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Center for Drug Evaluation and Research
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Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	20-272 SE 046, 20-272 SE 047, 20-588 SE 036, 20-588 SE 037, 21-444 SE 020, 21-444 SE 021
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Biometrics Division:	Biometrics I (HFD-710)
Statistical Reviewer:	John Lawrence
Concurring Reviewers:	Peiling Yang, Team Leader
	H. M. James Hung, Division Director
Medical Division:	Division of Psychiatric Drug Products
Clinical Team:	June Cai, Medical Reviewer
Project Manager:	Kimberly Updegraff

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrate that risperidone is effective in treating these subjects.

1.2 Brief Overview of Clinical Studies

There are three placebo-controlled randomized double blind studies in pediatric subjects. Studies RIS-SCH-302 and RIS-USA-231 evaluated the safety and efficacy of risperidone in adolescents with schizophrenia. RIS-BIM-301 evaluated the safety and efficacy of risperidone in adolescents with bipolar disorder.

1.3 Statistical Issues and Findings

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrated that risperidone is effective. There are no statistical issues for any of the three studies for the primary endpoint. However, no multiple comparison procedure was planned for secondary endpoints in any study. For each secondary endpoint, nominal p-values were reported. See Sections 3.1.1, 3.1.2, and 3.1.3 for the efficacy results of the individual studies.

2. INTRODUCTION

2.1 Overview

The sponsor submitted these studies to fulfill a pediatric written request.

Study RIS-SCH-302 (submitted under NDA 20-272) was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B). The study comprised 2 phases: a screening phase (with a possible washout period) and a 6-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 7; the investigator then titrated the dosage to the maximum tolerated dosage within the target dosage range up to Day 14 to optimize efficacy while minimizing adverse effects. Subjects could be enrolled as inpatients or outpatients as clinically indicated. A subject was considered as having completed the study if they had completed all assessments at Week 6 (Visit 6) of the double-blind treatment phase.

Study RIS-USA-231 (submitted under NDA 20-272) was an 8-week, randomized, double-blind, parallel-group, multicenter clinical study conducted at 41 sites in 8 countries. Subjects were randomly assigned to 1 of 2 treatment groups:
– Risperidone low dose group: oral risperidone 0.15–0.6 mg/day for subjects weighing ≥50 kg or 0.003-0.012 mg/kg/day for subjects weighing <50 kg
– Risperidone high dose: oral risperidone 1.5–6 mg/day for subjects weighing ≥ 50 kg or 0.03–0.12 mg/kg/day for subjects weighing <50 kg
The study comprised 2 phases: a screening phase (with a possible washout period) and an 8-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 12. The investigator could then adjust the dosage to achieve the maximum tolerated dose within the target dosage range; however, the dose was to remain stable during the last 4 weeks of the double-blind phase.

Study RIS-BIM-301 (submitted under NDA 20-272) evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy (0.5-2.5 mg/day and 3-6 mg/day) versus placebo in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of Bipolar I disorder who were experiencing a manic or mixed episode (Young Mania Rating Scale [YMRS] ≥20). Efficacy was primarily based on the improvement in severity of mania during the 3-week treatment period, measured by the change in total score (consensus final score) of the YMRS from baseline to endpoint.

2.2 Data Sources

Electronic study reports and data sets (\\Cdsesub1\n20272\S_046 and \\Cdsesub1\n20272\S_0467)

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 *Evaluation of Efficacy- RIS-SCH-302*

Study RIS-SCH-302 was a 6-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter clinical study conducted at 23 sites in 4 countries. Subjects were randomly assigned to 1 of 3 treatment groups: oral placebo tablets; oral risperidone tablets 1 to 3 mg/day (dosage group A); or oral risperidone tablets 4 to 6 mg/day (dosage group B). The study comprised 2 phases: a screening phase (with a possible washout period) and a 6-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 7; the investigator then titrated the dosage to the maximum tolerated dosage within the target dosage range up to Day 14 to optimize efficacy while minimizing adverse effects. Subjects could be enrolled as inpatients or outpatients as clinically indicated. A subject was considered as having completed the study if they had completed all assessments at Week 6 (Visit 6) of the double-blind treatment phase.

160 subjects are included in the intent-to-treat analysis set. The demographics for the ITT population appear in Table 1. The majority was white, roughly ⅔ were male, and all were older than 12 years old. There appeared to be roughly the same distribution in each treatment group.

Table 1 Patient Demographics (ITT analysis set)

	-- PLACEBO -- (N=54)	RIS 1-3 mg (N=55)	RIS 4-6 mg (N=51)	--- Total --- (N=160)
Age, years				
N	54	55	51	160
Mean (SD)	15.5 (1.38)	15.7 (1.33)	15.7 (1.29)	15.6 (1.33)
Median	16.0	16.0	16.0	16.0
Range	(13;17)	(13;17)	(13;17)	(13;17)
Sex, n (%)				
N	54	55	51	160
Female	19 (35)	25 (45)	14 (27)	58 (36)
Male	35 (65)	30 (55)	37 (73)	102 (64)
Race, n (%)				
N	54	55	51	160
American Indian/Alaskan Native	0	0	1 (2)	1 (1)
Asian	22 (41)	18 (33)	18 (35)	58 (36)
Black or African American	5 (9)	3 (5)	7 (14)	15 (9)
Mixed	0	1 (2)	1 (2)	2 (1)
White	27 (50)	33 (60)	24 (47)	84 (53)

Source: Study Report, p 73.

Roughly ¾ of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 2.

Table 2 Subject Disposition and Discontinuation Reasons (ITT analysis set)

State of Termination Term. Reason	PLACEBO (N=54) n (%)	RIS 1-3 mg (N=55) n (%)	RIS 4-6 mg (N=51) n (%)	Total (N=160) n (%)
Completed	36 (67)	45 (82)	44 (86)	125 (78)
Discontinued	18 (33)	10 (18)	7 (14)	35 (22)
Adverse event	2 (4)	3 (5)	4 (8)	9 (6)
Insufficient response	13 (24)	3 (5)	1 (2)	17 (11)
Subject ineligible to continue the trial	0	1 (2)	0	1 (1)
Subject withdrew consent	2 (4)	3 (5)	1 (2)	6 (4)
Other	1 (2)	0	1 (2)	2 (1)

Source: Study Report, p 72.

The primary efficacy measure was the change from baseline in the Positive and Negative Symptoms of Schizophrenia (PANSS) total score at the Day 43 (6-week) end point. The primary analysis used an ANCOVA model with factors for treatment, baseline value, and country. The last observed value was carried forward (from Day 8, 15, or 29) for subjects with missing values at Day 43. To account for multiple comparisons, a step-down sequential testing strategy was used. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 3. Both doses showed a significantly larger decrease in the PANSS total score compared to placebo.

Table 3 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores - Change From Baseline to Day 43 End Point- Efficacy Analysis Set.

	PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Baseline			
N	54	54	50
Mean (SD)	93.2 (10.27)	95.4 (11.01)	93.0 (11.87)
Median (Range)	94.0 (62;120)	96.0 (67;120)	90.0 (71;117)
Day 43 End Point			
N	54	54	50
Mean (SD)	84.4 (16.59)	74.1 (17.79)	71.8 (18.35)
Median (Range)	86.0 (42;126)	74.5 (34;124)	71.0 (34;117)
Change from Baseline			
N	54	54	50
Mean (SD)	-8.9 (16.11)	-21.3 (19.61)	-21.2 (18.29)
Median (Range)	-7.0 (-53;21)	-19.0 (-69;38)	-20.0 (-60;22)
P-value(minus PLACEBO)[a,b]		<0.001	<0.001
Diff. of LS Means (SE)		-12.0 (3.02)	-12.8 (3.07)
95% CI		(-17.95;-5.99)	(-18.83;-6.71)

Source: Study Report, p 86 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 4. There is a

numerical difference between each of the two risperidone groups and placebo at each visit in favor of the risperidone groups.

Table 4 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) – Efficacy Analysis Set.

	N	Mean	SD	Change from Baseline	
				Mean	SD
Placebo Group					
Baseline	54	93.2	10.27		
Day 8 OC	54	91.1	11.29	-2.1	7.23
Day 8 LOCF	54	91.1	11.29	-2.1	7.23
Day 15 OC	52	86.3	11.57	-6.8	9.48
Day 15 LOCF	54	86.9	11.94	-6.3	9.92
Day 29 OC	51	85.4	14.35	-7.9	13.66
Day 29 LOCF	54	86.0	14.47	-7.2	13.77
Day 43 OC	35	78.4	13.43	-14.8	13.70
Day 43 LOCF	54	84.4	16.59	-8.9	16.11
Risperidone 1-3 mg					
Baseline	54	95.4	11.01		
Day 8 OC	54	89.9	12.89	-5.5	10.19
Day 8 LOCF	54	89.9	12.89	-5.5	10.19
Day 15 OC	51	81.9	14.16	-13.8	12.30
Day 15 LOCF	54	82.9	14.93	-12.5	14.06
Day 29 OC	50	77.5	14.30	-18.2	14.33
Day 29 LOCF	54	79.0	15.32	-16.4	16.09
Day 43 OC	44	70.1	15.81	-26.6	16.22
Day 43 LOCF	54	74.1	17.79	-21.3	19.61
Risperidone 4-6 mg					
Baseline	50	93.0	11.87		
Day 8 OC	50	87.5	13.59	-5.5	9.29
Day 8 LOCF	50	87.5	13.59	-5.5	9.29
Day 15 OC	48	78.9	13.50	-14.0	12.35
Day 15 LOCF	50	79.9	14.36	-13.2	12.89
Day 29 OC	43	73.4	12.77	-19.1	11.25
Day 29 LOCF	50	76.8	15.52	-16.2	14.05
Day 43 OC	43	67.6	15.17	-24.9	15.73
Day 43 LOCF	50	71.8	18.35	-21.2	18.29

Source: Study Report, Attachment 2.1.1.2.

3.1.2 *Evaluation of Efficacy- RIS-USA-231*

Study RIS-USA-231 was an 8-week, randomized, double-blind, parallel-group, multicenter clinical study conducted at 41 sites in 8 countries. Subjects were randomly assigned to 1 of 2 treatment groups:
– Risperidone low dose group: oral risperidone 0.15–0.6 mg/day for subjects weighing ≥50 kg or 0.003-0.012 mg/kg/day for subjects weighing <50 kg
– Risperidone high dose: oral risperidone 1.5–6 mg/day for subjects weighing ≥ 50 kg or 0.03–0.12 mg/kg/day for subjects weighing <50 kg
The study comprised 2 phases: a screening phase (with a possible washout period) and an 8-week double-blind treatment phase. Study medication was to be titrated up to the assigned target dosage range by Day 12. The investigator could then adjust the dosage to achieve the maximum tolerated dose within the target dosage range; however, the dose was to remain stable during the last 4 weeks of the double-blind phase.

279 subjects are included in the intent-to-treat analysis set, 257 subjects in the mITT analysis set (diagnosis of schizophrenia and an age >12 years and ≤17 years at baseline), 255 subjects in the efficacy analysis set (excludes 2 subjects due to Good Clinical Practice noncompliance). The demographics for the mITT population appear in Table 5. The majority was white, roughly half were male, and all were older than 12 years old. There appeared to be roughly the same distribution in each treatment group.

Table 5 Patient Demographics (mITT analysis set)

	RIS LOW DOSE (N=132)	RIS HIGH DOSE (N=125)	--- Total --- (N=257)
Age, years			
N	132	125	257
Mean (SD)	15.6 (1.32)	15.6 (1.25)	15.6 (1.28)
Median	16.0	16.0	16.0
Range	(13;17)	(13;17)	(13;17)
Age in classes, n (%)			
N	132	125	257
>12 years	132 (100)	125 (100)	257 (100)
Sex, n (%)			
N	132	125	257
Female	52 (39)	60 (48)	112 (44)
Male	80 (61)	65 (52)	145 (56)
Race, n (%)			
N	131	123	254
Black or African American	20 (15)	17 (14)	37 (15)
Mixed	0	2 (2)	2 (1)
White	111 (85)	104 (85)	215 (85)

Source: Study Report, p 86.

Roughly ⅔ of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 6.

Table 6 Subject Disposition and Discontinuation Reasons (Intent-to-treat analysis set)

State of Termination Term. Reason	RIS LOW DOSE (N=141) n (%)	RIS HIGH DOSE (N=138) n (%)	Total (N=279) n (%)
Completed	87 (62)	97 (70)	184 (66)
Discontinued	54 (38)	41 (30)	95 (34)
Adverse event	6 (4)	8 (6)	14 (5)
Insufficient response	27 (19)	20 (14)	47 (17)
Subject ineligible to continue the trial	3 (2)	2 (1)	5 (2)
Subject lost to follow-up	3 (2)	0	3 (1)
Subject withdrew consent	10 (7)	6 (4)	16 (6)
Subject non-compliant	0	1 (1)	1 (<1)
Other	5 (4)	4 (3)	9 (3)

Source: Study Report, p 83.

The primary efficacy measure was the change from baseline in the Positive and Negative Symptoms of Schizophrenia (PANSS) total score at the Day 56 (8-week) end point. The primary analysis used an ANCOVA model with factors for treatment, baseline value, and country. The last observed value was carried forward (from Day 7, 14, 28, or 42) for subjects with missing values at Day 56. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 7. The high dose group showed a significantly larger decrease in the PANSS total score compared to the low dose.

Table 7 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores - Change From Baseline to Day 56 End Point- Efficacy Analysis Set.

	RIS LOW DOSE	RIS HIGH DOSE
Baseline		
N	131	124
Mean (SD)	93.3 (14.14)	96.4 (15.39)
Median (Range)	94.0 (61;119)	97.0 (63;126)
Day 56 End Point		
N	131	124
Mean (SD)	80.8 (24.33)	72.8 (22.52)
Median (Range)	80.0 (33;132)	71.0 (32;146)
Change from Baseline		
N	131	124
Mean (SD)	-12.5 (20.32)	-23.6 (22.83)
Median (Range)	-11.0 (-68;29)	-23.0 (-94;51)
P-value (minus RIS LOW DOSE)*		<0.001
Diff. of LS Means (SE)		-10.3 (2.65)
95% CI		(-15.53;-5.09)

Source: Study Report, p 103 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 8. There is a numerical difference between the two groups at each visit in favor of the high dose group.

Table 8 Positive and Negative Symptoms of Schizophrenia (PANSS) Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) - Modified ITT Analysis Set.

	Risperidone Low Dose					Risperidone High Dose				
				Change from Baseline					Change from Baseline	
	N	Mean	SD	Mean	SD	N	Mean	SD	Mean	SD
Baseline	131	93.3	14.14			124	96.4	15.39		
Day 7 OC	130	88.3	18.31	-5.0	10.86	123	87.7	16.34	-8.8	12.06
Day 7 LOCF	130	88.3	18.31	-5.0	10.86	123	87.7	16.34	-8.8	12.06
Day 14 OC	123	83.6	16.81	-9.9	11.34	121	80.6	16.05	-15.7	13.75
Day 14 LOCF	131	84.3	18.33	-9.0	12.56	124	81.5	17.07	-14.9	14.91
Day 28 OC	112	82.2	19.09	-11.5	14.10	113	75.4	17.05	-20.9	15.94
Day 28 LOCF	131	83.3	20.37	-9.9	15.14	124	76.6	18.39	-19.8	17.41
Day 42 OC	97	76.2	20.53	-16.1	17.68	97	71.3	18.56	-25.5	18.76
Day 42 LOCF	131	81.2	23.14	-12.0	18.92	124	74.9	21.04	-21.5	20.44
Day 56 OC	82	72.0	20.40	-19.5	18.98	87	66.5	18.16	-30.9	20.07
Day 56 LOCF	131	80.8	24.33	-12.5	20.32	124	72.8	22.52	-23.6	22.83

Source: Study Report, Attachment 2.1.1.3.

3.1.3 *Evaluation of Efficacy- RIS-BIM-301*

Study RIS-BIM-301 evaluated the safety and efficacy of 2 dose ranges of risperidone monotherapy (0.5-2.5 mg/day and 3-6 mg/day) versus placebo in children and adolescents with a Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV) diagnosis of Bipolar I disorder who were experiencing a manic or mixed episode (Young Mania Rating Scale [YMRS] ≥20). Efficacy was primarily based on the improvement in severity of mania during the 3-week treatment period, measured by the change in total score (consensus final score) of the YMRS from baseline to endpoint.

169 subjects are included in the intent-to-treat analysis set. The demographics appear in Table 9. The majority was white, roughly half were male, and 40% were under 12 years old. There appeared to be roughly the same distribution in each treatment group.

Table 9 Patient Demographics (Intent-to-treat analysis set)

	--- PLACEBO -- (N=58)	RIS 0.5-2.5 mg (N=50)	- RIS 3-6 mg - (N=61)	---- Total --- (N=169)
Age, years				
N	58	50	61	169
Mean (SD)	13.1 (2.20)	13.4 (2.03)	13.1 (2.12)	13.2 (2.11)
Median	13.0	13.0	13.0	13.0
Range	(10;17)	(10;17)	(10;17)	(10;17)
Age in classes, n (%)				
N	58	50	61	169
≤12 years	24 (41)	18 (36)	25 (41)	67 (40)
>12 years	34 (59)	32 (64)	36 (59)	102 (60)
Sex, n (%)				
N	58	50	61	169
Female	30 (52)	22 (44)	35 (57)	87 (51)
Male	28 (48)	28 (56)	26 (43)	82 (49)
Race, n (%)				
N	58	50	61	169
American Indian/Alaskan Native	1 (2)	2 (4)	0	3 (2)
Asian	0	1 (2)	0	1 (1)
Black or African American	10 (17)	10 (20)	9 (15)	29 (17)
Mixed	2 (3)	2 (4)	2 (3)	6 (4)
White	45 (78)	35 (70)	50 (82)	130 (77)

Source: Study Report, p 98.

Roughly 80% of the subjects completed the study. The reasons for discontinuation by treatment group appear in Table 10.

Table 10 Subject Disposition and Discontinuation Reasons (Intent-to-treat analysis set)

State of Termination Term. Reason **All subjects**	PLACEBO (N=58) n (%)	RIS 0.5-2.5 mg (N=50) n (%)	RIS 3-6 mg (N=61) n (%)	Total (N=169) n (%)
Completed	46 (79)	45 (90)	46 (75)	137 (81)
Discontinued	12 (21)	5 (10)	15 (25)	32 (19)
Adverse event	4 (7)	3 (6)	10 (16)	17 (10)
Insufficient response	2 (3)	0	2 (3)	4 (2)
Subject ineligible to continue the study	0	1 (2)	0	1 (1)
Subject lost to follow-up	1 (2)	0	2 (3)	3 (2)
Subject withdrew consent	2 (3)	1 (2)	1 (2)	4 (2)
Subject non-compliant	1 (2)	0	0	1 (1)
Other	2 (3)	0	0	2 (1)
	PLACEBO (N=24)	RIS 0.5-2.5 mg (N=18)	RIS 3-6 mg (N=25)	Total (N=67)
≤12 years	n (%)	n (%)	n (%)	n (%)
Completed	22 (92)	17 (94)	17 (68)	56 (84)
Discontinued	2 (8)	1 (6)	8 (32)	11 (16)
Adverse event	0	0	4 (16)	4 (6)
Insufficient response	0	0	1 (4)	1 (1)
Subject lost to follow-up	0	0	2 (8)	2 (3)
Subject withdrew consent	1 (4)	1 (6)	1 (4)	3 (4)
Other	1 (4)	0	0	1 (1)
	PLACEBO (N=34)	RIS 0.5-2.5 mg (N=32)	RIS 3-6 mg (N=36)	Total (N=102)
>12 years	n (%)	n (%)	n (%)	n (%)
Completed	24 (71)	28 (88)	29 (81)	81 (79)
Discontinued	10 (29)	4 (13)	7 (19)	21 (21)
Adverse event	4 (12)	3 (9)	6 (17)	13 (13)
Insufficient response	2 (6)	0	1 (3)	3 (3)
Subject ineligible to continue the study	0	1 (3)	0	1 (1)
Subject lost to follow-up	1 (3)	0	0	1 (1)
Subject withdrew consent	1 (3)	0	0	1 (1)
Subject non-compliant	1 (3)	0	0	1 (1)
Other	1 (3)	0	0	1 (1)

Source: Study Report, p 95.

The primary efficacy variable was the change in the total YMRS consensus final score from baseline to the Day 21 endpoint (i.e. the last post-baseline observation carried forward to the Day 21 endpoint). The primary analysis used an ANCOVA model with factors for treatment, baseline value, investigator, and diagnosis (mixed or manic). The last observed value was carried forward (from Day 7 or 14) for subjects with missing values at Day 21. To account for two comparisons, a sequential testing procedure was used starting with the high dose versus placebo. Results of the primary efficacy analysis (LOCF analysis) are shown in Table 11. Both risperidone treated groups show significantly lower scores at Day 21 compared to placebo.

Table 11 Young Mania Rating Scale Adolescent Version (YMRS) Consensus Total Scores - Change From Baseline to Day 21 Endpoint- ITT with a Post-Baseline Observation Analysis Set.

	PLACEBO	RIS 0.5-2.5 mg	RIS 3-6 mg
Baseline			
N	57	49	60
Mean (SD)	31.0 (7.46)	31.1 (5.97)	30.5 (5.92)
Median (Range)	31.0 (19;45)	31.0 (16;44)	31.0 (20;44)
Day 21 endpoint			
N	57	49	60
Mean (SD)	21.9 (9.51)	12.6 (7.22)	13.9 (9.70)
Median (Range)	22.0 (3;44)	12.0 (0;30)	11.5 (0;40)
Change from Baseline			
N	57	49	60
Mean (SD)	-9.1 (10.95)	-18.5 (9.70)	-16.5 (10.29)
Median (Range)	-8.0 (-36;22)	-17.0 (-39;-3)	-18.0 (-35;6)
P-value(minus PLACEBO)(a,b)		<0.001	<0.001
Diff. of LS Means (SE)		-9.2 (1.76)	-8.0 (1.70)
95% CI		(-12.69;-5.74)	(-11.33;-4.62)

Source: Study Report, p 120 and FDA analysis.

The mean PANSS Total Scores at each visit and the change from baseline for both the observed cases and with last observed value carried forward are in Table 12. There is a numerical difference between each of the two risperidone groups and placebo at each visit in favor of the risperidone groups.

Table 12 Young Mania Rating Scale Adolescent Version (YMRS) Consensus Total Scores at Each Visit, Observed Case (OC) and Last Observation Carried Forward (LOCF) – ITT with a Post-Baseline Observation Analysis Set.

	N	Mean	SD	Change from Baseline	
				Mean	SD
Placebo Group					
Baseline	57	31.0	7.46		
Day 7 OC	57	25.4	7.67	-5.6	8.06
Day 7 LOCF	57	25.4	7.67	-5.6	8.06
Day 14 OC	49	20.3	8.63	-11.0	9.83
Day 14 LOCF	57	21.7	8.98	-9.2	10.60
Day 21 OC	47	20.5	9.41	-10.0	10.12
Day 21 LOCF	57	21.9	9.51	-9.1	10.95
Risperidone 0.5-2.5 mg					
Baseline	49	31.1	5.97		
Day 7 OC	48	20.4	8.48	-10.6	9.75
Day 7 LOCF	48	20.4	8.48	-10.6	9.75
Day 14 OC	47	13.6	7.26	-17.5	9.36
Day 14 LOCF	49	13.8	7.19	-17.3	9.34
Day 21 OC	45	12.1	6.82	-18.8	9.71
Day 21 LOCF	49	12.6	7.22	-18.5	9.70
Risperidone 3-6 mg					
Baseline	60	30.5	5.92		
Day 7 OC	59	21.7	8.63	-8.7	6.71
Day 7 LOCF	59	21.7	8.63	-8.7	6.71
Day 14 OC	53	12.2	7.15	-18.1	7.30
Day 14 LOCF	60	14.0	8.58	-16.5	8.48
Day 21 OC	46	12.3	8.49	-18.0	9.17
Day 21 LOCF	60	13.9	9.70	-16.5	10.29

Source: Study Report, Attachment 2.1.1.1.

3.2 Evaluation of Safety

See medical officer's review.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

4.1.1 *Efficacy findings Gender, Race and Age- RIS-SCH-302*

The results for the primary endpoint in subgroups defined by gender and race appear in Table 13. Numerically, the results appear to show both the low and high dose groups were better than placebo in each subgroup.

Table 13 Results for primary endpoint in demographic subgroups

Demographic Subgroup		PLACEBO	RIS 1-3 mg	RIS 4-6 mg
Sex				
Female	N	19	24	14
	Mean (SD)	-11.6 (12.01)	-22.8 (23.62)	-26.3 (21.40)
	Diff. of LS means (95% CI)		-11.2 (-21.53;-0.88)*	-14.2 (-25.78;-2.52)'
Male	N	35	30	36
	Mean (SD)	-7.4 (17.94)	-20.2 (16.04)	-19.2 (16.85)
	Diff. of LS means (95% CI)		-11.8 (-19.32;-4.29)*	-12.2 (-19.33;-5.09)
Race				
Non-white	N	27	22	27
	Mean (SD)	-15.9 (17.61)	-30.1 (18.77)	-27.8 (21.33)
	Diff. of LS means (95% CI)		-11.1 (-21.39;-0.77)*	-13.4 (-23.18;-3.57)
White	N	27	32	23
	Mean (SD)	-1.9 (10.80)	-15.3 (18.08)	-13.5 (9.58)
	Diff. of LS means (95% CI)		-12.5 (-19.42;-5.65)***	-12.3 (-19.77;-4.77)'

Source: Study Report p. 101

4.1.2 *Efficacy findings Gender, Race and Age- RIS-USA-231*

The results for the primary endpoint in subgroups defined by gender and race appear in Table 14. Numerically, the results appear to favor the high dose groups over the low dose in each subgroup.

Table 14 Results for primary endpoint in demographic subgroups

	Change from baseline at Day 56 end point in total PANSS score			
	RIS LOW DOSE		RIS HIGH DOSE	
	N	Mean (SD)	N	Mean (SD) Diff. of LS Means (95% CI)
Sex				
Female	51	-14.5 (19.72)	59	-22.8 (25.88) -8.2 (-16.87;0.53)
Male	80	-11.2 (20.72)	65	-24.3 (19.85) -13.4 (-20.23;-6.55)***
Race#				
Non-White	20	-12.7 (19.16)	19	-30.6 (22.95) -17.0 (-31.76;-2.18)**
White	110	-12.7 (20.45)	103	-22.9 (22.50) -9.4 (-15.02;-3.80)*
Black	20	-12.7 (19.16)	17	-29.9 (24.16) -16.4 (-31.53;-1.23)*

Source: Study Report p. 116

4.1.3 *Efficacy findings Gender, Race and Age- RIS-BIM-301*

The results for the primary endpoint in subgroups defined by gender, race and age appear in Table 15. Numerically, the results appear to favor the risperidone treated groups over placebo in each subgroup.

Table 15 Results for primary endpoint in demographic subgroups

	Change From Baseline at Day 21 Endpoint in Total YMRS Score					
	PLACEBO		RIS 0.5-2.5 mg		RIS 3-6 mg	
	N	Mean (SD)	N	Mean (SD) Diff. of LS Means (95% CI)	N	Mean (SD) Diff. of LS Means (95% CI)
Sex						
Female	29	-10.7 (10.47)	22	-15.1 (7.06) -4.5 (-9.53;0.46)	35	-17.1 (9.98) -5.7 (-10.17;-1.22)*
Male	28	-7.5 (11.37)	27	-21.3 (10.77) -14.7 (-20.43;-8.95)***	25	-15.7 (10.85) -10.9 (-16.98;-4.78)***
Race						
Non-White	13	-7.8 (6.44)	14	-17.6 (9.92) -8.5 (-16.84;-0.11)*	10	-13.7 (12.52) -8.9 (-18.68;0.81)
White	44	-9.5 (11.99)	35	-18.9 (9.73) -9.0 (-13.25;-4.83)***	50	-17.1 (9.83) -8.5 (-12.40;-4.58)***
Race (Non-Black versus Black)						
Black	10	-6.8 (5.47)	9	-20.9 (9.60) -11.5 (-22.94;-0.12)*	9	-12.0 (11.99) -4.3 (-16.98;8.46)
Non-Black	47	-9.6 (11.77)	40	-18.0 (9.77) -8.6 (-12.58;-4.63)***	51	-17.3 (9.88) -8.6 (-12.35;-4.84)***
Age						
≤12 years	24	-6.1 (11.07)	18	-18.6 (10.00) -14.0 (-21.50;-6.54)***	24	-18.0 (9.51) -13.1 (-19.71;-6.40)***
>12 years	33	-11.3 (10.49)	31	-18.5 (9.69) -6.5 (-10.88;-2.03)*	36	-15.6 (10.80) -5.1 (-9.22;-1.03)*

Source: Study Report p. 139

4.2 Other Special/Subgroup Populations

None.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrated that risperidone is effective. There are no statistical issues for any of the three studies for the primary endpoint. However, no multiple comparison procedure was planned for secondary endpoints in any study. For each secondary endpoint, nominal p-values were reported. See Sections 3.1.1, 3.1.2, and 3.1.3 for the efficacy results of the individual studies.

5.2 Conclusions and Recommendations

Two studies in adolescents with schizophrenia and one study in adolescents with bipolar disorder demonstrate that risperidone is effective in treating these subjects.

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James Hung
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