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Health-related quality of life in acute schizophrenia patients treated with RBP-7000 once monthly risperidone: An 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study

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ABSTRACT

Background: There is increased interest in the impact of new long-acting treatments on health-related quality of life (HRQoL) in patients with schizophrenia. The aim of this study was to evaluate the impact of treatment with subcutaneous injections of RBP-7000, a new sustained-release formulation of risperidone, compared with placebo on health status, subjective well-being, treatment satisfaction, and preference of medicine in subjects with acute schizophrenia.
Methods: HRQoL data were derived from an 8-week double-blind, randomized, placebo-controlled, phase 3 study that assessed efficacy, safety, and tolerability of once monthly RBP-7000 (90 mg and 120 mg) compared with placebo in subjects with acute schizophrenia (n = 337). HRQoL was measured with the EuroQol EQ-5D-5L, well-being using the Neuroleptic Treatment-Short Version (SWN-S), satisfaction using the Medication Satisfaction Questionnaire (MSQ), and preference using the Preference of Medicine Questionnaire (POM).
Results: The EQ-5D-5L VAS increased significantly in the RBP-7000 120 mg group compared to Placebo ($p = 0.0212$). In RBP-7000 120 mg, subjects reported significant improvements in SWN-S physical functioning ($p = 0.0093$), social integration ($p = 0.0368$), and total score ($p = 0.0395$). Subjects were significantly more satisfied with RBP-7000 versus placebo (90 mg $p = 0.0009$, 120 mg $p = 0.0006$) and preferred RBP-7000 over their previous medication (90 mg $p < 0.0001$, 120 mg $p = 0.0619$).
Conclusions: Significantly greater improvements in HRQoL and overall well-being were demonstrated in patients randomized to RBP-7000 compared to placebo. The effect was more pronounced in the RBP-7000 120 mg group. Patient satisfaction improved significantly and patient preference for their medicine favored RBP-7000 90 mg and 120 mg versus Placebo.

1. Introduction

Schizophrenia is a severe and chronic brain disorder afflicting approximately 1% of the general population (Andreasen and Black, 2006; National Institute of Mental Health, 2015). Global estimates show that approximately 51 million people suffer from schizophrenia (Andreasen and Black, 2006). Since the introduction of long-acting injectable (LAI) formulations for treatment of schizophrenia in the 1960s, health-related quality of life (HRQoL) and patient-reported outcomes (PROs) measures have become increasingly important in demonstrating patients' response to treatment and their ability to restore well-being as well as social and family interactions (Nasrallah et al., 2004; Kane et al., 2003; Juckel et al., 2014). Symptoms of schizophrenia can be classified as positive (e.g., delusions, hallucinations, disorganized speech and behavior); negative (e.g., social withdrawal, avolition, blunted affect); cognitive (e.g., impaired sustained attention, executive function and working memory) and affective (e.g., anxiety and depression, hostility and aggression, increased risk of suicide).

With continuing advancements in treatment options, patients, physicians and payers have acknowledged the importance of HRQoL as measurable outcomes in defining the optimal framework for effectiveness of treatment. Improvements in HRQoL have been demonstrated in several studies assessing the efficacy of LAIs (Nasrallah et al., 2004; Kane et al., 2003). In a 12-week double-blind LAI trial of risperidone in the hospital setting, Nasrallah et al. (2004) demonstrated clinically meaningful improvements in mental health domains of the SF-36 that were not significantly different than the U.S. general population (Nasrallah et al., 2004). Subjective well-being has also been shown to be an important patient-centered measure in schizophrenia (Naber, 1995, 2008; Naber et al., 2001, 2005; de Haan et al., 2008; Karow et al., 2007; Mauriño et al., 2012; Mizrahi et al., 2009). As early as 2001, researchers began studying health states in schizophrenia and

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Table 1
Demographics and baseline characteristics.

	Statistic	Treatment group			
		RBP-7000 90 mg (N = 111)	RBP-7000 120 mg (N = 114)	Placebo (N = 112)	Total (N = 337)
Gender					
Male	n (%)	93 (83.8)	84 (73.7)	81 (72.3)	258 (76.6)
Female	n (%)	18 (16.2)	30 (26.3)	31 (27.7)	79 (23.4)
Age (years)					
20 and under	n (%)	1 (0.9)	2 (1.8)	1 (0.9)	4 (1.2)
21 to 30	n (%)	16 (14.4)	20 (17.5)	12 (10.7)	48 (14.2)
31 to 40	n (%)	36 (32.4)	32 (28.1)	28 (25.0)	96 (28.5)
41 to 50	n (%)	39 (35.1)	41 (36.0)	49 (43.8)	129 (38.3)
51 to 55	n (%)	19 (17.1)	19 (16.7)	22 (19.6)	60 (17.8)
	Mean (SD)	40.5 (9.52)	40.4 (9.52)	42.8 (8.65)	41.2 (9.27)
	Median	41.0	41.5	45.0	43.0
	Min, max	19, 55	18, 54	20, 55	18, 55
Race					
White	n (%)	28 (25.2)	30 (26.3)	25 (22.3)	83 (24.6)
Black or African American	n (%)	79 (71.2)	80 (70.2)	84 (75.0)	243 (72.1)
Asian	n (%)	1 (0.9)	3 (2.6)	1 (0.9)	5 (1.5)
American Indian or Alaska Native	n (%)	0	0	0	0
Native Hawaiian or other Pacific Islander	n (%)	1 (0.9)	1 (0.9)	1 (0.8)	3 (0.9)
Other	n (%)	2 (1.8)	0	1 (0.9)	3 (0.9)
Ethnicity					
Hispanic or Latino	n (%)	7 (6.3)	9 (7.9)	10 (8.9)	26 (7.7)
Not Hispanic or Latino	n (%)	104 (93.7)	104 (91.2)	101 (90.2)	309 (91.7)
Unknown	n (%)	0	1 (0.9)	1 (0.9)	2 (0.6)
Weight (kg)					
	Mean (SD)	90.89 (18.862)	88.54 (20.343)	92.62 (22.856)	90.67 (20.761)
	Median	88.30	83.00	87.73	86.80
	Min, max	52.2, 136.8	51.7, 161.9	51.7, 180.5	51.7, 180.5
Height (cm)					
	Mean (SD)	175.3 (9.05)	174.0 (9.88)	173.1 (10.81)	174.1 (9.95)
	Median	175.3	175.0	172.0	175.0
	Min, max	149, 197	151, 196	152, 201	149, 201
BMI (kg/m^2)					
	Mean (SD)	29.592 (5.963)	29.326 (6.723)	30.970 (7.289)	29.960 (6.702)
	Median	28.900	27.515	29.695	28.980
	Min, max	18.55, 49.95	17.70, 57.08	17.89, 55.51	17.70, 57.08
Abdominal fat measurement (waist to hip ratio)	Mean (SD)	0.949 (0.076)	0.935 (0.073)	0.948 (0.089)	0.944 (0.080)
	Median	0.950	0.935	0.940	0.940
	Min, Max	0.79, 1.14	0.70, 1.15	0.76, 1.33	0.70, 1.33

BMI = body mass index; max = maximum; min = minimum; SD = standard deviation. Note: one subject in the placebo group had a missing baseline abdominal fat measurement.

evaluating patient-reported utilities with standard gamble and willingness to pay methods (Sevy et al., 2001). Recently, researchers have relied on generic HRQoL instruments in disease-specific populations, in which successful use depends on whether the instrument will be sensitive enough to measure disease-specific changes in relevant HRQoL domains. In one study, the EuroQol (EQ-5D) was positively evaluated for construct validity and appropriateness for use in studies involving subjects with schizophrenia (Prieto et al., 2004). In another study assessing predictors of functional and symptomatic remission, researchers report the EQ-5D and the Subjective Well-being Under Neuroleptic Treatment Scale, short version (SWN-S) responses to be highly correlated ($r = 0.66$, 95% Confidence Interval 0.662 to 0.665, $p < 0.001$) (Lambert et al., 2006), lending further support for inclusion in clinical studies in schizophrenia. Clinical trials that include the evaluation of health state utilities with preference based standardized population norms will be invaluable for determining quality-adjusted life years for evaluation of reimbursement and coverage decisions.

RBP-7000 is the first once-monthly subcutaneous (SC) formulation of risperidone using the ATRIGEL® delivery system in late-stage clinical development (Gomeni et al., 2013; Laffont et al., 2014, 2015; Nasser et al., 2016). The aim of this study was to evaluate the impact of treatment with RBP-7000 compared with placebo (the ATRIGEL® delivery system only) on HRQoL, overall well-being, treatment satisfaction, and preference of medicine in subjects with acute schizophrenia.

2. Method

PROs were collected as part of the 8-week, multicenter, randomized, double-blind, placebo controlled trial to evaluate the efficacy, safety and tolerability of RBP-7000 (90 mg and 120 mg, once monthly) compared with placebo (United States National Library of Medicine Identifier: NCT02109562). The primary objective was to assess the efficacy of RBP-7000 (90 mg and 120 mg) on symptoms of acute schizophrenia using change from baseline to end of treatment in the total Positive and Negative Syndrome Scale (PANSS) score. PROs were specified as tertiary endpoints and included the EuroQol EQ-5D-5L (EQ-5D-5L), the Subjective Well-being Under Neuroleptic Treatment, short version (SWN-S), subject satisfaction with medication using the Medication Satisfaction Questionnaire (MSQ), and medication preference using the Preference of Medicine Questionnaire (POM).

2.1. Patients

Patients were between 18 and 55 years of age with a diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders 4th Edition, Text Revision (DSM-IV-TR) criteria. Patients were required to have baseline scores on the PANSS between 80 and 120, confirmed to be able to tolerate 0.25 mg tablet of oral risperidone prior to randomization, and admitted as hospital inpatients during the study. Additional criteria for eligibility included a score of >4 on at least two of the following four items: hallucinatory behavior, delusions, conceptual disorganization, or suspiciousness/persecution. Subjects were excluded if they were taking oral risperidone at a dose ≥6 mg/day, or taking any sustained release risperidone or 9-hydroxyrisperidone sustained release or depot formulation within the 120 days prior to study screening. Full details of the clinical trial including inclusion and exclusion criteria have been published elsewhere (Nasser et al., 2016). Both diagnosis of acute exacerbation of schizophrenia and a total PANSS score between 80 and 120 were confirmed by an experienced State, Assessability, Face, Ecological, and Rule (SAFER) rater of the Massachusetts General Hospital

Table 2
Change from baseline in EQ-5D-5L.

Treatment	LS mean (SE)	95% C.I.	p-Value[a]
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 center 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.

Table 3
Change from baseline in SWN-S.

Treatment	LS mean (SE)	95% C.I.	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 center 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.

(Desseilles et al., 2013). The study was conducted in accordance with the International Conference on Harmonisation Good Clinical Practice guidelines, Food and Drug Administration regulations governing clinical study conduct, and the Declaration of Helsinki (1996) and was approved by the Copernicus Group Institutional Review Board (Durham, NC, USA). An informed consent document, approved by the Independent Ethics Committee and Institutional Review Board for each study site, was signed by the subject and the Investigator before any study-related procedures were performed.

2.2. Trial design

Screening occurred during week 1, in which washout from restricted medications (including psychotropics) began. Eligible patients were placed into an inpatient setting and tapered completely off of their current oral antipsychotic medication. Successfully screened patients were randomly assigned to receive monthly SC injections of RBP-7000 (90 mg or 120 mg) or placebo over an 8-week treatment period.

2.3. Patient-reported outcomes

Administration of PROs was conducted prior to clinical assessments at screening, baseline and end of treatment. An additional assessment for the MSQ was collected at week 4 half way through the study for an early evaluation of the subjects' satisfaction with treatment.

2.3.1. EuroQol EQ-5D-5L

The EQ-5D-5L was collected to provide a simple descriptive profile and a single index value for health status (Herdman et al., 2011; The EuroQol Group, 1990). The instrument consists of the EQ-5D-5L descriptive system and Visual Analogue Scale (VAS). Validity of the EQ-5D has been demonstrated by positive association of EQ-5D index and VAS scores with Global Assessment in Function (R = 0.33 to 0.54), and with Clinical Global Impression descriptors (R = −0.31 to -0.54) in schizophrenic patients (Prieto et al., 2004). The descriptive system consists of 5 dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression), with five levels of severity (no problems, slight problems, moderate problems, severe problems, and extreme problems) within each dimension used to generate the EQ-5D Index score. Index scores range from 0 (really bad/death) to 1.0 (perfect health). The VAS records the respondent's self-rated health on a 20 cm vertical scale with endpoints labeled “the best health you can imagine” and “the worst health you can imagine.” The VAS scores range from 0 (worst health you can imagine) to 100 (best health you can imagine).

2.3.2. Subjective well-being under Neuroleptic Treatment Scale — Short Version (SWN-S)

The SWN-S scale is a 20-item (10 positive and 10 negative) instrument designed to capture a patient's subjective well-being (Naber et al., 2001). Reliability has been demonstrated in schizophrenic patients with Cronbach's alpha reported from 0.88 to 0.92 (Vothknecht et al., 2013). Each item is scored on a Likert-scale with 6 response categories (ranging from “not at all” to “very much”). Each item can have a value of 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). The SWN-S has a total score and 5 subscales: mental functioning, self-control, emotional regulation, physical functioning, and social integration.

2.3.3. Medication Satisfaction Questionnaire (MSQ)

The MSQ is a single-item questionnaire which evaluates satisfaction with antipsychotic medication in schizophrenia patients. It has been evaluated psychometrically for use in clinical research and found to be reliable in schizophrenic patients. A 1-point change is reported to be considered clinically meaningful (Vernon et al., 2010). The single-item scale is scored from 1 “Extremely Dissatisfied” to 7 “Extremely Satisfied.” In addition, the MSQ was evaluated dichotomously as dissatisfied (scores 1–4, including subjects who were neither satisfied nor dissatisfied) and satisfied (scores 5–7).

2.3.4. Preference of Medicine (POM) Questionnaire

The POM is a 2-item questionnaire assessing the preference for the current antipsychotic compared with the most recent pre-study antipsychotic (Tandon et al., 2006). Both items are identical; one is addressed to the subject and the other item to the subject's caregiver. In this study only subject responses were analyzed as the number of caregiver responses was too few in number. The item is scored from 1 “Much better; I prefer this mediation” to 5 “Much worse: I prefer my previous mediation.” The POM was also evaluated dichotomously as better (scores 1–2; subjects who preferred their medicine much better

Table 4
Impact of RBP-7000 90 mg on MSQ scores analyzed dichotomously.

MSQ	Screening			Week 4			EOS		
	90 mg (N = 111)	Placebo (N = 112)	p-Value[a]	90 mg (N = 111)	Placebo (N = 112)	p-Value[a]	90 mg (N = 111)	Placebo (N = 112)	p-Value[a]
Dissatisfied (scores 1–4), n (%)	72 (64.9)	69 (61.6)	0.4696	39 (35.1)	51 (45.5)	0.1348	30 (27.0)	55 (49.1)	0.0009
Satisfied (scores 5–7), n (%)	32 (28.8)	38 (33.9)		71 (64.0)	61 (54.5)		81 (73.0)	57 (50.9)	

[a] Fishers exact test comparing RBP-7000 90 mg versus placebo at screening, visit 6 and end of study (EOS) assessments.

Table 5
Impact of RBP-7000 120 mg on MSQ scores analyzed dichotomously.

MSQ	Screening			Week 4			EOT/EOS		
	120 mg (N = 114)	Placebo (N = 112)	p-Value[a]	120 mg (N = 114)	Placebo (N = 112)	p-Value[a]	120 mg (N = 114)	Placebo (N = 112)	p-Value[a]
Dissatisfied (scores 1–4), n (%)	80 (70.2)	69 (61.6)	0.1410	32 (28.1)	51 (45.5)	0.0125	30 (26.3)	55 (49.1)	0.0006
Satisfied (scores 5–7), n (%)	28 (24.6)	38 (33.9)		79 (69.3)	61 (54.5)		84 (73.7)	57 (50.9)	

[a] Fishers exact test comparing RBP-7000 120 mg versus placebo at screening, visit 6 and end of study (EOS) assessments.

and slightly better) and worse (scores 3, 4 and 5; subjects who preferred their medicine about the same, slightly worse and much worse).

2.4. Statistical analysis

Analysis of PROs was conducted on the intent-to-treat (ITT) population who received at least 1 injection during the trial and had at least 1 post-baseline PRO assessment. Categorical variables were summarized using frequencies and percentages. Continuous measures were summarized using descriptive statistics (mean, SD, median, minimum, maximum) by treatment group and dose. ANCOVA models were developed to test between-group comparisons at baseline and post-baseline visits for continuous measures, with effects for treatment group, study site and baseline HRQoL scores as covariates. Categorical variables were evaluated using Fisher's exact test for dichotomous analyses (Canuso et al., 2010) and Pearson's Chi-square test for analyses with greater than 2 categories. Missing data was imputed using the last observation carried forward.

3. Results

A total of 538 subjects were screened and 354 subjects were randomized to receive RBP-7000 or Placebo. Baseline demographics were similar across treatment groups as shown in Table 1, however, more Black or African Americans (72.6%), males (76.6%), and subjects aged 41 to 50 (38.0%) were recruited. The ITT population included 337 subjects, 111 received RBP-7000 90 mg, 114 received RBP-7000 120 mg, and 112 received Placebo.

3.1. Feasibility

The proportion of subject's completing ≥80% of their PRO assessments was high ranging from 87.5% to 100% in the Placebo group, 91.9% to 100% in the 90 mg group, and 84.2% to 100% in the 120 mg group. In all treatment groups combined, 316 subjects (93.8%) completed ≥80% of their PRO assessments, 5 subjects (1.5%) completed 70–79% of assessments, 9 subjects completed 60–69% of their assessments, and 7 subjects completed 50–59% of their assessments.

3.2. Placebo comparison

3.2.1. Impact of RBP-7000 on health status

At end of study (EOS), the change from baseline in EQ-5D-5L VAS and index scores improved more in RBP-7000 90 mg than in Placebo, but the difference was not statistically significant (Table 2). The change of VAS in the RBP-7000 90 mg group was greater than 5 points (5.156), almost double the improvement observed in Placebo (3.295). The change in index score of 0.067 was more than double the 0.031 observed in Placebo. In subjects receiving RBP-7000 120 mg, VAS scores improved significantly (8.184 in RBP-7000 120 mg versus 3.295 in Placebo, $p = 0.0212$).

3.2.2. Impact of RBP 7000 on overall well-being

Subjects receiving RBP-7000 90 mg reported nonsignificant improvements compared to placebo in mental functioning, self-control, physical functioning, emotional regulation and total SWN-S scores (Table 3). While modest, some improvement was observed in SWN-S total score in RBP-7000 90 mg compared to placebo (9.095 versus 6.942 respectively). Subjects who received RBP-7000 120 mg reported significantly greater improvements in the following scores compared to placebo: physical functioning (2.086 versus 0.750, $p = 0.0093$), social integration (2.868 versus 1.765, $p = 0.0368$) and total score (10.951 versus 6.942, $p = 0.0395$).

3.2.3. Impact of RBP 7000 on medication satisfaction

Subjects receiving RBP-7000 reported significant increases in medication satisfaction over the course of the trial. Subject satisfaction with their medication at screening was 28.8% in RBP-7000 90 mg versus 33.9% in Placebo, at week 4 improved to 64.0 % in RBP-7000 90 mg versus 54.5% in Placebo, and at EOS improved to 73.0 % in RBP-7000 90 mg compared to only 50.9% in Placebo (Table 4, $p = 0.0009$). The relationship of subjects' satisfaction in RBP-7000 120 mg was similar to that of RBP-7000 90 mg (Table 5), however, the proportion of subjects satisfied with their medication by week 4 increased by a larger proportion (69.3% in RBP-7000 120 mg versus 54.5% in Placebo [$p = 0.0125$]). At EOS the increase in medication satisfaction in the RBP-7000 120 mg group continued to 73.77% versus 50.9% in Placebo ($p = 0.0006$).

3.2.4. Impact of RBP 7000 on preference of medicine

The distribution of POM scores across all response categories is shown in Table 6 by treatment group. In both RBP-7000 90 mg and RBP-7000 120 mg groups, the distribution across all response categories is statistically different compared to Placebo ($p = 0.0001$ and $p = 0.0352$ respectively). In the POM dichotomous analysis (Table 7), 33% of placebo subjects rated their POM as “Slightly Better” or “Much Better” compared with 63.1% for RBP-7000 90 mg ($p < 0.0001$) and 45.6% for RBP-7000 120 mg ($p = 0.0619$) respectively. In contrast, 59.8% of placebo subjects rated their POM as “About the same or worse” compared

Table 6
Impact of RBP-7000 90 mg and 120 mg on POM scores.

Preference of medicine score	RBP-7000 90 mg (N = 111)	RBP-7000 120 mg (N = 114)	Placebo (N = 112)
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	–

[a] Pearson's chi square test comparing RBP-7000 90 mg or RBP-7000 120 mg versus placebo.

Table 7
Impact of RBP-7000 90 mg and 120 mg on POM scores analyzed dichotomously.

Preference of medicine score	RBP-7000 90 mg (N = 111)	RBP-7000 120 mg (N = 114)	Placebo (N = 112)
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[a]	<0.0001	0.0619	–

[a] Fisher's exact test comparing RBP-7000 90 mg or RBP-7000 120 mg versus placebo.

with 32.4% for RBP-7000 90 mg and 51.8% for RBP-7000 120 mg respectively.

4. Discussion

Subjects treated with RBP-7000 showed significant improvements among several HRQoL dimensions. The change in EQ-5D-5L VAS increased significantly in the RBP-7000 120 mg group. Subjects also reported improvements in subjective well-being in both RBP-7000 90 mg and 120 mg groups. An increase of 8–10 points on the SWN scale has been reported to represent a clinically relevant improvement in subjective well-being in subjects with schizophrenia (Naber et al., 2005). While no individual SWN-S score was statistically significant in the RBP-7000 90 mg group, improvement from baseline in SWN-S total score was clinically relevant at 9.095 points. The change from baseline in the RBP-7000 120 mg group was 10.951 points and statistically significant compared to 6.942 points in the Placebo group ($p = 0.0395$). Significant improvements in physical functioning and social integration scores were also reported in subjects who received RBP-7000 120 mg. No significant improvements were reported by subjects receiving Placebo on any HRQoL measure.

Subjects who received RBP-7000 also reported greater medication satisfaction compared to Placebo. Published results of randomized clinical trials measuring medication satisfaction are rare in schizophrenia. In a 6-week prospective blinded-initiation study of paliperidone versus suboptimally responsive risperidone patients, researchers found the MSQ responsive with significant improvements reported at week 2 based on dichotomized analyses (67.7% satisfied in immediate initiation versus 45.3% in the delayed group [$p = 0.002$]) (Canuso et al., 2010). Subjects receiving RBP-7000 90 mg improved to 64.0% satisfied at week 4 and 73% satisfied at EOS versus 50.9% of Placebo subjects ($p = 0.0009$). Similarly the RBP-7000 120 mg group improved to 69.3% satisfied at week 4 and 73.7% satisfied at EOS ($p = 0.0006$). Subjects also reported more preference for RBP-7000 than their previous antipsychotic medicine.

This 8-week study in adult subjects with acute schizophrenia was conducted entirely in the inpatient setting which may have had an impact on the subjects' ability to fully respond to HRQoL indicators. Clinical efficacy was demonstrated by superiority of both RBP-7000 90 and 120 mg over placebo based on change from baseline in PANSS total scores and change from baseline in CGI-S scores (Nasser et al., 2016). Thus, symptomatic control was clearly achieved in subjects randomized to RBP-7000 treatment groups, even with a relatively short treatment period of 2 months (2 doses of RBP-7000 or Placebo). Complete evaluation of change in HRQoL requires long-term exposure to normal daily activities and the benefits associated with improved health, social interactions, employment, and other daily activities. In the present study, subjects obviously had limited exposure to social interactions and/or activities related to normal everyday settings. This may explain why some of the HRQoL findings did not improve to statistical significance across all domains, even though in most cases the treatment effect was clear and improvement in HRQoL was observed. Upon completion of the present 8-week inpatient study, subjects had the opportunity to continue in an open-label one year safety study in which HRQoL will continue to be collected. The combined analysis will provide a unique opportunity to compare short-term treatment response in the present study to the long-term management of positive and negative symptoms in subjects treated with RBP-7000 and the impact on their HRQoL.

The findings from this study should be viewed in the context of certain limitations. All PRO endpoints were tertiary and based on power calculations for the primary endpoint (total PANSS). Trials designed with primary or secondary PRO endpoints that include validation analyses and measurement characteristics within the study would improve robustness of findings. The relatively short duration of the study is a limitation as symptom control and HRQoL may continue to change beyond 8 weeks. The HRQoL findings could also have been influenced by the institutional setting. Demographics and baseline characteristics were similar across treatment groups, but overall, subjects were mostly Black or African Americans, males, and subjects aged 31 to 50. Study results could vary by patient population and also with different comparators. Further studies evaluating HRQoL in the acute schizophrenia setting would clarify the generalizability of our results.

5. Conclusions

Improvements in HRQoL were demonstrated in patients who received RBP-7000, a SC injection of long-acting risperidone (90 mg or 120 mg versus Placebo) every 30 days for 8 weeks. Overall, the effect was more pronounced in subjects who received RBP-7000 120 mg. Patient satisfaction with their medication improved significantly over the course of the trial and patient preference for their medicine was statistically significant favoring both RBP-7000 90 mg and 120 mg compared to Placebo. Altogether these findings demonstrate that once monthly RBP-7000 improves HRQoL, patient satisfaction and preference of medicine in patients with acute schizophrenia.

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Contributors
Isitt JJ, Nadipelli VR, and Heidbreder C contributed to the concept and design of the study. All authors contributed to the interpretation of the data, revised the manuscript, and approved the final content of the manuscript.

Conflict of interest
At the time this manuscript was completed JJ Isitt, VR Nadipelli, Dr. Kouassi, and Dr. Heidbreder were employees of Indivior, Inc. Dr. Fava was a full-time employee of Massachusetts General Hospital, Harvard Medical School and a paid consultant for Indivior, Inc.

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References

Andreasen, N.C., Black, D.W., 2006. Introductory Textbook of Psychiatry. fourth ed. American Psychiatric Publishing, Inc., Washington, DC.

Canuso, C.M., Grinspan, A., Kalali, A., Damaraju, C.V., Merriman, U., Alphs, L., Awad, A.G., 2010. Medication satisfaction in schizophrenia: a blinded-initiation study of paliperidone extended release in patients suboptimally responsive to risperidone. Int. Clin. Psychopharmacol. 25, 155–164.

de Haan, L., van Nimwegen, L., van Amelsvoort, T., Dingemans, P., Linszen, D., 2008. Improvement of subjective well-being and enduring symptomatic remission, a 5-year follow-up of first episode schizophrenia. Pharmacopsychiatry 41, 125–128.

Desseilles, M., Witte, J., Chang, T.E., Iovieno, N., Dording, C., Ashih, H., Nyer, M., Freeman, M.P., Fava, M., Mischoulon, D., 2013. Massachusetts General Hospital SAFER criteria for clinical trials and research. Harv. Rev. Psychiatry 21, 269–274.

Gomeni, R., Heidbreder, C., Fudala, P.J., Nasser, A.F., 2013. A model-based approach to characterize the population pharmacokinetics and the relationship between the pharmacokinetic and safety profiles of RBP-7000, a new, long-acting, sustained-release formulation of risperidone. J. Clin. Pharmacol. 53, 1010–1019.

Herdman, M., Grudex, C., Lloyd, A., Janssen, M.F., Kind, P., Parkin, D., Bonsel, G., Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L). Qual. Life Res. 20, 1727–1736.

Juckel, G., de Bartolomeis, A., Gorwood, P., Mosolov, S., Pani, L., Rossi, L., Sanjuan, J., 2014. Towards a framework for treatment effectiveness in schizophrenia. Neuropsychiatr. Dis. Treat. 10, 1867–1878.

Kane, J.M., Eerdekens, M., Lindenmayer, J.P., Keith, S.J., Lesem, M., Karcher, K., 2003. Long-acting injectable risperidone: efficacy and safety of the first long-acting atypical antipsychotic. Am. J. Psychiatry 160, 1125–1132.

Karow, A., Czekalla, J., Dittmann, R.W., Schacht, A., Wagner, T., Lambert, M., Schimmelmann, B.G., Naber, D., 2007. Association of subjective well-being, symptoms, and side effects with compliance after 12 months of treatment in schizophrenia. J. Clin. Psychiatry 68, 75–80.

Laffont, C.M., Gomeni, R., Heidbreder, C., Fudala, P.J., Nasser, A.F., 2014. Population pharmacokinetics and prediction of dopamine D2 receptor occupancy after multiple doses of RBP-7000, a new sustained-release formulation of risperidone, in schizophrenia patients on stable oral risperidone treatment. Clin. Pharmacokinet. 53, 533–543.

Laffont, C.M., Gomeni, R., Zheng, B., Heidbreder, C., Fudala, P.J., Nasser, A.F., 2015. Population pharmacokinetic modeling and simulation to guide dose selection for RBP-7000, a new sustained-release formulation of risperidone. J. Clin. Pharmacol. 55, 93–103.

Lambert, M., Schimmelmann, B.G., Naber, D., Schacht, A., Karow, A., Wagner, T., Czekalla, J., 2006. Prediction of remission as a combination of symptomatic and functional remission and adequate subjective well-being in 2960 patients with schizophrenia. J. Clin. Psychiatry 67, 1690–1697.

Mauriño, J., Cordero, L., Ballesteros, J., 2012. The subjective well-being under neuroleptic scale - short version (SWN-K) and the SF-36 health survey as quality of life measures in patients with schizophrenia. Patient Prefer. Adherence 6, 83–85.

Mizrahi, R., Mamo, D., Rusjan, P., Graff, A., Houle, S., Kapur, S., 2009. The relationship between subjective well-being and dopamine D2 receptors in patients treated with a dopamine partial agonist and full antagonist antipsychotics. Int. J. Neuropsychopharmacol. 12, 715–721.

Naber, D., 1995. A self-rating to measure subjective effects of neuroleptic drugs, relationships to objective psychopathology, quality of life, compliance and other clinical variables. Int. Clin. Psychopharmacol. 10 (Suppl. 3), 133–138.

Naber, D., 2008. Subjective effects of antipsychotic drugs and their relevance for compliance and remission. Epidemiol. Psichiatr. Soc. 17, 174–176.

Naber, D., Moritz, S., Lambert, M., Pajonk, F., Holzbach, R., Mass, R., Andresen, B., 2001. Improvement of schizophrenia patients' subjective well-being under atypical antipsychotic drugs. Schizophr. Res. 50, 79–88.

Naber, D., Riedel, M., Klimke, A., Vorbach, E.U., Lambert, M., Kühn, K.U., Bender, S., Bandelow, B., Lemmer, W., Moritz, S., Dittmann, R.W., 2005. Randomized double blind comparison of olanzapine vs. clozapine on subjective well-being and clinical outcome in patients with schizophrenia. Acta Psychiatr. Scand. 111, 106–115.

Nasrallah, H.A., Duchesne, I., Mehnert, A., Janagap, C., Eerdekens, M., 2004. Health-related quality of life in patients with schizophrenia during treatment with long-acting, injectable risperidone. J. Clin. Psychiatry 65, 531–536.

Nasser, A.F., Henderson, D.C., Fava, M., Fudala, P.J., Twumasi-Ankrah, P., Kouassi, A., Heidbreder, C., 2016. Efficacy, safety, and tolerability of RBP-7000 once-monthly risperidone for the treatment of acute schizophrenia: an 8-week, randomized, double-blind, placebo-controlled, multicenter phase 3 study. J. Clin. Psychopharmacol. (Epub ahead of print).

National Institute of Mental Health, 2015. Schizophrenia. National Institutes of Health, Bethesda, MD (http://www.nimh.nih.gov/health/topics/schizophrenia/index.shtml, Accessed April 22, 2015).

Prieto, L., Sacristán, J.A., Hormaechea, J.A., Casado, A., Badia, X., Gómez, J.C., 2004. Psychometric validation of a generic health-related quality of life measure (EQ-5D) in a sample of schizophrenic patients. Curr. Med. Res. Opin. 20, 827–835.

Sevy, S., Nathanson, K., Schechter, C., Fulop, G., 2001. Contingency valuation and preferences of health states associated with side effects of antipsychotic medications in schizophrenia. Schizophr. Bull. 27, 643–651.

Tandon, R., Marcus, R.N., Stock, E.G., Riera, L.C., Kostic, D., Pans, M., 2006. A prospective, multicenter, randomized, parallel-group, open-label study of aripiprazole in the management of patients with schizophrenia or schizoaffective disorder in general psychiatric practice: broad effectiveness trial with aripiprazole (BETA). Schizophr. Res. 84, 77–89.

The EuroQol Group, 1990. EuroQol — a new facility for the measurement of health-related quality of life. Health Policy 16, 199–208.

Vernon, M.K., Revicki, D.A., Awad, A.G., Dirani, R., Panish, J., Canuso, C.M., 2010. Psychometric evaluation of the Medication Satisfaction Questionnaire (MSQ) to assess satisfaction with antipsychotic medication among schizophrenia patients. Schizophr. Res. 118, 271–278.

Vothknecht, S., Meijer, C., Zwinderman, A., Kikkert, M., Dekker, J., van Beveren, N., Schoevers, R., de Haan, L., For GROUP (Genetic Risk and Outcome of Psychosis), 2013. Psychometric evaluation of the subjective well-being under Neuroleptic Treatment Scale (SWN) in patients with schizophrenia, their relatives and controls. Psychiatry Res. 206, 62–67.