwide.	Schizophrenia is a serious condition, associated with significant disability and a shortened life expectancy. Evidence informing the analysis of the condition of schizophrenia is from published literature and psychiatric textbooks, as well as clinical experience with this population.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	- Antipsychotics are the first-line medication therapy for schizophrenia; current practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued indefinitely to reduce the risk of relapse. - Antipsychotics have been shown to be effective for reducing positive symptoms of schizophrenia (e.g., delusions, hallucinations, disorganized thinking and behavior). Negative symptoms and cognitive deficits of schizophrenia generally show little to no improvement from antipsychotic treatment. - Antipsychotics are broadly categorized as first-generation/typical antipsychotics (e.g., chlorpromazine, fluphenazine, haloperidol, etc.) and second-generation/atypical antipsychotics (e.g., clozapine, risperidone, olanzapine, quetiapine, and aripiprazole). In general, first-generation antipsychotics have a higher risk for causing extrapyramidal side effects than second-generation antipsychotics. - Adverse reactions from antipsychotics vary between drugs but may include weight gain, extrapyramidal side effects, increased prolactin, sedation, and QT prolongation. - Nonadherence to daily oral antipsychotic treatment is very common in individuals with schizophrenia. The consequences of medication nonadherence can include acute psychosis exacerbation, occupational and social problems, danger to self or others, and psychiatric hospitalization. - Long-acting injectable antipsychotic medications maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients	Antipsychotics reduce the severity of positive symptoms of schizophrenia and the risk of psychosis exacerbations. Nonadherence to daily oral antipsychotics is common in individuals with schizophrenia and can lead to psychiatric hospitalization and other adverse outcomes. Long-acting injectable antipsychotics may reduce the risk of schizophrenia exacerbations in patients who are nonadherent to oral antipsychotics. Risperidone is currently available in an intramuscular injection formulation (Risperdal Consta, NDA 21346) that is administered every 14 days. Risperdal Consta requires the continued administration of daily oral antipsychotic for three weeks after its initial injection. Long-acting injectable formulations of risperidone's active metabolite paliperidone (i.e., Invega Sustenna and Invega Trinza) require two weekly loading doses before proceeding to maintenance dosing. Overall, this patient population's needs are being only partially met by currently available therapies. Most patients do not achieve full

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	who are nonadherent to oral antipsychotics. • In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and side effects of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). • When integrated with pharmacotherapy, psychosocial interventions have been shown to improve the course of schizophrenia. These interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy.	remission of schizophrenia symptoms, and current medications are generally ineffective for negative symptoms and cognitive deficits of schizophrenia. Additional treatment options are needed that target unmet clinical needs and promote improved adherence.
Benefit	• In Study RB-US-09-0010, both doses of RBP-7000 (90 mg and 120 mg) were associated with statistically significant improvements, when compared to placebo, on the primary efficacy endpoint (change from baseline on PANSS total score at Day 57). The least square mean differences, when compared to placebo, were -6.50 and -10.24 points for the 90-mg and 120-mg groups, respectively. Analysis of the response distribution showed that a smaller percentage of subjects who received RBP-7000 had no change or worsening PANSS scores, and a larger percentage of subjects had improvements of 20 to 60 points, as compared to placebo. • In Study RB-US-09-0010, both doses of RBP-7000 (90 mg and 120 mg) were associated with statistically significant improvements, when compared to placebo, on the key secondary endpoint (change from baseline on CGI-S score at Day 57). The least square mean differences, when compared to placebo, were -0.35 and -0.58 points for the 90-mg	The Applicant has demonstrated RBP-7000 to be efficacious, as compared to placebo, on efficacy measures that are considered valid for the schizophrenia indication. The Phase 3 efficacy study was conducted with 354 randomized subjects who were experiencing an acute exacerbation of schizophrenia. In addition, pharmacokinetic studies demonstrated that the doses of RBP-7000 yield daily plasma concentrations of risperidone (and its active metabolite) that are equivalent to doses of oral risperidone with previously-established efficacy. Therefore, the Applicant has provided evidence that meets the standard to support marketing approval.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	and 120-mg groups, respectively. • The PANSS captures the severity of a range of psychiatric symptoms associated with schizophrenia (positive symptoms, negative symptoms, and general psychopathology) and has been used to support the approval of most antipsychotic drugs on the market. The CGI-S is also frequently used as a secondary endpoint, providing information on clinicians' global assessment of psychiatric illness severity. • Study RB-US-09-0010 demonstrated that RBP-7000 is efficacious without the need for an overlap period of daily oral antipsychotic administration or loading dose(s). • Although analyses of secondary efficacy measures assessing patient-reported quality of life, functioning, and medication satisfaction were not pre-specified in the Statistical Analysis Plan or controlled for multiple testing, their collective results suggest that study subjects may have appreciated clinical benefit from RBP-7000 and were generally satisfied with the treatment. • Analyses of subpopulations (i.e., age, sex, race, ethnicity, body mass index, baseline schizophrenia severity and duration of illness) did not raise generalizability concerns for the target population. Although Study RB-US-09-0010 did not include subjects over 55 years of age, there is no reason to believe RBP-7000 would be ineffective in this population.	It is anticipated that this product will fit into the therapeutic armamentarium as a long-acting injectable antipsychotic option that requires less frequent injections than the other risperidone product on the market. This fact, in addition to the lack of need for an overlap period with oral antipsychotic treatment, is anticipated to be appreciated by patients as well as caregivers. Because the RBP-7000 doses (90 mg and 120 mg subcutaneous monthly) approximate the exposure to risperidone 3 or 4 mg by mouth daily, this product will not be appropriate for individuals who require higher daily doses of risperidone to achieve clinical stability. This supports the postmarketing commitment to develop a dose of RBP-7000 that approximates risperidone 6 mg by mouth daily.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• RBP-7000 is associated with adverse reactions common to other formulations of risperidone (e.g., increased weight, increased prolactin, sedation/somnolence, and extrapyramidal symptoms), as well as musculoskeletal pain. • Although most subjects reported no pain or injection site reactions, a minority of subjects (23 to 30% in each arm of Study RB-US-13-0005) experienced transient injection site pain and/or erythema or inflammation/swelling at the injection site. Injection site tenderness with a maximum intensity of severe was reported for <1% of subjects at any time point. • Although it was not observed in the development program, there is a theoretical risk from improper product administration (i.e., intravenous administration), because RBP-7000 forms a solid mass upon contact with body fluids. This potential risk will be mitigated by labeling (Dosage and Administration, Instructions for Use, and Warnings and Precautions). The establishment of a REMS program is considered unnecessary to mitigate this risk, because RBP-7000 will be administered by healthcare professionals and there is limited risk that this antipsychotic will be self-administered by patients. • Although it did not occur in the RBP-7000 development program, we recognize the potential that providers may administer more than one dose of RBP-7000 at a time, in attempt to approximate higher daily oral doses of risperidone (e.g., 6 mg or 8 mg). Because the safety risks of administering multiple doses are unknown, product labeling will clearly instruct providers to administer no more than one dose (90 mg or 120 mg total) per month. The Applicant is also being asked to fulfill	The assessment of safety findings from the RBP-7000 development program did not reveal any unexpected safety signals when compared to other formulations of risperidone. The injection site reactions (pain, erythema, inflammation/swelling) were transient and tended to decrease with subsequent injections. Potential risks related to administration of this product will be described in labeling. There were no safety issues that would preclude approval of this NDA.

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Dimension	Evidence and Uncertainties	Conclusions and Reasons
	a postmarketing commitment to develop a (b) (4) dose of RBP-7000 that would be appropriate for patients requiring 6 mg risperidone by mouth daily.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that was submitted as part of the application include:	Section where discussed, if applicable
	X Clinical outcome assessment (COA) data, such as	
	X Patient reported outcome (PRO)	6.1.1, 6.1.2
	☐ Observer reported outcome (ObsRO)	
	X Clinician reported outcome (ClinRO)	6.1.1, 6.1.2
	☐ Performance outcome (PerfO)	
	☐ Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Natural history studies	
	☐ Patient preference studies (e.g., submitted studies or scientific publications)	
	☐ Other: (Please specify)	
☐	Patient experience data that were not submitted in the application, but were considered in this review:	
	☐ Input informed from participation in meetings with patient stakeholders	
	☐ Patient-focused drug development or other stakeholder meeting summary reports	
	☐ Observational survey studies designed to capture patient experience data	
	☐ Other: (Please specify)	
☐	Patient experience data was not submitted as part of this application.	

Reviewer's Comment: The Applicant assessed patient-reported health-related quality of life, subjective well-being, medication satisfaction, medication preference, and healthcare utilization, as well as clinician-reported measures of psychiatric symptom severity. Please refer to Section 6.1 for a description of endpoints and Section 6.1.2 for discussion of results for Study RB-US-09-0010.

2. Therapeutic Context

2.1. Analysis of Condition

Schizophrenia is a highly heritable psychiatric syndrome characterized by chronic or recurring psychosis. Diagnosis is made clinically, based on diagnostic criteria specified in Table 1. Accurate diagnosis requires ruling out other causes of psychosis, such as other chronic psychiatric illnesses (i.e., schizoaffective disorder, bipolar disorder), substance use, and other medical conditions.

Table 1: Diagnostic Criteria for Schizophrenia

- | |
|--|
| <p>A. Two (or more) of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated). At least one of these must be (1), (2), or (3):</p> <ol style="list-style-type: none">1. Delusions2. Hallucinations3. Disorganized speech (e.g., frequent derailment or incoherence)4. Grossly disorganized or catatonic behavior5. Negative symptoms (i.e., diminished emotional expression or avolition) <p>B. For a significant period of the time since the onset of the disturbance, level of functioning in one or more major areas, such as work, interpersonal relations, or self-care, is markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, there is failure to achieve expected level of interpersonal, academic, or occupational functioning).</p> <p>C. Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e., active-phase symptoms) and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or by two or more symptoms listed in Criterion A present in an attenuated form (e.g., odd beliefs, unusual perceptual experiences).</p> <p>D. Schizoaffective disorder and depressive or bipolar disorder with psychotic features have been ruled out because either 1) no major depressive or manic episodes have occurred concurrently with the active-phase symptoms, or 2) if mood episodes have occurred during active-phase symptoms, they have been present for a minority of the total duration of the active and residual periods of the illness.</p> <p>E. The disturbance is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition.</p> <p>F. If there is a history of autism spectrum disorder or a communication disorder of childhood onset, the additional diagnosis of schizophrenia is made only if prominent delusions or hallucinations, in addition to the other required symptoms of schizophrenia, are also present for at least 1 month (or less if successfully treated).</p> |
|--|

Source: Diagnostic and Statistical Manual of Mental Disorders (DSM-5) [1]

The pathogenesis of schizophrenia is not well-understood, possibly due to the heterogeneity of the syndrome, but it likely involves an interaction between genetic (e.g., multiple genes with additive small effects, copy number variants) and environmental risk factors (e.g., obstetrical complications, maternal infections, cannabis use, and traumatic life events) [2]. Hypothetical

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neurochemical models of schizophrenia include excessive mesolimbic dopaminergic activity, hypoactivity of N-methyl-D-aspartate (NMDA) glutamate receptors, and dysfunctional gamma-aminobutyric acid (GABA)-mediated modulation of pyramidal neurons [3].

Individuals who develop schizophrenia vary substantially in terms of onset, symptom presentation, and outcome. Though it is variable, the clinical course of schizophrenia may include a:

- Childhood premorbid phase (sometimes associated with subtle cognitive, motor, or social deficits), an
- Adolescent prodromal phase (that may be associated with attenuated psychotic symptoms and/or functional decline), an
- Initial episode of florid psychotic symptoms (or “first break”) in the second or third decade of life, a
- Period of exacerbations and remissions of psychosis (with variable degrees of psychiatric and functional recovery), and a
- Residual phase, often characterized by a decrease in positive symptom severity and an increase in negative symptoms [4].

Although the age of the initial episode of schizophrenia is typically in the second or third decade of life, schizophrenia can infrequently present in childhood or in old age. On average, the age of onset occurs 5 to 7 years later in females than males, and when the course of schizophrenia is compared between men and women, women tend to have better premorbid functioning and less prominent negative symptoms and cognitive impairment. [4]. After a psychotic episode, it has been estimated that 50% of patients with schizophrenia experience a relapse/exacerbation in psychotic symptoms within one year after an episode, and almost three quarters of patients with exacerbations requiring hospitalization were nonadherent to prescribed antipsychotic medications. Relapse rates are significantly reduced with maintenance antipsychotic treatment [5].

Schizophrenia is associated with significant impairments in social and occupational functioning and is the 11th leading cause of years lost due to disability worldwide [6]. Patients with schizophrenia have a significantly higher mortality rate than the general population, with proportionally higher rates of suicide (particularly in younger patients) and cardiovascular disease, as well as other natural causes [7]. The years of potential life lost in individuals with schizophrenia has been estimated to be 14.5 years [8]. Overall, schizophrenia is clearly a serious condition, associated with significant disability and a shortened life expectancy.

2.2. Analysis of Current Treatment Options

Antipsychotics are the first-line medication treatment for schizophrenia. Current psychiatric

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practice guidelines recommend that antipsychotics should be initiated as soon as possible in an acute schizophrenia exacerbation and continued through the stable/maintenance phase of the illness to reduce the risk of relapse [9]. Antipsychotics are broadly classified as first-generation/typical antipsychotics (FGAs) and second-generation/atypical antipsychotics (SGAs). FGAs include antipsychotics approved before clozapine (1989); representative medications of this class are chlorpromazine, fluphenazine, and haloperidol. SGAs include clozapine and other antipsychotics approved after 1989; representative SGAs are clozapine, risperidone, olanzapine, quetiapine, and aripiprazole.

Antipsychotics are primarily effective at reducing positive symptoms of schizophrenia, such as hallucinations and delusions, and do not appear to have clinically meaningful effects on negative symptoms or cognitive impairment associated with schizophrenia [10, 11]. The mechanism by which antipsychotics improve psychotic symptoms is not completely understood but may involve antagonism of dopamine D₂ receptors and/or 5-HT_{2A} receptors. Binding to other neurotransmitter receptors (e.g., α 1-adrenergic, muscarinic, and histaminergic receptors) generally corresponds to the adverse reaction profile for a given drug [12]. In general, FGAs have a higher risk for causing extrapyramidal side effects (EPS), such as dystonia, parkinsonism, and tardive dyskinesia, and many SGAs, including risperidone, are associated with significant weight gain and metabolic effects. A Bayesian-framework, multiple-treatments meta-analysis comparing the efficacy and tolerability of 15 antipsychotic drugs found that antipsychotics differ primarily in adverse reactions (e.g., weight gain, EPS, prolactin increase, QT prolongation, and sedation). Antipsychotics differed less in efficacy, with exception of clozapine (the most effective antipsychotic), followed by amisulpride (not approved in the U.S.), olanzapine, and risperidone, followed by the rest of the antipsychotics studied [13].

Long-acting injectable antipsychotics (LAIs) have been part of the antipsychotic treatment armamentarium since the development of enanthate and decanoate formulations of fluphenazine in the late 1960's. The primary clinical benefit of LAIs is that they maintain therapeutic blood levels of antipsychotics for extended periods (weeks to months) and may reduce the risk of schizophrenia exacerbation in patients who are nonadherent to oral medications [14]. Other potential benefits of LAIs include transparency of medication adherence and reduced risk of overdose. Potential disadvantages of LAIs include a longer time to achieve steady state blood levels, delayed resolution of adverse reactions, injection site reactions, and more frequent appointments for drug administration [15]. Please refer to Table 2 for a tabulation of LAIs currently available in the U.S.

In addition to antipsychotic medications, patients with schizophrenia are frequently treated with adjunctive medications to target depression, anxiety, obsessions and compulsions, and adverse reactions of antipsychotics (e.g., dystonia, parkinsonism, tardive dyskinesia, and akathisia). These adjunctive medications may include anticholinergic drugs (i.e., benztropine, diphenhydramine), beta-blockers (i.e., propranolol), benzodiazepines, and antidepressants [16].

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Beyond pharmacotherapy, several psychosocial treatments have substantial evidence bases and are recommended for use alongside antipsychotic therapy. Psychosocial treatments may reduce relapse risk, improve coping skills, improve social and vocational functioning, and help individuals with schizophrenia to function more independently. Recommended psychosocial interventions include cognitive behavioral therapy, assertive community treatment, supported employment, and social skills therapy [17].

Overall, I assess the current treatment armamentarium for schizophrenia to be suboptimal. Current antipsychotic medications are effective at reducing the severity of positive psychotic symptoms (which are a substantial source of disability from schizophrenia) but do not provide meaningful benefit for other symptoms frequently associated with schizophrenia. Antipsychotics also have a non-negligible adverse reaction profile, likely contributing to their substantial nonadherence rate. Long-acting injectable formulations of antipsychotics are clinically useful, particularly in patients who are nonadherent to daily oral antipsychotics. Psychosocial treatments, in conjunction with antipsychotics, can lessen the functional impacts of schizophrenia but are not widely available.

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Table 2: Summary of Long-Acting Injectable Antipsychotics Currently Available in the U.S.

Product Name	Relevant Indication	Year of Approval	Route and Frequency of Administration	Important Differentiating Safety and Tolerability Issues	Comments
Aripiprazole monohydrate (Abilify Maintena)	Schizophrenia in adults	2013	IM in (b) (4) gluteal muscle, monthly	N/A	In conjunction with first dose, need to continue oral antipsychotic for 14 days
Aripiprazole lauroxil (Aristada)	Schizophrenia in adults	2015	IM in deltoid or gluteal muscle, monthly, every 6 weeks, or every 2 months	N/A	In conjunction with first dose, need to continue oral antipsychotic for 3 weeks
Fluphenazine decanoate	Schizophrenia in adults	1972	IM or SC, every (b) (4)	First generation antipsychotic – higher EPS liability	Need to continue oral fluphenazine until effective decanoate dosage is established
Haloperidol decanoate	Schizophrenia in adults	1986	IM, monthly	First generation antipsychotic – higher EPS liability	Depending on initiation dose, may need to continue oral antipsychotic for up to (b) (4)
Olanzapine pamoate (Zyprexa Relprevv)	Schizophrenia in adults	2009	IM in gluteal muscle, every 2 or 4 weeks	Risk of post-injection delirium/sedation syndrome: drug available only through restricted distribution program; requires 3 hours monitoring post-injection	No overlap period needed with oral antipsychotic
Paliperidone palmitate (Invega Sustenna)	Schizophrenia in adults	2009	IM in deltoid or gluteal muscle; two weekly initiation doses followed by monthly maintenance doses	N/A	No overlap period needed with oral paliperidone
Paliperidone palmitate (Invega Trinza)	Schizophrenia in adults	2015	IM in deltoid or gluteal muscle; every 3 months	N/A	Can only be used if patient has received monthly injections of Invega Sustenna for ≥4 months
Risperidone microspheres (Risperdal Consta)	Schizophrenia in adults	2003	IM in deltoid or gluteal muscle, every 2 weeks	N/A	In conjunction with first dose, need to continue oral antipsychotic for 3 weeks

Source: Reviewer-created from product labeling; EPS = extrapyramidal symptoms

3. Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

RBP-7000 contains risperidone, which was initially approved in 1993 (as Risperdal oral tablets, Janssen Pharmaceuticals, NDA 020272) for the treatment of schizophrenia in adults. Additional indications specified in current Risperdal labeling include: treatment of schizophrenia in adolescents (age 13 to 17 years), treatment of irritability associated with autistic disorder in children and adolescents (age 5 to (b) (4) years), and treatment of acute manic or mixed episodes associated with bipolar I disorder in adults (as monotherapy in adults and children and adolescents age 10 to 17 years, and as an adjunct to lithium or valproate in adults).

In addition to oral tablets, risperidone is approved as orally disintegrating tablets (Risperdal M-TAB, NDA 021444) and as an oral solution (NDA 020588). Risperidone is also marketed as a long-acting injectable product that was initially approved in 2003 (Risperdal Consta, NDA 021346). Risperdal Consta is indicated for the treatment of schizophrenia and for the maintenance treatment of bipolar I disorder (as monotherapy or as an adjunct to lithium or valproate).

Risperdal labeling includes a boxed warning (common to all antipsychotic drugs) describing increased mortality in elderly patients with dementia-related psychosis. Safety-related labeling changes to Risperdal within the past five years include:

- February 23, 2017: class-based addition of Falls to Warnings and Precautions
- March 1, 2016: addition of hypersensitivity reactions to Highlights of Prescribing Information and Contraindications
- April 28, 2014: additions of ileus to Postmarketing Experience; and anaphylactic reaction to Postmarketing Experience (in Risperdal Consta labeling)

3.2. Summary of Presubmission/Submission Regulatory Activity

- September 11, 2009: Type B Pre-IND Meeting to obtain the Agency's comments on the Sponsor's development plans.

(b) (4)



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(b) (4)

- December 1, 2009: IND application received (IND 105623 for the treatment of schizophrenia), (b) (4)
The May Proceed letter was issued on January 7, 2010.
- February 27, 2013: Type C Guidance Meeting to discuss completed clinical studies and revisions to the clinical development plan.
 - The Division advised that the Sponsor must conduct a long-term, open-label study so that safety data are available from at least 300 patients exposed for at least 6 months and at least 100 patients exposed for at least 12 months, in accordance with International Conference on Harmonisation (ICH) E1 (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions).
 - The Division expressed concerns about the potential for dose dumping and queried whether potential causal factors had been evaluated.
 - The Division of Medication Error Prevention and Analysis (DMEPA) indicated that human factors studies would be required to support the usability of the product.
 - In discussion of a proposed Phase 3 trial design, the Sponsor noted that the proposed indication for RBP-7000 is for the treatment of schizophrenia (b) (4). The Division commented that the proposed Phase 3 study must indicate how three months of clinical stability on an antipsychotic drug would be verified, that patients who became clinically unstable during the oral risperidone phase should not be eligible for randomization, that the difference between treatment groups on the primary efficacy variable must be statistically significant and should be clinically meaningful, and that clinical worsening in the placebo group should follow a pattern over time and not show deterioration at just one time point.
- June 21, 2013: The Division provided written feedback on the draft protocol for Phase 3 Study RB-US-09-0010. The Division noted that the draft protocol was unacceptable, (b) (4)

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(b) (4) A study in which subjects would be randomized to a fixed dose of RBP-7000 or placebo was suggested. The Division also recommended that inclusion criteria should ensure the inclusion of patients with prominent positive psychotic symptoms, and that timing and follow-up on injection site reactions should be specified.

- September 18, 2013: End-of-Phase 2 Meeting.
 - The Division noted that analysis of Columbia-Suicide Severity Rating Scale (C-SSRS) data should include findings based on the Columbia Classification Algorithm of Suicide Assessment (C-CASA) classification of any events potentially related to suicidal thoughts or behavior.
 - The Sponsor proposed a revised design for Phase 3 Study RB-US-09-0010. In this study, patients with schizophrenia who are acutely ill would be randomized to receive placebo, RBP-7000 90 mg, or RBP-7000 120 mg every four weeks for eight weeks, following taper of existing antipsychotic medications and administration of two test doses of risperidone 0.25 mg by mouth. The primary efficacy endpoint would be (b) (4).

The Division noted that we would not accept the (b) (4) as a primary efficacy measure and recommended that an analysis method that could deal with missing data, such as Mixed-Effect Model Repeated Measure (MMRM), be considered. The Sponsor accepted this recommendation.
 - The Sponsor proposed a plan to evaluate dose dumping that included simulations. The Agency indicated that other in vitro modalities that may result in dose dumping (such as heat and pressure) must be tested. Blood levels of risperidone should also be monitored in subjects that exhibit severe adverse events, to help rule out a causal relationship with product malfunction.
 - The Sponsor proposed a Human Factors study plan. The Agency recommended that a group of participants who received no training should also be included to identify potential failures in end users who do not receive training. Participants in the verification study must not have participated in the validation study.
- March 5, 2015: Type C Written Responses Only Guidance Meeting to follow-up on questions from the End-of-Phase 2 Meeting.
 - The Division agreed that an in vivo rat study would be useful to help evaluate the risperidone dose dumping potential of heat, physical pressure, and exercise stress.
- December 3, 2015: Agreed Initial Pediatric Study Plan submitted. This plan requested a full waiver for RBP-7000 assessments in all pediatric age groups, on the basis that necessary studies are impossible or highly impractical (in patients up to 12 years old)

and that the product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients and is unlikely to be used in a substantial number of pediatric patients (age (b) (4) to 17 years old).

- February 6, 2016: Type C Written Responses Only Guidance Meeting to discuss the dissolution method to assess the extended release profile of RBP-7000, a strategy regarding syringe orientation during the primary stability program, and an approach for addressing leachables that contain a structural alert for mutagenicity.
- August 4, 2016: Pre-NDA Meeting. The face to face meeting was cancelled by the Sponsor after receiving preliminary comments and follow-up clarifications.
 - The Sponsor indicated that they will generate a population PK model using all the relevant clinical studies performed in the development program, as well as provide reports of individual clinical studies.
 - The listed drug for the proposed NDA will be risperidone oral tablets (NDA 020272).
 - Exposure data from the multiple ascending dose Study RB-US-09-0009 will be used to bridge RBP-7000 to oral risperidone.
 - The Agency agreed that an in vitro paradigm for assessing potential dose dumping effects of pressure and heat would be acceptable in the context of difficulties assessing these factors in rats.
 - The Sponsor planned to present a comprehensive assessment of dose dumping events in clinical studies as well as the results of dose dumping simulations in the NDA.
 - The Sponsor will include recommended dosing intervals and instructions for managing missed doses or dosage intervals outside the recommended interval.
 - The Sponsor confirmed that the final to-be-marketed formulation was used in the multiple ascending dose and Phase 3 studies.

3.3. Foreign Regulatory Actions and Marketing History

The listed drug, Risperdal (NDA 020272), is registered in approximately 120 countries worldwide. The NDA 020272 Periodic Safety Update Report for the period from June 1, 2016 to May 31, 2017 was reviewed; no marketing authorizations were noted to have been withdrawn, revoked, or suspended during this period.

4. Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

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The OSI was consulted to request clinical inspections for two sites that were part of Study RB-US-09-0010:

- #106: David Brown, MD; Community Clinical Research, Austin, TX (18 subjects enrolled)
- #134: Tram Tran-Johnson, MD; California Neuropsychopharmacology Clinical Research Institute, San Diego, CA (19 subjects enrolled)

The rationale for selecting these two sites was that they had relatively high subject enrollments and neither of these sites had been recently inspected by the OSI.

Based on the results of OSI inspections, both sites appeared to have conducted the study adequately, and the data generated by the sites appeared acceptable for review in support of the NDA. The final compliance classification for both sites was No Action Indicated (NAI). Please refer to the review by Dr. Jenn Sellers for additional details.

4.2. Product Quality

Please refer to the Office of Product Quality (OPQ) review (application technical lead: Dr. David Claffey) for the reviews of drug substance, drug product, process, microbiology, facility, biopharmaceutics, and laboratory issues. In the OPQ executive summary, Dr. Claffey recommends that this application be approved from a product quality perspective. There were no issues raised in the OPQ review that appear to affect the interpretation of clinical data or approval decision.

4.3. Clinical Microbiology

As detailed in the OPQ review, the microbiology review team found the microbiology manufacturing controls and (b) (4) sterilization process to be adequate.

4.4. Nonclinical Pharmacology/Toxicology

Please refer to the Nonclinical Pharmacology/Toxicology review for details. The following brief discussion of nonclinical findings is quoted from Dr. Sonia Tabacova's review.

In the pivotal, GLP-compliant, repeat-dose general toxicity studies in rats and dogs with SC monthly administration for 6- and 9-months, RBP-7000 was well tolerated at doses of up to 60 and 80 mg/kg in rats and dogs, respectively, and provided sustained exposure to risperidone active moiety with predictable systemic effects and minimal to moderate effects at the local injection site. Plasma exposure in male and female rats at the NOAEL of 60 mg/kg provides a safety margin of 10- to 20-times (for C_{max}), 8- to 14-times (for AUC_{0-24h}) and 3- to 4-times (for AUC_{0-28d}) the corresponding human exposure

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parameters at the maximal clinical dose of 120 mg risperidone; the safety margins at the dog NOAEL of 80 mg/kg are 42 to 60 times (for C_{max}), 62 to 91 times (for AUC_{0-24h}) and 45 to 57 times (for AUC_{0-28d}) the corresponding human exposure parameters at the maximal clinical dose of 120 mg risperidone (PK data from the multiple-dose clinical Study RB-US-09-0009).

RBP-7000 was negative when tested for genetic toxicity in a valid micronucleus assay in male and female rats by SC dosing. Micronuclei induction was also not present upon SC administration of ATRIGEL Delivery System alone (vehicle control) using the same dosing and sampling regime.

Carcinogenicity studies have not been conducted with RBP-7000. The Division waived the carcinogenicity study requirement for RBP-7000 based upon the composition, pharmacology and toxicology characteristics and the absence of pre-neoplastic lesions in the toxicity studies in rats and dogs (correspondence of 9 July 2012), as well as on the carcinogenicity studies already conducted in rat and mouse with risperidone under Risperdal Tablet NDA 20272 (see drug label).

Reproductive and developmental toxicology studies were not performed with RBP-7000, but were conducted with ATRIGEL Delivery System alone (without API) in rats and rabbits using a similar (but not identical) extended-release product (b) (4)

The safety margins for the maximal human dose of RBP-7000 (containing 800 mg ATRIGEL Delivery System) are 17 times the NOAEL values for male sperm parameters, pre- and postnatal developmental toxicity, and 34 times the NOAEL for female fertility, based on mg/m² body surface area.

Juvenile toxicity studies with RBP-7000 have not been conducted, but were performed for oral risperidone in juvenile rats and dogs (RISPERDAL Tablets Label 2017).

Dr. Tabacova recommends that, from a Nonclinical Pharmacology/Toxicology perspective, this application should be approved.

4.5. Clinical Pharmacology

This NDA submission was supported by three key clinical pharmacology studies:

- Study RB-US-09-0007 - Phase 1, single-dose PK, safety, and tolerability study at 60 mg in subjects with schizophrenia
- Study RB-US-09-0008 - Phase 1, single ascending dose study at 60 mg, 90 mg, and 120 mg to assess the PK, safety, and tolerability in subjects with schizophrenia
- Study RB-US-09-0009 -Phase 2A, multiple ascending dose study over a dose range of 60 to 120 mg to assess safety/tolerability and PK in subjects with stable schizophrenia. This

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was the PK-bridging study conducted to provide the relative bioavailability to oral risperidone.

Please refer to the Office of Clinical Pharmacology (OCP) review by Drs. Praveen Balimane, Kevin Krudys, and Hao Zhu for additional information.

The OCP findings are summarized below:

- After a single RBP-7000 injection, the concentration of total active moiety (risperidone + 9-hydroxyrisperidone) rises rapidly, reaching the first T_{max} at ~8 hours on Day 1, followed by a second T_{max} at ~Day 11. The first C_{max} is approximately 50% of the second C_{max} . The mean terminal half-life of total active moiety was approximately 8 days, and steady state concentrations were reached by the end of the second monthly injection, with minimal accumulation. The PK was proportional from a 60 to 120 mg dose range.
- The proposed RBP-7000 doses of 90 mg and 120 mg are acceptable because 1) Study RB-US-09-0010 demonstrated that both doses significantly improved PANSS total scores compared to placebo, and 2) average concentrations of total active moiety at steady state after daily administration of oral risperidone tablets and RBP-7000 SC injections were similar; 3 mg/day oral was similar to 90 mg RBP-7000 and 4 mg/day oral was similar to 120 mg RBP-7000. There was less fluctuation in concentration, at steady state, for RBP-7000 compared to oral risperidone.
- RBP-7000 does not require either a loading dose or an overlap period with supplemental oral risperidone.
- There was no evidence of dose dumping in PK data collected from 102 subjects across multiple studies.
- The to-be-marketed formulation was used in the pivotal Phase 3 efficacy/safety study, relative bioavailability/PK-bridging study, and the other two clinical pharmacology studies.

One issue discussed in the OCP review was that this NDA was filed as a 505(b)(2) application using the previously-approved Risperdal oral tablets (NDA 20272) as the listed drug. However, the pharmacokinetic (PK) bridging study (RB-US-09-0009) was not performed using the listed drug; it was performed using an FDA-approved “AB”-rated generic risperidone oral tablet (ANDA 78871, manufactured by Workhardt). OCP concluded that the PK of the generic product is comparable to the PK of the listed drug when compared across study and literature data.

A second issue is that although the Applicant could provide information on the generic drug used in the bridging study, documentation of the lot numbers of all dosed materials was not initially available. Thus, the Office of Study Integrity and Surveillance (OSIS) was consulted to inspect sites where Study RB-US-09-0009 was conducted (Woodland International Research Group, Little Rock, AR, and Collaborative Neuroscience Network, Long Beach, CA). The OSIS

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review team memo concluded that data from the audited sites were reliable, and the inspection classifications for both sites were No Action Indicated (NAI).

Overall, OCP determined that there is sufficient clinical pharmacology information in the NDA package to support a recommendation to approve RBP-7000 for marketing. No post-marketing studies were recommended by OCP.

4.6. Devices and Companion Diagnostic Issues

The Center for Devices and Radiological Health (CDRH) was consulted to review this combination drug/device product, which is provided as a kit including a 2-syringe system and detached needle. Please refer to the review by CDR Keith Marin, RN, MS, MBA for complete details.

In summary, the CDRH review documented that the device exhibited adequate performance with respect to dose accuracy, break loose force, and glide force. The device components met acceptability criteria on the performance tests. Validation of essential requirements was covered by clinical and human factors testing (rapid iterative instruction development, formative usability studies, and human factors validation). The to-be-marketed device was used in human factors studies and the pivotal clinical trial. The device reliability was deemed acceptable to support the indications of use. In the summary of risk analysis, the use-related hazards of critical tasks were deemed to be acceptable for this device type. CDR Marin noted two residual risks with this device based on how preparation and delivery occurs. One risk is that insufficient product will be transferred to the delivery syringe prior to disconnecting the syringes; preparation of the product requires mixing, and the fluid is substantially more viscous than a typical suspension, making it difficult to ensure that all drug has been transferred to the delivery syringe. The second risk is insufficient removal of excess air, either due to the lack of familiarity with this dosage form and/or conducting the SC injection prior to removing excess air. The Applicant believes that these residual risks can be mitigated through additional education, and CDR Marin concurs. Overall, CDRH reviewer CDR Marin recommends that this product be approved.

4.7. Consumer Study Reviews

The Division of Medication Error Prevention and Analysis (DMEPA) was consulted to review the human factors (HF) validation study report ("Human Factors Engineering Report for RBP-7000 (Horsetooth)") and proposed product labeling to determine if product labeling is acceptable from a medication error perspective. Please refer to the review by Dr. Loretta Holmes for full details. The DMEPA review determined that the risks associated with RBP-7000 use have been mitigated to the extent possible, and no additional HF studies are needed. Several recommendations were made on how the Applicant could improve labeling to minimize the risks of medication errors. These recommendations include revising the route of administration

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language to read, “Do not administer by any other route;” improving syringe/pouch/carton labeling to be more readable and understandable; and revising the Instructions for Use leaflet to ensure consistency with the Prescribing Information. The recommendations from DMEPA will be conveyed to the Applicant.

5. Sources of Clinical Data and Review Strategy

5.1. Table of Clinical Studies

The clinical development program for this 505(b)(2) NDA consisted of six completed studies: three Phase 1 studies, a Phase 2 open-label multiple ascending dose (MAD) study, a Phase 3 randomized, placebo-controlled efficacy and safety study, and a Phase 3 open-label long-term safety study. All six studies enrolled adults with schizophrenia. Please see Table 3 for a description of the two Phase 3 studies that were most relevant to this clinical review.

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Table 3: Listing of Phase 3 Trials Submitted with NDA 210655

Trial Identity¹	NCT no.	Trial Design	Regimen/schedule/route	Study Endpoints³	Treatment Duration/Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
09-0010	02109562	Phase 3, randomized, double-blind, placebo-controlled study	90 mg RBP-7000, 120 mg RBP-7000, or placebo SC ² every 28 days	<u>Primary</u> : PANSS total score – change from baseline to end of treatment (Day 57) <u>Key Secondary</u> : CGI-S – change from baseline to end of treatment (Day 57)	8 weeks (2 SC injections)	354	Adults (age 18 to 55 years) with schizophrenia, experiencing an acute exacerbation (PANSS total score 80 to 120, with scores ≥4 on at least two of: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness)	33, all in the US
13-0005	02203838	Phase 3, open-label, long-term safety and tolerability study	120 mg RBP-7000 SC every 28 days. Subjects could receive one taper to 90 mg RBP-7000 for tolerability	<u>Safety</u> : AE monitoring, injection site monitoring, vital signs, bodyweight, ECGs, clinical laboratory studies, SAS, BARS, AIMS, C-SSRS <u>Efficacy (uncontrolled)</u> : PANSS total score, CGI-S	52 weeks (13 SC injections)	500	Adults (age 18 to 65 years) with schizophrenia, with a PANSS total score ≤70 at Screening.	53, all in the US

¹Full trial identifiers include a prefix of RB-US-; ²subcutaneous; ³PANSS=Positive and Negative Syndrome Scale, CGI-S=Clinical Global Impression–Severity of Illness, AE=adverse event, ECG=electrocardiogram, SAS=Simpson-Angus Scale, BARS=Barnes Akathisia Rating Scale, AIMS=Abnormal Involuntary Movement Scale, C-SSRS=Columbia-Suicide Severity Rating Scale

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5.2. Review Strategy

Because this NDA was submitted under the 505(b)(2) pathway, much of the overall understanding of the safety and effectiveness of RB-7000 relies on the Agency's previous findings for oral risperidone (Risperdal, NDA 20272). However, because RBP-7000 is a new formulation of risperidone, with a different route of administration and dosing regimen, the Applicant was advised to conduct both an adequate and well-controlled clinical study to assess efficacy and a long-term safety study, in addition to conducting studies evaluating the PK of RBP-7000 and comparing it to oral risperidone. Given that this is a 505(b)(2) application, many sections of this review will be abbreviated or not applicable, as noted.

The review of efficacy focuses on Study RB-US-09-0010; this study, conducted in subjects who were experiencing an acute exacerbation of schizophrenia, was the only randomized, double-blind, placebo-controlled study designed to evaluate the efficacy of RBP-7000. The long-term, open-label study, RB-US-13-0005, collected efficacy outcome measure data for up to 52 weeks. However, this study is only considered adequate for assessing long-term safety, as opposed to efficacy, because it was open-label and lacked a control group. The efficacy review was based on analyses submitted by the Applicant, supplemented with confirmatory and additional analyses conducted by this reviewer and Biometrics reviewer, Dr. Kelly Yang. The Clinical Pharmacology team provided additional input that informed the review of efficacy, including the PK comparison between doses of RBP-7000 and oral risperidone (Section 4.5). The sources of analyses and Table/Figure content are clearly delineated in the text. Dr. Davis' analyses were conducted primarily using the software package JMP 12.1 (SAS Institute).

Dr. Qi Chen conducted the review of safety and wrote Chapter 8 (Review of Safety). The safety review is based on data submitted from Studies RB-US-09-0010 and RB-US-13-0005. For the safety analyses, the Chi-squared test was used to compare injection site reaction rates between treatment groups. Poisson regression was used to predict the relative risk of adverse events (preferred terms) in treatment vs. placebo, with treatment duration as exposure. For laboratory values and vital signs, a mixed effects model was used to predict random effect mean changes after treatment, relative to non-treatment, with subject ID as a random effect. Given the skewed distribution of some variables, analyses were conducted to predict both absolute mean change and geometric mean change. Please refer to Section 8.1 for additional details about the safety review approach.

Drs. Davis and Chen worked jointly on certain sections of this review (i.e., Benefit-Risk Assessment, Labeling Recommendations, etc.) that incorporated both efficacy and safety perspectives.

6. Review of Relevant Individual Trials Used to Support Efficacy

6.1. Study RB-US-09-0010

6.1.1. Study Design

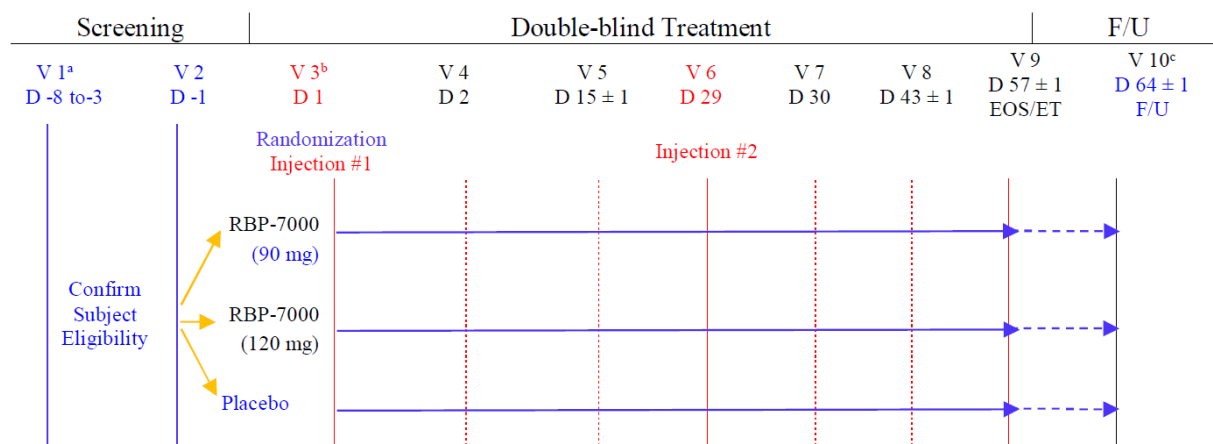
Overview and Objective

Study RB-US-09-0010 is entitled “A Phase 3 Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of RBP-7000 (90 mg and 120 mg) as a Treatment in Subjects with Acute Schizophrenia Over 8 Weeks (2 Subcutaneous Doses). Its stated primary objective was to assess the efficacy of RBP-7000 (90 mg and 120 mg), compared to that of placebo, on the symptoms of schizophrenia over an 8-week treatment period, using the change from baseline to the end of treatment in the Positive and Negative Syndrome Scale (PANSS) total score. Its secondary objectives were to assess efficacy using the Clinical Global Impression-Severity of Illness (CGI-S) scale and to establish a pharmacokinetic (PK)/pharmacodynamic (PD) model using a nonlinear mixed effect modeling approach. Its tertiary objectives were to assess health-related quality of life, subjective well-being, subject satisfaction, and subject and caregiver medication preference.

Trial Design

Basic Study Design: Study RB-US-09-0010 was a Phase 3, randomized, double-blind, placebo-controlled, multi-center study. The study duration was approximately 72 days per subject, including an up to 8-day screening period and a 56-day treatment period. Adults experiencing an acute exacerbation of schizophrenia were placed in an inpatient setting, if not already hospitalized, and initially administered one 0.25-mg tablet of oral risperidone on two subsequent days to assess whether they would have any intolerable reactions to risperidone. Subjects were then tapered off their prior oral antipsychotic medications at rates per the investigator’s discretion (but not exceeding 8 days). Subjects were then randomized (1:1:1) to receive either RBP-7000 (90 or 120 mg) or placebo SC on Days 1 and 29. Subjects remained in an inpatient setting for the entire study duration, except for one day pass after Day 29 (per the investigator’s discretion). Assessments for efficacy, safety, and pharmacokinetics occurred at scheduled intervals. Following the final assessment on Day 57, subjects had the option of entering the long-term safety study (RB-US-13-0005) or completing a follow-up phone call on Day 64. Please refer to Figure 1 for a schematic of the study design.

Figure 1: Study RB-US-09-0010 - Schematic of Study Design



D = Day; EOS/ET = End-of-Study/Early Termination; F/U = follow-up; V = Visit

- ^a Each subject who met the initial entry criteria at Visit 1 was placed into an inpatient setting if they were not already in an inpatient setting.
- ^b At Visit 3, eligible subjects were randomly assigned to 1 of the 3 treatment arms (active RBP-7000 [90 or 120 mg] or placebo).
- ^c Only those subjects who did not roll over into the long-term safety study completed this follow-up phone call.

Source: Study RB-US-09-0010 Clinical Study Report, page 21

Reviewer's Comment:

The design was reasonable for an inpatient acute schizophrenia study. The strength of this design is that subjects were in a controlled environment, so assessments were less likely to be confounded by factors such as disallowed concomitant medications or alcohol/substance use. A limitation of this design is that it is less representative of real-world clinical practice, in which patients with acute schizophrenia are typically hospitalized for shorter periods (mean length of stay ~ 9 days [18]) and thereafter followed in outpatient settings.

Trial Location: This study was conducted entirely in the United States.

Choice of Control Group: This study used a placebo control group, which was the ATRIGEL Delivery System (ADS) alone without risperidone (see Blinding section below for additional details). The use of a placebo control for comparison is acceptable and commonly used for efficacy studies for acute schizophrenia. Subjects were monitored on an inpatient unit, and rescue medications were allowed per investigator judgment; please refer to Section 6.1.2 for assessment of concomitant medications and rescue medication use in the study.

Diagnostic Criteria: Subjects needed to meet the Diagnostic and Statistical Manual for Mental Disorders (DSM-IV-TR) criteria for schizophrenia.

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Reviewer's Comment:

The DSM is the US standard for psychiatric diagnostic criteria. The DSM-IV-TR is one version older than current (DSM-5); however, the changes in the schizophrenia criteria (removal of special attribution to bizarre delusions and auditory hallucinations of two or more voices conversing, and the addition of a requirement that the individual must have at least one of the three symptoms of delusions, hallucinations, and disorganized speech) are not expected to significantly affect the generalizability of study findings.

Eligibility Criteria:

Key inclusion criteria were:

- Male and female adults between ages 18 and 55 years, inclusive
- PANSS total score between 80 and 120, inclusive, at Screening, and a score ≥ 4 on at least two of the following four items of the PANSS positive subscale: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness
- Experiencing an acute exacerbation of schizophrenia, as demonstrated by a recent marked deterioration from baseline status (impairment in functional capabilities secondary to schizophrenia symptoms); with start of exacerbation occurring ≤ 8 weeks prior to Screening; and subject would have benefited from psychiatric hospitalization or continued hospitalization for symptoms of schizophrenia

Key exclusion criteria were:

- Improvement in the PANSS total score of $\geq 20\%$ between Screening and Day 1 (first injection)
- Hospitalization for >14 days in the current episode prior to Screening
- Use of a LAI antipsychotic within 120 days prior to Screening
- Administration of daily oral risperidone at a dose ≥ 6 mg/day
- Administration of CYP2D6 inducers or inhibitors within 5 half-lives of the medication (or 30 days for fluoxetine)
- Treatment-resistant schizophrenia, as judged by the Investigator; or treatment at any time with clozapine for treatment-resistant schizophrenia; or documented failure of two or more antipsychotic medications; or prior documented failure to risperidone or paliperidone
- Suicidal ideation with intent or plan in the six months prior to Screening, suicidal behaviors within one year prior to Screening, significant risk of suicide per Investigator opinion, or uncontrolled depression per Investigator opinion
- Met DSM-IV-TR criteria for alcohol abuse or dependence or substance dependence (except for nicotine and caffeine) within 12 months prior to Screening; or tested positive for substances in a urine drug screen (except for cannabinoids if there was no dependence and the subject abstained for the duration of the study)
- Current DSM-IV-TR Axis I diagnosis other than schizophrenia, nicotine dependence, or

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- Mild or greater tardive dyskinesia, as assessed by a score of ≥ 2 on item 8 of the AIMS at Screening
- History of cancer (with exception of resected basal cell or squamous cell carcinoma of the skin) unless they had been disease free for ≥ 5 years; or any other medical condition or organ disease that could either compromise subject safety or interfere with evaluations. Exclusionary medical conditions included: HIV positive/AIDS, myocardial infarction, brain injury, insulin-dependent or unstable non-insulin-dependent diabetes mellitus, significant traumatic injury, major surgery or open biopsy within 30 days, seizure disorders, Parkinson's disease, dementia, neuroleptic malignant syndrome, or unstable thyroid disease
- Evidence or history within 6 months of Screening of a significant hepatic disorder, acute or chronic hepatitis, total bilirubin >1.5 x the upper limit of normal (ULN), or alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >2 x the ULN
- Absolute neutrophil count $\leq 1.5 \times 10^9/L$ (or $\leq 1.2 \times 10^9/L$ in African/African-Americans), or history of drug-induced leukopenia, or platelets $\leq 75,000/mm^3$, hemoglobin ≤ 9 g/dL, or creatine phosphokinase (CPK) >3 x ULN
- Congenital long-QT syndrome, history of prolonged QT in the 3 months prior to Screening, or QTcB >450 msec (in males) or >470 msec (in females) at Screening
- Women of childbearing potential with a positive pregnancy test at Screening or who were pregnant, breastfeeding, seeking pregnancy, or not using adequate contraceptive methods during the study

Reviewer's Comment:

The eligibility criteria are acceptable. It would have been ideal if the inclusionary age range was extended to 65 or greater to include representation from older adults with schizophrenia. The specified schizophrenia severity (PANSS cutoffs) ensured that subjects would be greater than "moderately ill" [19] and experiencing significant positive symptoms (which are most responsive to antipsychotic medications such as risperidone). This is consistent with the clinical status of patients who may require psychiatric hospitalization for stabilization. The exclusion criteria are reasonable in terms of reducing confounding factors (such as substance use) or safety risks to subjects (such as unstable medical conditions); however, they may be less representative of real-world schizophrenia patients, many of whom have comorbid alcohol or drug use, medical comorbidities, tardive dyskinesia, or a history of failing two or more antipsychotics. Overall, the exclusionary criteria are not considered too restrictive for generalizability to the target population.

Dose Selection: The Applicant selected two doses of RBP-7000 to compare with placebo (90 mg and 120 mg SC every four weeks). These doses were selected to provide similar average plasma concentrations of risperidone + 9-hydroxyrisperidone, across the dosage period, to a daily oral risperidone dosage of 3 mg or 4 mg. The 90 mg and 120 mg SC doses (but not a lower dose of

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60 mg SC) were also reported to predict dopamine D₂ receptor occupancy of 65-80%, which is believed to optimize antipsychotic efficacy while minimizing risks of extrapyramidal symptoms [20]. Please refer to the Clinical Pharmacology review for additional information on PK and PD modeling.

Reviewer's Comment:

Studying RBP-7000 doses that provide exposures comparable to 3 to 4 mg oral risperidone per day was reasonable, and these doses are expected to be appropriate for most patients with schizophrenia. However, it would have been ideal if the Applicant had studied additional doses of RBP-7000 that could provide exposures comparable to 2 mg, 6 mg, and 8 mg oral risperidone per day, because the optimal dose for some patients is lower or higher than 3 to 4 mg per day (i.e., the labeled target dose of risperidone for the treatment of schizophrenia in adults is 4 to 8 mg daily).

Study Treatments: The three study treatments were placebo SC every four weeks, 90 mg RBP-7000 SC every four weeks, and 120 mg RBP-7000 SC every four weeks. Prior to receiving the first injections, all subjects received one 0.25-mg tablet of oral risperidone on two consecutive days to assess the tolerability of risperidone. RBP-7000 consists of two syringes: syringe A contains the ATRIGEL Delivery System (a sterile, polymeric solution) and syringe B contains risperidone powder. Prior to administration, syringes A and B are coupled and the product is mixed by pushing the contents back and forth to produce a homogenous suspension. The syringes are then uncoupled, and a sterile, 18-gauge, 1-inch needle is affixed to syringe A for injection.

Assignment to Treatment: After signing the informed consent document (ICD), subjects were assigned a unique subject number (in numerical sequence per site). Subjects who met the eligibility criteria were randomized 1:1:1 to the three treatment groups (see Study Treatments above). Randomization, performed on Day 1, was controlled by an interactive web-response system (IWRS).

Blinding: Treatment assignments were tracked by the IWRS. Each study site had an unblinded study drug manager and an unblinded individual who administered the treatment injection (fulfilled by the same or multiple individuals). The study drug manager contacted the IWRS to determine the treatment assignment, obtain the study drug, and prepare the drug for administration. A blinding label was applied to the syringe, so subjects and blinded site personnel could not see the contents. In addition, the person administering the injection did so in a separate room from the blinded study staff. The placebo and RBP-7000 injections differed in appearance (the former being clear and the latter being milky white in color), and the injection volume differed between injections (placebo: 0.65 mL, RBP-7000 90 mg: 0.6 mL, and RBP-7000 120 mg: 0.8 mL). Prolactin levels and adverse events were reviewed by the unblinded team from (b) (4); this team was described as firewalled from other study personnel.

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Reviewer's Comment:

It would have been preferable if the placebo and active injections were identical in appearance and volume. However, the Applicant took steps such as using blinding syringe labels and administering injections in a different room to mitigate this factor. The difference between injection volumes (≤ 0.2 mL) seems small enough that it would be difficult for subjects to appreciate differences if comparisons were made. With the method described above, one or two staff members at each site were aware of the assigned treatment, so it seems that there would be a greater potential for disclosure than if all study staff were blinded to treatment. However, because the drug needed to be prepared prior to use and the solutions had different appearances, it was necessary to unblind at least one staff member. Overall, the blinding procedures are deemed acceptable.

Dose Modification and Discontinuation: Each subject received two doses of the investigational product (SC injection on Days 1 and 29). There were no pre-specified dose modifications. The Applicant specified that in the event of an emergency, or if a subject is withdrawn within the first 14 days of receiving an injection, a physician identified to perform surgery could attempt to remove the localized drug product (at the discretion of the Principal Investigator (PI)). The surgical procedure would require a small incision in the abdomen with a sterile scalpel where the drug product was injected, removal of the implant with forceps, irrigation of the incision with sterile normal saline, and closure of the incision with suturing.

Reviewer's Comment:

The Applicant's lack of a pre-specified plan for dose modification (for example, allowing the reduction of the second injection dose from 120 mg to 90 mg risperidone) is acceptable; the 120-mg dose produces exposure equivalent to risperidone 4 mg PO daily, which is at the lower end of the labeled target dose of 4 to 8 mg daily for adults with schizophrenia. It is a strength of the protocol that there was an allowable procedure for removing the implant (and this would not be possible with other LAI antipsychotic products).

Administrative Structure: Each study site had a designated PI, and the protocol was reviewed by an Institutional Review Board (IRB) with responsibility at that location. Each PI was responsible for ensuring that the clinical study was performed in accordance with the protocol, current ICH guidelines on good clinical practice (GCP), and applicable regulatory requirements. The Applicant assigned clinical monitors to periodically contact study sites and conduct on-site visits, as documented in the clinical monitoring plan and the site initiation visit report. There was no data monitoring committee (DMC) for this study.

Reviewer's Comment:

Although it was not required and the Applicant appeared to appropriately monitor the conduct of this study, a DMC may have been useful for additional oversight. FDA Guidance [The](#)

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[Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors](#) recommends that trial sponsors consider using a DMC when, in addition to other factors, the procedure for administering the treatment is particularly invasive, the study is being performed in a potentially vulnerable population, and the study is large, of long duration, and multi-center.

Procedures and Schedule: Please refer to Figure 1 for a schematic of the overall study design and Table 4 for a tabulation of study events.

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Table 4: Schedule of Assessments

Evaluation	Screening Period		Double-blind Treatment								Follow-up
	Visit number	1	2	3	4	5	6	7	8	9	10
	Day	-8 to -3	-1	1	2	15 ± 1	29	30	43 ± 1	57 ± 1	64 ± 1
Oral Risperidone Administration		X									
Treatment Injection				X			X				
Demographics, Medical History, Psychiatric History, SAFER Interview		X									
Efficacy Assessments (PANSS, CGI-S)		X		X		X	X		X	X	
EuroQol EQ-5D-5L		X		X						X	
SWN-S		X		X						X	
MSQ		X					X			X	
POM										X	
Physical and Neurological Examination		X		X						X	
Vital Signs ¹		X	X	X	X	X	X	X	X	X	
Body Weight ²		X		X			X			X	
Abdominal Fat Measurement (Waist-to-Hip Ratio)				X			X			X	
12-lead ECG		X		X			X			X	
Injection Site Evaluation				X	X		X	X			
Injection Site Pain Visual Analog Scale				X			X				
Chemistry ³ , Hematology ⁴ , and Urinalysis ⁵ Labs		X		X			X			X	
Serology Labs ⁶ , PT/INR, TSH		X									
Pregnancy Test ⁷		X	X							X	
Urine Drug Screen ⁸		X								X	
Pharmacokinetic Sample Collection ⁹				X	X	X	X	X	X	X	
C-SSRS (Baseline/Screening at Visit 1, Since-Last Visit at subsequent visits)		X		X	X	X	X	X	X	X	
EPS Assessments (AIMS, SAS, BARS)		X	X	X		X	X		X	X	
Adverse Event and Concomitant Medication Assessments		X	X	X	X	X	X	X	X	X	X

Source: Adapted from Study RB-US-09-0010 Protocol (Appendix 1).

Abbreviations: SAFER=State, Assessability, Face, Ecological, and Rule Interview; PANSS=Positive and Negative Syndrome Scale; CGI-S=Clinical Global Impression – Severity of Illness; EPS=extrapyramidal symptoms; AIMS=Abnormal Involuntary Movement Scale; SAS=Simpson-Angus Scale; BARS=Barnes Akathisia Rating

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Scale; SWN-S=Subjective Well-Being Under Neuroleptic Treatment, Short Version; MSQ=Medication Satisfaction Questionnaire; POM=Preference of Medicine Questionnaire; PT/INR=Prothrombin Time/International Normalized Ratio; TSH=Thyroid Stimulating Hormone; ECG=Electrocardiogram.

¹Performed <1 hour prior to injection and 12±4 hours post-injection on Visits 3 and 6; ²Height measured at Visit 3 for BMI calculations; ³Fasting for ≥8 hours except for Screening visit; includes glucose, sodium, potassium, calcium, chloride, carbon dioxide, blood urea nitrogen, creatinine, uric acid, phosphorus, magnesium, total protein, total cholesterol, albumin, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, creatine phosphokinase, gamma glutamyl transpeptidase, total bilirubin, and serum prolactin. Hemoglobin A1C measured at Visits 1 and 9; ⁴includes white blood cell count with differential, red blood cell count, hemoglobin, hematocrit, and platelet count; ⁴microscopic examination performed if results of white or red blood cell counts, casts, or crystals are abnormal; ⁶includes HIV 1/2, hepatitis B surface antigen, and hepatitis C virus antibody; ⁷FSH performed for post-menopausal subjects and serum pregnancy test used for female subjects of childbearing potential. Urine pregnancy tests were performed after subjects returned to the study site after a day pass was used; ⁸includes opioids, cocaine, amphetamines, methadone, barbiturates, benzodiazepines, methamphetamine, cannabinoids, and phencyclidine; ⁹includes samples collected on Days 1, 1-3, 8-15, 16-22, 29, 29-31, 36-42, 43-49, 55-57, and when subjects experience serious adverse events deemed related to the study drug. On injection days, the PK sample must be collected <12 hours prior to injection.

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Dietary Restrictions/Instructions: No dietary restrictions or instructions were specified in the protocol. Because subjects were hospitalized for most of the study, meals were provided by the inpatient sites. There is no reason to believe that dietary choices would impact the effectiveness of risperidone, though they could impact body weight and metabolic laboratory parameters.

Concurrent Medications: Subjects could take previously prescribed non-antipsychotic medications during the study, as directed by the Investigator. Non-antipsychotic medications could also be initiated during the study per Investigator discretion, except for those prohibited by the protocol. Concomitant use of lorazepam, propranolol, and anti-Parkinsonian medications were permitted during the study if they were not taken within 12 hours prior to administration of scales assessing efficacy or extrapyramidal symptoms. Study eligibility criteria excluded subjects who received any long-acting injectable antipsychotic within 120 days prior to Screening, mood stabilizers, inducers or inhibitors of CYP2D6 (within five half-lives of the medication or 30 days for fluoxetine), and any other medications that could be expected to significantly interact with risperidone or confound efficacy assessments. Tapering rates for washing out prohibited medications were at the discretion of the Investigator, if restricted medications were discontinued by Visit 2 (Baseline).

Reviewer's Comment:

Although the list of prohibited concomitant medications did not specifically exclude oral antipsychotics, these could be classified as mood stabilizers as well as medications that could confound efficacy assessments. The use of other antipsychotics in subjects who received the placebo injection could confound efficacy assessments by reducing the severity of schizophrenia symptoms, so it would have been ideal to explicitly exclude this class of medications. An Information Request was communicated to the Applicant on February 23, 2018, to clarify how other antipsychotics were intended to be used during the study. On March 5, 2018, the Applicant responded that the intent was that supplemental antipsychotics not be taken during the treatment period. The Applicant noted that the CSR classified any medication as concomitant if it was taken by subjects within 30 days prior to Screening through the end of study follow-up. The study design allowed subjects to be restarted on other antipsychotics after completion of the treatment period, and almost all the captured concomitant antipsychotic use occurred after the final efficacy assessment. The specification that concomitant use of benzodiazepines, propranolol, and anti-Parkinsonian medications could not be used within 12 hours of certain assessments was a reasonable approach for minimizing the confounding of safety and efficacy assessments.

Treatment Compliance: This study involved two subcutaneous injections of either placebo or RBP-7000, administered in an inpatient setting and documented accordingly. As such, monitoring treatment compliance was straightforward in this study.

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Rescue Medication: The protocol specified that rescue medications could be provided at the judgment of the site investigators. Concomitant use of a benzodiazepine, propranolol, or anti-parkinsonian medication was allowed for treatment of adverse reactions. Lorazepam was recommended as a treatment of agitation or anxiety due to psychosis, given in 1 to 2 mg divided doses, not to exceed 6 mg within 24 hours. Zolpidem (5 to 10 mg nightly) was recommended as an as-needed treatment for insomnia. Oral anticholinergic medications (≤ 4 mg benztropine equivalents per 24 hours) and propranolol (up to 60 mg/day) were suggested as treatments for emergent EPS.

Reviewer's Comment:

Rescue medication specifications seem reasonable, and specifying that they should not be used within 12 hours prior to efficacy or EPS scale administration should help reduce confounding.

Subject Completion, Discontinuation, or Withdrawal: Site investigators were permitted to withdraw subjects from the study for any of the following reasons: 1) protocol deviation that might compromise data integrity, protocol compliance, or safety; 2) AE occurrence that compromises or potentially compromises subject safety; 3) Applicant or investigator termination of the study; or 4) subject requests to be discontinued from the study (for any reason). If subjects were withdrawn from the study after receiving RBP-7000, the reason for withdrawal was to be documented and end-of-study procedures were to be performed. If subjects were withdrawn for safety reasons, they could be maintained in the inpatient setting for one week and treated as per standard of care. In the event of an emergency or if subjects withdrew within the first 14 days of an RBP-7000 injection, an attempt to surgically remove the implant could be made by the physician identified to perform surgery. All subjects were to be evaluated on their final study day (see Table 4), and subjects who completed the entire study could be eligible to enroll in the long-term safety study (RBP-US-13-0005). The Statistical Analysis Plan specified that no imputation was to be performed for missing/incomplete efficacy data, but a sensitivity analysis was to be conducted to investigate the impact of missing data assumptions.

Study Endpoints

Primary Efficacy

The primary efficacy endpoint was the change from baseline to end of treatment (Day 57) in the PANSS total score. The PANSS (see Appendix 13.3.1) is a scale used to evaluate positive symptoms, negative symptoms, and general psychopathology associated with schizophrenia [21]. The scale consists of 30 items, rated from 1 to 7. The total score, ranging from 30 to 210, is the sum of all item scores. The change in PANSS total score has been frequently used to support the approval of treatments for schizophrenia, with study durations typically between four and eight weeks.

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The baseline PANSS score was defined as the last non-missing value prior to the first dose of study medication on Day 1. As described in Section 3.2, the Division accepted the PANSS as the primary efficacy measure but recommended that the Applicant use an analysis method that could deal with missing data (such as MMRM). PANSS assessments were performed by an appropriately trained and certified individual at Screening and Days 1, 15, 29, 43, and 57. It was not noted whether the same individual conducted all ratings for a given subject, but the use of multiple raters could potentially increase measurement variability.

Reviewer's Comment:

The choice of primary efficacy endpoint is appropriate for this study, and the Applicant used an MMRM analysis model per the Division's suggestion. Of note, the PANSS is listed in the FDA Clinical Outcome Assessment (COA) Compendium for the condition of schizophrenia.

Key Secondary Efficacy

The pre-specified key secondary efficacy endpoint was the change from baseline to end of treatment (Day 57) of the CGI-S score. The CGI-S (see Appendix 13.3.2) asks the rater "Considering your total clinical experience with this particular population, how mentally ill is the patient at this time?" Score options are: 0=not assessed; 1=normal, not at all ill; 2=borderline mentally ill; 3=mildly ill; 4=moderately ill; 5=markedly ill; 6=severely ill; and 7=among the most extremely ill patients. The CGI-S was also administered by an appropriately trained and certified individual at the same visits as the PANSS. The CGI is frequently used as a key secondary endpoint (intended for labeling inclusion) in antipsychotic development programs, and it is included in the current Risperdal label.

Reviewer's Comment:

The choice of key secondary endpoint is also considered appropriate for this study, provided statistical analysis methods were used that account for multiple testing. A measure such as the CGI-S is useful for providing a global clinical assessment, but a limitation of this measure is that it depends on the rater's total clinical experience with the population. Therefore, it may be less meaningful if multiple raters are used to evaluate a subject over the course of a study and if study investigators vary in clinical experience across the sites.

Additional Secondary Endpoints

The following outcome measures were administered but not specified as efficacy outcomes in the Statistical Analysis Plan.

- EuroQol EQ-5D-5L (Appendix 13.3.3) – standardized, patient-reported instrument for measuring health status. This instrument includes a descriptive system with five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five levels of severity within each dimension), as well as a

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visual analog scale that records the subjects' self-rated health between "the best health you can imagine" and "the worst health you can imagine."

- Subjective Well-Being Under Neuroleptic Treatment Scale – Short Version (SWN-S, Appendix 13.3.4) – patient-rated instrument with 20 items designed to capture subjects' subjective well-being. Each item is scored on a Likert-scale with six response categories (ranging from "not at all" to "very much"). Each item is scored from 1 to 6, with a minimum total score of 20 (indicating low subjective well-being) and a maximum total score of 120 (indicating good subjective well-being). In addition to the total score, the SWN-S has five subscales (mental functioning, self-control, emotional regulation, physical functioning, and social integration).
- Medication Satisfaction Questionnaire (MSQ, Appendix 13.3.5) – single-item questionnaire that evaluates satisfaction with antipsychotic medications in patients with schizophrenia.
- Preference of Medicine Questionnaire (POM, Appendix 13.3.6) – two-item questionnaire assessing the preference for the current antipsychotic as compared with the most recent pre-study antipsychotic. One item is addressed to the subject and the other item to the subject's caregiver (if available).

Reviewer's Comment:

Because analysis of these additional scales was not planned, their results are not suitable for labeling. They may, however, provide useful exploratory information for review purposes.

Statistical Analysis Plan

Version 1.0 of the Statistical Analysis Plan (SAP) was dated July 29, 2014, and version 2.4 was dated February 18, 2015.

(b) (4)

(b) (4)

The SAP does not appear to have been formally submitted to the IND, but specific elements included in the SAP were reviewed by Biometrics reviewers Drs. Yeh Fong Chen and Andrejus Parfionovas between July 1, 2013, and January 2, 2015. On December 8, 2017, the Applicant responded to an information request submitted by the Agency that noted that the treatment effect was estimated in the CSR as the average treatment differences across all visits for both primary and key secondary efficacy endpoints; this was inconsistent with the treatment effect definition in the protocol and SAP (treatment difference at the end of study visit). The Applicant

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acknowledged this discrepancy and provided post-hoc efficacy analyses per the SAP. On March 14, 2018, the Division communicated to the Applicant that the PANSS scores assessed at the early termination visits should be excluded from the analysis sets for the primary and key secondary endpoints.

Please refer to the statistical review for additional details.

Analysis Populations

- All subjects randomized set (RND) – all subjects who were enrolled and randomized to study medication or placebo. Subjects were classified per the assigned treatment even if it differed from the received treatment.
- Intent-to-treat population (ITT) – all subjects in the RND set who received at least one dose of RBP-7000 or placebo and had data for at least one post-baseline total PANSS score, such that the change from baseline could be calculated. Subjects were classified per their randomized treatment.
- Per-protocol population (PP) – all subjects in the ITT population who did not experience any major protocol violations (defined as those that may affect the integrity of data as determined by the Applicant).
- Safety population (SAF) – all subjects in the RND set who received at least one dose of RBP-7000 or placebo. Subjects were classified per the treatment received.

Reviewer's Comment:

The analysis set definitions appear to be reasonable, though the RND population is technically more like a traditionally-defined ITT population and the Applicant's ITT population could be classified as a modified ITT population.

Missing Data

No imputation was planned for missing or incomplete PANSS assessments for the primary efficacy analysis. The Applicant planned to conduct sensitivity analyses to investigate the impact of missing data assumptions; these analyses consisted of a pattern mixture model and a multiple imputation approach.

Multiplicity

The SAP specifies that the significance level for the final analysis of the primary efficacy endpoint will be determined by Dunnett's procedure for controlling Type I error at 2.5% (one-sided), where each dose (90 mg and 120 mg) of RBP-7000 will be compared to placebo. The significance level for the key secondary endpoint will be compared across treatment groups using a decision tree based on the parallel gatekeeping procedure. If data did not support statistical superiority of RBP-7000 (90 mg or 120 mg) over placebo on the primary efficacy endpoint, no test would be performed for the key secondary endpoint.

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Interim Analysis

No interim analysis was planned for this study.

Planned Subgroup Analyses

No subgroup analyses were planned for this study.

Protocol Amendments

There were five amendments to this study protocol. The changes specified in the amendments were reviewed, with noteworthy changes highlighted below:

Amendment 1 (January 9, 2014)

- Addition of eligibility criteria excluding subjects who were previously taking oral risperidone at doses ≥ 6 mg/day.
- Addition of injection site pain visual analog scale measure to be completed 1, 5, 30, and 60 minutes after each injection.

Amendment 2 (February 19, 2014)

- A blinding label will be applied to study treatment syringes to help maintain the blind.
- Lorazepam, zolpidem, and anti-parkinsonian medications are to be restricted within the 12-hour period prior to administration of scales that could be confounded by their usage (PANSS, CGI-S, SAS, BARS, AIMS).
- The primary efficacy endpoint was updated to state that superiority of RBP-7000 over placebo will be demonstrated if one or both one-sided p-values for testing H01 or H02 satisfy $p\text{-value} < 0.0135$ (allowing for Dunnett's multiplicity adjustment). H01 is the difference in mean change from baseline in PANSS total score between RBP-7000 90 mg and placebo ≥ 0 , and H02 is the difference in mean change from baseline in PANSS total score between RBP-7000 120 mg and placebo ≥ 0 .
- Hypotheses and the parallel gatekeeping procedure were added for statistical evaluation of the key secondary endpoint (CGI-S).

Amendment 3 (April 9, 2014)

- Subjects who have been hospitalized for more than 14 days in the current episode prior to study screening will be excluded from the study.
- For the exclusion criterion of a positive urine drug screen, an exception was made for cannabinoids. The presence of cannabinoids may not be exclusionary if the investigator assesses there to be no dependence, the medical monitor approves the subject's continuation, and the subject agrees to abstain for the duration of the study.
- For the study treatments, text that "only unblinded personnel can prepare the study drug" was added.
- The use of mood stabilizers during the study will now not be permitted.

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Amendment 4 (August 6, 2014) – no noteworthy changes

Amendment 5 (August 14, 2014) – no noteworthy changes

Reviewer's Comment:

The protocol changes incorporated in the amendments seem to have been reasonable. The first subject in this study was randomized on (b) (6), and the last subject was completed on (b) (6). This indicates that changes that could theoretically affect interpretation of the study results were implemented before any subjects had been enrolled or very early in the study timeline.

6.1.2. Study Results

Compliance with Good Clinical Practices

The Applicant states that the study protocol, amendments, written study subject information, informed consent form, and other appropriate study-related information were reviewed by an independent ethics committee or institutional review board at each study site. The Applicant attests that the study was conducted in accordance with Good Clinical Practice.

Financial Disclosure

Please refer to Appendix 13.2 for details. There are no disclosed financial interests/arrangements or missing disclosures that raise questions about the integrity of study data.

Patient Disposition

Please refer to Table 5 for an overview of subject disposition. A total of 538 subjects were screened for participation at 33 sites, with 354 (65.8%) randomized to treatment. Of the 354 randomized subjects, there were 337 subjects in the ITT population. Of the 17 subjects who were randomized but not in the ITT population, 4 were identified as screen failures after randomization and never received treatment, and 13 received one dose of treatment but had no post-baseline efficacy measurements (withdrawing from the study one to three days after receiving treatment).

Reviewer's Comment:

The percentages of randomized subjects in the ITT population for each treatment arm were similar (94-96%), and 70-78% of subjects in each treatment arm completed the study, which is reasonable for a study of this nature. There do not appear to be significant imbalances in discontinuation reasons between the groups.

Table 5: Study RB-US-09-0010 - Subject Disposition (All Randomized Subjects)

Statistic		Treatment Group			Total (N=354)
		RBP-7000 90 mg (N=116)	RBP-7000 120 mg (N=119)	Placebo (N=119)	
Number of Subjects in the Safety Population	n (%)	115 (99.1)	117 (98.3)	118 (99.2)	350 (98.9)
Number of Subjects in the ITT Population	n (%)	111 (95.7)	114 (95.8)	112 (94.1)	337 (95.2)
Number of Subjects in the Per-Protocol Population	n (%)	96 (82.8)	96 (80.7)	99 (83.2)	291 (82.2)
Completed the Study	n (%)	90 (77.6)	85 (71.4)	84 (70.6)	259 (73.2)
Discontinued from the Study					
Withdrew consent	n (%)	20 (17.2)	25 (21.0)	21 (17.6)	66 (18.6)
Withdrawn by investigator	n (%)	3 (2.6)	4 (3.4)	5 (4.2)	12 (3.4)
Insufficient clinical response	n (%)	2 (1.7)	0	4 (3.4)	6 (1.7)
Adverse event	n (%)	0	2 (1.7)	3 (2.5)	5 (1.4)
Protocol deviation	n (%)	0	3 (2.5)	1 (0.8)	4 (1.1)
Lost to follow-up	n (%)	1 (0.9)	0	1 (0.8)	2 (0.6)
Sponsor discontinued study	n (%)	0	0	0	0
Continuing into Open-label Study	n (%)	31 (26.7)	34 (28.6)	29 (24.4)	94 (26.6)

ITT = intent-to-treat.

Notes: All subjects who were randomized and received at least 1 dose of study drug are in the Safety Population. All subjects who were randomized, received at least 1 dose of study drug, and had a baseline and at least 1 postbaseline efficacy measurement are in the ITT Population. All subjects who were in the ITT population and had no protocol deviations are in the Per-Protocol Population. All percentages are based on the number of randomized subjects.

Source: Clinical Study Report, Table 5 (p. 64)

Protocol Violations/Deviations

Please refer to Table 6 for a summary of protocol deviations. Overall, deviations occurred in a higher proportion of subjects in RBP-7000 treatment arms than placebo. The defined categories of deviations were reasonably well balanced between treatment arms.

Reviewer's Comment:

The incidence of protocol deviations across all treatment arms does not seem excessive for a trial of this nature (range: 11.6-15.8%) and do not raise significant concerns about the study conduct. Although some deviations might impact efficacy findings for individual subjects, I do not believe that they significantly affect the study conclusions, because they are fairly balanced

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across treatment arms and occurred at a relatively low rate compared to the overall study population.

Table 6: Study RB-US-09-0010 - Summary of Protocol Deviations (ITT Population)

Deviation	Statistic	Treatment Group			Total (N=337)
		RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)	Placebo (N=112)	
Subjects with at least 1 deviation	n (%)	15(13.5)	18(15.8)	13(11.6)	46(13.6)
Prohibited medications	n (%)	14(12.6)	13(11.4)	12(10.7)	39(11.6)
Randomized but did not meet all I/E criteria ^a	n (%)	9(8.1)	8(7.0)	8(7.1)	25(7.4)
Illicit drug use	n (%)	1(0.9)	2(1.8)	0	3(0.9)
Protocol deviation recorded on eCRF termination form	n (%)	0	2(1.8)	1(0.9)	3(0.9)
Critical or major site deviation	n (%)	1(0.9)	1(0.9)	0	2(0.6)
Received incorrect study treatment	n (%)	1(0.9)	1(0.9)	0	2(0.6)

eCRF = electronic case report form; I/E = inclusion/exclusion.

Notes: All subjects with protocol deviations are excluded from the Per-Protocol Population. Subjects with more than 1 type of protocol deviation are counted more than once in the table.

a One subject in the placebo group was found to be noncompliant with I/E criteria after conclusion of the study and database lock; this subject was not included in this analysis.¹

Source: Clinical Study Report, Table 6 (p. 65)

Prohibited Medications

In a response to an information request received on March 30, 2018, the Applicant provided additional details about deviations related to prohibited medications. Many of the subjects recorded as having prohibited medication protocol deviations in Table 6 were individuals that discontinued the restricted medications before Day -1 but did not have at least a 5-day washout period prior to this date. A post-hoc listing clarified which subjects took prohibited medications from Day 1 through Day 57/end-of-study; the Applicant believes that this group of subjects were those in whom prohibited medications could possibly affect efficacy and safety assessments. In this listing, there were six subjects who took prohibited medications (two in each treatment arm). The prohibited medications were ranitidine for acid reflux (two subjects), trazodone for insomnia (one subject), diphenhydramine for urticaria (one subject in the placebo group, and paliperidone and aripiprazole (discussed below in Concomitant Antipsychotic Use).

Concomitant Antipsychotic Use

As discussed in Section 6.1.1: Concurrent Medications, the Applicant did not explicitly exclude the use of oral antipsychotics during the study, raising concerns that their potential

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concomitant use could confound interpretation of efficacy and safety data. Antipsychotics are classified as medications that could confound efficacy assessments, so their concomitant use was a protocol violation. In Table 14.1.5.2 of the RB-US-09-0010 Clinical Study Report, the Applicant presented a tabulation of subjects with concomitant medications in the Safety population:

Table 7: Study RB-US-09-0010 - Concomitant Antipsychotic Use Described in Clinical Study Report

Drug	RBP-7000 90 mg (N=115 total), n (%)	RBP-7000 120 mg (N=117 total), n (%)	Placebo (N=118 total), n (%)
Aripiprazole	1 (0.9)	9 (7.7)	5 (4.2)
Asenapine	1 (0.9)	0	3 (2.5)
Haloperidol	3 (2.6)	4 (3.4)	4 (3.4)
Lurasidone	0	3 (2.6)	1 (0.8)
Olanzapine	4 (3.5)	4 (3.4)	4 (3.4)
Paliperidone	1 (0.9)	1 (0.9)	2 (1.6)
Quetiapine	18 (13.1)	9 (7.7)	17 (14.4)
Risperidone	13 (11.3)	10 (8.5)	8 (6.8)
Ziprasidone	0	2 (1.7)	1 (0.8)
All Antipsychotics	41 (35.7)	42 (35.9)	45 (38.1)

Source: Adapted from Clinical Study Report, Table 14.1.5.2. In the CSR, medications were classified as concomitant if taken by subjects within 30 days prior to Screening through the end of study follow-up.

On face, although there was no clear imbalance in concomitant antipsychotic use between the treatment groups, the fact that over one third of the subjects appeared to be receiving a concomitant medication that could clearly confound efficacy and safety assessments was initially concerning in review. In response to an Information Request submitted on February 23, 2018, the Applicant clarified that the CSR captured medications as concomitant if taken by subjects within 30 days prior to Screening through the end of study follow-up. Subjects could be restarted on other antipsychotics after completing the study treatment period. Accordingly, almost all subjects specified as taking concomitant antipsychotics (Table 7) started the medications after the final efficacy assessment.

The Applicant identified only two subjects ((b) (6)) who received supplemental antipsychotics during the treatment period and were included in the primary efficacy analysis. Subject (b) (6) randomized to receive RBP-7000 120 mg, started taking aripiprazole (10 mg PO daily) 13 days prior to the final efficacy assessment. Subject (b) (6), randomized to receive RBP-7000 90 mg, took paliperidone (3 mg PO QHS) for the first 7 days of the treatment period.

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Reviewer's Comment:

The use of concomitant oral antipsychotics during the treatment period was infrequent, occurring in only one subject in each RBP-7000 dose arm. Although it is possible that the use may have confounded efficacy assessments (hypothetically improving PANSS scores), its occurrence in two subjects is unlikely to impact overall study conclusions. The Applicant submitted a per protocol analysis of the primary efficacy endpoint that excluded the two subjects who received supplemental antipsychotics (Study RB-US-09-0010 Clinical Study Report, Post Hoc Table 14.2.1.2.1a), and both 90 mg and 120 mg doses of RBP-7000 remained superior to placebo (nominal $p = 0.0041$ and $p < 0.0001$, respectively).

Subjects Randomized but Did Not Meet All Inclusion and Exclusion Criteria

The Applicant provided additional details about the 25 subjects that were recorded as being randomized but not meeting all inclusion/exclusion criteria. Of these subjects, 22 of 25 did not meet exclusion criterion 6 (taking mood stabilizers or inducers or inhibitors of CYP2D6 within five half-lives (or 30 days for fluoxetine) prior to Day -1). There was some overlap between these subjects and those with prohibited medication deviations, as described under Prohibited Medications above.

Reviewer's Comment:

It is unlikely that these subjects affected overall study conclusions, as it hypothetically might make it more difficult to observe an RBP-7000 treatment effect if the prohibited medications lowered baseline schizophrenia symptom severity.

Critical or Major Site Deviations

The Applicant provided additional information about the two “critical or major site deviation” cases, which were both incorrect treatment doses. Subject (b) (6) received the first RBP-7000 injection at 90 mg instead of 120 mg, and Subject (b) (6) received the first injection at 120 mg instead of 90 mg. These subjects corresponded to those identified as having received incorrect study treatments in Table 6.

Reviewer's Comment:

If this error occurred more frequently, it could have potentially diminished the observed dose-response of RBP-7000. However, because it happened only twice, both to subjects who were randomized to receive active treatment rather than placebo, and both at only the first injection, these deviations are unlikely to significantly impact study conclusions.

Table of Demographic Characteristics

Please refer to Table 8 for a summary of demographic information across the treatment groups. There were approximately three times as many male as female subjects in the study, and this imbalance was evident in all treatment arms. The placebo group trended slightly older than the

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RBP-7000 treatment groups, but the differences do not appear substantial, and the age range approximates the patient population who would use this drug. Race and ethnicity demographics did not reflect the overall U.S. population, as Black or African American patients were overrepresented in the sample (72.1% overall), and other races and Hispanic ethnicity were underrepresented in the sample.

Reviewer's Comment:

Overall, assessment of demographic parameters did not reveal significant imbalances between the treatment groups. It would have been ideal if women and other races/ethnicities were better represented in the sample as compared to the U.S. population, but the sample appears adequate for assessing product efficacy. Some degree of underrepresentation of women may be expected, because women are reported to have a later age of illness onset as well as have a more favorable illness course (i.e., hospitalization rate and duration) than men until they reach menopause. The difference in schizophrenia expression between genders has been hypothesized to be related to estrogen levels, which may have antipsychotic properties [22]. The racial representation may, in part, reflect racial variations in the psychopharmacologic management of schizophrenia as reported in the literature; African-American patients may be nearly three times as likely to receive depot antipsychotic medications than Caucasian patients [23]. The authors speculate that this discrepancy might be due to multiple patient, provider, and administrative factors that influence prescribing decisions. Under Efficacy Results, I analyze results per demographic and other baseline characteristics and assess whether there are obvious differences in treatment effects between groups.

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Table 8: Study RB-US-09-0010 - Demographic Characteristics, ITT Population

Demographic Parameters	Placebo (N=112) n (%)	RBP-7000 90 mg (N=111) n (%)	RBP-7000 120 mg (N=114) n (%)	Total (N=337) n (%)
Sex				
Male	81 (72.3)	93 (83.8)	84 (73.7)	258 (76.6)
Female	31 (27.7)	18 (16.2)	30 (26.3)	79 (23.4)
Age				
Mean years (SD)	42.8 (8.7)	40.5 (9.5)	40.4 (9.5)	41.2 (9.3)
Median (years)	45.0	41.0	41.5	43.0
Min, max (years)	20, 55	19, 55	18, 54	18, 55
Age Group				
18 to 40 years	41 (36.6)	53 (47.7)	54 (47.4)	148 (43.9)
41 to 55 years	71 (63.4)	58 (52.3)	60 (52.6)	189 (56.1)
Race				
White	25 (22.3)	28 (25.2)	30 (26.3)	83 (24.6)
Black or African American	84 (75.0)	79 (71.2)	80 (70.2)	243 (72.1)
Asian	1 (0.9)	1 (0.9)	3 (2.6)	5 (1.5)
American Indian or Alaska Native	0	0	0	0
Native Hawaiian or Other Pacific Islander	1 (0.9)	1 (0.9)	1 (0.9)	3 (0.9)
Other	1 (0.9)	2 (1.8)	0	3 (0.9)
Ethnicity				
Hispanic or Latino	10 (8.9)	7 (6.3)	9 (7.9)	26 (7.7)
Not Hispanic or Latino	101 (90.2)	104 (93.7)	104 (91.2)	309 (91.7)
Unknown	1 (0.9)	0	1 (0.9)	2 (0.6)

Source: Adapted from Clinical Study Report, Table 14.1.3.1

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Other Baseline Characteristics

Please refer to Table 9 for a summary of other baseline characteristics across the treatment groups. Overall, the sample was generally overweight to obese, with greater than moderate schizophrenia severity at baseline. The subjects' age at first diagnosis was generally in their 20s, and they had a duration of illness of approximately 15 years.

Though not displayed in the table below, all but two subjects had previously been treated with antipsychotics, and all but seven subjects had other preexisting medical and/or psychiatric conditions. Noteworthy preexisting comorbidities included insomnia (79%), anxiety (66%), depression (17%), prior drug abuse (6%), hypertension (26%), diabetes mellitus (7%), and lipid disorders (8%). Approximately 95% of patients were taking other medications at study entry. The most widely used category of prior medications were of the nervous system class (used by approximately 95% of patients); this class included benzodiazepines, antipsychotics, antiparkinsonian, antidepressants, anxiolytics, and mood stabilizers. The tabulation of prior medications was reviewed in the Clinical Study Report, and there were no clear imbalances between treatment arms.

Reviewer's Comment:

Overall, the assessed baseline characteristics seem consistent with the anticipated target patient population and were generally equivalent across treatment arms. There were no clear differences that would be anticipated to impact the interpretation of study results.

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Table 9: Study RB-US-09-0010 - Other Baseline Characteristics, ITT Population

Characteristic	Placebo (N=112)	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)
Weight			
Mean (kg) (SD)	90.7 (20.8)	90.9 (18.9)	88.5 (20.3)
Min, max (kg)	51.7, 180.5	52.2, 136.8	51.7, 161.9
Body Mass Index			
Mean (kg/m ²) (SD)	31.0 (7.3)	29.6 (6.0)	29.3 (6.7)
Min, max (kg/m ²)	17.9, 55.5	18.6, 50.0	17.7, 57.1
PANSS Total Score			
Mean (SD)	94.1 (8.9)	95.5 (9.2)	94.9 (8.1)
CGI-S Score			
Mean (SD)	4.8 (0.6)	4.8 (0.6)	4.8 (0.6)
Schizophrenia Course			
Age at first diagnosis (years) (SD)	26.7 (9.1)	25.7 (8.3)	26.9 (8.5)
Duration of illness (years) (SD)	16.0 (10.1)	14.8 (9.5)	13.5 (9.5)

Adapted from Clinical Study Report, Tables 14.1.3.1, 14.2.1.3, 14.2.2.2, and analysis dataset ADSL.XPT

Treatment Compliance, Concomitant Medications, and Rescue Medication Use

The Applicant defined treatment compliance as receiving both SC injections during the study. In the ITT population, compliance rates, assessed using the COMPFL (Overall Compliance Flag) variable in ADSL.XPT, were 75% for both placebo and RBP-7000 120 mg groups and 81% for RBP-7000 90 mg.

In response to an information request, the Applicant submitted a post-hoc tabulation of subjects in the ITT population who used concomitant medications. Overall, 96.4% of subjects assigned to RBP-7000 90 mg, 95.6% assigned to 120 mg, and 98.2% assigned to placebo received at least one concomitant medication during the study. I assessed the tabulation for medications that in the nervous system category, as these could hypothetically impact interpretation of efficacy or safety findings. Overall, a slightly higher percentage of subjects assigned to placebo (97.3%) received medications in the nervous system category than those assigned to RBP-7000 90 mg (92.8%) or 120 mg (90.4%). Please see Table 10 for a summary of subjects who received concomitant benzodiazepines, non-benzodiazepine GABA_A agonists, or antiparkinsonian agents.

Table 10: Study RB-US-09-0010 - Selected Concomitant Medication Use, ITT Population

	Placebo (N=112)	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)
Benzodiazepines (e.g., alprazolam, clonazepam, diazepam, lorazepam) n= (%)	92 (82.1%)	83 (74.8%)	90 (78.9%)
Non-benzodiazepine GABA_A agonists (e.g., zolpidem, eszopiclone) n= (%)	82 (73.2%)	75 (67.6%)	88 (77.2%)
Antiparkinsonian agents (i.e., benztropine, diphenhydramine, trihexyphenidyl) n= (%)	14 (12.5%)	14 (12.6%)	12 (10.5%)

Source: Adapted from Post-hoc Table 14.1.5.2.1 (pp. 10-18, in a Response to Information Request received on March 30, 2018)

Reviewer's Comments:

- Compliance rates were similar between treatment arms in the ITT population and were reasonable for a study of this nature.
- The percentages of subjects who received concomitant benzodiazepines or non-benzodiazepine GABA_A agonists were similar between the treatment arms. These medications are frequently used for anxiety, agitation, and insomnia in inpatient psychiatric units, so the high incidence is not unexpected for a two-month hospital stay. Because these drugs could not be administered within 12 hours of efficacy and EPS assessments, it is unlikely that the scores were confounded by acute drug effects.
- The percentages of subjects who received concomitant antiparkinsonian agents were approximately equal between treatment arms and considered relatively low for a study of this nature. Because these drugs could not be administered within 12 hours of efficacy and EPS assessments, it is unlikely that scores were confounded by acute drug effects.

Efficacy Results – Primary Endpoint

Analysis of the primary efficacy endpoint was conducted as specified in the SAP, except subjects who had early termination visits were treated as dropouts, and only scores prior to early termination visits were used in the primary analysis set for these subjects. Please refer to Table 11 for PANSS total score changes from baseline at each time point and Figure 2 for a graphical depiction, as analyzed and prepared by Biometrics reviewer Kelly (Yang) Yang, PhD. Each dose of RBP-7000 were found to be statistically superior to placebo on the primary efficacy measure after applying Dunnett's procedure for multiple treatment comparisons (90 mg: adjusted p=0.0273; 120 mg: adjusted p <0.0001). These results provide evidence of effectiveness for both tested doses of RBP-7000.

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Visual inspection of the time course of response (Figure 2) suggests apparent treatment benefit with RBP-7000 at the first efficacy assessment (Day 15), and a dose-response relationship began to appear by the second efficacy assessment (Day 29). Inspection of the treatment – placebo differences (Table 11) suggests that maximal drug effects are achieved by Day 43. Further improvements in PANSS total scores at Day 57 seen in all treatment groups may be attributable to factors such as the structure or supportive milieu of the hospital environment.

Table 11: Study RB-US-09-0010 - PANSS Total Score Change from Baseline to Day 57, MMRM Analysis, ITT Population

Time Point	Treatment Group	n	Adjusted Mean Change from Baseline	SE	Difference in Adjusted Means (placebo-active)	95% CI	P-value
Day 15	RBP-7000 90 mg	106	-11.17	1.07	-4.54	(-7.51, -1.56)	0.0029
	RBP-7000 120 mg	108	-11.23	1.06	-4.60	(-7.55, -1.64)	0.0024
	Placebo	107	-6.63	1.07			
Day 29	RBP-7000 90 mg	102	-14.75	1.38	-5.42	(-9.25, -1.59)	0.0057
	RBP-7000 120 mg	96	-16.61	1.39	-7.28	(-11.12, -3.43)	0.0002
	Placebo	100	-9.34	1.38			
Day 43	RBP-7000 90 mg	93	-18.27	1.44	-7.78	(-11.77, -3.78)	0.0002
	RBP-7000 120 mg	88	-21.23	1.45	-10.74	(-14.75, -6.73)	<0.0001
	Placebo	95	-10.49	1.43			
Day 57	RBP-7000 90 mg	90	-19.86	1.56	-6.50	(-10.87, -2.13)	0.0037
	RBP-7000 120 mg	85	-23.61	1.58	-10.24	(-14.64, -5.85)	<0.0001
	Placebo	84	-13.37	1.58			

Source: Biometrics reviewer Dr. Yang (Kelly) Yang. Abbreviations: ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; n=number of subjects; SE=standard error. Estimates, SEs, two-sided confidence intervals (CI) and p-values are based on a repeated measures linear regression model of the change from baseline score, with fixed effects for visit as a categorical variable, baseline score, and treatment and treatment by visit interaction, assuming an unstructured covariance matrix. Tabulated CIs and p-values are unadjusted for multiple treatment comparisons.

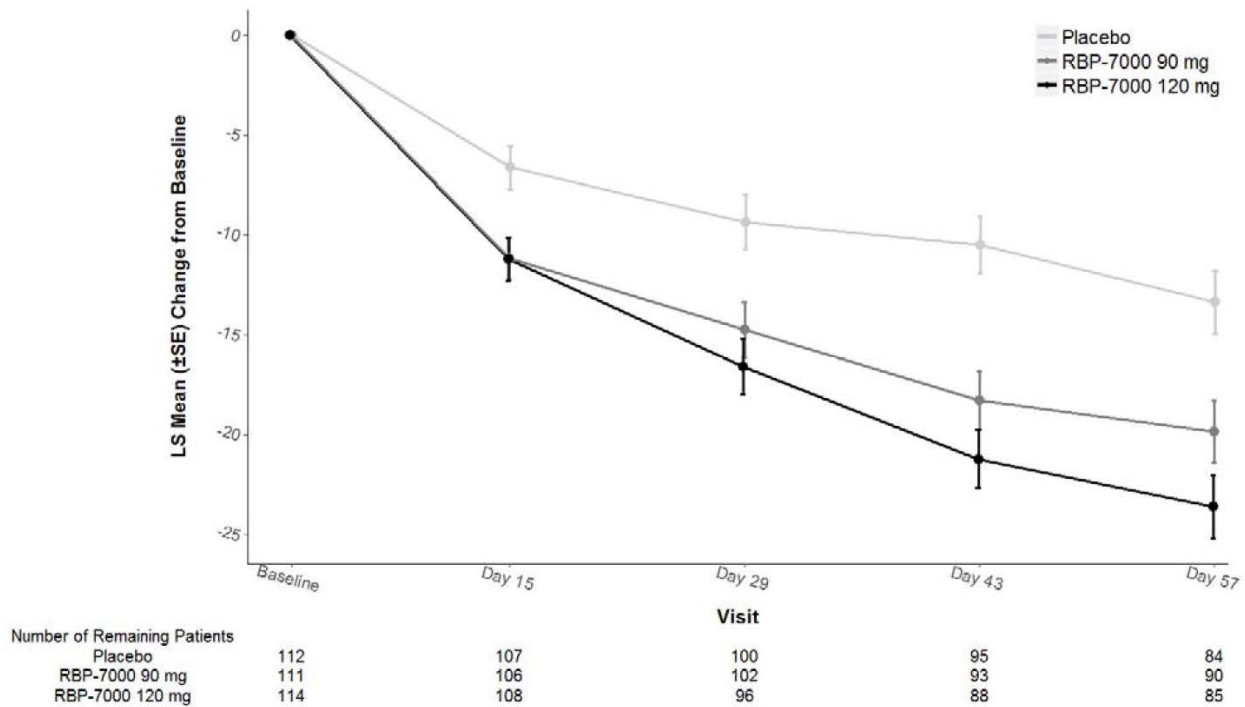
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Figure 2: Study RB-US-09-0010 - PANSS Total Score Change from Baseline, MMRM Analysis, ITT Population



Source: Biometrics reviewer Dr. Yang (Kelly) Yang

On March 23, 2018, the Applicant submitted an information amendment with revised efficacy analyses that excluded scores from early termination visits. The least squares mean treatment differences and p-values (Table 12) were similar to those calculated by Dr. Yang in Table 11. The slight differences between the analyses are attributable to the Applicant including early termination visit data for six subjects who discontinued at a scheduled study visit. Dr. Yang has indicated that the Applicant's approach is acceptable, and the minor differences do not change overall conclusions.

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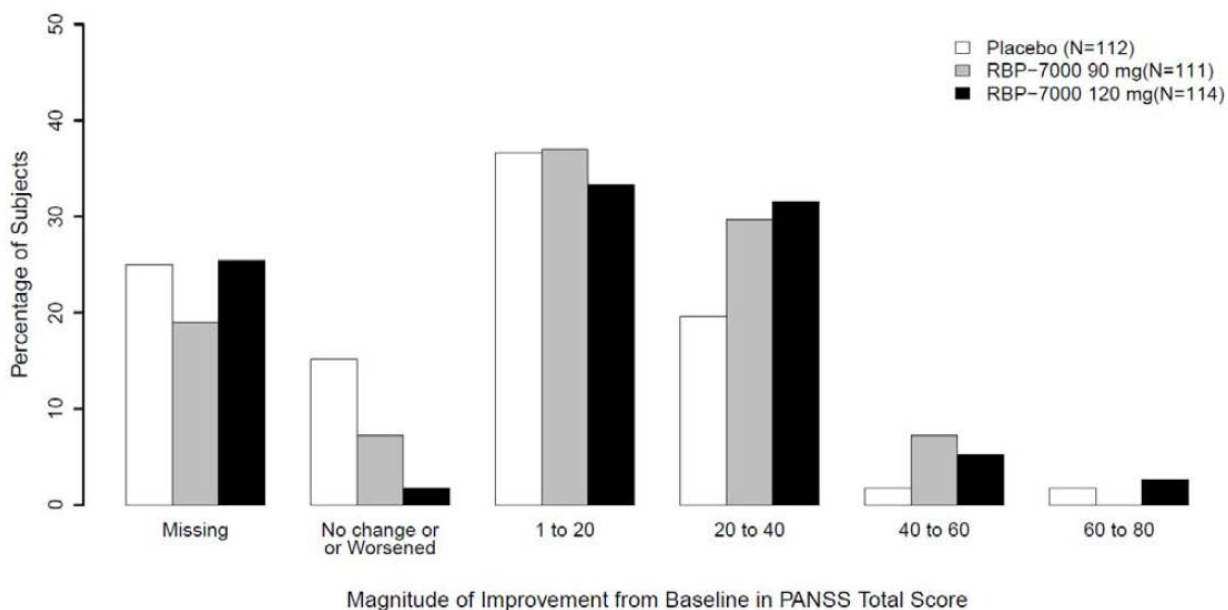
Table 12: Study RB-US-09-0010 - Applicant-submitted PANSS Total Score Change from Baseline, MMRM Analysis, ITT Population

Visit	Statistic	Treatment Group					
		RBP-7000 90 mg (N=111)		RBP-7000 120 mg (N=114)		Placebo (N=112)	
		Observed	Change	Observed	Change	Observed	Change
Day 57	n	90		85		84	
	Mean (SD)	74.69 (15.560)	-20.68 (15.288)	70.84 (13.821)	-23.48 (15.339)	78.33 (17.453)	-15.27 (17.275)
	LSmean (SE)		-19.86 (1.563)		-23.61 (1.584)		-13.37 (1.576)
	95% CI of LS mean		(-22.94, -16.79)		(-26.73, -20.49)		(-16.47, -10.27)
	LSmean Diff (SE)		-6.50 (2.220)		-10.24 (2.234)		
	95% CI		(-12.51, -0.49)		(-16.29, -4.20)		
	P-value		0.0037		<0.0001		

Source: Applicant-submitted information amendment, March 23, 2018, page 7; as per Dr. Yang's review, the Applicant's reported confidence intervals, but not the p-values, were adjusted for multiplicity.

In addition to MMRM analysis, Dr. Yang analyzed the primary efficacy measure using a pattern mixture model (PMM). This analysis supported the overall efficacy conclusions for both doses of RBP-7000. Dr. Yang also analyzed the efficacy results by creating a histogram with the percentage of subjects that achieved specified magnitudes of improvement for each treatment arm (Figure 3). This analysis illustrates that a smaller percentage of subjects receiving RBP-7000 treatment had no change or worsening PANSS total scores, and a larger percentage of subjects receiving RBP-7000 had improvements of 20 to 60 points, as compared to placebo.

Figure 3: Study RB-US-09-0010 - Percentage of Subjects with Specified Magnitudes of Improvements in PANSS total scores at Day 57, ITT Population



Source: created by Biostatistics reviewer, Dr. Kelly Yang

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To further explore the primary efficacy results, I conducted a subpopulation analysis to assess whether demographic or other baseline patient characteristics appear to be associated with differences in efficacy. The analysis dataset ADSL.XPT was used to group patients by age range, sex, race, ethnicity, BMI, baseline PANSS total score, age at first diagnosis of schizophrenia, and duration of schizophrenia illness. Only subjects who completed the study (n=259), having both baseline and Day 57 PANSS scores, were included in this analysis. The mean change from baseline to Day 57 on the PANSS total score was compared across subgroups, and the mean active treatment minus placebo difference is presented below in Table 13.

Both doses of RBP-7000 were numerically superior in almost every subgroup, with the only exceptions being groups with very small numbers, such as races other than Black or White (n=7). Similarly, there was a numerical superiority of the 120 mg vs. 90 mg dose of RBP-7000 in most subgroups, with exceptions only in groups with small numbers. Although the study was not designed to support efficacy conclusions across subgroups, factors that hypothetically might be associated with a lower magnitude of treatment effect were younger age (18 to 40 years), higher BMI (obese classification), lower baseline total PANSS score (<95), and higher age at initial schizophrenia diagnosis (≥ 24 years old).

Table 13: Study RB-US-09-0010 - Exploratory Subpopulation Efficacy Analysis, Completers

			Day 57 PANSS Total Score Change from Baseline									Mean RBP-7000 - placebo difference	
			Placebo			RBP-7000 90 mg			RBP-7000 120 mg			90 mg	120 mg
		n= (% of population)	n=	mean	SEM	n=	mean	SEM	n=	mean	SEM		
All Completers		259 (100)	84	-15.3	1.9	90	-20.7	1.6	85	-23.5	1.7	-5.4	-8.2
Age Group	18-40 years	110 (42)	29	-17.0	3.8	43	-20.7	2.5	38	-23.3	2.6	-3.7	-6.3
	>40 years	149 (58)	55	-14.4	2.1	47	-20.7	2.1	47	-23.7	2.2	-6.3	-9.3
Sex	F	58 (22)	23	-13.1	3.6	13	-20.6	4.8	22	-20.9	2.3	-7.5	-7.7
	M	201 (78)	61	-16.1	2.2	90	-20.7	1.6	85	-23.5	1.7	-4.6	-7.4
Race	Black	188 (73)	64	-15.4	2.2	65	-20.5	1.8	59	-24.5	2.0	-5.0	-9.0
	White	64 (25)	19	-14.5	4.2	22	-22.5	3.7	23	-21.5	3.2	-8.0	-7.0
	Other	7 (3)	1	-20.0	0.0	3	-11.7	6.0	3	-19.3	7.0	8.3	0.7
Ethnicity	Hispanic/Latino	20 (8)	7	-7.4	3.7	4	-16.5	6.8	9	-11.2	3.8	-9.1	-3.8
	Not Hispanic/Latino	239 (92)	77	-16.0	2.0	86	-20.9	1.7	76	-24.9	1.7	-4.9	-8.9
BMI	<30 kg/m ²	149 (58)	47	-16.3	2.1	50	-23.6	2.1	52	-24.5	2.4	-7.3	-8.2
	≥30 kg/m ²	110 (42)	37	-14.0	3.4	40	-17.0	2.4	33	-21.9	2.1	-3.0	-7.9
Baseline PANSS Total Score	<95	129 (50)	48	-12.3	2.0	42	-15.9	2.0	39	-19.0	2.0	-3.5	-6.7
	≥95	130 (50)	36	-19.2	3.4	48	-24.9	2.3	46	-27.3	2.4	-5.7	-8.1
Age at First Diagnosis of Schizophrenia	<24 years	117 (45)	38	-16.1	2.7	43	-23.4	2.5	36	-27.2	3.1	-7.4	-11.1
	≥24 years	142 (55)	46	-14.6	2.7	47	-18.1	2.0	49	-20.8	1.7	-3.5	-6.1
Schizophrenia Illness Duration	<10 years	97 (37)	26	-13.6	2.5	31	-18.2	2.7	40	-22.8	2.3	-4.6	-9.2
	≥10 years	162 (63)	58	-16.0	2.5	59	-22.0	2.0	45	-24.1	2.4	-6.0	-8.0

Source: Reviewer-created, as described in text. Sample includes patients in the ITT population who completed the study (N=259).

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Data Quality and Integrity

Please refer to Section 4.1 for discussion of OSI inspections for two sites that participated in this study. OSI concluded that the data generated from both sites appeared acceptable in support of the NDA. During the review, the Applicant complied with several requests for additional information about study data and provided additional tabulations and analyses in a timely manner. Overall, the quality and integrity of study data appears to be acceptable.

Efficacy Results – Secondary and other relevant endpoints

Per the SAP, analysis of the key secondary endpoint (CGI-S change from baseline at Day 57) was permitted because the primary efficacy endpoints were statistically significant for both doses of RBP-7000. Both 90-mg and 120-mg doses of RBP-7000 were demonstrated to be statistically superior to placebo on the key secondary endpoint (Table 14). Adjusted p-values for the key secondary endpoint, as calculated by Dr. Yang, were p=0.0425 for 90 mg and p=0.0001 for 120 mg RBP-7000.

Table 14: Study RB-US-09-0010 - Key Secondary Efficacy Analysis (CGI-S change from baseline to Day 57), ITT Population

PANSS Total Score	Placebo (N=112)	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)
Day 57			
N	90	85	84
LS Mean (SE)	-1.12 (0.090)	-1.35 (0.092)	-0.77 (0.091)
Difference of LS Mean (SE) (vs. Placebo)		-0.35 (0.128)	-0.58 (0.129)
Unadjusted 95% CI of Difference ^a		(-0.61, -0.10)	(-0.83, -0.32)
Unadjusted p-value (vs. Placebo) ^b		0.0061	<0.0001

Abbreviations: ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; n=number of subjects; SE=standard error a. Estimates, standard errors (SE), unadjusted two-sided confidence intervals (CIs) and p-values are based on a repeated measures linear regression model of the change from Baseline score, with fixed effects for visit as a categorical variable, baseline score, treatment and treatment by visit interaction, assuming an unstructured covariance matrix.

Source: Adapted from Applicant-submitted information amendment, March 23, 2018 (Table 14.2.2.1.1a); ^{a,b}unadjusted confidence intervals and p-values are from Dr. Yang's review

Reviewer's Comment:

Statistical significance for both doses of RBP-7000 on the key secondary endpoint, CGI-S change from baseline to Day 57, support conclusions from primary efficacy analyses and suggest that clinician raters can appreciate greater global clinical improvement from RBP-7000 than placebo.

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Results from additional secondary endpoints (described in Section 6.1.1: Additional Secondary Endpoints) will be discussed only briefly, because their analyses were not pre-specified in the SAP and statistical testing was uncontrolled for multiple comparisons.

EQ-5D-5L

Please refer to Table 15 for the Applicant's tabulation of results on the EQ-5D-5L. Subjects who received RBP-7000 had a numerically-greater improvement on the visual analog scale component of this measure than placebo, suggesting that RBP-7000 treatment might improve patients' self-reported overall perception of their health. Likewise, the numerical change on the EQ-5D-5L Index Score was greater for both doses of RBP-7000 over placebo, although a dose-response was not seen for the Index Score.

Table 15: Study RB-US-09-0010 - EQ-5D-5L Change from Baseline, ITT Population

Treatment	LS Mean (SE)	95% CI	P-value
EQ-5D-5L VAS			
Placebo (N=112)	3.295 (1.730)	-0.109, 6.700	--
RBP-7000 90 mg (N=111)	5.156 (1.753)	1.706, 8.605	0.3824
RBP-7000 120 mg (N=114)	8.184 (1.643)	4.949, 11.418	0.0212
EQ-5D-5L Index Score			
Placebo (N=112)	0.031 (0.016)	-0.000, 0.063	--
RBP-7000 90 mg (N=111)	0.067 (0.016)	0.035, 0.099	0.0697
RBP-7000 120 mg (N=114)	0.056 (0.015)	0.027, 0.086	0.1945

a From ANCOVA model with covariates of centre and baseline EQ-5D-5L scores; P-values for RBP-7000 90 mg or RBP-7000 120 mg versus placebo change from baseline EQ-5D-5L scores.

Source: Applicant-submitted Summary of Clinical Efficacy, p. 110. VAS=visual analog scale; LS=least squares; CI=confidence interval. P-values are nominal, uncontrolled for multiplicity.

SWN-S

Please refer to Table 16 for the Applicant's tabulation of results on the SWN-S. Subjects who received RBP-7000 had a dose-dependent numerically-greater improvement on the SWN-S Self-control, Physical Functioning, Emotional Regulation, and Total score. This suggests that RBP-7000 treatment might improve several components of subjective mental and physical well-being.

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Table 16: Study RB-US-09-0010 - SWN-S Change from Baseline, ITT Population

Score/Treatment	LS Mean (SE)	95% CI	P-value ^a
SWN-S Mental Functioning			
Placebo (N=112)	2.181 (0.462)	1.272, 3.090	–
RBP-7000 90 mg (N=111)	3.027 (0.468)	2.106, 3.948	0.1372
RBP-7000 120 mg (N=114)	2.678 (0.439)	1.814, 3.543	0.3786
SWN-S Self-control			
Placebo (N=112)	1.130 (0.356)	0.429, 1.831	–
RBP-7000 90 mg (N=111)	1.492 (0.362)	0.780, 2.204	0.4108
RBP-7000 120 mg (N=114)	1.703 (0.338)	1.037, 2.368	0.1883
SWN-S Physical Functioning			
Placebo (N=112)	0.750 (0.416)	–0.069, 1.570	–
RBP-7000 90 mg (N=111)	1.675 (0.421)	0.847, 2.503	0.0713
RBP-7000 120 mg (N=114)	2.086 (0.395)	1.310, 2.863	0.0093
SWN-S Emotional Regulation			
Placebo (N=112)	1.135 (0.431)	0.287, 1.983	–
RBP-7000 90 mg (N=111)	1.699 (0.439)	0.835, 2.562	0.2897
RBP-7000 120 mg (N=114)	1.884 (0.408)	1.081, 2.687	0.1544
SWN-S Social Integration			
Placebo (N=112)	1.785 (0.424)	0.951, 2.619	–
RBP-7000 90 mg (N=111)	1.298 (0.430)	0.451, 2.145	0.3517
RBP-7000 120 mg (N=114)	2.868 (0.402)	2.077, 3.659	0.0368
SWN-S Total Score			
Placebo (N=112)	6.942 (1.586)	3.821, 10.064	–
RBP-7000 90 mg (N=111)	9.095 (1.607)	5.933, 12.258	0.2705
RBP-7000 120 mg (N=114)	10.951 (1.509)	7.980, 13.921	0.0395

^a From an ANCOVA model with covariates of centre and baseline SWN-S scores; P-values for RBP-7000 90 mg or RBP-7000 120 mg versus placebo change from baseline SWN-S scores.

Source: Applicant-submitted Summary of Clinical Efficacy, p. 111. LS=least squares; SE=standard error; CI=confidence interval. P-values are nominal, uncontrolled for multiplicity.

MSQ

Please refer to Table 17 for the Applicant's tabulation of results on the MSQ. A greater percentage of patients receiving RBP-7000 were somewhat, very, or extremely satisfied with their treatment at the End of Study than those receiving placebo and, overall, nearly three quarters of subjects receiving RBP-7000 reported being satisfied with their treatment.

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Table 17: Study RB-US-09-0010 - Medication Satisfaction (Dichotomous Analysis of MSQ), ITT Population

Time Point/Score Range	RBP-7000 90 mg (N=111) n (%)	Placebo (N=112) n (%)	P-value ^a	RBP-7000 120 mg (N=114) n (%)	Placebo (N=112) n (%)	P-value ^b
Screening						
Dissatisfied (Scores 1-4)	72 (64.9)	69 (61.6)	0.4696	80 (70.2)	69 (61.6)	0.1410
Satisfied (Scores 5-7)	32 (28.8)	38 (33.9)		28 (24.6)	38 (33.9)	
Week 4						
Dissatisfied (Scores 1-4)	39 (35.1)	51 (45.5)	0.1348	32 (28.1)	51 (45.5)	0.0125
Satisfied (Scores 5-7)	71 (64.0)	61 (54.5)		79 (69.3)	61 (54.5)	
End of Study						
Dissatisfied (Scores 1-4)	30 (27.0)	55 (49.1)	0.0009	30 (26.3)	55 (49.1)	0.0006
Satisfied (Scores 5-7)	81 (73.0)	57 (50.9)		84 (73.7)	57 (50.9)	

a Fisher's exact test comparing RBP-7000 90 mg versus placebo at screening, Visit 6 and end of study (EOS) assessments.

b Fisher's exact test comparing RBP-7000 120 mg versus placebo at screening, Visit 6 and EOS assessments.

Source: Applicant-submitted Summary of Clinical Efficacy, p. 112. P-values are nominal, uncontrolled for multiplicity.

POM

Please refer to Table 18 for the Applicant's tabulation of results on the POM. A greater percentage of patients receiving RBP-7000 expressed preference for their investigational treatment over their previous antipsychotic, as compared to those receiving placebo. The 90-mg dose of RBP-7000 was preferred by a higher percentage of subjects than the 120-mg dose.

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Table 18: Study RB-US-09-0010 - Medication Preference (Dichotomous Analysis of POM), Day 57, ITT Population

	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)	Placebo (N=112)
Preference of Medicine Score			
Much better; I prefer this medication, n (%)	42 (37.8)	31 (27.2)	25 (22.3)
Slightly better, n (%)	28 (25.2)	21 (18.4)	12 (10.7)
About the same, n (%)	25 (22.5)	43 (37.7)	34 (30.4)
Slightly worse, n (%)	6 (5.4)	11 (9.6)	19 (17.0)
Much worse, n (%)	5 (4.5)	5 (4.4)	14 (12.5)
P-value ^a	0.0001	0.0352	–
POM Scores Analysed Dichotomously			
Prefer medication much better and slightly better (scores = 1-2), n (%)	70 (63.1)	52 (45.6)	37 (33.0)
Prefer medication about the same or worse (scores = 3-5), n (%)	36 (32.4)	59 (51.8)	67 (59.8)
P-value ^b	0.0001	0.0619	–

a Pearson's Chi-square test comparing RBP-7000 90 mg or RBP-7000 120 mg versus placebo

b Fisher's exact test comparing RBP-7000 90 mg or RBP-7000 120 mg versus placebo

Source: Applicant-submitted Summary of Clinical Efficacy, p. 113. P-values are nominal, uncontrolled for multiplicity.

Reviewer's Comment:

The results on the EQ-5D-5L, SWN-S, MSQ, and POM should be interpreted with caution because the endpoints were not pre-specified in the SAP and the statistical tests were not controlled for multiple testing. The collective results on these measures suggest that subjects may appreciate benefit from RBP-7000 and were generally satisfied with the treatment, often preferring RBP-7000 over their prior antipsychotic treatment. The value of these results is that they capture subjects' subjective experience of receiving investigational treatment (see Section 1.4 – Patient Experience Data).

Dose/Dose Response

Please refer to Section 7.1.4 for an integrated summary of dose-response information. In this study, both 90-mg and 120-mg doses of RBP-7000 exhibited superior efficacy as compared to placebo. Although the doses were not compared statistically, the 120-mg dose was numerically superior to the 90-mg dose on the primary and key secondary efficacy measures (Table 11, Table 14), which is consistent with the known dose-response relationship of risperidone.

Durability of Response

The clinical benefit associated with RBP-7000 appeared to be durable over the course of this study, as illustrated by Table 11 and Figure 2; the magnitude of placebo-subtracted treatment effect appeared to increase up to Day 43 and then plateau for the remainder of the study.

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Results from this study do not suggest that treatment benefits from RBP-7000 decrease with time.

Persistence of Effect

Persistence of RBP-7000 treatment was not assessed in this study, as there were no scheduled efficacy assessments after the end of treatment. Of note, 92 subjects from this study continued into the 1-year open-label safety study, RB-US-13-0005, and there was no evidence suggesting that the treatment benefit diminished over time.

Additional Analyses Conducted on the Individual Trial

I did not conduct any additional analyses on this trial that have not been described in previous sections.

7. Integrated Review of Effectiveness

7.1. Assessment of Efficacy Across Trials

This 505(b)(2) application relies on the FDA's previous conclusions of efficacy for risperidone oral tablets (NDA 20272), in conjunction with the Phase 3 study RB-US-09-0010 (discussed in Section 6.1) and the clinical pharmacology program that established the PK bridge between RB-7000 and oral risperidone. Because there was only one adequate and well controlled study assessing the efficacy of RBP-7000, many subsections of Chapter 7.1 will not be applicable to this review.

7.1.1. Primary Endpoints

Please refer to Section 6.1.2 for a discussion of primary efficacy results from Study RB-US-09-0010.

7.1.2. Secondary and Other Endpoints

Please refer to Section 6.1.2 for a discussion of secondary efficacy results from Study RB-US-09-0010.

7.1.3. Subpopulations

Please refer to Section 6.1.2 for a discussion of efficacy results per patient subpopulation in Study RB-US-09-0010.

7.1.4. Dose and Dose-Response

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As discussed in the Clinical Pharmacology review (summarized in Section 4.5), circulating levels of total active moiety (risperidone plus 9-hydroxyrisperidone) were comparable between oral risperidone and RBP-7000. Average concentrations at steady state were similar between RBP-7000 90 mg SC monthly and risperidone 3 mg PO daily and RBP-7000 120 mg SC monthly and risperidone 4 mg PO daily. Based on PK analyses and the results from Study RB-US-09-0010, RBP-7000 does not require a loading dose or an overlap period with supplemental oral risperidone to achieve efficacy. PK was noted to be dose-proportional for the dose range from 60 mg to 120 mg RBP-7000. Although Study RB-US-09-0010 was not designed to compare the 90 mg and 120 mg doses of RBP-7000 on efficacy, the 120-mg dose was numerically superior to the 90-mg dose on the primary and key secondary endpoints, as expected from the known dose-response relationship of risperidone.

7.1.5. Onset, Duration, and Durability of Efficacy Effects

Please refer to Section 6.1.2 for a discussion of RBP-7000 onset, duration, and durability of efficacy effects.

7.2. Additional Efficacy Considerations

7.2.1. Considerations on Benefit in the Postmarket Setting

Please refer to Section 6.1.1 for a discussion of the eligibility criteria for Study RB-US-09-0010 and its generalizability to the target patient population and Section 6.1.2 for discussion of efficacy results per patient subpopulation. Of note, the studied doses of RBP-7000 are appropriate for patients who would be stable on the equivalent of 3 to 4 mg daily oral risperidone. Patients who are stable on higher doses of oral risperidone (which has a labeled recommended dosage range for the treatment of schizophrenia of 4 to 8 mg PO daily) may not receive adequate clinical benefit from 90 or 120 mg RBP-7000 monthly. In addition, Study RB-US-09-0010 was conducted in an inpatient setting with subjects who consented to receiving study treatments. Effectiveness in the postmarket setting may be affected by patient nonadherence and delays in medication administration (which can occur in outpatient clinics).

7.2.2. Other Relevant Benefits

RBP-7000 is a long-acting injectable formulation of risperidone that is proposed to be administered monthly, as compared to administrations every two weeks with the existing risperidone long acting injectable product (Risperdal Consta, NDA 21346). In addition, Risperdal Consta requires a 3-week overlap period in which an oral antipsychotic needs to be continued after the initial injection. In contrast, RBP-7000 does not require an overlap period with an oral antipsychotic to achieve efficacy. Both factors are expected to provide convenience for patients as well as care providers.

7.3. Integrated Assessment of Effectiveness

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The Applicant's submitted evidence to support marketing approval of RBP-7000 appears to meet the statutory requirement for new drug approval as described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act. Substantial evidence of effectiveness is provided by the Agency's finding of effectiveness for Risperdal oral tablets (NDA 20272), in conjunction with the results from Study RB-US-09-0010 (see Section 6.1.2) and the clinical pharmacology program that established the PK bridge between oral risperidone and RBP-7000. Study RB-US-09-0010 is considered to be an adequate and well-controlled study, and its results support the conclusion that RBP-7000 will have its purported effect under the conditions of use recommended in the proposed labeling.

Furthermore, the benefits are expected to be clinically meaningful. Although the magnitudes of change on the primary efficacy measure (PANSS total score) cannot be directly compared between Study RB-US-09-0010 and previous studies of oral risperidone (due to differences in trial design), they appear to be generally similar. In addition, Study RB-US-09-0010 collected patient-reported outcome measures on quality of life, different aspects of physical and mental well-being, and satisfaction with the investigational treatment. Although their results are not conclusive (because the endpoints were not pre-specified in the SAP and the statistical tests were not controlled for multiple testing), they collectively support the judgment that the effects of RBP-7000 will be clinically meaningful to patients.

I recommend that the efficacy results be presented in Section 14 of the Prescribing Information labeling as a line graph illustrating the change in PANSS total score over time for the treatment arms, as well as a tabulation comparing the baseline PANSS total scores, change from baseline at Day 57, and placebo-subtracted differences with confidence intervals.

8. Review of Safety (Dr. Qi Chen)

8.1. Safety Review Approach

The safety evaluation of the NDA for RBP-7000 90 and 120 mg subcutaneous (SC) injection is based on the pooled integrated summary of safety (ISS) and the Phase 3 study RB-US-09-0010 and RB-US-13-0005.

Risperdal oral tablet was approved in US in 2003 and its safety profile is well-characterized. Unsurprisingly, there is significant overlap in the safety profile of the proposed product and the labeled safety information described in the Risperdal package inserts. However, because of the form of SC injection of RBP-7000, this safety review focuses primarily on adverse events of local reaction and dose dumping effect.

The following physical findings were used to assess safety:

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- Physical examination
- Adverse events (AEs)
- Body weight, height, body mass index, and waist-to-hip ratio
- Vital signs: blood pressure, pulse, respiratory rate, oral temperature
- ECG parameters: heart rate, RR, QT, QTcF, QTcB, PR, and QRS intervals
- Laboratory parameters: hematology, chemistry, prothrombin time with international normalized ratio (PT/INR), thyroid stimulating hormone, glycosylated hemoglobin (HbA1c), serum pregnancy test, follicle-stimulating hormone, prolactin, and urinalysis, urine pregnancy test and urine drug screen.

In addition, the following structured interviews and questionnaires were used to assess safety:

- Columbia-Suicide Severity Rating Scale (C-SSRS)
- Abnormal Involuntary Movement Scale (AIMS)
- Barnes Akathisia Rating Scale (BARS)
- Simpson-Angus Scale (SAS)
- Injection Site Grading Scale
- Injection Site Pain Visual Analogue Scale

8.2. Review of the Safety Database

8.2.1. Overall Exposure

The composition of each safety population in the study is described in Table 19. Please refer to Table 20 for a tabulation of exposure duration in Phase 3 clinical trials.

Table 19: Composition of Safety Population

Safety Population	N			
	RBP-7000 90 mg	RBP-7000 120 mg	Placebo	Total
Primary safety study- study 09-0010	115	117	118	350
Long-term safety – study 13-0005	0	439	0	500

Table 20: Drug Exposure and Duration in Phase 3 Clinical Trials

	Number of patients exposed to the study drug:			
Dosage	>= 1 day	>=29 days	>=169 days	>=337 days

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dose 90 mg	114	101		
dose 120 mg	524	454	257	198

8.2.2. Relevant characteristics of the safety population

Patient demographics for the primary safety study and long-term safety study are presented in Section 6.1.2. Most subjects were male (67%-83%) and African American (72%-79%) with mean age 40-45 years. It is reported that male African Americans have higher diagnostic rates of schizophrenia but not to the extent that they are represented in these studies. By treatment group, mean subject weights were 86 to 91 kg and mean BMIs were 28 to 31 kg/m². Patient demographics are evenly distributed between the placebo, RBP-7000 90mg and RBP-7000 120 mg treatment groups. The primary study and long-term safety study were conducted in 33 and 53 clinical sites respectively in US. It is reasonable to accept that the demographics of above two safety studies are representative of patients with schizophrenia, which is the population that would receive this drug.

8.2.3. Adequacy of the safety database

The Primary Safety Study includes 350 patients. The Long-term Safety Study includes 500 patients. The size of the safety database appears adequate to draw meaningful conclusions from the study results. In addition, risperidone is a currently marketed drug, with a known safety profile.

8.3. Adequacy of Applicant's Clinical Safety Assessments

8.3.1. Issues Regarding Data Integrity and Submission Quality

There are no issues, from a safety perspective, regarding data integrity and submission quality.

8.3.2. Categorization of Adverse Events

Adverse events were coded by system organ class (SOC) and preferred term (PT) using the Medical Dictionary for Regulatory Activities (MedDRA) Version 17.0. Treatment-emergent adverse events (TEAEs) were defined as AEs that either commenced following injection of study drug (i.e., RBP-7000 or placebo) or was present prior to injection but increased in frequency or severity following injection, regardless of causality. The number and percentage of subjects with any TEAEs, drug-related TEAEs, TEAEs by severity (mild, moderate, and severe), serious TEAEs, AEs leading to discontinuation and AEs leading to death were summarized by treatment group. Causality of AEs are reported as "related" or "not related" to study drug. Applicant used injection site grading scale and injection site pain visual analogue scale to evaluate local injection site tolerability.

8.3.3. Routine Clinical Tests

The schedule for collection of routine clinical tests is presented in Section 6.1.1. The scheduling of clinical tests appears adequate to support the clinical safety review.

8.4. Safety Results

8.4.1. Deaths

There were no deaths during the short-term clinical studies, including the primary safety study. During long-term safety study 13-0005, four patients treated with RBP-7000 120 mg experienced SAEs leading to death. I reviewed the narrative summary for each death case. These patients generally had multiple predisposing factors that were likely to have significantly contributed to the fatal outcome. Cause of death was not identified in two cases. For the other two cases, with listed cause of death, not enough detailed information for further analysis was available.

- Patient (b) (6), a 53-year-old black man with history of hyperlipidemia, died of cardiac arrest 15 days after the seventh (last) injection of RBP-7000. No autopsy or toxicology tests were performed. Patient's has history of smoking 1 pack of cigarettes every 2-3 days.

Reviewer's comment: unknown death cause, might be of myocardial infarction or ventricular tachycardia. Sponsor had evaluated the potential of RBP-7000 to dose-dump through pressure to the depot, increased temperature and exercise. It is not likely caused by dose-dumping hypothetically induced by abdominal trauma. Risperidone has an established safety profile that has no cardiovascular correlation.

- Patient (b) (6) a 39-year-old black woman with history of obesity, smoking, cocaine use and cannabis use, died 6 days after the eleventh (last) injection of RBP-7000 due to massive bilateral pulmonary embolism. Patient was not taking birth control pills. Autopsy reported pulmonary thromboembolism and venous stasis change in the distal lower extremities. Toxicological examination findings were insignificant.

Reviewer's comment: patient's risk factor for PE includes obesity, smoking, standing for long hours prior to the incident. Although there are several observational and case history studies indicating possible risk increase of hypercoagulation and risperidone use, the evidence is not enough for causality. In this fatal case, the information is not enough to determine causality as well.

- Patient (b) (6), a 36-year-old black man had a history of drug abuse, alcohol use and rehabilitation therapy. He was hospitalized for increased psychosis 28 days after the

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sixth (last) injection of RBP-7000. Patient died for unknown reason in hospital at 21 hours in hospital. No autopsy reports were provided. The toxicology assessment on admission was reported as negative for opiates, amphetamines, barbiturates, cocaine, PCP, and THC. Serum alcohol, salicylate, and acetaminophen were reported within normal limits. No image test was done in hospital.

Reviewers comments: Hospital record reviewed. Patient died for unclear reasons. Not enough information to determine causality. Onset occurred 28 days after the last injection makes drug involvement unless the worsening psychosis was the result of diminished efficacy.

- Patient (b) (6) a 52-year-old black man died after hitting his head, 3 days after the sixth (last) injection of RBP-7000. Autopsy details were not reported.

Reviewer's comment: Details of the head injury and patient's subsequent symptoms were not reported. Cause of hitting of his head was not reported. No further details were available as the family was not cooperative. No enough information to determine causality, yet being dizzy or having low blood pressure caused by the drug cannot be excluded.

8.4.2. Serious Adverse Events

During the primary safety study (09-0010), two SAEs were reported. One participant in the RBP-7000 120-mg group experienced chest pain and was hospitalized; the chest pain turned out to be non-cardiac. The other participant in the placebo group also developed chest pain, was hospitalized, and eventually ruled out cardiac cause and diagnosed dyspepsia. In the long-term safety study (13-0005), there were 46 SAEs reported in 34 (6.8%) of subjects overall during the treatment period. I summarized the SAEs in following table:

Table 21: Study RB-US-13-0005 - Serious Adverse Events (by Actual Treatment Group)

SAEs by PT term	Actual treatment				Total (N=500)
	De Novo (N=408)	Roll-Over 120mg (N=28)	Roll-Over 90mg (N=31)	Roll-Over Placebo (N=33)	
ABDOMINAL PAIN	1	0	0	0	1
ACCIDENTAL OVERDOSE	0	0	0	1	1
AGITATION	0	0	1	0	1
ANGINA UNSTABLE	1	0	0	0	1
ASTHMA	1	0	0	0	1
CARDIAC ARREST	1	0	0	0	1
CHRONIC OBSTRUCTIVE PULMONARY DISEASE	1	0	0	0	1

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SAEs by PT term	Actual treatment				Total (N=500)
	De Novo (N=408)	Roll-Over 120mg (N=28)	Roll-Over 90mg (N=31)	Roll- Over Placebo (N=33)	
DEATH	1	0	0	0	1
DEEP VEIN THROMBOSIS	0	0	1	0	1
DEPRESSIVE SYMPTOM	1	0	0	0	1
DIARRHOEA	1	0	0	0	1
DIVERTICULITIS	1	0	0	0	1
DYSPNOEA	1	0	0	0	1
FACIAL PARESIS	1	0	0	0	1
HAND FRACTURE	1	0	0	0	1
HYPERGLYCAEMIA	1	0	0	0	1
HYPOGLYCAEMIA	1	0	0	0	1
HYPOKALAEMIA	1	0	0	0	1
HYPOTENSION	1	0	0	0	1
MUSCULAR WEAKNESS	1	0	0	0	1
NAUSEA	1	0	0	0	1
NON-CARDIAC CHEST PAIN	1	0	0	0	1
PSYCHOTIC DISORDER	4	1	0	0	5
PULMONARY EMBOLISM	0	0	0	1	1
PYREXIA	1	0	0	0	1
SCHIZOPHRENIA	5	1	0	1	7
STRESS	1	0	0	0	1
SUBSTANCE USE	1	0	0	0	1
SUBSTANCE-INDUCED PSYCHOTIC DISORDER	1	0	0	0	1
SUICIDAL IDEATION	3	0	1	0	4
SUICIDE ATTEMPT	1	0	0	0	1
UTERINE LEIOMYOMA	0	1	0	0	1
VOMITING	1	0	0	0	1
Total	37	3	3	3	46

Source: Reviewer-created

All the SAEs preferred terms were reported for one subject only, except for schizophrenia exacerbation, psychotic disorder and suicidal ideation, which are considered related with the treated condition, not the medication.

Reports of serious TEAEs in the supportive safety studies (MAD, MW, SAD and FTIH) did not raise any new safety concerns.

8.4.3. Dropouts and/or Discontinuations Due to Adverse Effects

Adverse events that resulted in discontinuation were reported for 58 (11.6%) of patients during long-term safety study with treatment of RBP-2000 120mg, and for 3 (2.5%) of the placebo group and 2 (1.7%) of the RBP-2000 120mg group during the double-blind, placebo controlled study. No discontinuation due to adverse events was reported in other clinical studies (studies 09-0007, 09-0008, 09-0009 or 15-0001). The most commonly reported AEs that led to discontinuation were related to worsening of schizophrenia, akathisia, weight increased and galactorrhea, which are consistent with oral risperidone safety profile. Table 22 summarizes the adverse events that resulted in discontinuation for at least two patients during the study.

Table 22: Studies RB-US-09-0010 and RB-US-13-0005 - Reasons for Discontinuation (by Actual Treatment Groups)

Adverse Reaction	Study 09-0010				Study 13-0005							
	Placebo		RBP-7000 120mg		De Novo		Roll-Over 120mg		Roll-Over 90mg		Roll-Over Placebo	
	(N=118)	n(%)	(N=117)	n(%)	(N=408)	n(%)	(N=33)	n(%)	(N=31)	n(%)	(N=28)	n(%)
SCHIZOPHRENIA	0	0.0	0	0.0	7	1.7	1	3.0	0	0	2	7.1
AKATHISIA	0	0.0	0	0.0	4	1.0	0	0.0	0	0	0	0.0
WEIGHT INCREASED	0	0.0	0	0.0	4	1.0	0	0.0	0	0	0	0.0
GALACTORRHOEA	0	0.0	0	0.0	3	0.7	0	0.0	0	0	0	0.0
PSYCHOTIC DISORDER	2	1.7	0	0.0	1	0.2	0	0.0	0	0	0	0.0
TREMOR	0	0.0	0	0.0	1	0.2	0	0.0	0	0	2	7.1
AGITATION	0	0.0	0	0.0	1	0.2	0	0.0	1	3.2	0	0.0
BLOOD GLUCOSE INCRE..	0	0.0	0	0.0	1	0.2	1	3.0	0	0.0	0	0.0
BLOOD PROLACTIN INC..	0	0.0	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0
DYSKINESIA	0	0.0	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0
GAMMA-GLUTAMYLTRANS..	0	0.0	0	0.0	1	0.2	1	3.0	0	0.0	0	0.0
INSOMNIA	0	0.0	0	0.0	1	0.2	0	0.0	0	0.0	1	3.6
LIBIDO DECREASED	0	0.0	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0
SEDATION	0	0.0	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0
SOMNOLENCE	0	0.0	0	0.0	2	0.5	0	0.0	0	0.0	0	0.0
SUICIDAL IDEATION	0	0.0	0	0.0	1	0.2	0	0.0	1	3.2	0	0.0

Source: Reviewer-created

8.4.4. Significant Adverse Events

RBP-7000 is the first subcutaneous injection form of risperidone. Injection site reaction and dose dumping effects were of particular interest during this review.

Injection site adverse reactions affected about 22%-30% participants, and occurred an average of 2-2.6 times in each affected participant. Of the injection site reactions observed, the most

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common adverse effect in both studies is injection site pain, affecting 15%-22% participants. In the long-term safety study, the next most common adverse effects are injection site nodule and injection site induration, affecting about 6% of participants each. There is no meaningful difference among different treatment groups in incidence of each type of injection site adverse events as well as the proportion of subjects with injection site adverse events (Table 23, Table 24).

Participants maximumly received two injections in primary safety study and over 50% of them received ten injections in the long-term safety study. If the injection reaction rate (the proportion of affected subjects who reported any injection site reaction) is constant after each injection, we would expect the more injections a study group received, the higher injection reaction rate would be. However, there are no meaningful differences in injection reaction rates across three treatment groups in primary study and in the De Novo group in long-term safety study, which indicates most injection reactions happened the first couple of times, then diminished in subsequent injections. Consistent with this explanation, the injection reaction rates in roll-over groups are smaller than the De Novo group in the long-term safety study and all groups in the primary safety study. The De Novo group had no previous injection and the roll-over placebo group had previous injection with only diluent. In Chi-squared test, the odds ratio of the injection reaction rate is 1.7 with $P=0.069$ between De Novo group and roll-over groups all together and 1.6 with $P=0.14$ between De Novo group and roll-over placebo vs. roll-over 90mg and roll-over 120mg. These results suggest the injection reaction rate is likely smaller in groups of participants who had previous injection than no previous injections, but no meaningful difference between groups of participants who received previous injections with drugs vs. with diluent only, which indicate the reaction is likely caused by the procedure and/or the diluent, rather than a response to the active ingredient.

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Table 23: Study RB-US-09-0010 - TEAEs Associated with Injection

Preferred Term	Treatment Group					
	Placebo (N=118)		RBP-7000 90mg (N=115)		RBP-7000 120mg (N=117)	
	n	%	n	%	n	%
INJECTION SITE BRUISING	1	0.8	0	0	2	1.7
INJECTION SITE ERYTHEMA	6	5.1	7	6.1	5	4.3
INJECTION SITE INDURATION	4	3.4	2	1.7	5	4.3
INJECTION SITE INFECTION	0	0	0	0	1	0.9
INJECTION SITE INFLAMMATION	1	0.8	0	0	0	0
INJECTION SITE IRRITATION	0	0	1	0.9	0	0
INJECTION SITE NODULE	3	2.5	1	0.9	2	1.7
INJECTION SITE PAIN	23	19.5	18	15.7	26	22.2
INJECTION SITE PRURITUS	1	0.8	1	0.9	2	1.7
INJECTION SITE REACTION	4	3.4	3	2.6	5	4.3
INJECTION SITE SWELLING	1	0.8	1	0.9	4	3.4
NODULE	6	5.1	3	2.6	4	3.4
Total	35	9.7	26	22.6	35	29.9

Source: Reviewer-created

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Table 24: Study RB-US-13-0005 - TEAEs Associated with Injection

Preferred Term	Treatment Groups							
	De Novo (N=408)		Roll-Over RBP-7000 Placebo (N=28)		Roll-Over RBP-7000 90mg (N=31)		Roll-Over RBP-7000 120mg (N=33)	
	by affected participants		by affected participants		by affected participants		by affected participants	
	n	%	n	%	n	%	n	%
DEVICE MALFUNCTION	2	0.5	0	-	0	-	0	-
IMPLANT SITE NODULE	1	0.2	0	-	0	-	0	-
INFUSION SITE BRUISING	1	0.2	0	-	0	-	0	-
INJECTION SITE BRUISING	5	1.2	0	-	0	-	0	-
INJECTION SITE DISCOLORATION	1	0.2	0	-	0	-	1	3.0
INJECTION SITE DISCOMFORT	2	0.5	0	-	0	-	0	-
INJECTION SITE ERYTHEMA	4	1.0	0	-	2	6.5	0	-
INJECTION SITE INDURATION	26	6.4	0	-	0	-	3	9.1
INJECTION SITE IRRITATION	1	0.2	0	-	0	-	0	-
INJECTION SITE NODULE	29	7.1	1	3.6	1	3.2	3	9.1
INJECTION SITE PAIN	52	12.7	2	7.1	4	12.9	7	21.2
INJECTION SITE PRURITUS	21	5.1	1	3.6	0	-	1	3.0
INJECTION SITE REACTION	3	0.7	0	-	0	-	0	-
INJECTION SITE SWELLING	0	-	0	-	1	3.2	0	-
INJECTION SITE ULCER	1	0.2	0	-	0	-	0	-
Total	113	27.7	4	14.3	5	16.1	8	24.2

Source: Reviewer-created

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For dose dumping effect, we haven't found any anomalies in AEs or vital signs that would be consistent with dose dumping.

8.4.5. Treatment Emergent Adverse Events and Adverse Reactions

In the primary safety study, Treatment-emergent adverse events (TEAEs) were reported for 77.8% in the RBP-7000 120-mg group compared with the 70.4% in the RBP-7000 90-mg group and 68.6% in the placebo group (Table 25). The most common TEAEs, occurring $\geq 10\%$, were injection site pain, headache and weight increased in the primary safety study, and injection site pain, schizophrenia (exacerbation) and weight increased in the long-term safety study. The TEAEs reported by at least 5% of patients are shown in Table 25 for primary safety study and Table 26 for long-term safety study.

In the primary safety study, the proportions of subjects with weight increased, musculoskeletal pain and somnolence are more than twice as high in treatment groups compared to placebo. Constipation and toothache are marginally higher in treatment group compared with the placebo. I conducted statistical analysis with Poisson regression between TEAEs and treatment group vs. placebo group, with treatment duration as exposure. Weight increased was the only adverse effect that was statistically more frequent in treatment group compared to control group.

Table 25: Study RB-US-09-0010 - TEAEs Reported for ≥5% of Patients

	Treatment Group					
	RBP-7000 120 mg		RBP-7000 90 mg		Placebo	
	N=117		N=115		N=118	
Preferred Term	N Rows	Percent	N Rows	Percent	N Rows	Percent
Subjects With ≥1 TEAE	91	77.8%	81	70.4%	81	68.6%
GASTROINTESTINAL DISORDERS						
CONSTIPATION	9	7.7%	8	7.0%	6	5.1%
DYSPEPSIA	7	6.0%	4	3.5%	11	9.3%
NAUSEA	6	5.1%	5	4.3%	10	8.5%
TOOTHACHE	8	6.8%	9	7.8%	7	5.9%
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS						
BACK PAIN	8	6.8%	4	3.5%	5	4.2%
MUSCULOSKELETAL PAIN	6	5.1%	6	5.2%	3	2.5%
PAIN IN EXTREMITY	9	7.7%	1	0.9%	6	5.1%
NERVOUS SYSTEM DISORDERS						
AKATHISIA	8	6.8%	3	2.6%	5	4.2%
HEADACHE	18	15.4%	20	17.4%	28	23.7%
SOMNOLENCE	5	4.3%	6	5.2%	.	.
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS						
INJECTION SITE ERYTHEMA	5	4.3%	7	6.1%	6	5.1%
INJECTION SITE PAIN	26	22.2%	18	15.7%	23	19.5%
INVESTIGATIONS						
WEIGHT INCREASED	15	12.8%	15	13.0%	4	3.4%
PSYCHIATRIC DISORDERS						
ANXIETY	8	6.8%	3	2.6%	6	5.1%
SKIN AND SUBCUTANEOUS TISSUE DISORDERS						
PRURITUS	5	4.3%	6	5.2%	9	7.6%

Source: Reviewer-created

Table 26: Study RB-US-13-0005 - TEAEs Reported for ≥5% of Patients

Preferred Term	Treatment Group							
	De Novo		Roll-Over 120 mg		Roll-Over Placebo		Roll-Over 90 mg	
	N=408		N=33		N=28		N=31	
	N	Percent	N	Percent	N	Percent	N	Percent
	Rows		Rows		Rows		Rows	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS								
FATIGUE	12	2.9%	1	3.0%	1	3.6%	3	9.7%
INJECTION SITE NODULE	29	7.1%	3	9.1%	1	3.6%	1	3.2%
INJECTION SITE PAIN	52	12.7%	7	21.2%	2	7.1%	4	12.9%
INJECTION SITE PRURITUS	21	5.1%	1	3.0%	1	3.6%	.	.
INJECTION SITE ERYTHEMA	4	1.0%	.	.	.	.	2	6.5%
INJECTION SITE INDURATION	26	6.4%	3	9.1%	.	.	.	.
NERVOUS SYSTEM DISORDERS								
AKATHISIA	25	6.1%	1	3.0%	2	7.1%	2	6.5%
HEADACHE	20	4.9%	1	3.0%	.	.	4	12.9%
SOMNOLENCE	17	4.2%	3	9.1%	2	7.1%	.	.
PSYCHIATRIC DISORDERS								
INSOMNIA	27	6.6%	3	9.1%	1	3.6%	4	12.9%
SCHIZOPHRENIA	32	7.8%	1	3.0%	4	14.3%	2	6.5%
GASTROINTESTINAL DISORDERS								
TOOTHACHE	4	1.0%	1	3.0%	1	3.6%	2	6.5%
INFECTIONS AND INFESTATIONS								
UPPER RESPIRATORY TRACT INFECTION	23	5.6%	.	.	1	3.6%	2	6.5%
INVESTIGATIONS								
WEIGHT INCREASED	60	14.7%	3	9.1%	1	3.6%	.	.
METABOLISM AND NUTRITION DISORDERS								
INCREASED APPETITE	16	3.9%	2	6.1%	.	.	1	3.2%
REPRODUCTIVE SYSTEM AND BREAST DISORDERS								
GALACTORRHOEA	11	2.7%	2	6.1%	1	3.6%	.	.

Source: Reviewer-created

I also analyzed the recurrence of adverse events in affected subjects in both primary and long-term safety studies (Table 27 and Table 28). The proportion of affected subjects with adverse events occurring more than 2 times among treatment groups has no clinically important difference.

Table 27: Study RB-US-09-0010 - Number of Subjects with Adverse Events Occurring >2 Times

	Treatment Groups		
Preferred Term	Placebo	RBP-7000 90mg	RBP-7000 120mg
	N=118	N=115	N=117
Anxiety	1	0	0
Contusion	1	0	0
Dizziness	0	1	1
Dyspepsia	1	0	0
Headache	4	3	1
Injection site pain	3	3	1
Injection site Pruritus	0	0	1
Injection site reaction	0	1	0
Muscle tightness	0	0	1
Musculoskeletal stiffness	0	0	1
Rash	1	0	0
Toothache	1	2	0
Vomiting	1	0	0

Source: Reviewer-created

Table 28: Study RB-US-13-0005 - Number of Subjects with Adverse Events Occurring >2 Times

	Treatment Groups			
Preferred Term	De Novo	Roll-Over Placebo	Roll-Over RBP- 7000 90mg	Roll-Over RBP-7000 120mg
	N=408	N=28	N=31	N=33
Asthma	1	0	0	0
Back pain	1	0	0	0
Blood CR increased	1	0	0	0
Dermatitis atopic	1	0	0	0
Injection site inudration	8	0	0	0
Injection site nodule	7	0	0	3
Injection site pain	11	1	1	1
Melanocytic naevus	1	0	0	0
Tremor	0	1	0	0

Source: Reviewer-created

In the primary safety study, two subjects experienced severe TEAEs: one in the RBP-7000 90-mg group had toothache, and one in the RBP-7000 120-mg group had dystonia. In the long-term

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safety study, the most common severe TEAE reported were schizophrenia (5 subjects, 1.0%), weight increased (2 subjects, 0.4%) and hypotension (2 subjects, 0.4%) (Table 29).

Table 29: Study RB-US-13-0005 - Severe TEAEs, by Treatment Group

Preferred Term	Actual Treatment				Total
	De Novo	Roll-Over RBP-7000 120mg	Roll-Over RBP-7000 90mg	Roll-Over Placebo	
ANGINA UNSTABLE	1	0	0	0	1
BREAST PAIN	1	0	0	0	1
CARDIAC ARREST	1	0	0	0	1
DEATH	1	0	0	0	1
DEEP VEIN THROMBOSIS	0	0	1	0	1
DEPRESSIVE SYMPTOM	1	0	0	0	1
DIVERTICULITIS	1	0	0	0	1
DRY MOUTH	1	0	0	0	1
GALACTORRHOEA	1	0	0	0	1
HYPOTENSION	2	0	0	0	2
LIBIDO DECREASED	1	0	0	0	1
PARKINSONISM	1	0	0	0	1
PSYCHOTIC DISORDER	1	0	0	0	1
PULMONARY EMBOLISM	0	0	0	1	1
SCHIZOPHRENIA	3	1	0	1	5
SEDATION	1	0	0	0	1
SUICIDE ATTEMPT	1	0	0	0	1
TOOTHACHE	1	0	0	0	1
URINARY INCONTINENCE	0	0	1	0	1
VERTIGO	1	0	0	0	1
WEIGHT INCREASED	2	0	0	0	2
Total	22	1	2	2	27

Source: Reviewer-created

The TEAEs of schizophrenia reported in both clinical studies most likely do not represent new psychotic symptoms caused by the drug, but episodes of worsening of the patient's underlying disease, which is commonly observed over the chronic course of the illness in patients with schizophrenia, and is consistent with the oral risperidone safety profile.

8.4.6. Laboratory Findings

To detect the possible different effect on lab values between RBP-7000 treatment and placebo, I used a mixed effects model to analyze primary safety study data and combined data from the

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primary and long-term safety studies.

Metabolic Parameters

The estimated mean of cholesterol, glucose and HgA1C is significantly increased in treatment group compared to control group in primary safety study, which is consistent with oral risperidone profile.

Electrolytes (calcium, chloride, potassium, sodium, magnesium), total protein, and uric acid have statistical significant difference between treatment group and placebo group, however, the magnitude of the estimated difference is not clinically significant.

In the primary safety study, the least squares geometric mean change of phosphorus was significantly decreased (6.2%), bicarbonate significantly decreased (3.7%) and blood urea nitrogen significantly increased (5.5%) in treatment group compared to placebo. The change of phosphorus and blood urea nitrogen became insignificant in analysis of the combined data. Above analytic results may indicate possible drug effect on acute renal function, which may attenuate with long term use (Table 30).

I further conducted dose (Table 31) and threshold analyses (Table 32) on cholesterol. In the 120mg treatment group, the least squares mean change relative to placebo is 5.2 mg/dL and 3.0%. However, the change in 90mg treatment group is not significant, which indicates threshold effects on cholesterol of RBP-7000. When markedly abnormal value of cholesterol is defined as above or equal 300mg/dL, the odds ratio for a markedly abnormal value is not significant in either dose treatment group.

Table 30: Least Squares Mean Change and Least Squares Geometric Mean Change of Metabolic Parameters in Treatment Relative to Placebo in Study RB-US-09-0010 and Combined Data

Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Cholesterol (mg/dL)								
primary safety study	3.08	0.43	5.73	0.02	1.8%	0.4%	3.15%	0.01
combined data	0.51	-0.97	1.99	0.5	0.3%	-0.5%	1.1%	0.4
Glucose (mg/dL)								
primary safety study	5.84	3.61	8.06	0	4.8%	3.0%	6.7%	0
combined data	5.56	4.23	6.90	0	4.4%	3.3%	5.6%	0
HgA1C (%)								
primary safety study	0.21	0.14	0.28	0	3.6%	2.6%	4.6%	0
combined data	0.15	0.13	0.18	0	2.5%	2.1%	2.9%	0
Bicarbonate (mEq/L)								
primary safety study	-0.96	-1.22	-0.70	0	-3.7%	-4.7%	-2.7%	0
combined data	-0.95	-1.09	-0.82	0	-3.8%	-4.4%	-3.3%	0
Calcium (mg/dL)								
primary safety study	-0.04	-0.08	-0.0005	0.047	-0.4%	-0.8%	0.02%	0.06

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Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
combined data	-0.01	-0.04	0.01	0.22	-0.2%	-0.4%	0.1%	0.2
Chloride (mEq/L)								
primary safety study	-0.35	-0.61	-0.08	0.01	-0.3%	-0.6%	-0.1%	0.01
combined data	-0.16	-0.32	0.00	0.04	-0.2%	-0.3%	0.0%	0.04
Potassium (mEq/L)								
primary safety study	-0.05	-0.09	-0.01	0.007	-1.1%	-1.9%	-0.3%	0.009
combined data	-0.08	-0.11	-0.06	0	-1.8%	-2.3%	-1.3%	0
Phosphorus (mg/dL)								
primary safety study	0.23	0.17	0.28	0	6.2%	4.7%	7.7%	0
combined data	0.05	0.02	0.08	0.003	1.2%	0.3%	2.0%	0.005
Sodium (mEq/L)								
primary safety study	-0.29	-0.54	-0.04	0.02	-0.2%	-0.4%	0.0%	0.02
combined data	-0.31	-0.46	-0.15	0	-0.2%	-0.3%	-0.1%	0
Magnesium (mEq/L)								
primary safety study	-0.04	-0.05	-0.03	0	-2.4%	-3.1%	-1.6%	0
combined data	-0.02	-0.03	-0.02	0	-1.4%	-1.7%	-1.0%	0

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Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Protein total (g/dL)								
primary safety study	-0.06	-0.10	-0.01	0.02	-0.6%	-1.3%	0.0%	0.06
combined data	-0.03	-0.05	0.00	0.05	-0.3%	-0.7%	0.0%	0.07
Uric acid (mg/dL)								
primary safety study	0.29	0.20	0.37	0	5.5%	3.9%	7.1%	0
combined data	0.23	0.17	0.28	0	3.8%	2.9%	4.7%	0

Source: Reviewer-created

Table 31: Least Squares Mean Change and Geometric Mean Change in Cholesterol in Treatment by Dose, Relative to Placebo, in Study RB-US-09-0010

	Least squares mean change relative to placebo (mg/dL)	95% confidence interval (mg/dL)		P	Least squares geometric mean change relative to placebo	95% confidence interval		P
RBP-7000 90mg	0.8	-2.8	4.5	0.65	0.5%	-1.4%	2.5%	0.6
RBP-7000 120mg	5.2	1.5	8.8	0.006	3.0%	1.1%	4.9%	0.002

Source: Reviewer-created

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Table 32: Study RB-US-09-0010 - Markedly Abnormal Cholesterol Values, Relative to Placebo, in Study RB-US-09-0010

Cholesterol ≥300	Odd ratio for post-baseline measurement	95% confidence interval		P
RBP-7000 90mg	1.2	0.3	5.1	0.8
RBP-7000 120mg	0.8	0.1	4.8	0.8

Source: Reviewer-created

Hematology

Least squares mean changes of red blood cell count and hemoglobin are significantly lower in treatment group compared to placebo group (Table 33). Otherwise no meaningful significant findings require further analysis.

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Table 33: Least squares Mean Change and Geometric Least Squares Mean Change of Hematological Parameters in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Data

Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Hematocrit (%)								
primary safety study	-0.78	-1.04	-0.53	0	-1.8%	-2.4%	-1.2%	0
combined data	0.04	-0.11	0.18	0.6	0.1%	-0.2%	0.5%	0.5
Hemoglobin (g/dL)								
primary safety study	-0.26	-0.33	-0.18	0	-1.8%	-2.3%	-1.2%	0
combined data	-0.09	-0.13	-0.04	0	-0.6%	-0.9%	-0.3%	0.001
Red blood cell count (X10E6/uL)								
primary safety study	-0.07	-0.10	-0.04	0	-1.4%	-2.0%	-0.9%	0
combined data	0.01	-0.005	0.03	0.2	0.3%	-0.04%	0.6%	0.09
Red cell distribution width (%)								
primary safety study	-0.29	-0.37	-0.20	0	-1.9%	-2.4%	-1.4%	0
combined data	-0.29	0.00	0.03	0.2	0.3%	0.0%	0.6%	0.09
Mean corpuscular hemoglobin (pg/cell)								
primary safety study	-0.13	-0.21	-0.06	0	-0.4%	-0.7%	-0.2%	0
combined data	-0.12	-0.19	-0.05	0.001	-0.4%	-0.6%	-0.1%	0.002
Mean corpuscular hemoglobin concentration (g/dL)								
primary safety study	-0.01	-0.10	0.08	0.8	-0.02%	-0.3%	0.3%	0.9
combined data	-0.01	-0.03	0.07	0.7	-0.03%	-0.3%	0.2%	0.8
Mean corpuscular volume (fL)								

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Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
primary safety study	-0.37	-0.55	-0.19	0	-0.4%	-0.6%	-0.2%	0
combined data	-0.30	-0.03	-0.12	0.001	-0.3%	-0.5%	-0.1%	0.001
White blood cell count (X10E3/uL)								
primary safety study	0.12	-0.04	0.29	0.1	1.6%	-0.4%	3.7%	0.1
combined data	0.01	-0.09	0.10	0.9	0.1%	-1.1%	1.2%	0.9
Neutrophils (%)								
primary safety study	-0.55	-1.32	0.21	0.2	-0.9%	-2.3%	0.5%	0.2
combined data	-0.04	-0.46	0.39	0.9	0.1%	-0.7%	0.8%	0.9
Neutrophils Absolute (X10E3/uL)								
primary safety study	0.06	-0.09	0.20	0.5	0.7%	-2.2%	3.7%	0.6
combined data	0.00	-0.08	0.08	1.0	0.1%	-1.5%	1.7%	0.9
Eosinophils (%)								
primary safety study	0.14	-0.04	0.32	0.1	4.1%	-1.5%	10.1%	0.2
combined data	0.09	0.00	0.18	0.06	2.3%	-1.1%	5.8%	0.2
Eosinophils Absolute (X10E3/uL)								
primary safety study	0.01	-0.001	0.02	0.08	5.7%	0.3%	11.4%	0.04
combined data	0.01	0.00	0.01	0.02	2.1%	-1.1%	5.4%	0.2
Basophils (%)								
primary safety study	-0.04	-0.07	-0.004	0.03	-6.9%	-12.5%	-0.8%	0.03
combined data	-0.03	-0.05	-0.02	0	-3.5%	-6.8%	-0.1%	0.05
Basophils Absolute (X10E3/uL)								
primary safety study	-0.002	-0.004	0.001	0.2	-5.5%	-11.2%	0.6%	0.08

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Parameter (units)	least squares mean changes (treatment vs. placebo)	95% confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
combined data	-0.002	-0.004	-0.001	0.001	-3.3%	-6.7%	0.1%	0.06
Monocytes (%)								
primary safety study	0.44	0.25	0.63	0	7.3%	4.0%	10.7%	0
combined data	0.19	0.09	0.30	0	3.3%	1.5%	5.3%	0
Monocytes Absolute (X10E3/uL)								
primary safety study	0.04	0.02	0.05	0	9.2%	5.5%	13.1%	0
combined data	0.01	0.00	0.02	0.002	3.4%	1.4%	5.5%	0.001
Lymphocytes (%)								
primary safety study	0.03	-0.62	0.68	0.9	0.2%	-2.0%	2.4%	0.9
combined data	-0.23	-0.59	0.13	0.2	-0.5%	-1.8%	0.7%	0.4
Lymphocytes Absolute (X10E3/uL)								
primary safety study	0.03	-0.02	0.08	0.3	1.9%	-0.2%	4.1%	0.08
combined data	-0.01	-0.04	0.01	0.3	-0.5%	-1.6%	0.7%	0.4
Platelet count (X10E3/uL)								
primary safety study	-2.18	-5.36	1.00	0.2	-0.5%	-1.7%	0.7%	0.4
combined data	-5.58	-7.52	-3.63	0	-1.9%	-2.6%	-1.2%	0

Source: Reviewer-created

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I conducted threshold analysis with hemoglobin less than 11g/dL and 12 g/dL (Table 34). Odds ratio of markedly decreased hemoglobin to less than 11g/dL and 12g/dL is not significant in treatment group compared to placebo. Decreased hemoglobin and red blood cell count wasn't observed after oral risperidone or Risperdal Consta. This finding might be random error or multiple comparison problem in the mixed model. Fluid retention secondary to a hypothesized drug induced acute renal function effect I discussed before is also one of the possible causes.

Table 34: Markedly Abnormal Hemoglobin Values, Related to Placebo, in Study RB-US-09-0010

	Odd ratio for post-baseline measurement	95% confidence interval		P
Hemoglobin < 11 g/dL	0.97	0.19	4.96	0.97
Hemoglobin < 12 g/dL	1.57	0.67	3.68	0.3

Source: Reviewer-created

Liver-Related Tests

Hepatic enzyme increases were observed in oral risperidone clinical trials (Table 35). The least squares mean changes between treatment group and placebo are statistically significant for albumin, alkaline phosphatase, alanine transaminase and gamma-glutamyl transpeptidase. However, the differences are relatively small in magnitude and in different directions; the findings may be caused by random error instead of drug effect.

In the primary safety study, least squares geometric mean change are 9.7% for alanine transaminase and 6.5% for gamma-glutamyl transferase. However, as discussed above, this finding may due to random error and is not likely clinically significant.

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Table 35: Least Squares Mean Change and Least Squares Geometric Mean Change of Liver Function Parameters in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Data

Parameter (units)	Least squares mean changes (treatment vs. placebo)	95% Confidence interval		P value	Least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Albumin (g/dL)								
primary safety study	-0.03	-0.06	-0.004	0.03	-0.6%	-1.3%	0.05%	0.07
combined data	-0.02	-0.04	-0.01	0.007	-0.5%	-0.8%	-0.1%	0.01
Alkaline Phosphatase (U/L)								
primary safety study	-2.22	-3.66	-0.79	0.002	-2.9%	-4.8%	-1.1%	0.002
combined data	0.12	-0.54	0.79	0.7	0.4%	-0.4%	1.2%	0.3
Alanine transaminase (U/L)								
primary safety study	3.24	1.36	5.12	0.001	9.7%	5.0%	14.5%	0
combined data	1.33	0.52	2.15	0.001	0.2%	-1.9%	2.4%	0.8
Aspartate transaminase (U/L)								
primary safety study	-0.28	-1.69	1.14	0.7	-0.6%	-3.9%	2.8%	0.7
combined data	0.20	-0.36	0.75	0.5	-1.0%	-2.7%	0.7%	0.2
Gamma-glutamyl transferase (GGT)								
primary safety study	2.47	0.84	4.11	0.003	6.5%	3.2%	9.9%	0
combined data	2.16	1.05	3.27	0	2.6%	0.9%	4.4%	0.002

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Parameter (units)	Least squares mean changes (treatment vs. placebo)	95% Confidence interval		P value	Least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Bilirubin total (mg/dL)								
primary safety study	-0.01	-0.03	0.01	0.4	-0.2%	-4.7%	4.5%	0.9
combined data	0.00	-0.01	0.01	0.5	0.0%	-2.4%	2.4%	1
INR								
primary safety study	0.05	-0.07	0.16	0.4	4.3%	-6.1%	15.9%	0.4
combined data	0.02	-0.02	0.05	0.4	1.6%	-1.7%	5.1%	0.4
Prothrombin time (seconds)								
primary safety study	0.50	-0.71	1.71	0.4	4.5%	-6.0%	16.1%	0.4
combined data	0.16	-0.27	0.58	0.5	1.5%	-1.9%	5.1%	0.4

Source: Reviewer-created

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Renal function tests and Creatine Phosphokinase

In primary safety study, least squares geometric mean change is 5.5% for blood urea nitrogen in treatment group compared to placebo, and the change decreased to 0.8% and insignificant in analysis of combined data (Table 36). This result is consistent with hypothesis of acute drug induced renal function effect as I discussed above in metabolic parameters analysis, and this effect attenuate with long term drug use.

The least squares mean change for creatine phosphokinase is 16.96 U/L or 15.5% in treatment group relative to placebo in primary safety study, which was not observed after oral risperidone or Risperdal Consta use. The change became insignificant in combined data analysis. One possible cause of the increased creatine phosphokinase is muscle damage after the subcutaneous injection and the existence of a lump after injection, and this side effect gradually subsides after the body gets adjusted with the drug.

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Table 36: Least Squares Mean Change and Least Squares Geometric Mean Change of Renal Function Parameters in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Data

Parameter (units)	least squares mean changes (treatment vs. placebo)	95% Confidence interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% confidence interval		P value
Blood urea nitrogen (mg/dL)								
primary safety study	0.68	0.34	1.02	0	5.5%	2.7%	8.4%	0
combined data	0.14	-0.05	0.32	0.2	0.8%	-0.7%	2.4%	0.3
Creatinine (mg/dL)								
primary safety study	0.00	-0.01	0.01	0.7	-0.1%	-1.1%	1.0%	0.9
combined data	0.01	0.01	0.02	0	1.1%	0.5%	1.7%	0
Creatine Phosphokinase (U/L)								
primary safety study	16.96	-39.83	73.74	0.6	15.5%	8.8%	22.6%	0
combined data	-2.46	-27.57	22.65	0.8	2.9%	-0.1%	6.0%	0.06

Source: Reviewer-created

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Prolactin and Thyroid stimulating hormones

The least squares mean changes of Prolactin is significantly higher in treatment group compared to placebo group, which is consistent with the oral risperidone safety profile. There is no significant difference between treatment and placebo for thyroid-stimulating hormone.

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Table 37: Least Squares Mean Change and Least Squares Geometric Mean Change of Prolactin and Thyroid Stimulating Hormone in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Data

	least squares mean changes (treatment vs. placebo)				least squares geometric mean changes (treatment vs. placebo)	geometric 95% confidence interval		
Parameter (units)		95% Confidence interval		P value				P value
Prolactin (ng/mL)								
primary safety study	24.21	22.04	26.38	0	257.5%	232.0%	284.8%	0
combined data	12.58	11.20	13.96	0	122.4%	111.8%	133.5%	0
Thyroid-stimulating hormone (uIU/mL)								
primary safety study	-0.14	-1.08	0.79	0.8	-6.9%	-45.3%	58.3%	0.8
combined data	0.05	-0.25	0.36	0.7	2.8%	-14.5%	23.6%	0.8

Source: Reviewer-created

8.4.7. Vital Signs

I conducted mixed effects model analysis on primary safety study data and combined data to detect the possible differential effect on vital signs values between RBP-7000 treatment and placebo (Table 38). In the mixed model, systolic and diastolic blood pressure were significantly lower in treatment group compared to placebo group in combined data analysis, and pulse is significantly higher in treatment group compared to placebo group in primary safety study analysis. These findings are consistent with the oral risperidone safety profile, probably reflecting its alpha-adrenergic antagonistic properties.

The least squares mean change of weight in treatment group relative to control group is 4.22 kg in the primary safety study analysis and 3.16 kg in combined data analysis, which is consistent with oral risperidone safety profile. The estimated waist-to-hip ratio are also significantly higher in treatment group than in placebo group, which indicates that increased fat tissue may deposit more in waist area than be evenly distributed.

In dose dependent analysis (Table 39), using primary safety data and combined data, blood pressure change is not consistent between 90mg and 120mg doses and with small magnitude, the statistical significant results are likely caused by random error among multiple comparisons. In the primary safety study, the least squares mean change of pulse is significantly increased with dose effect tendency, however, the pulse increase magnitude is larger in primary safety study than in combined data, which indicates the pulse increase effect may attenuate with long term drug use. I further conducted threshold analysis of heart rate using EKG data in section 8.4.8.

Least squares mean change of weight is significantly increased in the treatment group, and the data show a dose-effect tendency, yet weight increase and dose-effect seems attenuated in long term treatment. In weight threshold analysis, the relative risk of $\geq 7\%$ increase of weight from baseline is significantly higher in treatment group compared to placebo, with an odds ratio of 2.63 for 90mg RBP-7000 and 2.96 for 120mg RBP-7000.

Mixed effect model analysis using combined data for rest of the parameters (Table 40) showed no significant dose response effect.

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Table 38: Least Squares Mean Change and Least Squares Geometric Mean Change of Vital Signs in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Safety Data

Parameter (units)	least squares mean changes (treatment vs. placebo)	95% Confidence Interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% Confidence Interval		P value
Systolic blood pressure (mmHg)								
Primary safety study	-0.57	-1.21	0.06	0.08	-0.4%	-0.9%	0.1%	0.09
studies combined	-1.20	-1.51	-0.89	0	-1.0%	-1.2%	-0.7%	0
Diastolic blood pressure (mmHg)								
Primary safety study	-0.36	-0.85	0.14	0.2	-0.4%	-1.0%	0.3%	0.3
studies combined	-0.28	-0.51	-0.05	0.02	-0.3%	-0.6%	-0.04%	0.03
Pulse (beats/min)								
Primary safety study	3.47	2.81	4.12	0	4.7%	3.8%	5.6%	0
studies combined	-0.05	-0.34	0.25	0.8	-0.1%	-0.5%	0.3%	0.6
Respiratory rate (breaths/min)								
Primary safety study	0.04	-0.08	0.16	0.5	0.3%	-0.3%	1.0%	0.4
studies combined	0.002	-0.05	0.05	0.9	-0.02%	-0.3%	0.3%	0.9
Temperature ©								
Primary safety study	0.002	-0.02	0.02	0.9	0.005%	-0.1%	0.1%	0.9
studies combined	0.03	0.02	0.04	0	0.1%	0.01%	0.1%	0.03
Body mass index (kg/m2)								
Primary safety study	1.38	1.23	1.54	0	4.7%	4.1%	5.3%	0
studies combined	1.00	0.86	1.15	0	3.2%	2.8%	3.7%	0
Weight (kg)								
Primary safety study	4.22	3.74	4.70	0	4.7%	4.1%	5.3%	0

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Parameter (units)	least squares mean changes (treatment vs. placebo)	95% Confidence Interval		P value	least squares geometric mean changes (treatment vs. placebo)	95% Confidence Interval		P value
studies combined	3.02	2.58	3.46	0	3.2%	2.8%	3.7%	0
Waist-to-hip ratio								
Primary safety study	0.01	0.004	0.02	0.002	1.3%	0.1%	2.4%	0.03
studies combined	0.01	0.01	0.01	0	1.1%	0.6%	1.6%	0

Source: Reviewer-created

Table 39: Least Squares Mean Change and Least Squares Geometric Mean Change of Blood Pressure, Heart Rate, and Weight in Treatment by Dose, Relative to Placebo, in Study RB-US-09-0010 and Combined Safety Data

Parameter (units)	mean difference (treatment vs. placebo)	geometric 95% Confidence interval		P value	geometric mean difference (treatment vs. placebo)	geometric 95% confidence interval		P value
Systolic blood pressure (mmHg)								
primary safety study								
90 mg	-0.8	-1.6	0.1	0.1	-0.6%	-1.3%	0.1%	0.1
120 mg	-0.4	-1.3	0.5	0.4	-0.3%	-1.0%	0.4%	0.5
combined studies								
90 mg	-2.0	-2.9	-1.1	0	-1.6%	-2.3%	-0.9%	0
120 mg	-1.0	-1.3	-0.7	0	-0.8%	-1.1%	-0.6%	0
Diastolic blood pressure (mmHg)								
primary safety study								
90 mg	-0.8	-1.5	-0.1	0.02	-1.0%	-1.9%	-0.1%	0.03
120 mg	0.1	-0.6	0.8	0.8	0.3%	-0.6%	1.2%	0.6

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Parameter (units)	mean difference (treatment vs. placebo)	geometric 95% Confidence interval		P value	geometric mean difference (treatment vs. placebo)	geometric 95% confidence interval		P value
combined studies								
90 mg	-1.2	-1.8	-0.6	0	-1.5%	-2.3%	-0.7%	0
120 mg	-0.1	-0.3	0.1	0.4	-0.1%	-0.4%	0.2%	0.4
PULSE (beats/min)								
primary safety study								
90 mg	3.2	2.3	4.1	0	4.4%	3.1%	5.6%	0
120 mg	3.8	2.9	4.7	0	5.1%	3.8%	6.3%	0
combined studies								
90 mg	1.9	1.1	2.7	0	2.6%	1.5%	3.7%	0
120 mg	0.01	- 0.28	0.30	0.9	-0.1%	-0.5%	0.3%	0.7
Weight (kg)								
primary safety study								
90 mg	3.6	2.9	4.3	0	3.8%	3.0%	4.7%	0
120 mg	4.8	4.3	5.4	0	5.6%	5.0%	6.2%	0
combined								
90 mg	3.1	2.0	4.1	0	3.3%	2.2%	4.5%	0
120 mg	3.1	2.6	3.5	0	3.3%	2.8%	3.7%	0

Source: Reviewer-created

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Table 40: Least Squares Mean Change and Least Squares Geometric Mean Change of Other Vital Signs in Treatment, Relative to Placebo, in Study RB-US-09-0010 and Combined Safety Data

Parameter (units)	least squares mean changes (treatment vs. placebo)	geometric 95% Confidence interval		P value	geometric least squares mean changes (treatment vs. placebo)	geometric 95% Confidence interval		P value
Body mass index (kg/m2)								
90 mg	1.0	0.6	1.3	0	3.2%	2.1%	4.4%	0
120 mg	1.0	0.9	1.2	0	3.2%	2.8%	3.7%	0
Respiratory rate (breaths/min)								
90 mg	0.09	-0.05	0.23	0.2	0.7%	-0.2%	1.6%	0.1
120 mg	-0.05	-0.10	-0.004	0.04	-0.4%	-0.7%	-0.1%	0.02
Temperature ©								
90 mg	0.02	-0.02	0.05	0.3	0.1%	-0.1%	0.3%	0.3
120 mg	0.02	0.01	0.03	0	0.0%	0.0%	0.1%	0.3
Waist-to-hip ratio								
90 mg	0.009	-0.0001	0.018	0.05	1.0%	-0.2%	2.2%	0.09
120 mg	0.010	0.006	0.014	0	1.1%	0.6%	1.6%	0

Source: Reviewer-created

Orthostatic hypotension is well established in oral risperidone and Risperdal Consta. Syncope was reported in 0.8% (12/1499 patients) of patients treated with Risperdal Consta in multiple-dose studies, and 0.2% (6/2607) of Risperdal-treated patients in Phase 2 and 3 studies in adults with schizophrenia. In clinical trials of RBP-7000, syncope was not reported in primary safety study or Phase II open-label, multiple ascending dose study, but one case in long-term safety study. No cause of dehydration was reported.

8.4.8. Electrocardiograms (ECGs)

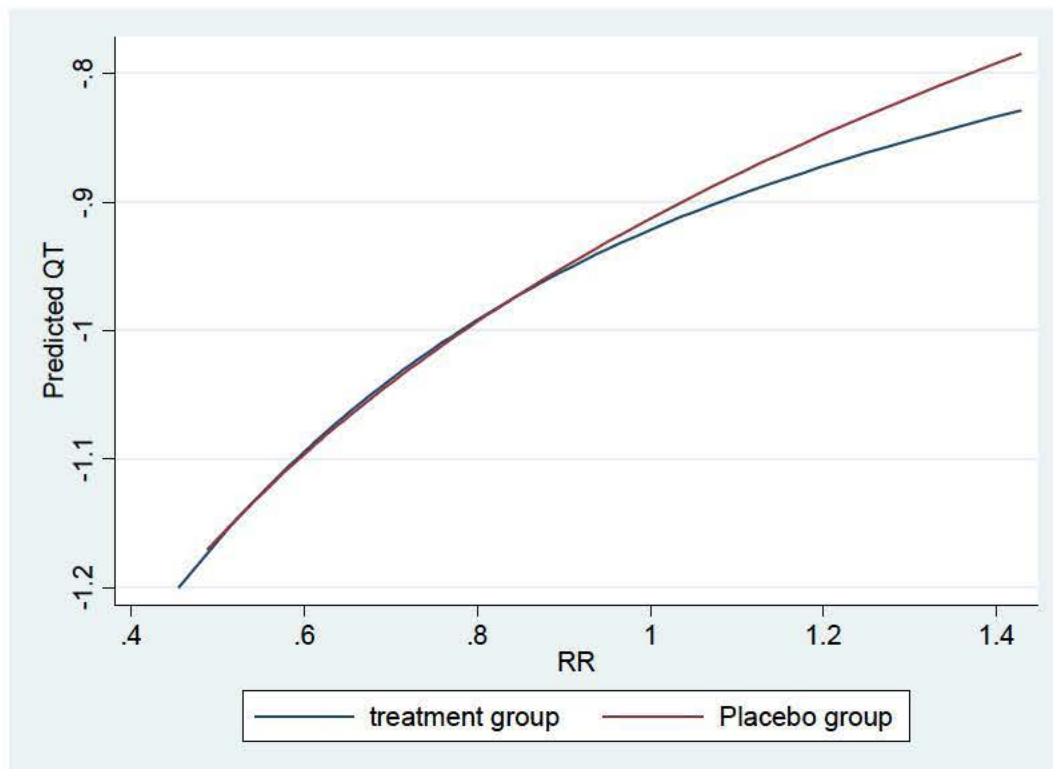
In the mixed effects model, the least squares mean change of heart rate in treatment group is 3.47 beats/min (SD 0.48, P 0.000), significantly higher than control group in the primary safety study, which is consistent with statistical analysis of heart rate using vital sign data.

In threshold analysis, the odds ratio for a heart rate over 100 beats/minute is 3.3 (confidence interval 1.5-7.1) for the treatment group relative to placebo.

8.4.9. QT

The relationship between QT and RR is frequently different than what is given by Fridericia's correction. To reduce this noise, I conducted statistical analysis using a mixed effects model with the slope of the $\ln(QT)$ to $\ln(RR)$ relationship represented in the model as random normal variable to represent variation in slopes at subject level. Furthermore, I fit a cubic spline model to avoid the assumption that the relationship between $\ln(QT)$ and $\ln(RR)$ is linear. As Figure 4 showed, predicted QT is slightly decreased in treatment group compared to placebo group.

Figure 4: Predicted QT by RR interval, Primary Safety Data



Source: Reviewer-created using a mixed-effects model with fitted cubic splines, in treatment relative to placebo in the primary safety data.

8.4.10. Immunogenicity

No data on immunogenicity submitted with this application.

8.5. Analysis of Submission-Specific Safety Issues

Injection site tolerability was evaluated by an injection site tolerability assessment (grading from 1-4), subject-reported injection site pain VAS (100-point scale) in primary safety study, proportion of subjects reporting injection site burning/stinging in Phase III studies and injection site reaction TEAEs. No meaningful difference was observed across the treatment groups and no meaningful difference in the pattern of injection site reactions following the first injection compared with subsequent injections. Most subjects who experienced pain, burning/stinging immediately after dosing reported the symptoms resolved by 3 hours post-dose. No subjects had reported of injection site pain, inflammation/swelling or erythema with a maximum

intensity of severity. Injection site tenderness with a maximum intensity of severity was reported for <1% of subjects at any time point.

8.6. Safety Analyses by Demographic Subgroups

The sponsor submitted subgroup analysis by age (18-34, 35-44, 45-54 and 55-65), sex (female and male), and race (black/African American and not black/African American) on TEAE and TEAE related discontinuation and death. There were no significant differences between strata for any demographic variable.

I conducted analysis using the same demographic subgroup for each TEAE reported by at least 5% of RBP-7000 users during the primary safety study and at a rate at least higher than the placebo rate. There are no significant differences among subgroups for each TEAE, including “weight increased, constipation, toothache, musculoskeletal pain, and somnolence”.

8.7. Specific Safety Studies/Clinical Trials

No specific human safety studies or clinical trials were submitted with this application.

8.8. Additional Safety Explorations

8.8.1. Human Carcinogenicity or Tumor Development

No new human carcinogenicity studies were submitted with this application.

8.8.2. Human Reproduction and Pregnancy

No new human reproduction or pregnancy data was submitted with this application.

8.8.3. Pediatrics and Assessment of Effects on Growth

No pediatric patients were enrolled in studies conducted in association with this application.

8.8.4. Overdose, Drug Abuse Potential, Withdrawal, and Rebound

No assessments related to these issues were submitted with this application.

8.9. Safety in the Postmarket Setting

8.9.1. Safety Concerns Identified Through Postmarket Experience

Not applicable.

8.9.2. Expectations on Safety in the Postmarket Setting

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In the instructions for use, the powder medication and liquid diluent should be mixed in between two syringes back and forth for total 60 cycles for complete mixing and the sponsor notes that “failure to fully mix the medication could result in incorrect dosage”. I am concerned the mixing process cannot be accurately performed every time in clinical practice. More post marketing information is needed to prove its applicability.

8.9.3. Additional Safety Issues From Other Disciplines

No additional safety issues have been raised by other disciplines.

8.10. Integrated Assessment of Safety

The only potential safety issue that has emerged during clinical trials is the increased creatine kinase, which may indicate muscle damage caused by the injection and local lump. This issue will be followed up in post-marketing. This safety review has not identified any safety issues that would preclude the approval of this NDA.

9. Advisory Committee Meeting and Other External Consultations

Not applicable; the Division did not convene an Advisory Committee to discuss this application.

10. Labeling Recommendations

10.1. Prescription Drug Labeling

At the time of review completion, the Prescribing Information is in negotiation with the Applicant. The following clinical recommendations for changes to the initially-proposed label have been made to the Applicant:

- Indications and Usage: The patient population (adults) was added to describe the population for whom the drug is indicated.
- Dosage and Administration:
 - Language clarifying that Perseris is not to be administered by any other route than abdominal subcutaneous injections was added to support safe product use.
 - Language describing the PK-based average daily concentrations of risperidone and total active moiety, with correspondence to daily oral risperidone dosage, was added to help guide dose selection.
 - Language that no more than one 90-mg or 120-mg dose should be administered per month was added to reduce the chance that providers will administer two

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doses in attempt to approximate higher daily oral doses of risperidone (i.e., 6 mg or 8 mg).

- Warnings and Precautions:
 - The warning (b) (4) .
 - Metabolic Changes: Data tables updated based on Safety Review.
- Clinical Trials Experience: Safety information updated based on review.
- Use in Specific Populations: Language in Pregnancy, Lactation, and Females and Males of Reproductive Potential sections were updated in accordance with the Pregnancy and Lactation Labeling Rule (PLLR).
- Clinical Studies:
 - The National Clinical Trial number was added to the description of Study RB-US-09-0010.
 - (b) (4) was removed because (b) (4) (b) (4)
 - A summary statement about subgroup effects in age, gender, and racial subgroups will be added in the discussion of results from Study RB-US-09-0010.
 - (b) (4) were removed from this section, because (b) (4)

10.2. Nonprescription Drug Labeling

Not applicable.

11. Risk Evaluation and Mitigation Strategies (REMS)

Based on clinical review, the use of a REMS does not appear to be necessary, and a favorable benefit-risk balance will be maintained through appropriate labeling. Perseris labeling includes antipsychotic class boxed warning of increased mortality of elderly patients with dementia-related psychosis. (b) (4)

(b) (4) the label emphasizes that Perseris must not be administered by a route other than subcutaneous injection in the abdomen. Perseris is labeled to only be administered by healthcare professionals, and their clinical training, in conjunction with the labeled Instructions for Use, is expected to adequately facilitate safe product administration. Of note, another product with a similar delivery system (Sublocade, NDA 209819) presents the risk of serious harm or death with intravenous administration as a boxed warning and includes a REMS program. This

approach was considered but determined to be unnecessary for Perseris, which, in contrast to Sublocade, is not a controlled substance and is therefore very unlikely to be administered by means other than a healthcare professional.

12. Postmarketing Requirements and Commitments

RBP-7000 has been developed in 90-mg and 120-mg formulations that approximate daily oral risperidone dosages of 3 mg and 4 mg, respectively. The listed drug, Risperdal tablets, specifies a target daily oral dosage of 4 to 8 mg for the treatment of schizophrenia in adults. A review article by Davis, et al., discussing the dose response and dose equivalence of antipsychotics, states that the dose-response curve for risperidone plateaus at around 4 mg per day for most patients and that the optimal daily dose of risperidone in adults with schizophrenia is 4 to 6 mg per day [24].

The Office of Surveillance and Epidemiology was consulted to provide real-world drug utilization data on the daily doses used to treat schizophrenia in adults. Their analysis of U.S. office-based physician survey data from 2014 to 2017 suggests that around 43% of adults with schizophrenia treated with oral risperidone receive 3 to 4 mg/day oral risperidone, 28% receive less than 3 mg/day, 18% receive 6 mg/day, and 5% receive greater than 6 mg/day (the dose was unspecified for the remainder of adults in the sample). Because patients who are prescribed LAI antipsychotics generally have greater illness severity than those prescribed oral antipsychotics [25], it is anticipated that there will be a significant number of patients who would benefit from an RBP-7000 dose that approximates 6 mg/day oral risperidone. In anticipation of this need, we have added language to product labeling indicating that no more than one dose of Perseris (90 mg or 120 mg total) should be given per month, because the safety and efficacy of administering two doses simultaneously has not been evaluated.

Accordingly, as a Postmarketing Commitment, we are asking the Applicant to develop a dose of RBP-7000 that approximates 6 mg/day oral risperidone. (b) (4)

13. Appendices

13.1. References

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13.2. Financial Disclosure

The Applicant appears to have adequately disclosed financial interests/arrangements with clinical investigators. There were 62 investigators identified in Form 3454 as submitted with the NDA. The Applicant certified that the listed clinical investigators did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study; had no proprietary interest in this product or significant equity interest in the sponsor of the covered study, and were not the recipient of significant payments of other sorts.

Covered Clinical Study (Name and/or Number): RB-US-09-0010 – A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study to Evaluate the Efficacy, Safety, and Tolerability of RBP-7000 (90 mg and 120 mg) as a Treatment in Subjects with Acute Schizophrenia Over 8 Weeks (2 Subcutaneous Doses)

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: <u>62</u>		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>0</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR		

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54.2(a), (b), (c) and (f):		
Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____		
Significant payments of other sorts: _____		
Proprietary interest in the product tested held by investigator: _____		
Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant)

13.3. Outcome Measure Scales

The following primary and key secondary outcome measure scales were used in Study RB-US-09-0010:

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page

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MICHAEL C DAVIS
07/08/2018

QI N CHEN
07/09/2018

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07/09/2018

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07/10/2018