SYNOPSIS

Name of Sponsor/Company: Janssen Pharmaceutica Products, LP Name of Finished Product: RISPERDAL® Name of Active Ingredient(s): Risperidone (R064766)	
Protocol No.: CR002143	
Title of Study: A Study to Evaluate the Efficacy, Safety and Maintenance Effect of Risperidone Augmentation of SSRI Monotherapy in Young and Older Adult Patients with Unipolar Treatment-Resistant Depression	
Coordinating Investigator: Multicenter Study	
Publication (Reference): None	
Study Period: 25 June 2002 to 18 March 2004	**Phase of development:** 3
Objectives: The objectives of the Open-Label phase were to evaluate the efficacy and safety of oral risperidone as augmentation therapy in adult subjects with unipolar treatment-resistant depression (TRD), and secondarily to evaluate the efficacy of using risperidone as augmentation therapy in TRD on associated symptoms of anxiety; to evaluate the effect of risperidone as augmentation therapy on cognition, health-related quality of life and functional outcomes in subjects with TRD. The primary study objective was to demonstrate the long-term maintenance effect of risperidone as augmentation therapy in subjects with unipolar TRD as compared with placebo augmentation over a 6-month double-blind period (Double Blind phase).	
Methodology: This was a multi-center, international, prospective study designed to evaluate the short- and long-term efficacy and safety of risperidone as augmentation therapy in young (18-54 years of age, inclusive) and older (55-85 years of age, inclusive) adult subjects with TRD. The study consisted of three phases: Pre-Treatment, Open-Label, and Double-Blind maintenance. The Pre-Treatment phase consisted of a Screening visit and a Baseline visit. The Open-Label phase consisted of an SSRI Confirmation period (Period S) and a Risperidone Augmentation period (Period A). The SSRI Confirmation period (Period S; Weeks S-1 to S-6) was designed to prospectively confirm treatment resistance to SSRI monotherapy. During the Risperidone Augmentation period (Period A) risperidone was added to the SSRI taken at the completion of Period S. This period was designed to prospectively evaluate the safety and efficacy of risperidone in conjunction with the SSRI. The Double-Blind maintenance phase consisted of a Relapse Prevention period (Period R) followed by a post-study Taper period (Period T). Patients were randomized to either continuing treatment with risperidone or switch to placebo. The Relapse Prevention period (Period R) was designed to evaluate the maintenance effect of risperidone augmentation, as compared to placebo, on the prevention of relapse. The optional Taper period (Period T), which followed Period R, was of two weeks duration, and was designed to gradually reduce and then discontinue risperidone (or placebo) dose for those subjects who chose not to continue treatment.	
Number of Subjects (planned and analyzed): 633 subjects were screened. During Period S, 502 subjects enrolled, 489 were analyzed for efficacy in the Intent-to-Treat (ITT) population, and 500 were analyzed for safety. During Period A, 390 subjects enrolled, 386 were analyzed for efficacy (ITT), and 388 were analyzed for safety. During Period R, 243 subjects enrolled (123 risperidone, 120 placebo), 241 subjects (122 risperidone, 119 placebo) were analyzed for efficacy (ITT), and 241 subjects (122 risperidone, 119 placebo) were analyzed for safety.	
Diagnosis and Main Criteria for Inclusion: Subjects were between 18 and 85 years of age; had a diagnosis of unipolar Major Depressive Disorder, single or recurrent episode, with or without psychotic features according to DSM-IV criteria; had a reliable history of resistance to antidepressant pharmacotherapy defined as failure to respond in the current episode to at least one antidepressant medication other than citalopram, given at adequate doses for a minimum period; and a threshold score on the HAM-D-17 at both screening and baseline visits Major exclusion criteria were pregnancy or breast-feeding; a DSM-IV Axis I diagnosis of Major Depressive Disorder confounded by physiological effects of a substance, a medically unstable condition, or other disorders; current suicidal ideation; a history of failure to more than three antidepressant treatments, including electroconvulsive therapy (ECT), for the current episode; or failure on a therapeutic course of citalopram or any antidepressant pharmacotherapy with risperidone augmentation therapy in the past.	
Test Product, Dose and Mode of Administration, Batch No.: Risperidone was orally administered as 0.25 mg	

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(batch numbers 01C27/F070 and 02J07/F070), 0.5 mg (batch number 01L03/F009), 1.0 mg (batch numbers 01E22/F005 and 01L04/F005) or 2.0 mg (batch numbers 01E23/F013 and 01L05/F013) tablets. Young subjects received 0.5, 1.0, and 2.0 mg/day; older subjects received 0.25, 0.5, and 1.0 mg/day.

Reference Therapy, Dose and Mode of Administration, Batch No.: Citalopram was orally administered as 20 mg (batch numbers J7126, J7780, A185E, A186E, A680B, and A800E) or 40 mg (batch numbers J7216, J7780, A797, and A127B) tablets. Young subjects received 20, 40, and 60 mg/day; older subjects received 20 and 40 mg/day. Placebo tablets (batch numbers 01C26/F007 and 01E21/7007) were orally administered.

Duration of Treatment: During Period S, subjects received SSRI for 4 to 6 weeks. During Period A, subjects received risperidone as augmentation for 4 to 6 weeks. During Period R, subjects received risperidone or placebo augmentation to SSRI for 24 weeks.

Criteria for Evaluation:

Efficacy: The Montgomery and Asberg Depressive Rating Scale (MADRS) served as the primary efficacy measure during the Open-Label Treatment Phase of the study. For the double-blind Relapse Prevention Period, the primary outcome measure was relapse measured by 'time to relapse.' In this period, relapse was defined as the occurrence of any one of the following: substantial clinical deterioration, as indicated by scores of 7 or 8 on the Clinical Global Impression of Change (CGI-C) scale; HAM-D-17 total score of >16; discontinuation due to lack of therapeutic effect; or deliberate self-injury or suicidal intent accompanied by a plan that was clinically significant, as determined by the Investigator.

Secondary efficacy variables throughout all periods included HAM-D-17 scale, CGI-C scale, Hamilton Rating Scale of Anxiety (HAM-A), Quality of Life and Enjoyment Questionnaire (Q-LES-Q), and a computerized cognitive assessment scale.

Safety: Assessment of safety was based on the frequency of treatment-emergent adverse events (AEs), scores on extrapyramidal symptoms (EPS) scales (Simpson-Angus Rating Scale [SAS], Barnes Akathisia Scale [BAS], and Abnormal Involuntary Movement Scale [AIMS]) and sexual function measures (Global Impressions of Sexual Function [GISF]), laboratory parameters, vital signs, ECG and physical examination findings.

Statistical Methods:

The change from baseline to each post-baseline visit in Period S was tested using a paired t-test or by using the Wilcoxon Signed Rank test, for the Period S ITT population. In addition, the proportions of responders and remitters based on the MADRS were summarized. The analyses conducted for Period A were similar to those done for Period S. The change from baseline (Day A-0) to each post-baseline assessment, including the LOCF endpoint, was tested for each of the efficacy variables listed above using a paired t-test for the Period A ITT population. These evaluations were also performed for the HAM-A and Q-LES-Q. The change in total scores on the MADRS and HAM-D-17 were also analyzed using the Period S baseline values. Categorical outcomes (e.g., CGI-S) were evaluated using the appropriate rank tests.

The primary efficacy analysis of time-to-relapse was analyzed using the Kaplan-Meier method of survival analysis with Day R-0 as the origin. Subjects who did not experience a relapse during Period R were considered censored at the time of their withdrawal or at the completion of Period R,. The primary efficacy analysis was a log-rank test for the Period R ITT population. Observed times to relapses were graphically summarized for Period R and summary statistics were provided. A Cox proportional hazards regression model to assess the effect of baseline covariates was performed, with treatment, age group, pooled site, and Period R baseline CGI-S and HAM-D-17 total scores included in the model. The planned analyses included separate evaluation of patients who met a priori criteria for full non-response to SSRI.

Secondary efficacy analyses included summary statistics on changes from baseline (Day R-0, if appropriate) and observed values for the secondary efficacy variables. Analysis of covariance (ANCOVA) were used to analyze change scores on measures, and the within group differences were evaluated using paired t-test. Actual scores at baseline were compared between the treatment arms using the analysis of variance (ANOVA). Categorical variables were evaluated using the Cochran-Mantel-Haenszel (CMH) test stratifying on site. . The correlation between changes in the Q-LES-Q and the MADRS were examined using parametric (Pearson) and non-parametric (Spearman) methods.

SUMMARY - CONCLUSIONS

DISPOSITION AND DEMOGRAPHICS

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Overall, 91% of subjects completed Period S. 390 subjects were enrolled in Period A, with 90.2% of subjects completing Period A. The number of subjects who completed Period R was similar between the risperidone and placebo groups (35% vs 36.1%, respectively). The population was primarily Caucasian. Approximately three fourths of all subjects entered were of a younger age group (18 - 54 years of age). Approximately two thirds of the subjects were female.

EFFICACY RESULTS:

In subjects whose depression had not benefited from an adequate treatment trial with antidepressant medication, a prospective trial of SSRI (Period S) provided clinically relevant benefit in less than 13% of subjects. Addition of risperidone to SSRI monotherapy in those subjects who had improved by less than 50% over their baseline symptoms was associated with a robust clinical benefit, as noted by the proportion of subjects (59%) meeting criteria for symptom resolution. In contrast to results seen with SSRI monotherapy, risperidone augmentation increased the proportion of subjects who were considered remitters based on the MADRS to over 60%. Statistically significant improvements were noted in a variety of depressive symptoms, anxiety-related features, and somatic and vegetative symptoms. Sub-analyses on the HAM-D-17 scale indicated significant benefits on the anxiety/somatization subscale, retardation subscale, sleep disturbance subscale, depressed mood item and feelings of guilt item.

Approximately 50% of the subjects enrolled in the trial, and 62% of those considered partially or fully non-responsive to SSRI and who entered Period A, achieved symptom resolution following risperidone augmentation of citalopram, and qualified to enter the 24-week randomized withdrawal period of the trial. Approximately 54% of subjects in both groups experienced relapse during this period. The median time to relapse was numerically longer in the risperidone group (102 days) than in the placebo group (85 days), although this difference did not reach statistical significance in Kaplan-Meier analysis. As the Kaplan-Meier curves for the two groups intersected, violating the assumptions of the proportional hazards model, alternative analyses were performed that estimated the effect of treatment using a linear function of time (putting greater weight on earlier events). These linear rank tests indicated a significant difference between the two treatment groups. A planned analysis was also performed on the ~60% of subjects enrolled in the trial who met operational criteria for full non-response (<25 % improvement on the HAM-D-17). Approximately 58% of these fully non-responsive subjects responded to risperidone augmentation, achieved symptom resolution, and continued in the 6-month double-blind period. Over the course of the 6-month randomized period, 56.0% of the risperidone-treated subjects relapsed, while 63.6% of those subjects receiving placebo experienced relapse. There was a large difference in median time to relapse (97 days for the risperidone group and 56 days for the placebo group). A Wilcoxon p-value was p=0.0512 for this smaller subpopulation, indicating borderline statistical significance in difference in time to relapse.

SAFETY RESULTS:

	Period S (n = 500)	Period A (n = 388)
No. (%) of deaths	0	0
No. (%) with one or more serious AE	14 (2.8)	10 (2.6)
No. (%) treatment stopped due to AE	17 (3.5)	18 (4.6)
No. (%) with one or more AE	371 (74.2)	302 (77.8)
Adverse events (AE) Most frequently reported AE (≥5% of patients)	n (% of patients)	n (% of patients)
• Headache	97 (19.4)	45 (11.6)
• Nausea	55 (11.0)	19 (4.9)
• Dry mouth	45 (9.0)	49 (12.6)
• Insomnia	40 (8.0)	11 (2.8)
• Somnolence	35 (7.0)	32 (8.2)
• Diarrhea	33 (6.6)	19 (4.9)
• Dizziness	27 (5.4)	33 (8.5)
• Tremor	11 (2.2)	30 (7.7)
• Weight increase	10 (2.0)	24 (6.2)
• Appetite increase NOS	9 (1.8)	22 (5.7)
Period R	RISPERIDONE (n = 122)	PLACEBO (n = 119)

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No. (%) of deaths	1	0	
No. (%) with one or more serious AE	5 (4.1)	2 (1.7)	
No. (%) treatment stopped due to AE	5 (4.1)	3 (2.5)	
No. (%) with one or more AE	76 (62.3)	67 (56.3)	
Adverse events (AE) Most frequently reported AE (≥5% of patients)	n (% of patients)	n (% of patients)	
• Headache	14 (11.5)	7 (5.9)	
• Weight increase	9 (7.4)	5 (4.2)	
• Dizziness	7 (5.7)	3 (2.5)	
• Fatigue	6 (4.9)	9 (7.6)	
• Insomnia	4 (3.3)	7 (5.9)	

Both citalopram (20 - 60 mg/day) and risperidone (0.25 - 2.0 mg/day) were well tolerated in this population. Citalopram monotherapy and the augmentation of citalopram with risperidone treatment were both associated with an approximately 6% discontinuation rate due to adverse events; approximately 75% of subjects experienced an AE on either treatment. The most frequent (incidence >10%) AEs on citalopram were headache (19.4%) and nausea (11%), while the most frequent AEs on the combination of citalopram and risperidone were dry mouth (12.6%) and headache (11.6%). Comparison of tolerability of the risperidone/citalopram combination to citalopram monotherapy (placebo group) during the randomized double-blind period indicated that the discontinuation rate due to AEs was low (4.9% and 3.4%, respectively). The percentage of subjects who experienced at least one AE was also similar in the two groups (62.3% and 56.3 %, respectively). Headache was the most frequently reported symptom on the combination therapy, with an incidence of 11.5%, compared to 5.9% on citalopram alone.

Treatment with citalopram was associated with a small, but statistically significant worsening on the BAS; augmentation with risperidone was not associated with any statistically significant or clinically relevant worsening of EPS, as measured by the AIMS, BAS and SAS. Citalopram treatment was associated with a statistically significant worsening of sexual functioning in male subjects, as measured by the GISF. Addition of risperidone resulted in a minor improvement in sexual function in both male and female subjects. During long-term treatment, female subjects treated with the combination showed worsening, compared with subjects treated with citalopram alone

Citalopram treatment was not associated with any clinically relevant changes in vital signs or physical examination findings. Risperidone augmentation of citalopram was accompanied by a statistically significant increase of 1.4 kg body weight, compared to baseline; 12 (3.1%) of the subjects receiving risperidone in Period A experienced clinically notable weight increase (≥ 7% of body weight). During long-term treatment, subjects receiving the citalopram/risperidone combination experienced a mean weight increase of 1.3 kg, while subjects on citalopram alone lost 0.5 kg; this difference was statistically significant. Clinically notable weight increases were observed in 8.3% and 2.6% of subjects treated with citalopram/risperidone and citalopram/placebo, respectively.

No clinically relevant change was detected in any clinical chemistry or hematology parameters during citalopram monotherapy. Risperidone augmentation of citalopram in Period A, however, was associated with a significant mean increase of 42 ± 48.0 ng/ml in prolactin levels. During long-term treatment, prolactin levels increased on average by 35.4 ± 53.4 ng/ml in the risperidone group, and by 6.6 ± 21.0 ng/ml in the placebo group.

Overall, no consistent pattern of deleterious change was detected in subjects treated with citalopram alone, or in combination with risperidone, except for the increase in plasma prolactin and the 1.3-kg weight gain during long-term treatment.

CONCLUSION:

Patients enrolled in this study suffered from chronic, poorly responsive major depressive illness, with over two thirds being fully non-responsive to prospective treatment with citalopram, a standard antidepressant therapy. Despite having full or partial non-response to standard treatment, over 60% of patients rapidly achieved not only improvement but symptom resolution with open-label risperidone augmentation. Irrespective of treatment group, at the end of the 24-week maintenance phase, a majority of patients achieving symptom resolution after initial risperidone augmentation remained relapse-free. The time to relapse among patients achieving symptom resolution with risperidone augmentation was statistically similar with risperidone and placebo augmentation. A large subgroup (69%) of patients entering the double-blind phase was fully non-responsive to citalopram monotherapy. In this common and difficult-to-treat population, a subgroup analysis showed that relapse was substantially delayed with ongoing maintenance of risperidone augmentation compared with placebo augmentation.

Conclusions regarding the maintenance of effect of risperidone augmentation of citalopram treatment may be limited by methodology that evaluates time to a single event (relapse) in an illness characterized by fluctuating

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symptomatology. Data from continued treatment and follow-up of the patients who met the relapse criteria on a single occasion suggest the possibility that further treatment with risperidone augmentation may produce a positive clinical response in many patients.

Maintenance therapy with risperidone augmentation appears to be safe and well tolerated in patients who are partially or fully non-responsive to standard antidepressant therapy and achieve symptom resolution with risperidone augmentation. As expected, some patients experienced prolactin elevations or weight gain in response to risperidone treatment; however, the incidence of EPS was very low.

Thus, risperidone may play a role in the treatment of this common and clinically challenging population of patients with resistant depression, in particular, those patients who experience the least benefit from conventional treatment.

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