CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210655Orig1s000

STATISTICAL REVIEW(S)

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/BLA #:	NDA 210655 (SN 0001, SN 006, SN 0011, SN 0026)
Drug Name:	RBP-7000
Indication(s):	Schizophrenia
Applicant:	INDIVIOR Inc.
Date(s):	Receipt Date: September 28, 2017
	PDUFA Date: July 28, 2018
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Yang (Kelly) Yang, Ph.D.
Concurring Reviewers:	Peiling Yang, Ph.D. Team Leader
	Hsien Ming J Hung, Ph.D. Division Director
Medical Division:	Division of Psychiatry Products
Clinical Team:	Michael Davis, M.D. Clinical Reviewer
Project Manager:	Latrice Wilson, Pharm.D.

Table of Contents

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

Both RBP-7000 doses (90 mg and 120 mg) showed statistically significant improvement in change from baseline on both the primary (PANSS Total Score at Day 57) and the key secondary endpoints (CGI-S score at Day 57) compared with placebo after multiple comparison adjustment using Dunnett's procedure. The least square mean differences when compared to placebo group were -6.50 and -10.24 points in PANSS Total Score for 90 mg and 120 mg RBP-7000 treatment group, and were -0.35 and -0.58 points in CGI-S score. Although the results suggested additional improvement of the 120 mg over the 90 mg dose on both the primary and the key secondary endpoints, the observed treatment differences in CGI-S appeared to be very small.

2 INTRODUCTION

2.1 Overview

RBP-7000 is a long-acting formulation of risperidone for subcutaneous (SC) administration under development by INDIVIOR for the treatment of acute schizophrenia. The oral formulation of risperidone tablet has been approved by the FDA for the treatment of schizophrenia in December 1993 (NDA 020272). RBP-7000 is being currently submitted to address the compliance issues associated with oral risperidone treatment. It includes a phase III, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study, RB-US-09-0010.

The original protocol was reviewed under IND 105623.

Table 1: List of All Studies Included in Review

	Phase and Design	Treatment Period	Follow-up Period	# of Subjects per Arm	Study Population
RB-US-09-0010	*Phase 3*	*8 weeks*	*1 week*	*119 subjects in placebo, 116 subjects in RBP-7000 90 mg, and 119 subjects in RBP-7000 120 mg*	*Subjects with Acute Schizophrenia at the ages of 18 to 55 years*

[Source: reviewer's table]

The primary objective of this study was to evaluate the efficacy of RBP-7000 (90 mg and 120 mg) compared with placebo as a treatment in subjects with acute schizophrenia over 8 weeks.

2.2 Data Sources

The datasets for Study B210655 is located at

\\Cdsesub1\evsprod\NDA210655\0001\m5\datasets\rb-us-09-0010\analysis\adam\datasets

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

The sponsor has complied with our requests for providing necessary datasets, definition files, and statistical programs for their analyses. This reviewer found the quality of their submissions acceptable and was able to replicate the primary results from the sponsor's Response to Information Request (Multiple Module Information Amendment, SN 0026).

3.2 Evaluation of Efficacy

3.2.1 Study Design and Endpoints

It was a double-blind, randomized, placebo-controlled, Phase 3 study performed at 33 sites in the US. The study was designed to evaluate the efficacy, safety, and tolerability of RBP-7000 (90 and 120 mg) compared with placebo in subjects with acute schizophrenia. Subjects were required to have a (e)CRF Positive and Negative Syndrome Scale (PANSS) score of 80 to 120, inclusive, at Visit 1 (the initial screening visit, which occurred 3 to 8 days before start of double-blind treatment) without an

improvement in the total PANSS score of ≥20% between Visit 1 and Visit 3 (Day 1 of double-blind treatment/predose).

The study duration was approximately 72 days per study subject, including an up to 8-day screening period and a 56-day treatment period. At the conclusion of the treatment period, subjects who complete the study may be offered entry into a long-term safety study for RBP-7000.

The primary efficacy endpoint was change from baseline to end of treatment (Day 57) in the total PANSS score, which was recorded on the PANSS form and was the sum of all 30 PANSS items. The key secondary endpoint was change from Baseline in Clinical Global Impression Severity (CGI-S) scale at Day 57. CGI-S was a 7-point clinician-rated scale for assessing the global severity of the subject's illness.

3.2.2 Statistical Methodologies

The sample size calculation was based on the total PANSS score, assuming a standard deviation (SD) of 17.5. A total of 90 subjects randomized to each treatment arm was considered to be sufficient to demonstrate a mean difference of 8.1 in change from baseline to end of treatment in the total PANSS score between RBP-7000 (at the least effective dose) and placebo, at the one-sided significance level of 0.025 and a power of 80%, and taking into account Dunnett's multiplicity adjustment for two dose comparisons with placebo. Accounting for 20% screen failure and an additional buffer of 20% attrition rate to cover uncertainties in our assumptions, the total number of subjects to be screened would be 423.

The primary analysis was conducted on the change from baseline in the total PANSS score at Day 57 (primary time point) based on the ITT population. A mixed-effects model for repeated measures (MMRM) was used with treatment, visit, interaction of treatment and visit as fixed effects and the baseline total PANSS score as a covariate. Data from Days 15, 29, 43, and 57 were used. The unstructured covariance matrix was be used to model the within-subject variance-covariance errors.

Comparison of each dose group with placebo for the final analysis of the primary efficacy endpoint (change in total PANSS score from baseline) was performed using Dunnett's procedure for controlling Type I error. The significance level for the key secondary efficacy endpoint (change in CGI-S score from baseline to end of study) was compared across treatment groups using a decision tree that was based on the parallel gatekeeping procedure associated with the Dunnett's method. A conservative value of 0.01 was assumed to be the correlation between the primary efficacy endpoint and the key secondary efficacy endpoint.

In addition to the model-based missing data approach of the MMRM model, the primary efficacy analysis was also analyzed using a pattern mixture model (PMM) and a multiple imputation approach as sensitivity analyses. The PMM proposed by the sponsor assumed that the distribution of the responses Y (difference in PANSS score from baseline to a follow up visit) at different time points was a mixture of normal distributions over the patterns of missing data. To consider some Missing Not At Random (MNAR) scenarios for missing data mechanism, the parameters defining the mean of the normal distribution within each pattern were assumed to vary. Hence, the assumption of missing at random (MAR) was explored by assessing the consistency between the coefficients across the missing patterns. Multiple imputation method was done to fill in the missing values using data for the corresponding group with the observed values shifted by the estimated "departure" (the difference between the observed change from baseline in total PANSS score at each time point and the corresponding LSMEAN for the treatment group derived from the MMRM analysis) for the subject.

The imputed datasets were analyzed with an MMRM model analogous to that used to estimate departure. The impact of missing data was assessed by comparing the resulting estimates with the original MMRM estimates based on available data to assess.

3.2.3 Patient Disposition, Demographic and Baseline Characteristics

A total of 354 subjects were randomized to treatment with placebo (N=119), RBP-7000 90mg (N=116), or RBP-7000 120mg (N=119). A total of 337 subjects were included in the ITT population: 112 subjects in the placebo group, 111 subjects in RBP-7000 90mg group and 114 subjects in the RBP-7000 120mg group.

The proportions of subjects in the placebo, RBP-7000 90mg, and RBP-7000 120mg treatment groups who discontinued from treatment during the double-blind treatment period were 29.4%, 22.4% and 28.6%- respectively. The most common reason for discontinuation for all three groups was withdrew consent (17.6%, 17.2% and 21%, respectively). A total of 259 (73.2%) subjects completed the treatment phase.

Table 2: Subject Disposition (All Randomized Subjects)

		Treatment Group			
	Statistic	**RBP-7000 90 mg (N=116)**	**RBP-7000 120 mg (N=119)**	**Placebo (N=119)**	**Total (N=354)**
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: Sponsor's clinical study report RB-US-09-0010 Table 5, verified by the reviewer.]

Table 3: Demographic Characteristics (Intent-to-Treat Population)

		Treatment Group			
	Statistic	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)	Placebo (N=112)	Total (N=350)
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 (0.9)	3 (0.9)
Other	n (%)	2 (1.8)	0	1 (0.9)	3 (0.9)
Weight (kg)					
	Mean (SD)	90.89 (18.862)	88.54 (20.343)	92.62 (22.856)	90.67
	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)	174.3 (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

[Source: Sponsor's clinical study report RB-US-09-0010 Table 14.1.3.1, verified by the reviewer.]

The RBP-7000 90 and 120 mg and placebo groups were similar in most demographic and baseline characteristics. The overall median age of 43 years was comparable among treatment arms. Overall, 76.6% subjects were male and 23.4% were female, 24.3% were white and 72.6% were black. However, the proportion of male subjects was higher for the RBP-7000 90 mg group compared with the RBP-7000 120 mg and placebo groups.

3.2.4 Primary Efficacy Analysis and Sensitivity Analysis

The change from baseline in PANSS total scores was summarized for the ITT population in Table 4 and presented in Figure 1. The primary objective was met for both RBP-7000 dose groups. The LS mean change (± SE) from Baseline to End of Study (Day 57) for the PANSS total score based on an MMRM model was -23.61 ± 1.58 for the RBP-7000 120 mg, -19.86 ± 1.56 for the RBP-7000 90 mg, and -13.37± 1.58 for the placebo group. Both doses showed statistically significant improvement in change from baseline in PANSS total score at Day 57 compared with placebo.

Table 4: Primary Analysis: Changes from Baseline of PANSS total scores, through Day 57 Using MMRM Analysis (ITT Population)

Time Point	Treatment Group	n	Adjusted Mean Change from Baseline	SE	Difference in Adjusted Means	Unadjusted 95% CI [a]	Unadjusted P-value [b]
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			

Abbreviations: ITT=intent-to-treat; MMRM=mixed-effects model for repeated measures; n=number of subjects; SE=standard error a. Estimates, standard errors (SE), two-sided confidence intervals (CIs) and two-sided 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.

Note: [a]: The confidence intervals (CIs) were adjusted for multiple comparisons using Dunnett's procedure in the sponsor's table. The unadjusted CIs in the table above were calculated by the reviewer.

[b]: The p-values were marked as adjusted for multiple comparisons using Dunnett's procedure in the sponsor's table, but the reviewer found that they were unadjusted p-values.

[Source: Table 14.2.1.1.1a on Multiple Module Information Amendment - Clinical Response of Biometrics except unadjusted CIs and unadjusted p-values in the last two columns of the table because the sponsor reported the adjusted CIs and mislabeled the unadjusted p-values as the adjusted p-values.]

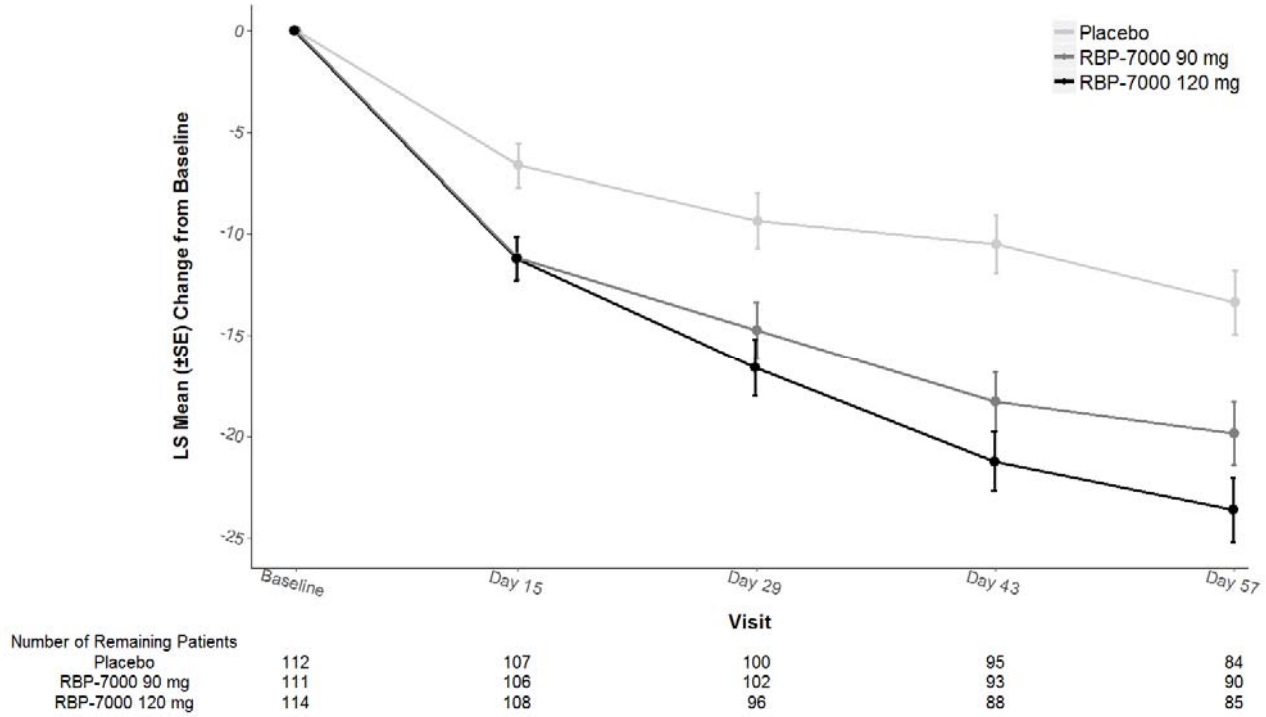
As shown in Figure 1, the LS mean decreases in the PANSS total score in both RBP-7000 groups were numerically greater than placebo beginning at Day 15 and continuing through Day 57. The mean decrease in RBP-7000 120mg group was also numerically greater than 90mg group at later visits. Overall, compared to placebo, the plot supported that both doses of RBP-7000 improved the PANSS total score after 57 days of treatment.

A PMM method was conducted to explore the missing at random (MAR) assumption underlying the primary efficacy MMRM analyses (ITT population). The results of this analysis were in line with MMRM results for the primary efficacy variable. Based on the sponsor's statistical analysis plan (SAP), the MAR assumption required for MMRM analysis was also tested by assessing the consistency between the coefficients across the missing patterns and the test did not suggest a violation of the assumption (results were not shown). However, the reviewer thought that this

analysis was not useful for the reason that the regression coefficients looked quite different but the test cannot tell, maybe caused by a low power.

A second sensitivity analysis based on a multiple imputation method was performed to assess the impact of missing data. The estimates, confidence intervals (CIs) and p-values from the multiple imputation method were shown in Table 6.

Figure 1: Change from Baseline (LS Mean ± SE) in the PANSS total scores over Time-Mixed Model for Repeated Measures (ITT Population)



[Source: Reviewer's Plot]

Table 5: Sensitivity Analysis: Pattern Mixture Model for Primary Efficacy Analysis of PANSS Total Score (ITT Population)

Analysis	Statistic	Placebo (N=112)	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)
Pattern Mixture Model Result at Day 57	LS Mean	-11.19	-17.06	-20.38
	Difference from Placebo			
	LS Mean Difference		-5.87	-9.19
	Unadjusted 95% CI of Difference		(-10.27, -1.47)	(-13.66, -4.72)
	Unadjusted p-value		0.0046	<0.0001

Abbreviations: ITT = Intent-to-Treat; LS = least squares.

Note: Estimate, confidence intervals (CIs) and p-values are based on a repeated measures linear regression model of the change from baseline, with fixed effects for treatment (as a categorical variable), visit, monotone missing pattern (as a categorical variable), baseline total PANSS score, monotone missing pattern*baseline total PANSS score interaction, and treatment*visit interaction assuming an unstructured covariance matrix.

[Source: Reviewer's Table]

Table 6: Sensitivity Analysis: Multiple Imputation Method for Primary Efficacy Analysis of PANSS Total Score (ITT Population)

Analysis	Statistic	Placebo (N=112)	RBP-7000 90 mg (N=111)	RBP-7000 120 mg (N=114)
[a] Departure (Prior to Multiple Imputation) Result at Day 57	LS Mean	-0.27	-0.92	-3.08
	Difference from Placebo			
	LS Mean Difference		-0.65	-2.82
	Unadjusted LS Mean Difference 95% CI		(-5.14, 3.83)	(-7.34, 1.70)
	Unadjusted p-value		0.77	0.22
[b] Departure (After Multiple Imputation) Result at Day 57	LS Mean	0.74	0.16	0.66
	Difference from Placebo			
	LS Mean Difference		-0.58	-0.08
	Unadjusted LS Mean Difference 95% CI		(-5.14, 3.99)	(-4.64, 4.48)
	Unadjusted p-value		0.83	0.97

Abbreviations: ITT = Intent-to-Treat; LS = least squares.

Note: [a] Estimate, confidence intervals (CIs) and p-values are based on a repeated measures linear regression model of the change in departure from baseline, with fixed effects for treatment, reason for dropping from study (as a categorical variable), treatment duration, visit (as a categorical variable), treatment by visit interaction and reason for dropping by visit interaction assuming an unstructured covariance matrix.

[b] Estimate, confidence intervals (CIs) and p-values are based on fitting model for [a] on five imputed datasets and combining the results assuming a t distribution with the reported degrees of freedom.

[Source: Reviewer's Table]

***Reviewer's Note**: This reviewer opines that the multiple imputation method does not appear to be a sensible sensitivity analysis to assess the impact of the deviation from the missing data mechanism assumed in the primary analysis because it is still based on the same assumption as for the primary analysis.*

3.2.5 Key Secondary Efficacy Analysis

The key secondary endpoint was the change in CGI-S score from Baseline to Day 57. Because the primary objective was met for both of the RBP-7000 doses, confirmative testing for the key secondary endpoint was performed. The improvement in the CGI-S scores at Day 57 were statistically significantly different from placebo for both the RBP-7000 90 mg/day (-0.35 ± 0.128) and RBP-7000 120 mg/day (-0.58 ± 0.129) treatment groups. Thus, treatment with RBP-7000 demonstrated a statistically significant improvement over placebo in the CGI-S after 57 days of treatment.

Table 7: Key Secondary Analysis: Changes from Baseline of CGI-S scores, through Day 57 Using MMRM Analysis (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.
Note: [a]: The confidence intervals (CIs) were adjusted for multiple comparisons using Dunnett's procedure in the sponsor's table. The unadjusted CIs in the table above were calculated by the reviewer.
[b]: The p-values were marked as adjusted for multiple comparisons using Dunnett's procedure in the sponsor's table, but the reviewer found that they were unadjusted p-values.

[Source: Table 14.2.2.1.1a on Multiple Module Information Amendment - Clinical Response of Biometrics except unadjusted CIs and unadjusted p-values in the last two rows of the table because the sponsor reported adjusted CIs and mislabeled unadjusted p-values as adjusted p-values.]

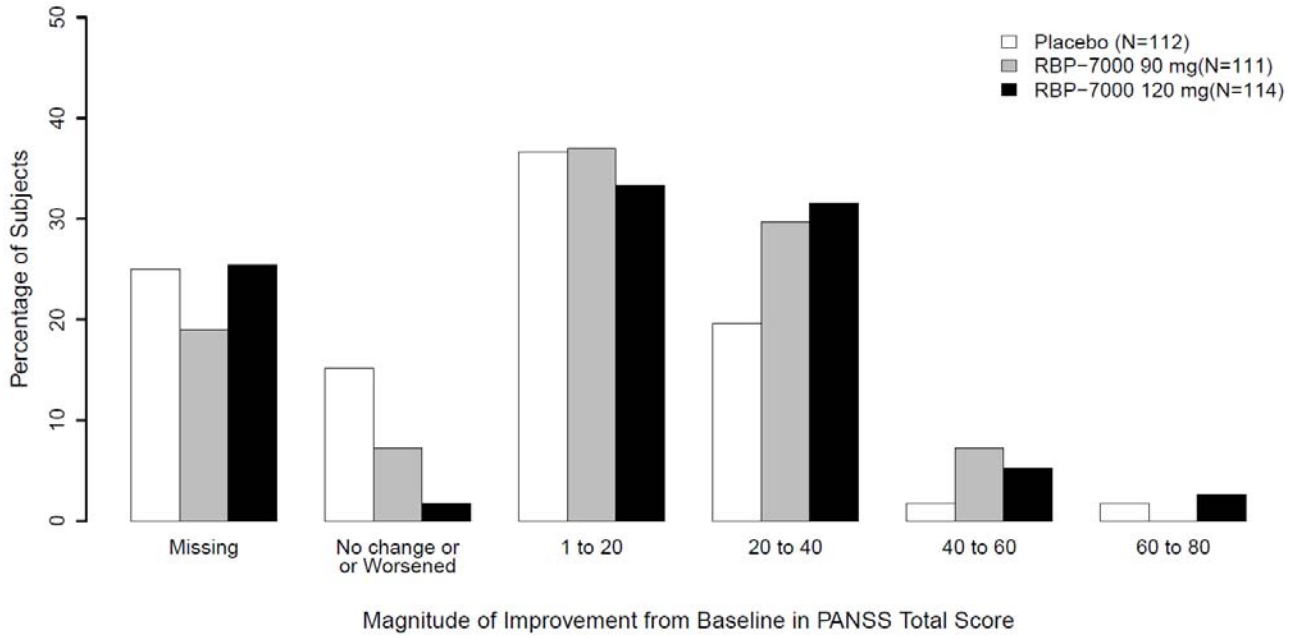
3.2.6 Reviewer's Results and Comments

Based on the dataset that the sponsor provided for the primary efficacy analyses, this reviewer confirmed the sponsor's analysis results for the primary and key secondary endpoints. The sponsor's results were based on the unadjusted p-values compared with pre-specified nominal alpha levels adjusting for multiplicity. This reviewer obtained adjusted p-values for both the primary and the key secondary endpoints as following:

Primary endpoint (PANSS Total Score at Day 57): 90 mg: adjusted p=0.0273; 120 mg: adjusted p <0.0001.
Key secondary endpoint (CGI-S score at Day 57): 90 mg: adjusted p= 0.0425; 120mg: adjusted p=0.0001.

Based on this reviewer's analysis, Figure 2 suggested that the improvements observed on both RBP-7000 groups were generally better compared with placebo.

Figure 2: Percentage of Subjects with Specific Magnitudes of Improvement in PANSS total scores at Day 57 (ITT Population)

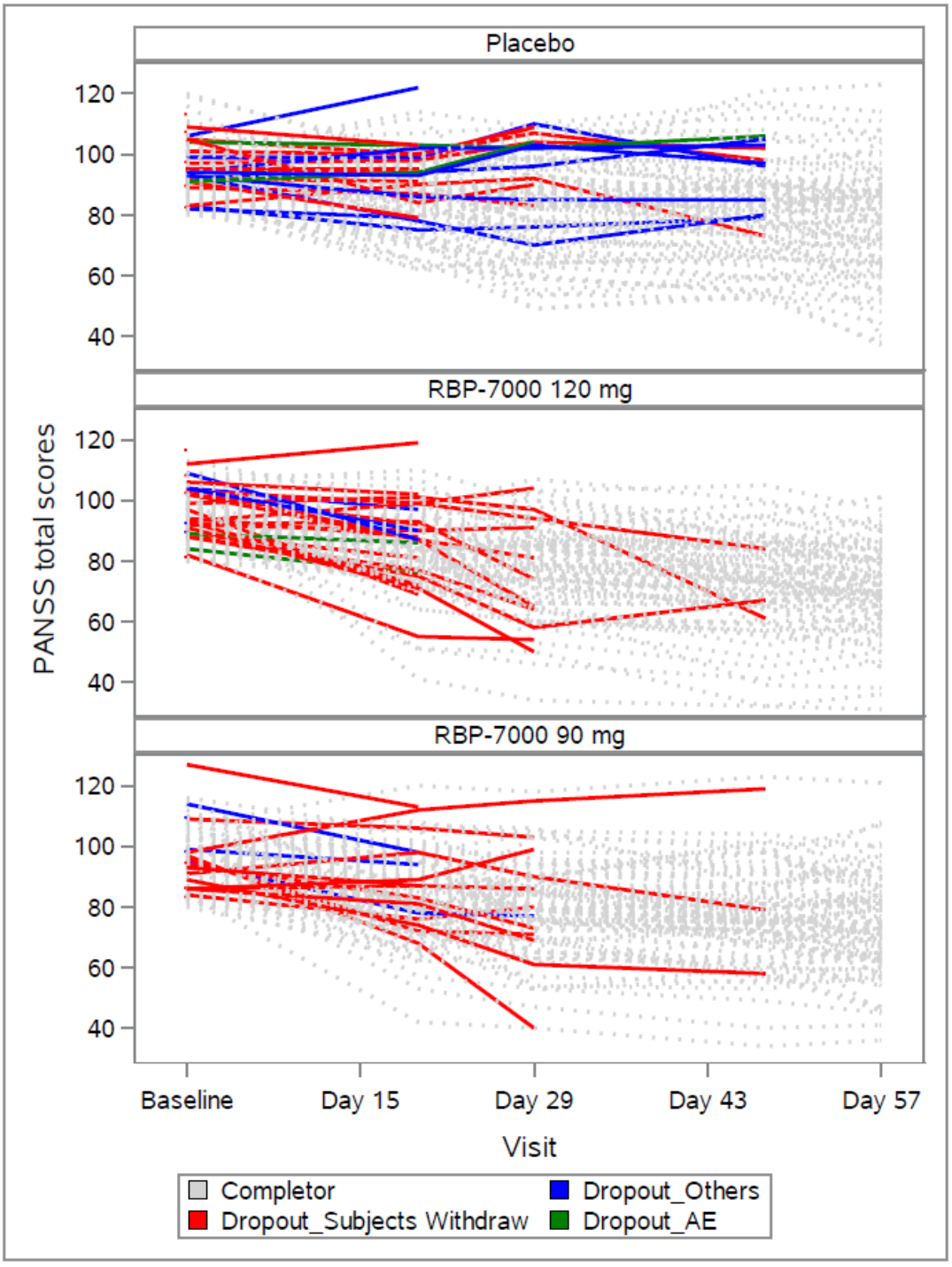


[Source: Reviewer's Plot]

Reviewer's Note: *It is noted that the 90mg group had a slightly smaller dropout rate. In this case, if missing values are treated as failures (e.g., imputed by worst scores) regardless of dropout reasons, the efficacy results could be biased in favor of 90mg group. Hence, such an analysis may not be appropriate to assess efficacy, but it may be considered as "utility" analysis to explore how useful the treatment is in real life.*

The reviewer also explored the assumption of missing at random (MAR) by plotting the observed individual-patient longitudinal profiles in PANSS total scores for each drug arm. Most of the dropouts had the similar patterns with the completers in each treatment group before they discontinued from the study. Thus, it was reasonable to suspect that most of the dropouts would continue to have a similar PANSS response as those subjects who remained in the study. Moreover, among those dropouts, only a few had the worsening PANSS responses (measured as a positive change in PANSS) before they discontinued from the study. It is likely that the treatments were not useful for those patients and they dropped out because of the lack of usefulness. In Figure 2, note that the dropout rates were similar between 120 mg group and placebo. However, in Figure 3, there were noticeably more dropouts who had the worsening PANSS responses in placebo group compared to those in both RBP-7000 dose groups. The positive finding based on the PANSS responses of the dropouts for both RBP-7000 dose groups supports the usefulness of RBP-7000. In this case, if missing values were just treated as failures regardless whether the PANSS responses became worsening or not, the efficacy results could be biased. Hence, Figure 3 may be considered as an exploratory analysis to aid in the analysis of RBP-7000's usefulness in treating Schizophrenia.

Figure 3: Individual-patient longitudinal profiles in PANSS total scores for drug arms (ITT Population)



[Source: Reviewer's Plot]

3.3 Evaluation of Safety

Safety was not evaluated in this review. Please refer to the clinical review for details on the safety evaluation.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

The purpose of the following subgroup analyses was to assess the consistency of treatment effects across subgroups. The change from Baseline to Day 57 in the PANSS total score was examined by gender and race to explore whether there was a consistent trend in treatment effect across subgroups. Mean differences from placebo in PANSS total score for gender and race were shown in Table 8. The trends appeared consistent in favor of RBP-7000 across subgroups. In terms of dose response relationship, there was a noticeable trend in favor of 120 mg for the male group, as compared to the seemly-flat trend for the female subgroup. Since the majority (76.6%) of the patient population in this trial was male, the overall treatment effects were largely driven by this subgroup. The dose response relationship in favor of 120 mg was also observed for both African American and other race subgroups. The results did not suggest apparent treatment-by-subgroup interactions with respect to gender or race.

Table 8: PANSS total score: Subgroup Analysis by Age group, Gender and Race in Changes from Baseline to Day 57 (ITT Population)

Subgroup Treatment	Treatment	n	LS Mean (SE)	Difference in Adjusted Means (95% CI)
Gender				
Male	RBP-7000 90 mg	93	-19.61 (1.70)	-5.30 (-10.26,-0.34)
	RBP-7000 120 mg	84	-24.59 (1.85)	-10.29 (-15.44, -5.13)
	Placebo	81	-14.31 (1.86)	-
Female	RBP-7000 90 mg	18	-21.06 (3.97)	-10.06 (-19.85,-0.28)
	RBP-7000 120 mg	30	-20.78 (3.09)	-9.78 (-18.25, -1.30)
	Placebo	31	-11.00 (3.00)	-
Race				
Black or African American	RBP-7000 90 mg	79	-20.37 (1.84)	-6.45 (-11.56, -1.34)
	RBP-7000 120 mg	80	-24.85 (1.89)	-10.93 (-16.10, -5.76)
	Placebo	84	-13.92 (1.83)	-
Other	RBP-7000 90 mg	32	-18.58 (2.98)	-6.86 (-15.40, 1.68)
	RBP-7000 120 mg	34	-20.50 (2.95)	-8.78 (-17.29, -0.27)
	Placebo	28	-11.72 (3.16)	-

Note: LS Means, LS Mean Difference, associated 95% CI and p-value are based on model with treatment, and treatment-by-subgroup interaction as fixed factors, and baseline PANSS total score as a covariate.

[Source: Reviewer's Table]

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

There are no statistical issues that impact the overall conclusions.

5.2 Collective Evidence

Both RBP-7000 doses (90 mg and 120 mg) showed statistically significant improvement in change from baseline in both the primary (PANSS Total Score at Day 57) and the key secondary endpoints (CGI-S score at Day 57) compared with placebo after multiple comparison adjustment using Dunnett's procedure. The least square mean differences when compared to placebo group were -6.50 and -10.24 points in PANSS Total Score for 90 mg and 120 mg RBP-7000 treatment group, and were -0.35 and -0.58 points in CGI-S score. When compared to placebo, 120 mg dose seemed to have a greater observed treatment effect than 90 mg dose on the primary and the key secondary endpoint.

5.3 Conclusions and Recommendation

Both RBP-7000 treatment groups showed statistical significance when compared with the placebo group on the primary and the key secondary endpoints. The results also suggested additional benefit of the 120 mg over the 90 mg dose on both the primary and the key secondary endpoints. However, the observed treatment differences in CGI-S appeared to be very small.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

YANG YANG
05/15/2018

PEILING YANG
05/16/2018

HSIEN MING J HUNG
05/16/2018