SYNOPSIS

NAME OF SPONSOR/COMPANY: Janssen L.P. NAME OF FINISHED PRODUCT: RISPERDAL® NAME OF ACTIVE INGREDIENT(S): risperidone	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Anonymized Protocol ID: CR004696

Title of Study: A double-blind, randomized, prospective study to evaluate adjunctive risperidone versus adjunctive placebo in Generalized Anxiety Disorder sub-optimally responsive to standard psychotropic therapy

Principal Investigator: H. Mikel Thomas, M.D. – CTT Research, 4121 W. 83rd St., Prairie Village, Kansas, 66208; USA

Publication (Reference): Not applicable

Study Initiation/Completion Dates: Study initiated on 18 June 2004, study completed on 16 June 2005	**Phase of development:** 3B

Objectives: The primary objective was to demonstrate the superiority of adjunctive risperidone therapy added to standard anxiolytic pharmacotherapy over placebo in subjects with sub-optimally responding GAD, as measured by the Most Troubling Symptoms (MTS) scale. The MTS scale, completed by the subject at baseline and weekly thereafter via an interactive voice response system (IVRS), was derived from the DSM-IV criteria for GAD and includes the following 7 symptoms: excessive anxiety or worry, feeling restless, keyed up or on edge, getting tired easily, mind going blank/trouble concentrating, muscle tension, irritability, and trouble sleeping. The sum of the subject's top 4 self-rated MTS scores constitutes the MTS total score. Symptom severity was rated on a scale of 0 to 10 (0 = resolved (absent); 1 to 3 = mild; 4 to 6 = moderate; 7 to 9 = marked; 10 = extreme). The secondary objectives were to evaluate the safety of adjunctive risperidone to standard anxiolytic therapy in subjects with treatment-resistant GAD; to evaluate the subject's anxiety symptoms, as measured by the HAM-A; to evaluate subject functioning and quality of life, as assessed by the PGIS, CGI-S, SDS, and Q-LES-Q SF.

Methodology: This was a six-week, double-blind, randomized, prospective, placebo-controlled, multi-site trial. It evaluated the efficacy and safety of up to and including 2 mg/day adjunctive risperidone versus adjunctive placebo in subjects undergoing standard treatment with antidepressant and/or anxiolytic medication for GAD. All subjects completing at least four weeks of double-blind treatment were offered four weeks of open-label adjunctive risperidone therapy. Leading into this trial, subjects received standard anxiolytic medication for at least eight weeks, and for the last four weeks their anxiolytic pharmacotherapy was maintained at a clinically effective dose(s) without dose change. They were judged to exhibit a sub-optimal response to this therapy at baseline, as reflected by a CGI-S score of 4 or greater, and continued on this dose of anxiolytic therapy throughout adjunctive risperidone treatment.

Number of Subjects (planned and analyzed): Approximately 432 subjects were planned to be randomized to either risperidone (n=216) or placebo (n=216). The total number of subjects randomized is 417; 211 subjects were assigned to risperidone treatment and 206 subjects were randomized to receive placebo.

Diagnosis and Main Criteria for Inclusion: Subjects were to have: (i) a diagnosis of GAD; (ii) judged to be healthy; (iii) treated for at least eight weeks with one or more allowed anxiolytic mediation(s): *either* monotherapy with one of the allowable medications, including an antidepressant alone, a benzodiazepine alone or buspirone alone *or* an allowed antidepressant plus a benzodiazepine *or* an allowed antidepressant plus buspirone; (iv) maintained on a stable, therapeutic dose(s) of the allowed medications(s) for at least the past four weeks; (v) judged by the clinician to have shown a sub-optimal response to his/her current treatment (CGI-S score of $\geq$4).

Duration of Treatment: 6 weeks (4 weeks minimal) of double-blind treatment with risperidone or placebo; optional 4 weeks of open-label treatment with risperidone

Criteria for Evaluation:

Efficacy: the primary efficacy parameter was the MTS, based on the change between baseline and double-blind Week 4 in the sum of the subject's top 4 self-rated MTS scores. The secondary efficacy rating scales used in this study were the HAM-A, PGIS, CGI-S, SDS, Q-LES-Q SF.

Safety: the safety assessments used in this study included monitoring and recording of all treatment-emergent adverse events and serious adverse events; performance of physical examination; and monitoring of vital signs, fasting blood glucose testing, and urine pregnancy test.

SUMMARY – CONCLUSIONS

EFFICACY RESULTS:

Primary Efficacy: The primary efficacy outcome in this study was the mean change from baseline to Week 4 in the total score of the 4 most troubling symptoms (MTS Total Score). The 4 symptoms most frequently selected at baseline as one of the 4 most troubling (based on subjects' rating of severity) were 'excessive anxiety or worry', 'feeling restless, keyed up or on edge', 'trouble sleeping', and 'getting tired easily.' Statistically significant ($p<0.001$) improvements from baseline in the MTS Total Score were noted at all time points in both the risperidone and placebo groups, though no statistically significant difference in the MTS Total Score was noted between the risperidone and placebo groups at the Week 4 (LOCF) evaluation; there was a significant difference favoring risperidone at Week a ($p=0.040$) and a trends at non-study site visits (Weeks 3 & 5).

Secondary Efficacy: Results similar to those for the MTS Total Score mean change were observed for secondary analyses of the MTS. Statistically significant improvements from baseline at all post-baseline assessments, but no statistically significant between-group differences, were noted for the following analyses: MTS Total Score expressed as a percent change from baseline, change from baseline in the MTS Percent from Maximum (total score for the 4 most troubling symptoms with a rating of ≥4, expressed as a percent of the total possible score); and MTS Total Global Score (total of all 7 symptoms), either as a mean change or percent change from baseline. A trend for greater improvement on the MTS Percent from Maximum was observed, with mean reductions from baseline being numerically greater in the risperidone group, compared to the placebo group, at all time points (OC and LOCF).

Analysis of individual MTS symptom scores, either by mean change from baseline or by categories of severity, indicated that the only symptom significantly improved by risperidone treatment, compared to placebo, was 'trouble sleeping' at the Week 6 evaluation (OC and LOCF).

An additional analysis for the MTS was performed, which evaluated the mean change from baseline in the scores for each symptom, but only when it was rated as one of the 4 most troubling symptoms at baseline. In this analysis, significantly greater ($p<0.05$) improvement was observed in the risperidone group, compared to the placebo group, for 'feeling restless' (Weeks 1 and 3), 'getting tired easily' (Weeks 1, 5, and 6), and 'muscle tension' (Week 4).

The observation that MTS scores appeared to favor the risperidone-treated groups during non-study site visits (e.g., Weeks 1, 3, and 5) is of some clinical interest. It appears that the difference may be accounted for by greater improvements in the placebo groups on visits during which they visited the study site. An analysis of MTS "Responders", defined as subjects having a 50% or greater reduction from baseline in their MTS Total Score was numerically higher in the risperidone group (11-43%), than in the placebo group (10-35%); though not statistically different.

Results for the mean change from baseline in the HAM-A total score paralleled those of the MTS Total Score, with statistically significant improvements being noted at each evaluation in both the risperidone and placebo groups, but no significant differences between groups being observed at any time point. Similar results were obtained for the Somatic and Psychic subscales of the HAM-A. When changes from baseline in scores on individual items of the HAM-A were analyzed, only sporadic differences between groups were observed on a few items at selected time points. The proportion of subjects meeting HAM-A criteria for responder (≥ 50% improvement from baseline) or remitter (total score ≤7) increased over time in both treatment groups; however, no between-group differences were observed.

Data from the HAM-A were also analyzed for the 4-week Open-Label Period, during which all subjects received risperidone. At the Open-Label Period endpoint, patients originally randomized to placebo, as well as those receiving risperidone throughout, showed statistically significant improvement of a similar magnitude on the HAM-A total score, the Somatic and Psychic subscales, and most individual items of the HAM-A, compared to the double-blind endpoint. On average, subjects randomized to risperidone in the double-blind period had an almost 14-point improvement in the HAM-A total score from the double-blind baseline to the Open-Label Period endpoint.

The results of the analysis of the data from the CGI-S, a global assessment of the severity of the subjects' anxiety performed by a clinician, indicated significant improvement from baseline (~1 point) in both the risperidone and placebo groups at Weeks 4 and 6. However, as observed for other measures, there was no significant difference between groups in the magnitude of the improvement or in the categorical distribution of ratings of severity for the CGI-S.

Secondary Efficacy (continued): The self-rated PGIS, which is a global assessment of change from baseline in the subject's anxiety, showed greater benefit with risperidone, compared to placebo. In both groups, mean scores at all time points were less than 4, indicating improvement from baseline. At Weeks 1, 3 and 4 (LOCF) the mean rating of change was significantly lower in the risperidone group than in the placebo group, indicating greater level of improvement. A similar effect was observed in the analysis of the categorical ratings of the PGIS, which showed a significant difference between groups at Weeks 1, 3 and 4 (OC and LOCF), reflecting a greater proportion of subjects in the risperidone group having ratings of 'very much improved' or 'much improved.'

Assessment of a subject's impairment/disability due to their anxiety, performed using the self-rated SDS, did not show any differences between treatment groups. Both risperidone- and placebo-treated subjects showed significant improvements from baseline on the SDS Total Score and on the three dimension scores (work/school; social life; family life/home responsibilities) at Weeks 4 and 6, but no significant between-group differences were observed.

Subjects' overall quality of life was not affected by treatment with risperidone, as evident from the results of the total score on the self-rated Q-LES-Q SF. The mean change from baseline on the total score for items 1-14 indicated significant improvement in both the risperidone and placebo groups at Weeks 4 and 6; the magnitude of the improvement was similar in both groups. For the Medication Satisfaction item of the Q-LES-Q SF, however, significantly greater ($p<0.05$) improvement from baseline was noted in the risperidone group at the Week 4 evaluation, but not at Week 6. Similar results were obtained for the Overall Life Satisfaction item, with greater improvement being observed at Week 4, in the risperidone-treated subjects. These effects of risperidone on ratings of the latter two items are reflected in the categorical distribution of ratings, with a greater proportion of subjects in the risperidone group rating their Medication Satisfaction and Overall Life Satisfaction as 'good' or 'very good' at the Week 4 evaluation.

SAFETY RESULTS: In general, the tolerability of risperidone was comparable to that of placebo in the population of subjects with anxiety that were enrolled in this study. The proportion of subjects experiencing any treatment emergent adverse event was similar in the risperidone (57%) and placebo (52%) groups. Adverse events related to the gastrointestinal system and infections and infestations were more frequent in the placebo group, whereas as a slightly greater incidence of weight increase (6.4% vs. 5.4%) was observed in the risperidone group.

The most frequently reported adverse events were related to the nervous system, for which a higher incidence was reported in the risperidone group (23.2%), compared to the placebo group (16.3%). Nervous system adverse events reported in a greater proportion of risperidone-treated subjects included dizziness, lethargy, paraesthesia, sedation and somnolence. There was no evidence of movement disorders related to risperidone treatment; the incidence of extrapyramidal symptoms was low and comparable between groups. The proportion of subjects experiencing psychiatric disorders was also similar in risperidone (12.8%) and placebo (12.4%) treated subjects. The placebo group had a higher incidence of abnormal dreams, and the only report of suicidal ideation was for a placebo-treated subject. Depression was reported for 3 subjects in the risperidone group, but none in the placebo group.

The incidence of adverse events that were rated severe was lower in the risperidone group (4.9%) than in the placebo group (6.4%); however, severe psychiatric disorders were more common with risperidone treatment (2.5%) than with placebo (0.5%). The proportion of subjects who had their study medication discontinued due to a treatment-emergent adverse event was higher in the risperidone group (11.3%) than in the placebo group (7.9%). The most common adverse events leading to discontinuation were related to the nervous system, with 7.4% of subjects in the risperidone group and 3.5% of subjects in the placebo group experiencing these events.

Only 9 serious treatment-emergent adverse events were reported in the study, 4 events in 3 subjects in the risperidone group, and 5 events in 4 subjects in the placebo group. The serious adverse events reported in risperidone-treated patients comprised hospitalization for ileus, depression and drug dependence (both reported in the same subject), and syncope; the latter two subjects were permanently discontinued from treatment due to these events.

Vital signs assessments at and physical examinations were conducted at baseline and endpoint. Statistically significant mean reductions in systolic blood pressure (~3 mm Hg), and mean increases in pulse rate (~2 bpm) were noted at endpoint in both the risperidone and placebo groups; however, these were not considered to be clinically significant. Significant increases in mean body weight were also observed at endpoint in both treatment groups; though the increase in the risperidone group (2.5 lbs) was significantly greater ($p<0.001$) than placebo (0.8 lbs). The incidence of clinically notable vital signs changes, including weight gain, was low and similar in both treatment groups. There were no clinically important treatment emergent findings on the physical examination at endpoint in either group.

For subjects who entered the 4-week Open-Label Period, during which all subjects received treatment with risperidone, the proportion of subjects who discontinued prematurely was lower in the original risperidone group, compared to the placebo group (11.3% vs. 15.5%). The proportion of subjects discontinuing due to an adverse event was also lower in the risperidone group (5.6% vs. 8.8%). The pattern of adverse events that was observed during the Open-Label Period was similar to that of the double-blind period. Of note was the fact that a greater proportion of subjects from the placebo group, compared to the risperidone group, experienced psychiatric adverse events (4.7% vs. 0.7%) and weight gain (2.7% vs. 0.7%) after switching from placebo to risperidone. The effect on body weight was also noted in the vital signs assessment, with the placebo group gaining on average 1.8 lbs. at Open-Label endpoint, compared to 0.3 lbs. in the risperidone group.

CONCLUSIONS:

In this population of patients with GAD, who were not responding well to their current treatment regimen, adjunctive treatment with either risperidone or placebo resulted in statistically significant improvement from baseline on all efficacy measures at virtually all timepoints in the double–blind period (Weeks 1-6).

Assessing subjects' anxiety, based on their rating of their 4 most troubling symptoms, appears to be comparable to other standard measures, as the MTS Total Score and change from baseline correlated well with results from other scales, both those assessed by clinicians, i.e., HAM-A and CGI-S, and those that were self-rated, i.e., SDS, Q-LES-Q SF, and PGIS.

Risperidone was not superior to placebo on the primary outcome, the mean change from baseline at Week 4 (LOCF) in the MTS Total Score. Greater improvement with risperidone was noted on the MTS Total Score only at Week 1, though a trend favoring risperidone treatment was noted for non-study visit weeks.

Other secondary analyses of the MTS data did not indicate greater benefit with risperidone treatment, compared to placebo. The only individual symptom from the 7 MTS for which significantly greater improvement in the risperidone group was noted was "trouble sleeping" (only at Week 6). However, when only those symptoms selected by each subject as one of their 4 MTS at baseline were analyzed, significantly greater improvement was observed with risperidone for "feeling restless", "getting tired easily", and "muscle tension", at selected timepoints.

Results from the HAM-A, CGI-S and SDS did not show any additional benefit of risperidone over that of placebo with regard to symptoms of anxiety, global severity of disease, or disability due to disease, respectively.

Risperidone treatment led to greater improvement on subject-rated assessments of global change from baseline and quality of life, i.e., the PGIS and Q-LES-Q SF – Medication Satisfaction and Overall Life Satisfaction items, which was observed at the Week 4 assessment for all three measures.

Risperidone was generally well tolerated, with the incidence of TEAEs, SAEs, and severe TEAEs in the risperidone group being comparable to that of placebo. A higher incidence of nervous system TEAEs and discontinuations due to adverse events, as well as greater weight gain, were observed with risperidone; however, there was no evidence of treatment-induced movement disorders.

In summary, adjunctive treatment with risperidone at doses of 1-2 mg/day, although well tolerated, showed no consistent pattern of benefit in this population of patients with GAD responding sub-optimally to their current anxiolytic therapy. Methodological constraints, such as the large number of centers, use of investigators with limited experience with assessment tools, and telephone self-ratings may have contributed to the blurring of the potential efficacy of risperidone in these GAD patients.

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