SYNOPSIS
Issue Date: Final – 22 July 2009
[**Document No.:** EDMS-PSDB-9245102]

Name of Sponsor/Company	Janssen-Cilag EMEA Medical Affairs a division of Janssen Pharmaceuticals N.V.
Name of Finished Product	Risperdal® Consta®
Name of Active Ingredient(s)	risperidone

Protocol No.: RIS-BMN-3001

Title of Study: A randomized, double-blind, placebo- and active-controlled, parallel-group study to evaluate the efficacy and safety of risperidone long-acting injectable for the prevention of mood episodes in the treatment of subjects with bipolar I disorder

EudraCT Number: 2006-001490-15

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Publication (Reference): none at the time of reporting

Study Period: 14 November 2006 – 13 April 2009 [date of first study-related procedure – study termination date]

Phase of Development: III

Objectives:

The primary objective of this study was to evaluate the efficacy of risperidone long-acting injectable (LAI) monotherapy versus placebo in the prevention of a mood episode (recurrence event) in subjects with bipolar I disorder after a 12-week (3-month) open-label stabilization period on risperidone LAI, as measured by the time to recurrence of any mood episode.

Secondary objectives were: to evaluate the prevention of a mood episode (sustained efficacy of maintenance treatment) with risperidone LAI versus placebo, as measured by (1) the time to recurrence of an elevated mood episode (hypomanic, manic, or mixed) and (2) the time to recurrence of a depressive episode; to evaluate overall duration of treatment of risperidone LAI versus placebo, as measured by the time to early discontinuation from study medication for any reason (including recurrence) except termination of the study by the sponsor; to evaluate the sustained efficacy of maintenance treatment with risperidone LAI versus placebo, using the Young Mania Rating Scale (YMRS), the Montgomery Åsberg Depression Rating Scale (MADRS), the Clinical Global Impressions – Severity (CGI-S) scale, and Personal and Social Performance scale (PSP); to evaluate the sustained efficacy of maintenance treatment with risperidone LAI versus placebo on mental health status, using the SF-36® Health Survey (Medical Outcomes Study Short Form 36); and to evaluate the long-term safety of risperidone LAI in subjects with bipolar I disorder.

Methods:

This was a randomized, double-blind, double-dummy, multicenter study with 3 parallel treatment arms (risperidone LAI, placebo, and olanzapine) conducted at multiple sites in Europe, Asia, Latin-America, and Africa. The study included 3 periods, i.e., the screening period (Period I, up to 2 weeks), the open-label treatment period (Period II, 12 weeks), and the double-blind treatment period (Period III, up to 18 months).

At screening, subjects who met all entry criteria were classified into 2 groups according to their mood and medication status at screening: acute subjects experiencing a manic or mixed episode (YMRS >20 and CGI-S ≥4 [moderate]), or non-acute subjects in-between mood episodes (YMRS <12 and CGI-S ≤3 [mild]) who had been receiving an antipsychotic or mood stabilizer for at least 4 weeks prior to screening.

During Period I, acute subjects were allowed to receive any medication for the treatment of their manic symptoms, as considered clinically appropriate (excluding clozapine and depot neuroleptics). Non-acute subjects were to continue the treatment they were receiving for at least 4 weeks prior to screening.

The beginning of Period II was marked by the first injection of risperidone LAI. Acute subjects were to discontinue treatment of all antipsychotics other than oral risperidone and tapering-off was to be completed within the first week of Period II. In addition to risperidone LAI, subjects experiencing an acute manic or mixed episode were administered oral risperidone at whole-milligram doses between 1 and 6 mg/day, as needed to treat the symptoms of the acute episode, during the first 3 weeks and this was to be tapered off within the 2 weeks thereafter. Non-acute subjects who had been receiving an antipsychotic or mood stabilizer for at least 4 weeks prior to screening were to continue this previous treatment during the first 3 weeks of Period II, in addition to risperidone LAI; tapering-off of this antipsychotic or mood stabilizer was to be completed within the 2 weeks thereafter. No changes were to be made to the regimens of non-acute subjects on an antipsychotic or mood stabilizer unless there was a concern about efficacy or safety.

Subjects who did not show response to treatment (for acute subjects at baseline) or who did not maintain efficacy of treatment (for non-acute subjects at baseline) during the 12-week open-label risperidone LAI stabilization period (Period II) were to be discontinued from the study. Subjects who did show response during the 12-week open-label risperidone LAI stabilization period (Period II) were eligible for entry into the fixed-dose double-blind period (Period III).

In Period III, subjects were randomized to one of 3 treatment arms (risperidone LAI, placebo, and olanzapine) in a 1:1:1 ratio. Using the double-dummy design, all subjects received an intramuscular injection (risperidone LAI or placebo) every 14 days and took oral medication (olanzapine or placebo) every day.

Subjects who presented with a recurrence of a mood episode during Period III, as defined in the protocol, were considered as meeting the endpoint of the study. Subjects could remain in the double-blind treatment period until they had a recurrence, until they had received 18 months of double-blind treatment without a mood episode in Period III, until they met any of the withdrawal criteria, or until the study ended. The study was to end once 158 subjects had a recurrence of a mood episode in Period III or if the study was terminated based on the decision of the sponsor.

Number of Subjects (planned and analyzed):

The null hypothesis was that there is no difference in time to recurrence between risperidone LAI and placebo. The power and sample size calculations were based on a 2-sided test with a 5% significance level. No adaptation of the alpha-level was required as the olanzapine versus placebo comparison was not involved in the primary hypothesis.

If in Period III 100 subjects were randomized to each of the 2 relevant treatment arms (risperidone LAI and placebo), this study would have had approximately 90% power to detect a clinically meaningful difference of 23% in recurrence rates of a mood episode between the risperidone and placebo arms (i.e., a recurrence rate at 9 months of approximately 45% in the risperidone LAI arm and 68% in the placebo arm). With 100 subjects in each treatment arm, these recurrence rates would have translated into approximately 45 and 68 events, respectively, i.e., a total of 113 recurrence events. However, the third treatment arm also was to be taken into account because this was a double-blind study and the treatment group of a subject with recurrence was not known prior to unblinding. If it was assumed that the recurrence rate in the olanzapine arm was the same as in the risperidone LAI arm (45%), a further 45 recurrence events were to be expected in the olanzapine arm and 300 subjects were to be randomized in Period III. The study was to end once 158 recurrence events were observed in Period III.

Given the assumption that the dropout or non-response rate during the 12-week open-label treatment period (Period II) in the present study was approximately 65%, in order to have 300 subjects entering Period III, the study would have needed to enroll 860 subjects. However, during the study, careful statistical review of the Period II data showed a lower dropout rate than was expected. As a consequence, the protocol was amended to reflect that the number of subjects that was screened at the time of review (N=667) was sufficient to have 300 subjects randomized into Period III, taking into account the observed screening failure rate of 10%.

The actual number of subjects that were enrolled in the study was 585. The predefined analysis sets consisted of

- Intent-to-treat set of Period II, i.e., all subjects who received at least one injection of risperidone LAI and who had at least one post-baseline visit;

- Intent-to-treat set of Period III, i.e., all randomized subjects who received at least one dose of double-blind study medication and who had at least one post-baseline visit;
- Safety set for Period II, i.e., all subjects who received at least one injection of risperidone LAI;
- Safety set for Period III, i.e., all randomized subjects who received at least one dose of double-blind study medication.

	Period II: Open-Label			Period III: Double-Blind, Randomized			
	Risperidone LAI			Risperi-	Placebo	Olanza-	Total
Parameter, n	Acute	Non-acute	Total	done LAI		pine	
Screened	-	-	667	-	-	-	-
Enrolled (all treated subjects)	415	170	585	-	-	-	-
Entered in Period II	415	170	585	-	-	-	-
Intent-to-treat Period II	412	166	578	-	-	-	-
Safety Period II	415	170	585	-	-	-	-
Entered in Period III	-	-	-	137	140	138	415
Intent-to-treat Period III	-	-	-	135	138	137	410
Safety Period III	-	-	-	137	140	138	415

n=number of subjects

Diagnosis and Main Criteria for Inclusion:

Subjects, male or female, 18 to 65 years of age (inclusive), with a diagnosis of bipolar I disorder as defined by DSM-IV-TR criteria, who were either experiencing a manic or mixed episode (acute; defined as having YMRS >20 and CGI-S ≥4 [moderate]) or who were in-between mood episodes (non-acute; defined as having YMRS <12 and CGI S ≤3 [mild]) and had been receiving an antipsychotic or mood stabilizer for at least 4 weeks prior to screening (i.e., non acute subjects were to have received an unchanged dose of antipsychotic or mood stabilizer for a minimum of 4 weeks prior to screening and were to be experiencing problems of safety or tolerability with this antipsychotic or mood stabilizer, or requesting for a change in medication, except for oral risperidone), who did not meet the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text revised (DSM-IV-TR) criteria for a depressive episode, who were in good general physical health, and who met the entry criteria.

Test Product, Dose and Mode of Administration, Batch Numbers:

Risperidone LAI was started in Period II at the recommended dose of 25 mg. If judged clinically appropriate, subjects could start with 37.5 mg. Injections were repeated every 14 days.

During the first 8 weeks of Period II, upward dosage adjustments of risperidone LAI were allowed in acute subjects, but they were not to be made more frequently than every 4 weeks. In non-acute subjects, only one dose increase and only one dose decrease of risperidone LAI was allowed during the first 8 weeks of Period II. No dose adjustments were allowed after Week 8 of Period II. The dose of risperidone LAI could be increased (up to a maximum dose of 50 mg every 14 days) if the CGI-S score had increased by ≥1 over 2 consecutive assessments at least 2 weeks apart and there was symptom exacerbation that could not be treated adequately with short-term (14-day) benzodiazepine medication; if a subject did not respond to a 14-day course of benzodiazepine medication, the risperidone LAI dose was to be increased. One 12.5-mg decrease in risperidone LAI dose was permitted by the investigator if tolerability was considered to be a factor. However, the dose could not subsequently be increased for a subject that had a dose decrease and the dose was to remain ≥25 mg.

During Period III, risperidone LAI was to be administered at the dose reached at the end of Period II. No supplementation with oral risperidone and no dose titration was allowed during this period.

Oral risperidone was added in the following scenarios:

- In case subjects were risperidone-naïve, they were to receive an oral risperidone test dose (2x1 mg/day) on 2 consecutive days prior to the first injection of risperidone LAI, in order to establish tolerability.
- Acute subjects received oral risperidone in addition to risperidone LAI, in a flexible dosage regimen at whole-milligram dosages of 1 to 6 mg/day during the first 3 weeks of Period II and this was to be tapered off within the 2 weeks thereafter (non-acute subjects were to continue their previous antipsychotic therapy during the first 3 weeks of Period II, in addition to risperidone LAI).

- If an increase in risperidone LAI dose was necessary, oral risperidone (1 to 2 mg/day) was to be added during 3 weeks after the first injection of the higher dose, i.e., until release from the microspheres occurred.

Risperidone LAI Batches: 164-3714-BC, 164-3714-BB, and 164-3714-BA
Oral Risperidone Batches: 06A27/F005, 06D20/F005, 07C05/F005, 07I18/F005

Reference Therapy, Dose and Mode of Administration, Batch Numbers:

In Period III, subjects were randomized to one of 3 treatment arms (risperidone LAI, placebo, or olanzapine) in a 1:1:1 ratio. Using the double-dummy design, all subjects received an intramuscular injection every 14 days and took oral medication every day. Oral placebo and injectable placebo were used.

Reference treatment was olanzapine (Zyprexa®), administered at a standard dose of 10 mg/day.

Olanzapine Batches: 06F01/F292, 07A17/F292, 07K08/F292, 08C17/F292
Oral placebo Batches: 06L06/F125, 06F08/F125, 06F09/F125, 06F12/F125, 06F13/F125, 08E23/F125
Injectable placebo Batches: 421-0416AA, 421-2446BA

Duration of Treatment:

The study included 3 periods, i.e., the screening period (Period I, up to 2 weeks), the open-label treatment period (Period II, 12 weeks), and the double-blind treatment period (Period III, up to 18 months). The study was to end once 158 subjects had a recurrence of a mood episode in Period III.

Criteria for Evaluation:

Subjects who presented with a recurrence of a mood episode during Period III were considered as meeting the endpoint of the study. Primary efficacy criterion of the study was the time to recurrence of a mood episode in the double-blind period (Period III).

Other efficacy assessments were based on:

- Young Mania Rating Scale: the YMRS was administered at all visits.
- Montgomery Åsberg Depression Rating Scale: the MADRS was administered at all visits.
- Clinical Global Impression – Severity: the CGI-S was administered at all visits.
- SF-36® Health Survey: Medical Outcomes Study Short Form 36 was administered at baseline of Period II, end of Period II/baseline of Period III, at all visits throughout Period III, and at completion of Period III or upon early discontinuation.
- Personal and Social Performance scale: the PSP was administered at baseline of Period II, end of Period II/baseline of Period III, at all visits throughout Period III, and at completion of Period III or upon early discontinuation.
- Resource use questionnaire: the RUQ was administered by all subjects who entered Period III, at all visits throughout Period III and at completion of Period III or upon early discontinuation.

Safety assessments were based on:

- Adverse events (AEs): AEs were reported by the subjects from signing of informed consent onwards until the last study-related procedure. Serious AEs (SAEs) were reported until 45 days after the last injection of study medication or until the last study-related procedure (whichever occurred later). AEs occurring after the end of the study were captured by spontaneous reporting.
- Clinical laboratory tests: blood samples for hematology and biochemistry and a random urine sample for urinalysis were taken at screening and at completion of Period III or upon early discontinuation.
- Vital signs measurements: blood pressure and pulse were measured at screening, at baseline of Period II, baseline of Period III, at all visits throughout Period III, and at completion of Period III or upon early discontinuation.
- Body weight and BMI: height was measured at screening; body weight was measured at screening, at baseline of Period II, at baseline of Period III, at 12-week intervals throughout Period III, and at completion of Period III or upon early discontinuation; Body Mass Index (BMI) was calculated.
- Electrocardiogram (ECG) evaluations: heart rate and PR, QRS, and QT measured intervals were analyzed at baseline of Period II and at baseline of Period III. QTc Bazett (QTcB), QTc Fridericia (QTcF), and QTc linear-derived (QTcLD) were calculated.
- Physical examinations were performed at screening and at completion of Period III or upon early discontinuation.

- Extrapyramidal symptoms: ESRS was administered at screening, at baseline of Period II, at end of Period II/baseline of Period III, at 12-week intervals throughout Period III, and at completion of Period III or upon early discontinuation.

Statistical Methods: Descriptive statistics, intent-to-treat, Kaplan-Meier, log-rank test, ANCOVA, Van Elteren test, Wilcoxon signed-rank test, Cochran-Mantel-Haenszel test

RESULTS:

STUDY POPULATION

The actual number of subjects that entered the open-label stabilization period (Period II) was 585. Twenty-nine percent of these subjects were discontinued from the study during open-label stabilization. The majority of subjects that were discontinued during Period II (103 of the 170 subjects that discontinued; 61%) had been identified as non-responder. Four hundred and fifteen (71%) subjects completed Period II and were randomized to either the risperidone LAI (N=137), placebo (N=140), or olanzapine (N=138) double-blind treatment arm in Period III.

The study was stopped once the predetermined number of recurrences of a mood episode in Period III, needed to detect a clinically meaningful difference in recurrence rate in the risperidone LAI arm compared to the placebo arm, was reached; 161 subjects (39% of the subjects in Period III) had met at least one of the criteria for recurrence.

Study Completion/Withdrawal Information During Open-Label Treatment
(Study RIS-BMN-3001: *Safety Set Period II*)

Parameter, n (%)	Acute N=415	Non-acute N=170	Total N=585
Completed Period II	**281 (67.7)**	**134 (78.8)**	**415 (70.9)**
Discontinued Period II	**134 (32.3)**	**36 (21.2)**	**170 (29.1)**
Non-responder	89 (21.4)	14 (8.2)	103 (17.6)
Reason other than non-response	45 (10.8)	22 (12.9)	67 (11.5)
Withdrawal of consent	19 (4.6)	8 (4.7)	27 (4.6)
Adverse event(s)	8 (1.9)	2 (1.2)	10 (1.7)
Lost to follow-up	5 (1.2)	1 (0.6)	6 (1.0)
Other	13 (3.1)	11(6.5)	24 (4.1)

Study Completion/Withdrawal Information During Double-Blind Treatment
(Study RIS-BMN-3001: *Safety Set Period III*)

Parameter, n (%)	Ris LAI N=137	Placebo N=140	Olanzapine N=138	Total N=415
Recurrence	**52 (38.0)**	**77 (55.0)**	**32 (23.2)**	**161 (38.8)**
Completed without recurrence	**55 (40.1)**	**40 (28.6)**	**81 (58.7)**	**176 (42.4)**
18 months treatment	13 (9.5)	8 (5.7)	14 (10.1)	35 (8.4)
Ongoing	42 (30.7)	32 (22.9)	67 (48.6)	141 (34.0)
Discontinued Period III without recurrence	**30 (21.9)**	**23 (16.4)**	**25 (18.1)**	**78 (18.8)**
Withdrawal of consent	16 (11.7)	12 (8.6)	8 (5.8)	36 (8.7)
Adverse event(s)	6 (4.4)	2 (1.4)	4 (2.9)	12 (2.9)
Lost to follow-up	2 (1.5)	4 (2.9)	4 (2.9)	10 (2.4)
Non-compliance	0	2 (1.4)	3 (2.2)	5 (1.2)
Pregnancy	0	2 (1.4)	0	2 (0.5)
Other	6 (4.4)	1 (0.7)	6 (4.3)	13 (3.1)

At screening, subjects were classified into subgroups based upon their YMRS and CGI-S scores and medication status. At Period II baseline, median YMRS and CGI-S scores in the subgroup of acute subjects were 25.0 (range: 10-46) and 4.0 (range: 3-6), respectively, whereas they were 4.0 (range: 0-26) and 2.0 (range: 1-4), respectively, in the subgroup of non-acute subjects. Median Period II baseline MADRS score in acute and non-acute subjects was 5.0 (range: 0-25) and 2.0 (range: 0-14), respectively.

For subjects in the ITT population randomized to double-blind treatment, the most recent episode was 'manic' for 378 (92%) subjects and 'mixed' for 32 (8%) subjects. Note that at screening, subjects meeting the DSM-IV-TR criteria for a hypomanic or depressive episode were not enrolled in the study.

No differences in demographic data and baseline disease characteristics were apparent among subjects randomized to the risperidone LAI, placebo, and olanzapine arms (Period III), nor between subjects in the

acute and non-acute subgroups (Period II), apart from differences attributable to the subgroup classification.

Demographic Characteristics
(Study RIS-BMN-3001: *ITT Sets Period II and III*)

	Open-Label	Double-Blind			
	All subjects	Ris LAI	Placebo	Olanzapine	All subjects
Parameter	**N=578**	**N=135**	**N=138**	**N=137**	**N=410**
Age (years)					
N	574	133	137	137	407
Mean (SD)	36.8 (11.41)	35.5 (11.16)	36.5 (10.83)	36.4 (11.04)	36.1 (10.99)
Median	36.0	34.0	35.0	35.0	35.0
Range	18-64	18-63	18-61	18-62	18-63
Sex, n (%)					
N	578	135	138	137	410
Male	276 (47.8)	56 (41.5)	67 (48.6)	74 (54.0)	197 (48.0)
Female	302 (52.2)	79 (58.5)	71 (51.4)	63 (46.0)	213 (52.0)
Race, n (%)					
N	578	135	138	137	410
Asian	250 (43.3)	53 (39.3)	52 (37.7)	55 (40.1)	160 (39.0)
White	226 (39.1)	61 (45.2)	60 (43.5)	57 (41.6)	178 (43.4)
Black	11 (1.9)	2 (1.5)	3 (2.2)	3 (2.2)	8 (2.0)
Other	91 (15.7)	19 (14.1)	23 (16.7)	22 (16.1)	64 (15.6)
BMI (kg/m^2)					
N	575	135	138	136	409
Mean (SD)	25.8 (5.02)	26.5 (5.37)	25.6 (4.38)	26.0 (5.20)	26.0 (5.00)
Median	25.0	25.4	25.2	25.3	25.3
Range	14.9-50.8	17.7-48.6	17.0-37.7	16.0-43.4	16.0-48.6

EFFICACY RESULTS:

Efficacy analyses were performed on an ITT analysis set for each relevant period in the study. The ITT set for Period II included all subjects who received at least one injection of risperidone LAI and who had at least one post-baseline visit; these were 578 subjects (7 were excluded because they did not have a post-baseline visit in Period II). The ITT set for Period III included all randomized subjects who received at least one dose of double-blind study medication and who had at least one post-baseline visit; these were 410 subjects of whom 135 were randomized to the risperidone LAI arm, 138 to the placebo arm, and 137 to the olanzapine arm (5 subjects were excluded because they did not have a post-baseline visit in Period III).

PRIMARY EFFICACY VARIABLE: TIME TO RECURRENCE OF A MOOD EPISODE IN PERIOD III

In total 161 subjects (39% of the subjects in the ITT set for Period III) met any of the criteria for recurrence during double-blind treatment in the study. The percentage of subjects experiencing a recurrence was lower in the risperidone LAI arm than in the placebo arm, i.e., 39% versus 56%.

No statistically significant difference in time to recurrence of any mood episode with risperidone LAI versus placebo was found by means of a log-rank test adjusting for subject type at screening (acute or non-acute) and geographic region (p=0.062). The Kaplan-Meier estimate provided a median time to recurrence of a mood episode of 206 days in the placebo arm, whereas the median was not defined in the risperidone LAI arm since the 50^{th} percentile had not been reached. The 25^{th} percentile of estimated time to recurrence was 98 days in the risperidone LAI arm and 97 days in the placebo arm.

In the olanzapine arm, 23% of the subjects experienced a recurrence of a mood episode. The 50^{th} percentile of estimated time to recurrence in the olanzapine arm had not been reached. The 25^{th} percentile in the olanzapine arm was 459 days.

The randomization for this study was stratified by subject type at screening and country. The pre-planned primary efficacy analysis took these stratification factors into account by employing a log-rank test stratified by subject type at screening and geographic region. Post-hoc investigation into the effect on recurrence rates of each stratum individually and the interaction between the 2 factors suggested that stratifying the log-rank test by geographic region only was a more appropriate method than stratifying by both geographic region and subject type. A log-rank test stratified by geographic region only indicated a statistically significant difference in time to recurrence of any mood episode between risperidone LAI and placebo (p=0.032). This result was consistent with an analysis of simple recurrence percentages between

risperidone LAI and placebo controlling for both subject type and region (p=0.006; Cochran-Mantel-Haenszel test).

SECONDARY EFFICACY VARIABLES:

The percentage of subjects with an elevated mood episode in the risperidone LAI arm was half of that in the placebo arm (20% versus 39%). The contribution of manic episodes was lower in the risperidone LAI arm than in the placebo arm (13% versus 31%). The percentage of subjects with manic or hypomanic episodes was similar between the risperidone LAI and olanzapine arms. Statistically significant difference in time to recurrence of an elevated mood episode with risperidone LAI versus placebo was found in favor of risperidone LAI (p=0.005; log-rank test adjusting for subject type at screening and geographic region and p=0.002; log-rank test and adjusting for geographic region alone).

The percentage of subjects with a depressive episode in the risperidone LAI arm (19%) was similar to that in the placebo arm (17%) and more than the percentage in the olanzapine arm (9%). No statistically significant difference in time to recurrence of a depressive episode with risperidone LAI versus placebo was found (p=0.587; log-rank test adjusting for subject type at screening and geographic region and p=0.652; log-rank test adjusting for geographic region alone).

No statistically significant difference in time to clinically relevant decline in mental health status, as measured by the SF-36® Health Survey, with risperidone LAI versus placebo was found (p=0.371; log-rank test adjusting for subject type at screening and geographic region). Median time to clinically relevant decline was 86 days in the risperidone LAI arm and 77 days in the placebo arm. The 25th percentile of estimated time to relevant decline was 30 days in the risperidone LAI arm and 29 days in the placebo arm.

Efficacy and Quality of Life Scales During Open-Label Treatment
(Study RIS-BMN-3001: *ITT Set Period II*)

Parameter	**Acute N=412**	**Non-acute N=166**
YMRS score		
Actual value at baseline, mean (SE)	25.7 (0.23)	4.6 (0.31)
Change from baseline[a], mean (SE)	-18.5 (0.46)	-1.8 (0.41)
MADRS score		
Actual value at baseline, mean (SE)	5.7 (0.21)	3.2 (0.27)
Change from baseline[a], mean (SE)	-0.3 (0.40)	0.7 (0.53)
CGI-S score		
Actual value at baseline, mean (SE)	4.4 (0.03)	1.9 (0.07)
Change from baseline[a], mean (SE)	-1.9 (0.07)	-0.1 (0.09)
SF-36®: Mental Health Domain score		
Actual value at baseline, mean (SE)	66.8 (1.00)	67.6 (1.61)
Change from baseline[a], mean (SE)	-1.5 (1.13)	1.3 (1.77)
SF-36®: MCS score		
Actual value at baseline, mean (SE)	43.7 (0.39)	42.8 (0.57)
Change from baseline[a], mean (SE)	-1.5 (0.47)	-0.1 (0.61)
SF-36®: PCS score		
Actual value at baseline, mean (SE)	48.4 (0.34)	47.9 (0.45)
Change from baseline[a], mean (SE)	-0.2 (0.37)	0.7 (0.48)
PSP score		
Actual value at baseline, mean (SE)	56.1 (0.64)	77.8 (0.89)
Change from baseline[a], mean (SE)	14.4 (0.88)	2.7 (0.92)

[a] change from Period II baseline to Period II endpoint

At Period II endpoint, 78% of acute subjects had shown response to treatment and 90% of non-acute subjects had maintained efficacy of treatment and were eligible to continue in Period III.

Efficacy and Quality of Life Scales During Double-Blind Treatment
(Study RIS-BMN-3001: *ITT Set Period III*)

Parameter	Risperidone LAI N=135	Placebo N=138	Olanzapine N=137
YMRS score			
Actual value at baseline, mean (SE)	3.6 (0.33)	3.3 (0.31)	2.9 (0.30)
Change from baseline[a], mean (SE)	2.8 (0.85)	7.9 (1.13)	1.8 (0.74)
MADRS score			
Actual value at baseline, mean (SE)	2.4 (0.24)	2.3 (0.26)	2.8 (0.28)
Change from baseline[a], mean (SE)	5.0 (0.84)	5.8 (0.97)	1.9 (0.62)
CGI-S score			
Actual value at baseline, mean (SE)	1.9 (0.07)	1.7 (0.07)	1.7 (0.06)
Change from baseline[a], mean (SE)	0.7 (0.14)	1.5 (0.17)	0.4 (0.12)
SF-36®: Mental Health Domain score			
Actual value at baseline, mean (SE)	68.3 (1.71)	72.5 (1.46)	68.1 (1.70)
Change from baseline[a], mean (SE)	-3.8 (2.09)	-5.2 (2.00)	1.1 (1.84)
SF-36®: MCS score			
Actual value at baseline, mean (SE)	42.4 (0.63)	44.1 (0.57)	42.9 (0.61)
Change from baseline[a], mean (SE)	-0.4 (0.66)	-1.4 (0.78)	0.4 (0.69)
SF-36®: PCS score			
Actual value at baseline, mean (SE)	49.3 (0.48)	48.8 (0.46)	48.7 (0.48)
Change from baseline[a], mean (SE)	-0.5 (0.55)	-0.4 (0.58)	0.8 (0.57)
PSP score			
Actual value at baseline, mean (SE)	78.0 (0.88)	79.2 (0.96)	78.2 (0.92)
Change from baseline[a], mean (SE)	-4.4 (1.52)	-12.2 (1.84)	0.4 (1.37)

[a] change from Period III baseline to Period III endpoint

SAFETY RESULTS:

Safety analyses were performed on a safety analysis set for each relevant period in the study. The safety set for Period II included all subjects who received at least one injection of risperidone LAI (585 subjects). The safety set for Period III included all randomized subjects who received at least one dose of double-blind study medication (415 subjects).

ADVERSE EVENTS:

Subjects With Adverse Events
(Study RIS-BMN-3001: *Safety Sets Period II and III*)

	Open-label	Double-blind		
Parameter, n (%)	All subjects N=585	Ris LAI N=137	Placebo N=140	Olanzapine N=138
One or more AEs	385 (65.8)	108 (78.8)	99 (70.7)	119 (86.2)
One or more treatment-emergent AEs	356 (60.9)	98 (71.5)	87 (62.1)	105 (76.1)
Deaths	0	0	0	0
One or more treatment-emergent SAEs	34 (5.8)	20 (14.6)	32 (22.9)	13 (9.4)
Treatment stopped due to AEs	10 (1.7)	6 (4.4)	2 (1.4)	5 (3.6)

No deaths were reported during any treatment period in this study. The majority of treatment-emergent AEs in Period II and in any treatment arm in Period III were mild or moderate in severity.

Treatment-emergent SAEs were reported in 6% of the subjects during Period II and in 15% of subjects in the risperidone LAI arm, 23% of subjects in the placebo arm, and 9% of subjects in the olanzapine arm during Period III. Treatment-emergent SAEs were most often mania; their incidence throughout the study was low.

During open-label treatment with risperidone LAI, most frequent treatment-emergent AEs (incidence ≥5%) were insomnia (15%), akathisia (7%), headache and weight increased (both 6%), and anxiety and extrapyramidal disorder (both 5%). Most frequent treatment-emergent AEs reported with risperidone LAI treatment during the double-blind period were weight increased (24%) and insomnia (16%), followed by amenorrhea (8%), galactorrhea, somnolence, depression (all 6%), mania, and anxiety (both 5%). The incidences of TEAEs during Period III in the risperidone LAI arm were comparable to those in the placebo and olanzapine arms, with a few exceptions.

Incidences of AEs leading to permanent stop of study medication were low.

Incidences of Treatment-Emergent AEs Reported in More Than 10% of Subjects During Period II or in Any Treatment Arm During Period III
(Study RIS-BMN-3001: *Safety Sets Period II and III*)

	Open-label	Double-blind		
	All subjects	Ris LAI	Placebo	Olanzapine
System Organ Class Lower-Level Term, n (%)	**N=585**	**N=137**	**N=140**	**N=138**
Psychiatric disorders	**169 (28.9)**	**44 (32.1)**	**63 (45.0)**	**35 (25.4)**
Insomnia	88 (15.0)	22 (16.1)	24 (17.1)	14 (10.1)
Mania	20 (3.4)	7 (5.1)	23 (16.4)	6 (4.3)
Nervous system disorders	**172 (29.4)**	**41 (29.9)**	**32 (22.9)**	**57 (41.3)**
Somnolence	18 (3.1)	8 (5.8)	4 (2.9)	19 (13.8)
Investigations	**47 (8.0)**	**41 (29.9)**	**22 (15.7)**	**43 (31.2)**
Weight increased	32 (5.5)	33 (24.1)	12 (8.6)	35 (25.4)
Reproductive system and breast disorders	**40 (6.8)**	**20 (14.6)**	**6 (4.3)**	**7 (5.1)**
Infections and infestations	**45 (7.7)**	**15 (10.9)**	**12 (8.6)**	**15 (10.9)**
Gastrointestinal disorders	**58 (9.9)**	**13 (9.5)**	**17 (12.1)**	**18 (13.0)**
Metabolism and nutrition disorders	**17 (2.9)**	**11 (8.0)**	**7 (5.0)**	**15 (10.9)**
General disorders and administration site conditions	**33 (5.6)**	**10 (7.3)**	**7 (5.0)**	**17 (12.3)**

EPS-related treatment-emergent AEs were reported in 20% of the subjects in Period II and in 17% of the subjects with risperidone LAI, 14% of the subjects with olanzapine, and 9% of the subjects with placebo during Period III. EPS-related treatment-emergent AEs were most often akathisia (7% and 4%), tremor (5% and 4%), and parkinsonism (3% and 4%) during both open-label and double-blind risperidone LAI treatment, respectively.

The ESRS total score decreased (improved) from a mean (SE) of 1.4 (0.14) at baseline to 1.1 (0.11) at endpoint during open-label risperidone LAI treatment and from 0.9 (0.18) to 0.7 (0.16) at endpoint during double-blind risperidone LAI treatment. No change in mean ESRS total score from Period III baseline to endpoint was documented in the placebo arm.

Potentially prolactin-related treatment-emergent AEs were reported in 6% of the subjects in Period II and in 14% of the subjects with risperidone LAI, 6% of the subjects with olanzapine, and 3% of the subjects with placebo during Period III. Combinations of potentially prolactin-related treatment-emergent AEs were low in frequency and consisted of the combinations amenorrhea/galactorrhea and breast enlargement/galactorrhea.

CLINICAL LABORATORY EVALUATION:

Blood prolactin levels increased during open-label risperidone LAI treatment (medians from 24.5 ng/mL to 54.6 ng/mL). The median changes in blood prolactin level in acute and non-acute subjects were comparable. During open-label risperidone LAI treatment followed by double-blind risperidone LAI period, blood prolactin levels increased from baseline to endpoint (medians from 32.0 ng/mL to 39.4 ng/mL), whereas decreases in prolactin levels were observed from baseline to endpoint in subjects receiving open-label risperidone LAI treatment followed by double-blind olanzapine or placebo treatment.

OTHER SAFETY OBSERVATIONS:

In all treatment periods, mean changes from baseline in all vital signs parameters were small.

The most frequently reported vital signs-related AE was blood pressure increased, reported in 3% of subjects randomized to the olanzapine arm. Other vital signs-related AEs were reported in less than 2% of the subjects during Period II or in any treatment arm during Period III.

Increases in body weight and BMI were observed during any active treatment; mean (SE) changes in body weight from baseline to endpoint ranged from +1.1 (0.19) to +3.0 (0.82) kg, with the largest changes in female subjects randomized to olanzapine treatment. Mean decreases in body weight were observed in the placebo arm (-1.0 [4.54] in female subjects and -0.8 [2.48]) in male subjects). Abnormal weight increase

(i.e., ≥7%) during Period III was seen in 18% of subjects in the risperidone LAI arm, 26% of subjects in the olanzapine arm, and 5% of subjects in the placebo arm.

Mean changes from baseline in ECG parameters during open-label treatment were small.

Treatment-emergent ECG-related AEs were reported in at most 2 (<1%) subjects during open-label treatment and in at most one (1%) subject in either double-blind treatment.

CONCLUSION:

After 12 weeks of stabilization treatment, continued treatment with risperidone LAI significantly delayed the time to recurrence of any mood episode compared to placebo in subjects with bipolar I disorder. Greatest efficacy was demonstrated in the prevention of manic episodes. Long-term risperidone LAI treatment was generally safe and well-tolerated. The findings from this study and two previous studies support the efficacy and general safety and tolerability of risperidone LAI in the maintenance treatment of bipolar I disorder.

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