Supplementary Information

An Open-Label Study to Assess Monthly Risperidone Injections (180 mg) Following Switch from Daily Oral Risperidone (6 mg) in Stable Schizophrenic Patients

David P. Walling, PhD[a]; Sunita N. Shinde, MD[b]; Janice M. Pogoda, PhD[b]; Jahnavi Kharidia, PhD[b*]; Celine M. Laffont, PhD[b]

[a]Collaborative Neuroscience Network, LLC, Garden Grove, CA USA

[b]Indivior Inc., North Chesterfield, VA USA

*Formerly employed by Indivior.

Corresponding Author:

Celine M Laffont, celine.laffont@indivior.com

Online Resource 1

Full List of Inclusion/Exclusion Criteria

The following criteria must have been met to be eligible for this study:

1. Sex: male and female, Age: ≥18 to ≤65 years
2. Diagnosis of schizophrenia, as defined by DSM-5 criteria.
3. Status: clinically stable participants defined as participants with no hospitalizations for acute exacerbations within 3 months of screening and screening total PANSS score ≤70.
4. Participants with a body mass index (BMI) between 18.0 and 35.0 kg/m^2 and who weigh at least 49.9 kg.
5. Participants who had given written informed consent.

Participants who met any of the following criteria were ineligible for participation in the study:

1. Participants who had received a once-monthly LAI antipsychotic within 60 days of screening and a once-every-3-month LAI antipsychotic within 120 days of screening.
2. Participants taking the following concurrent medication/over-the-counter (OTC) products:
   a. Inducers or inhibitors of CYP2D6 within 14 days or 5 half-lives whichever was greater prior to study screening.
   b. Bupropion, chlorpheniramine, cimetidine, clomipramine, doxepin, or quinidine within 30 days prior to study screening.
   c. Clozapine, phenothiazines, aripiprazole, haloperidol, or any other antipsychotic other than oral risperidone within 14 days prior to study screening.
   d. Selective serotonin reuptake inhibitors (SSRIs) or serotonin norepinephrine reuptake inhibitors (SNRIs) within 30 days prior to study screening.
   e. Opioids or opioid-containing analgesics within 14 days prior to study screening.
   f. Medications, in the addition to those listed above which in the opinion of the investigator in conjunction with the medical monitor, were expected to significantly interfere with the metabolism or excretion of risperidone and/or 9- hydroxyrisperidone, that were associated with a significant drug interaction with risperidone, or that may pose a significant risk to participants' participation in the study. The medical monitor was to be contacted with any questions regarding the use of CYP2D6 or 3A4 inducers or inhibitors in particular.
3. Participants with a history of cancer (with the exception of resected basal cell or squamous cell carcinoma of the skin) unless they had been disease free for ≥5 years.
4. Participants with another active medical condition or organ disease that may have either compromised participant safety or interfered with the safety and/or outcome evaluation of the study drug.

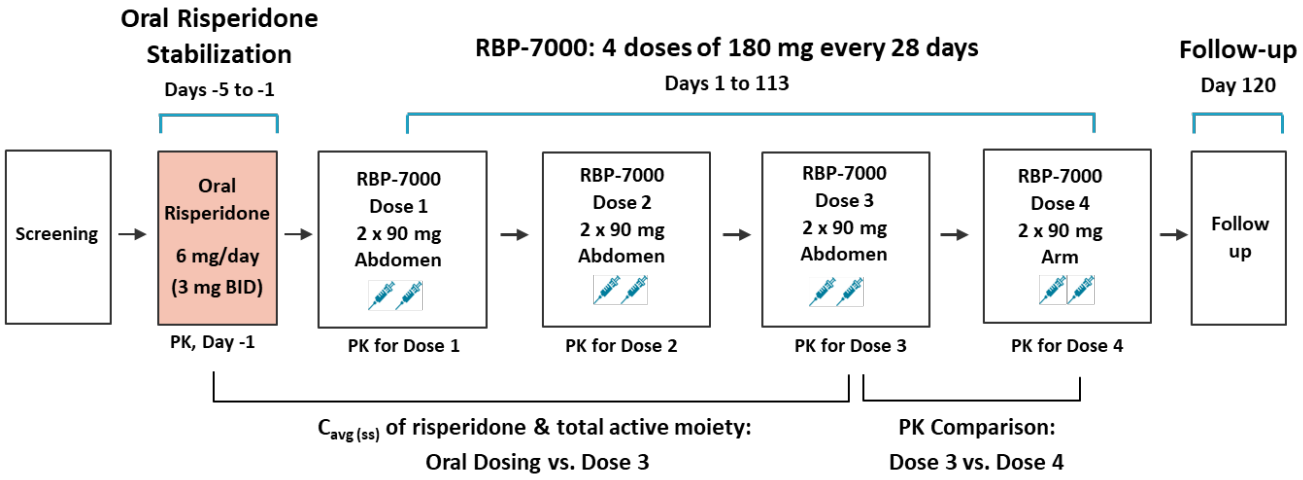
5. Participants with evidence or history of a significant hepatic disorder that may have either compromised participant safety or interfered with the safety and/or outcome evaluation of the study drug. Individuals with acute or chronic hepatitis (including but not limited to hepatitis B or C); or individuals with 1) total bilirubin >1.5x the upper limit of normal (ULN) and/or 2) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >3x ULN was excluded.
6. Participants with a history of renal disease, or a creatinine clearance of less than 60 mL/min (as determined by the Cockcroft-Gault formula).
7. Participants with a history of orthostatic hypotension, syncope, significant low white blood cell (WBC) count (i.e., absolute neutrophil count < 1.5 x 10^9 /L), or drug-induced leukopenia or other medical conditions including, but not limited to, history of heart attack (i.e., myocardial infarction) or brain injury (i.e., traumatic with loss of consciousness and/or cardiovascular accident) within a year of screening and clinically significant low blood pressure or arrhythmias as interpreted by the principal investigator (PI).
8. Participants with corrected QT interval [Fridericia's calculation (QTcF)] >450 msec (male) or >470 msec (female) at screening or prior to administration of the first dose of RBP-7000, or with a known history of Torsades de Pointes, or family member with sudden unexplained cardiac death.
9. Participants who were known to have AIDS (acquired immunodeficiency syndrome) or were to be HIV (human immunodeficiency virus) positive.
10. Participants with suicidal ideation with intent and plan (C-SSRS affirmative answers to questions 4 and 5 of the ideation section) or suicide attempts within the last 6 months, as noted on the C-SSRS, or participants with uncontrolled depression in the opinion of the investigator.
11. Participants with a known diagnosis of type 1 diabetes or participants with hemoglobin A1c (HbA1c) >8.0% at screening.
12. Participants who had participated in a clinical trial within 30 days prior to study screening.
13. Participants with significant traumatic injury, major surgery, or open biopsy within 30 days prior to study screening.
14. Participants who met the criteria for the diagnosis of current moderate or severe substance use disorder, by DSM-5 criteria.
15. Participants with prior allergic reactions, sensitivities, or other known contraindications to any component of RBP-7000 (i.e., risperidone, PLG, PLGH, or NMP).
16. Women of childbearing potential who were pregnant or breastfeeding, seeking pregnancy, or failing to use adequate contraceptive methods during the study.

a. Acceptable forms of contraception for female participants included: oral, transdermal, injectable, or implanted contraceptives, intrauterine device, or double barrier method (e.g., condom, diaphragm, cervical cap) with spermicide. Abstinence (defined abstaining from heterosexual intercourse for the duration of the study) was an acceptable form of contraception only if it was the participant's pre-existing method of contraception.
b. A woman of childbearing potential was defined as any female who was less than 2 years postmenopausal or has not undergone a hysterectomy or surgical sterilization (e.g., bilateral tubal ligation, bilateral ovariectomy [oophorectomy]). Postmenopausal status was confirmed by follicle stimulating hormone (FSH) test at initial screening.
c. Male participants with partners of childbearing potential should have utilized a double barrier contraceptive method with spermicide to prevent pregnancy. Note: Following study termination or completion, it was recommended that all participants maintain their current form of contraception for at least 30 days after the last dose of RBP-7000.

17. Participants with a positive urine drug screen (UDS) anytime through Day -1 for opioids, cocaine, amphetamines, methadone, cannabinoids, barbiturates, benzodiazepines, methamphetamine, and phencyclidine, unless the positive screen was determined to be secondary to an allowable concomitant medication. If a positive UDS was possibly the result of a participant's use of OTC or prescription medications, a repeat UDS may be permissible. Study site personnel should have contacted the medical monitor for approval to retest.
18. Participants with tardive dyskinesia as assessed by a score of ≥2 on Item 8 of the AIMS at screening.
19. Participants with epilepsy or other seizure disorders, Parkinson's disease, or dementia.
20. Participants with a history of neuroleptic malignant syndrome.
21. Participants who have been previously injected with RBP-7000 within 6 months prior to screening.
22. Participants who were unable, in the opinion of the PI, to comply fully with the study requirements.
23. Participants who were determined to be poor metabolizers, intermediate metabolizers, or ultrarapid metabolizers for CYP2D6 genotype.

Online Resource 2

Study Design



Subcutaneous administration of RBP-7000 occurred on Days 1, 29, 57 and 85.

Online Resource 3

Incidence and Number of Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

System Organ Class Preferred Term	All Subjects (N=23)	
	Number of Subjects (%)	Number of Events
Any TEAE	16 (69.6)	34
Eye disorders	1 (4.3)	1
Eye irritation	1 (4.3)	1
Gastrointestinal disorders	3 (13.0)	3
Dry mouth	1 (4.3)	1
Dyspepsia	1 (4.3)	1
Vomiting	1 (4.3)	1
General disorders and administration site conditions	2 (8.7)	2
Injection site pain	1 (4.3)	1
Sluggishness	1 (4.3)	1
Infections and infestations	3 (13.0)	4
Gastroenteritis	1 (4.3)	1
Upper respiratory tract infection	3 (13.0)	3
Injury, poisoning and procedural complications	4 (17.4)	5
Exposure via direct contact	1 (4.3)	1
Fall	2 (8.7)	2
Joint injury	1 (4.3)	1
Skin laceration	1 (4.3)	1
Investigations	3 (13.0)	4
Blood pressure increased	1 (4.3)	1
Blood prolactin increased	2 (8.7)	2
Weight increased	1 (4.3)	1
Metabolism and nutrition disorders	3 (13.0)	4
Decreased appetite	2 (8.7)	2
Hypercholesterolaemia	1 (4.3)	1
Increased appetite	1 (4.3)	1
Musculoskeletal and connective tissue disorders	1 (4.3)	1
Back pain	1 (4.3)	1

Nervous system disorders	5 (21.7)	7
Akathisia	1 (4.3)	1
Dyskinesia	2 (8.7)	2
Headache	2 (8.7)	2
Parkinsonian gait	1 (4.3)	1
Tremor	1 (4.3)	1
Respiratory, thoracic and mediastinal disorders	1 (4.3)	1
Nasal congestion	1 (4.3)	1
Skin and subcutaneous tissue disorders	1 (4.3)	1
Rash	1 (4.3)	1
Surgical and medical procedures	1 (4.3)	1
Tooth extraction	1 (4.3)	1

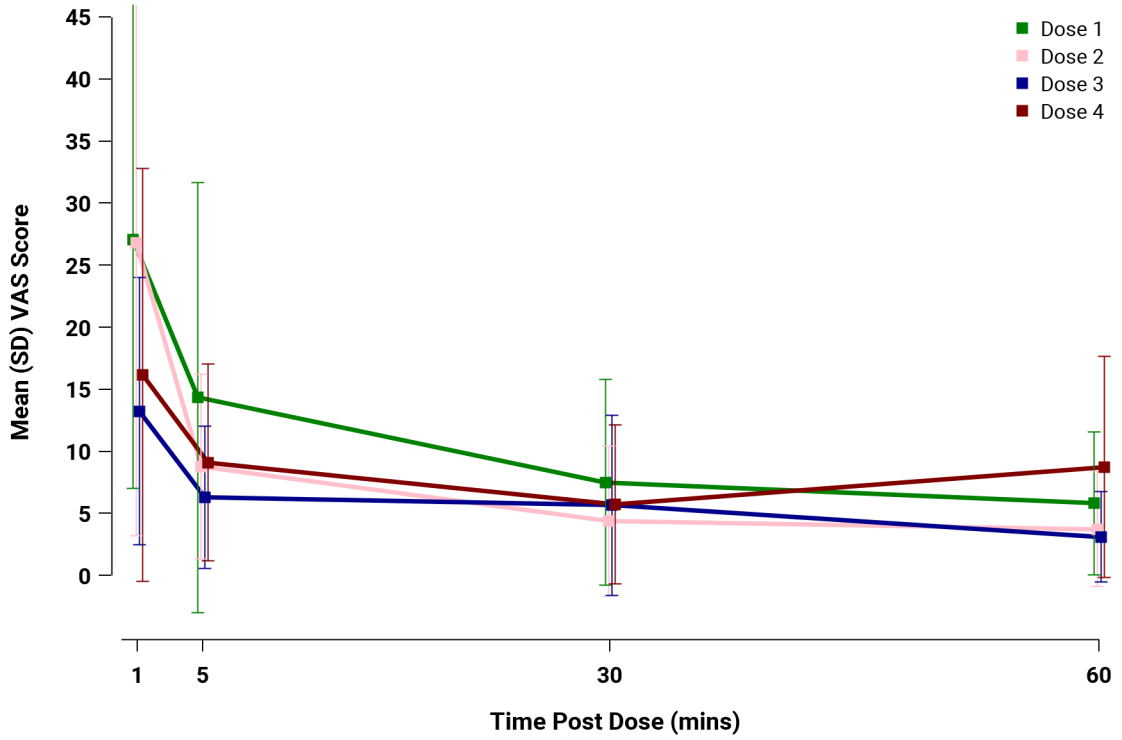
Online Resource 4

Incidence and Number of Treatment-Related Treatment-Emergent Adverse Events (TEAEs) (Safety Population)

System Organ Class Preferred Term	All Subjects (N=23)	
	Number of Subjects (%)	Number of Events
Any Treatment-Related TEAE	6 (26.1)	10
General disorders and administration site conditions	1 (4.3)	1
Injection site pain	1 (4.3)	1
Injury, poisoning and procedural complications	1 (4.3)	1
Fall	1 (4.3)	1
Investigations	3 (13.0)	3
Blood prolactin increased	2 (8.7)	2
Weight increased	1 (4.3)	1
Metabolism and nutrition disorders	1 (4.3)	1
Decreased appetite	1 (4.3)	1
Nervous system disorders	3 (13.0)	4
Akathisia	1 (4.3)	1
Dyskinesia	1 (4.3)	1
Parkinsonian gait	1 (4.3)	1
Tremor	1 (4.3)	1

Online Resource 5

Mean (±SD) Injection Site Pain Score Measured on a 100-mm Visual Analogue Scale (VAS)



Online Resource 6

Observed Values and Changes from Baseline for Positive and Negative Syndrome Scale (PANSS) Total Score (Efficacy Population)

Visit	Statistic	All Subjects (N=23)	
		Observed	Change from Baseline
SCREENING	n	23	-
	Mean (SD)	60.4 (6.94)	-
	Median	61.0	-
	Min, Max	49, 70	-
DAY -1	n	23	-
	Mean (SD)	59.6 (7.04)	-
	Median	58.0	-
	Min, Max	49, 70	-
BASELINE	n	23	-
	Mean (SD)	59.6 (7.04)	-
	Median	58.0	-
	Min, Max	49, 70	-
DOSE 1/DAY 2	n	23	23
	Mean (SD)	59.4 (6.72)	-0.2 (3.52)
	Median	60.0	1.0
	Min, Max	49, 71	-10, 4
DOSE 1/DAY 8	n	23	23
	Mean (SD)	60.5 (6.69)	0.9 (3.91)
	Median	58.0	1.0
	Min, Max	48, 77	-9, 7
DOSE 1/DAY 15	n	22	22
	Mean (SD)	60.5 (8.02)	0.7 (4.81)
	Median	60.0	1.5
	Min, Max	46, 79	-7, 9
DOSE 1/DAY 22	n	22	22
	Mean (SD)	59.4 (7.45)	-0.4 (4.16)
	Median	58.0	-0.5
	Min, Max	45, 71	-6, 8
DOSE 2/DAY 29	n	22	22
	Mean (SD)	59.0 (6.99)	-0.9 (5.05)
	Median	57.5	0.0
	Min, Max	46, 73	-13, 9
DOSE 2/DAY 50	n	19	19
	Mean (SD)	59.4 (7.74)	-0.5 (7.21)
	Median	58.0	-1.0
	Min, Max	50, 77	-11, 15

DOSE 3/DAY 57	n	16	16
	Mean (SD)	56.9 (6.90)	-2.9 (4.92)
	Median	57.0	-2.5
	Min, Max	46, 70	-13, 4
DOSE 4/DAY 85	n	16	16
	Mean (SD)	58.9 (6.46)	-0.9 (6.00)
	Median	60.0	-0.5
	Min, Max	46, 67	-14, 9
EOS	n	14	14
	Mean (SD)	61.1 (10.93)	1.6 (6.22)
	Median	58.0	-1.0
	Min, Max	47, 79	-6, 15

Online Resource 7

Observed Values and Changes from Baseline for Clinical Global Impression - Severity of Illness (CGI-S) (Efficacy Population)

Visit	Statistic	All Subjects (N=23)	
		Observed	Change from Baseline
SCREENING	n	23	-
	Mean (SD)	3.3 (0.49)	-
	Median	3.0	-
	Min, Max	3, 4	-
DAY -1	n	23	-
	Mean (SD)	3.3 (0.45)	-
	Median	3.0	-
	Min, Max	3, 4	-
BASELINE	n	23	-
	Mean (SD)	3.3 (0.45)	-
	Median	3.0	-
	Min, Max	3, 4	-
DOSE 1/DAY 2	n	23	23
	Mean (SD)	3.2 (0.39)	-0.1 (0.29)
	Median	3.0	0.0
	Min, Max	3, 4	-1, 0
DOSE 1/DAY 8	n	23	23
	Mean (SD)	3.3 (0.47)	0.0 (0.21)
	Median	3.0	0.0
	Min, Max	3, 4	0, 1
DOSE 1/DAY 15	n	22	22
	Mean (SD)	3.3 (0.48)	0.0 (0.38)
	Median	3.0	0.0
	Min, Max	3, 4	-1, 1
DOSE 1/DAY 22	n	22	22
	Mean (SD)	3.3 (0.55)	0.0 (0.44)
	Median	3.0	0.0
	Min, Max	2, 4	-1, 1
DOSE 2/DAY 29	n	22	22
	Mean (SD)	3.3 (0.46)	0.0 (0.44)
	Median	3.0	0.0
	Min, Max	3, 4	-1, 1
DOSE 2/DAY 50	n	19	19
	Mean (SD)	3.3 (0.45)	0.0 (0.47)
	Median	3.0	0.0
	Min, Max	3, 4	-1, 1

DOSE 3/DAY 57	n	16	16
	Mean (SD)	3.3 (0.48)	0.1 (0.44)
	Median	3.0	0.0
	Min, Max	3, 4	-1, 1
DOSE 4/DAY 85	n	16	16
	Mean (SD)	3.4 (0.62)	0.1 (0.50)
	Median	3.0	0.0
	Min, Max	3, 5	-1, 1
EOS	n	14	14
	Mean (SD)	3.3 (0.73)	0.0 (0.55)
	Median	3.0	0.0
	Min, Max	2, 4	-1, 1