SYNOPSIS

NAME OF SPONSOR/COMPANY: Ortho-McNeil Janssen Scientific Affairs, LLC 1125 Trenton-Harbourton Road Titusville, NJ 08560-0200	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER	(FOR NATIONAL AUTHORITY USE ONLY)
NAME OF FINISHED PRODUCT: Invega™ NAME OF ACTIVE INGREDIENT(S): Paliperidone ER	Volume: Page:	

Protocol No.: R076477-SCH-3015 CR010501

Title of Study: A randomized, double-blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of paliperidone ER compared to quetiapine in subjects with an acute exacerbation of schizophrenia

[Coordinating] [Principal] Investigator: There were a total of 48 investigators in this study. See Appendix 1.4.1. for the list of study investigators.

Publication (Reference): Not applicable

Study Initiation/Completion Dates: 30 May 2006 – 12 July 2007	**Phase of development:** IIIb

Objectives:

Primary objective

The primary objective of this study was to demonstrate superior short-term efficacy of paliperidone extended release (ER) over quetiapine in the treatment of subjects with an acute exacerbation of schizophrenia.

Secondary objectives

The secondary objectives were to determine the time to response (defined as 30% Positive and Negative Syndrome Scale (PANSS) reduction plus Clinical Global Impression-Change Scale (CGI-C) of 1 or 2) in subjects receiving paliperidone ER versus quetiapine (key secondary); to determine time to readiness for discharge in subjects receiving paliperidone ER versus quetiapine; to evaluate polypharmacy use in subjects receiving paliperidone ER versus quetiapine; to evaluate the safety of paliperidone ER as compared with quetiapine in the treatment of subjects with an acute exacerbation of schizophrenia; and to evaluate the utilization of healthcare resources associated with treatment with paliperidone ER as compared with treatment with quetiapine in the treatment of subjects with an acute exacerbation of schizophrenia.

In addition to the clinical and pharmacoeconomic objectives listed above, subjects in countries where pharmacogenomic testing was permitted were also given the option to participate in genetic research.

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Methodology: This was a double-blind, parallel group, randomized, multicenter placebo and active-controlled study designed to compare the efficacy and safety of paliperidone ER versus quetiapine. Subjects with a recent acute exacerbation of symptoms of schizophrenia were randomized to paliperidone ER, quetiapine, or placebo in a 2:2:1 fashion. Following randomization, subjects remained hospitalized for at least 10 days. The study involved 2 phases: a 2-week Monotherapy phase followed by a 4-week Additive Therapy phase.

During the Monotherapy phase, study medication dosing began on Day 1. From Day 1 through Day 3, subjects randomized to paliperidone ER took paliperidone ER 6 mg orally each day. On Day 4, all paliperidone ER subjects had their dose increased to 9 mg. On Day 8, if indicated by unchanged or worsened clinical condition, the investigator had a one-time option of increasing the subject's dose of paliperidone ER to 12 mg. Subjects assigned to the quetiapine group received 50 mg (25 mg twice daily [BID]) on Day 1. The quetiapine dose was doubled daily to 100 mg (50 mg BID) on Day 2, 200 mg (100 mg BID) on Day 3 and 400 mg (200 mg BID) on Day 4. On Day 5, the dose of quetiapine was increased to 600 mg (300 mg BID). On Day 8, if indicated by unchanged or worsened clinical condition, the investigator had a one-time option of increasing the dose of quetiapine to 800 mg per day (400 mg BID).

During the Additive Therapy phase, beginning on Day 15 and proceeding through Day 42, subjects were maintained on the dose of study medication taken in the Monotherapy phase. During this phase, additional psychotropic medication could be used, as clinically necessary, to control symptomatology in subjects who remained sufficiently symptomatic.

Subjects participated in 10 study visits (Days 0 [Baseline], 1, 3, 5, 7, 9, 14, 21, 28, and 42). Prior/concomitant medications, vital signs, weight, and adverse events (AEs) were assessed at all study visits. The PANSS, Clinical Global Impression - Severity scale (CGI-S), and UKU Sleepiness and Sedation scale were administered at Baseline and at all study visits except Day 1. The CGI-C and Readiness for Discharge Questionnaire were administered on Day 3 and all subsequent study visits. Movement disorder scales (Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BAS], and Abnormal Involuntary Movement Scale [AIMS]) were administered at Baseline and on Days 14, 28, and 42. Laboratory assessments, urinalysis, urine drug screen, and electrocardiogram (ECG) were conducted at Baseline and on Days 14 and 42. The Study Medication Satisfaction Questionnaire was administered on Days 14 and 42. Additional psychotropic medication use was assessed on Days 21, 28, and 42. Additional information regarding study procedures is presented in Table 3-4 of this report.

Effort was made to maintain all randomized subjects on their study medication. Subjects who discontinued study medication but did not withdraw consent, had all final (scheduled for Day 42) assessments completed at the time of discontinuation and were thereafter treated according to usual clinical practice. Those subjects also had their assessments continued according to the original assessment schedule for the remainder of the study.

Number of Subjects (planned and analyzed):
Planned: Approximately 395 subjects at approximately 40 sites. A total of 399 subjects were analyzed from 48 study centers in the United States, India, Russia, and the Ukraine.

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Diagnosis and Main Criteria for Inclusion:

- Were aged 18 to 65 years, inclusive;
- Females were at least 1 year postmenopausal, irreversibly surgically sterilized, willing to practice abstinence, or were using adequate and reliable contraception;
- Met diagnostic criteria (Diagnostic and Statistical Manual of Mental Disorders, Verson IV [DSM-IV]) for schizophrenia paranoid type, disorganized type, or undifferentiated type (confirmed by the Mini International Neuropsychiatric Interview – Plus Version [M.I.N.I. Plus])
- Had a score of ≥ 4 on at least two of the following PANSS items: Hostility (P7); Excitement (P4); Tension (G4); Uncooperativeness (G8); and Poor Impulse Control (G14) AND a total score on these five items of ≥ 17;
- Were currently experiencing an acute exacerbation of symptoms of schizophrenia that was less than 4 weeks but greater than 4 days in duration.
- Had a score of ≥ 5 (markedly ill) on the CGI-S.
- Had a body mass index (BMI) equal to or greater than 18 kg/m^2 at study entry.
- Were either hospitalized or were outpatients in need of hospitalization at Day 0 and willing to remain hospitalized for a minimum of 10 days

Test Product, Dose and Mode of Administration, Batch No.: Paliperidone ER 6, 9, or 12 mg/day by mouth (p.o.) in 3 or 6 mg tablets

Reference Therapy, Dose and Mode of Administration, Batch No.: Quetiapine 50 to 800 mg/day p.o. in 25, 100, or 200 mg tablets

Duration of Treatment: The study involved 2 phases: a 2-week Monotherapy phase followed by a 4-week Additive Therapy phase

Criteria for Evaluation:

Pharmacogenomics: ADME genes

Efficacy: PANSS, Readiness for Discharge Questionnaire, CGI-S, CGI-C, Medication Satisfaction Questionnaire, and additional psychotropic medication.

Safety: Treatment-emergent adverse events (TEAEs) and serious AEs (SAEs); hematology, biochemistries, and urinalysis; vital signs; movement disorders and Udvalg for Kliniske Undersøgelser (UKU) Sleepiness/sedation scale, physical examinations, and ECG findings.

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Statistical Methods:

Baseline characteristics, disease-related characteristics, and Baseline values of efficacy variables were summarized by treatment group and overall. Continuous variables were summarized using descriptive statistics (e.g., mean, standard deviation, median, minimum, and maximum). Categorical variables were summarized using frequencies and percentages. Any variable found to differ among treatment groups could be used as a covariate in efficacy analyses, to assess the variable's impact on observed differences between the treatment groups. Prior medication use, including types, doses, and durations, was summarized using frequencies and percents. These analyses were carried out for the safety, ITT, and Additive Therapy phase efficacy populations.

The primary efficacy variable was the change from Baseline (Day 0) to the end of the Monotherapy phase (Day 14) in the PANSS total score. The primary efficacy analysis population was the ITT population. The primary efficacy analysis was an analysis of covariance (ANCOVA) with treatment and site as main effects with the baseline PANSS total score as a covariate. The endpoint analysis for PANSS total score change from baseline used the last observation carried forward (LOCF) procedure.

The primary null hypothesis was that there is no difference in PANSS total score change from baseline to the monotherapy endpoints between paliperidone ER and quetiapine in the treatment of subjects with an acute exacerbation of schizophrenia. Rejection of the null hypothesis at a two-tailed alpha level of 0.05, together with a greater estimated mean decrease from Baseline to Day 14 in the PANSS total score in the paliperidone ER group than in the quetiapine group, was taken to establish that paliperidone ER is more effective than quetiapine.

A composite response analysis for ≥30% reduction from Baseline on PANSS total score and a score of 1 or 2 on CGI-C over the study was performed. The key secondary outcome, time to first composite response, was specified in the analysis plan to cover the entire study duration, rather than the Monotherapy phase, up to Day 14. As a result, the gatekeeper testing procedure specified in the analysis plan was not implemented in the final interpretation of results. The time to first composite response was analyzed using Kaplan-Meier methodology and the difference between the survival curves for the treatment groups was assessed using an unstratified log-rank test. Subjects who did not meet criteria for the composite response event during the study were censored at the time of the withdrawal or completion of the study at Day 42. Kaplan-Meier statistics (25th percentile, median, mean, and 75th percentile) and their corresponding 95% CIs were presented.

The proportions of subjects who satisfied the composite response criteria in each treatment group were analyzed using 3 timepoints: 1) Day 14 Endpoint, 2) Day 42 Endpoint, and 3) the timepoint corresponding to best response at any time during the study. The percentage of responders at each post-Baseline visit was compared between treatment groups using CMH Chi-Square testing controlling for country or Fisher's exact test (depending on sample size) for the ITT population.

The ANCOVA model described for the primary analysis was utilized to analyze change from Baseline to scheduled visits for the other secondary measures of efficacy (e.g., PANSS subscale and factor scores, CGI-S, CGI-C, UKU and Study Medication Satisfaction). Additional ordinal parameters (e.g., CGI, UKU, Medication Satisfaction) were summarized using frequencies and percents. LOCF methodology was used where appropriate for endpoint analyses. Similar methods were applied to changes from Day 14 to Day 42 in efficacy variables, for the Additive Therapy phase efficacy population.

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The sample size calculations for this study were based on information from previous studies of paliperidone ER and quetiapine, as well as from other relevant studies currently in the literature for the treatment of acute exacerbation of schizophrenia disorder.

A sample size of approximately 134 subjects in each active comparison group was calculated to have at least 90% power to detect an effect size of 0.4 with a mean difference of 7.2 and a standard deviation of 18.0 in PANSS total change from Baseline to Day 14 using a 2-group t-test with an assumption of equal variance at a 0.05 2-sided significance level. In addition, this sample size gave a 90% power to detect an effect size of 0.3 using a 1-sample paired t-test with a 0.05 2-sided significance level testing whether the mean change from Baseline in the quetiapine group was 0, so that improvement within this active control arm could be examined. With a 2:2:1 randomization ratio for the paliperidone ER, quetiapine, and placebo groups, respectively, before attrition, a total of 335 subjects were needed. Assuming approximately 15% of subjects would not complete the 14-day Monotherapy phase, approximately 395 total planned subjects were to be randomized (158 paliperidone ER subjects, 158 quetiapine subjects, and 79 placebo subjects).

Additional information on statistical methodology is presented in Section 3.11 of this report.

SUMMARY – CONCLUSIONS

SUBJECT DISPOSITION:

A total of 399 subjects were randomized into the study (160 subjects, paliperidone ER; 159 subjects, quetiapine; 80 subjects, placebo). The ITT population consisted of 394 subjects; 397 subjects were analyzed in the safety population. A total of 116 subjects (29.1%) prematurely withdrew from the study. The most common reaons for premature withdrawal were AEs (7.8%), withdrawal of consent (7.3%), lack of efficacy (5.8%), and loss to follow-up (5.3%). The incidence of discontinuation due to AEs was higher in the quetiapine group compared with the paliperidone ER and placebo groups (10.1% vs. 6.3% vs. 6.3%). Discontinuation due to lack of efficacy was higher in the placebo group (paliperidone ER vs. quetiapine vs. placebo: 1.9% vs. 6.3% vs. 12.5%). A total of 90% of subjects completed Day 14 (90.6% vs. 88.7% vs. 91.3%), and 76.2% (81.3% vs. 72.3% vs. 73.8%) of subjects completed Day 42. Overall, significant differences in all-cause discontinuation rates were evident between paliperidone ER and quetiapine (p=0.036) and between paliperidone ER and placebo (p=0.032).

DEMOGRAPHICS:

The mean age of subjects was 36.3 years of age (range of 18 to 64), 66.5% of subjects were male, and 44.7% were Caucasian. The mean PANSS total scores for the paliperidone ER, quetiapine, and placebo groups were similar and reflect the severity of the symptoms in the subject population (102.8 vs. 101.3 vs. 103.8). The mean last daily dose for the Monotherapy phase was 10.4 mg for the paliperidone ER group and 690.9 mg for the quetiapine group. The mean daily dose for the entire study period was 9.8 mg for the paliperidone ER group and 599.1 mg for the quetiapine group.

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EFFICACY RESULTS:

PANSS Total Score ITT Population	Paliperidone ER (N=157) LS Mean (SE)	Quetiapine (N=157) LS Mean (SE)	Placebo (N=80) LS Mean (SE)
Primary Efficacy Measure: Change from Baseline to Day 14 (Monotherapy Endpoint)	-23.4 (1.8)	-17.1 (1.8)	-15.0 (2.2)
Primary Comparison – at Monotherapy Endpoint LOCF			
Paliperidone ER vs. quetiapine (p-value)	<0.001*		
Treatment vs. placebo (p-value)	<0.001*	0.333	
Secondary Comparison at Additive Therapy Endpoint LOCF			
Paliperidone ER+ vs. quetiapine+ (p-value)	0.023*		
Treatment+ vs. placebo+ (p-value)	0.002*	0.214	

*Statistically significant.
+ Refers to treatment during the Additive Therapy period in which subjects were allowed usage of additional psychotropics, including antipsychotics.

During the Monotherapy phase, subjects in the paliperidone ER group had a significant reduction of symptoms compared to quetiapine ($p<0.001$), as determined by the PANSS total score.

Paliperidone ER demonstrated a rapid onset of action. Significant differences were observed by Day 5 between paliperidone ER vs. quetiapine and paliperidone ER vs. placebo.

The paliperidone ER group also had a significantly reduced time to composite treatment response over the entire study period (total score >=30% improvement from Baseline with CGI-C <=2) compared to the placebo group ($p=0.008$).

During the Monotherapy phase, superior efficacy was observed for subjects treated with paliperidone ER compared with quetiapine or placebo on subscales of the PANSS assessing positive and negative symptoms and general psychology, and factors of the PANSS assessing positive and negative symptoms, disorganized thought, and uncontrolled hostility/excitement. Paliperidone ER treatment was associated with a greater rate of clinically meaningful improvement compared with quetiapine or placebo and also showed significantly greater improvement in overall clinical status as measured by the CGI-C. When subjects were asked to rate their satisfaction with study medication, they rated paliperidone ER with significantly higher (better) satisfaction scores as compared to quetiapine or placebo. Overall there was no difference observed between subjects treated with quetiapine and placebo on any of the measures described above.

Despite the allowance and substantial usage of additional psychotropics in the Additive Therapy phase, superior treatment effects observed in the Monotherapy phase persisted for subjects treated with paliperidone ER+ compared with quetiapine+ or placebo+ in the Additive Therapy phase. Similar to the Monotherapy phase, subjects treated with quetiapine+ generally did not demonstrate significant improvements compared with placebo+.

An additional sensitivity analysis excluding data from 2 Good Clinical Practice (GCP) compliance deficient sites was conducted and yielded results consistent with the analysis of the ITT population for the primary endpoint.

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SAFETY RESULTS:

Incidence of Adverse Events Occurring in ≥5% of Subjects in Any Treatment Group During the Monotherapy Phase (Safety Population)

System Organ Class/Preferred Term	Treatment Group		
	Paliperidone ER N = 158	Quetiapine N = 159	Placebo N = 80
Number of Subjects With At Least 1 TEAE	97 (61.4%)	85 (53.5%)	37 (46.3%)
Gastrointestinal Disorders	27 (17.1%)	35 (22.0%)	12 (15.0%)
Constipation	4 (2.5%)	8 (5.0%)	2 (2.5%)
Dry Mouth	3 (1.9%)	9 (5.7%)	1 (1.3%)
Vomiting	8 (5.1%)	8 (5.0%)	2 (2.5%)
General Disorders and Administrative Site Conditions	13 (8.2%)	14 (8.8%)	7 (8.8%)
Asthenia	7 (4.4%)	6 (3.8%)	4 (5.0%)
Nervous System Disorders	64 (40.5%)	54 (34.0%)	20 (25.0%)
Akathisia	7 (4.4%)	8 (5.0%)	2 (2.5%)
Dizziness	4 (2.5%)	11 (6.9%)	1 (1.3%)
Headache	19 (12.0%)	12 (7.5%)	11 (13.8%)
Hypertonia	13 (8.2%)	4 (2.5%)	1 (1.3%)
Sedation	5 (3.2%)	13 (8.2%)	2 (2.5%)
Somnolence	14 (8.9%)	19 (11.9%)	1 (1.3%)
Tremor	22 (13.9%)	8 (5.0%)	6 (7.5%)
Psychiatric Disorders	22 (13.9%)	33 (20.8%)	16 (20.0%)
Insomnia	16 (10.1%)	15 (9.4%)	9 (11.3%)
Schizophrenia	2 (1.3%)	8 (5.0%)	4 (5.0%)

Note: Percentages are based on the number of subjects in the Safety population.
Note: A subject experiencing more than 1 AE within a system organ class/preferred term is counted once within that system organ class/preferred term for incidence.
Note: Treatment-emergent AEs are defined as AEs with onset date on or after the start of treatment and prior to 30 days after the stop of treatment or AEs starting prior to the start of treatment and increasing in severity or relationship after the start of treatment.
Note: Monotherapy TEAEs are defined as AEs with onset date on or after the start of treatment and prior to the Visit 7 (Day 14) date.
Cross-reference: Display SAF 01.1

During the Monotherapy phase, the percentage of subjects who experienced at least 1 TEAE was highest in the paliperidone ER group (61.4%, 97 subjects) followed by the quetiapine group (53.5%, 85 subjects), and the placebo group (46.3%, 37 subjects). The most common TEAEs (≥10% of subjects in any group) were headache (12.0% vs. 7.5% vs. 13.8%), somnolence (8.9% vs. 11.9% vs. 1.3%), tremor (13.9% vs. 5.0% vs. 7.5%), and insomnia (10.1% vs. 9.4% vs. 11.3%).

No subject in the paliperidone ER+ or quetiapine+ group experienced the TEAE of stroke or stroke-related events of blood clots or hemorrhage, or a transient ischemic attack during the Monotherapy phase. No subject in the paliperidone ER+ or quetiapine+ group experienced the TEAE of diabetes mellitus. One subject in the paliperidone ER+ group experienced a TEAE of blood glucose increased, and 1 subject in the quetiapine+ group experienced a TEAE of glucose urine.

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The percentage of subjects who experienced at least 1 TEAE during the entire study period was higher in the paliperidone ER+ (75.3%, 119 subjects) and quetiapine+ (77.4%, 123 subjects) groups compared with the placebo+ group (67.5%, 54 subjects). The most common TEAEs (≥10% of subjects in any group) were headache (14.6% vs. 11.9% vs. 16.3%), tremor (19.6% vs. 7.5% vs. 15.0%), somnolence (11.4% vs. 15.1% vs. 2.5%), insomnia (12.0% vs. 10.1% vs. 15.0%), dizziness (3.8% vs. 15.1% vs. 1.3%), hypertonia (12.0% vs. 3.8% vs.3.8%), and sedation (4.4% vs. 10.7% vs. 3.8%).

Most TEAEs were mild or moderate in severity. With the exception of events coding to neurological disorders, the majority of TEAEs were considered by the investigator to be "not related" or "doubtfully related" to study medication. Prolactin-related and metabolic-related events were infrequent and comparable to placebo+ for the paliperidone ER+ and quetiapine+ groups. The percentage of EPS-related TEAEs was low and comparable across the paliperidone ER+, quetiapine+, and placebo+ groups with the exception of tremor, hypertonia, and to a lesser extent dystonia, which occurred more often in the paliperidone ER+ group.

A total of 22 subjects experienced 29 SAEs during the study. The incidence of subjects with at least 1 SAE was greatest in the paliperidone ER+ group followed by the quetiapine+ and placebo+ groups (8.2% vs. 4.4% vs. 2.5%). The most commonly reported SAE was schizophrenia (3.8% [6 subjects] vs. 1.9% [3 subjects] vs. [0 subjects]). A total of 37 subjects discontinued from the study due to a TEAE. The percentage of subjects with at least 1 TEAE that led to discontinuation was higher in the quetiapine+ (12.6%) and placebo+ group (10.0%) compared with the paliperidone ER+ group (5.7%). The majority of individual TEAEs leading to discontinuation were reported by ≤1 subject each within a treatment group.

One subject in the placebo+ group died of unknown causes on Day 35 of the study. She had discontinued study medication due to lack of efficacy, was stabilized clinically, and discharged from the hospital the day prior to the event. Her medical history included previous suicide attempts.

No clinically relevant changes were noted in the biochemistry analytes. Notable increases in prolactin were observed in the paliperidone ER group while decreases were observed in the quetiapine and placebo groups. Decreases in Total T3, Free T3, Total T4 and Free T4, and increases in TSH were seen in quetiapine group. These differences in prolactin and thyroid hormones were also reflected in a greater percentage of paliperidone ER subjects with shifts from normal to high in prolactin, and a greater percentage of quetiapine subjects with shifts from normal to low in T3, T4, and Free T4. In general, shifts from normal to high in liver analytes and lipids were also more common in quetiapine subjects relative to placebo and paliperidone ER subjects.

With the exception of heart rate changes and weight gain, vital signs were generally stable relative to Baseline and no clinically relevant differences were detected between treatment groups. Clinically notable increases in pulse rate were seen in all 3 treatment groups and had the highest incidence in the quetiapine group. This was also reflected in a higher incidence of abnormally high heart rate in the quetiapine group compared with the paliperidone ER and placebo groups, however the incidence of TEAEs of increased heart rate was similar across treatment groups. The incidence of subjects with abnormally low heart rate was greater in the paliperidone ER group compared with the quetiapine and placebo groups, however the incidence of TEAEs of bradycardia/sinus bradycardia remained low across treatment groups. There was a greater mean increase in weight seen in the quetiapine group compared with the paliperidone ER and placebo groups, which was also reflected in a greater incidence of subjects with clinically notable weight gain of ≥7% in the quetiapine group compared with the paliperidone ER and placebo groups.

No subject met criteria for prolonged QTcLD or QTcF intervals. The incidence of subjects meeting criteria for prolonged QTcB intervals was low and comparable across treatment groups. No clinically relevant differences between treatment groups were noted in physical findings.

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Overall, there were no clinically meaningful differences among treatment groups in SAS, BAS, or AIMS scores. Statistically significant differences were noted between the paliperidone ER and quetiapine groups, favoring quetiapine in LS mean change in SAS total score (Day 14 and Monotherapy Endpoint), however neither group differed significantly from placebo at these time points. At Study Endpoint there was a trend towards a significant difference in SAS total score between the quetiapine+ and placebo+ groups, favoring quetiapine+, however this did not reach statistical significance (p=0.052). Statistically significant differences were noted between the paliperidone ER and placebo groups for some BAS ratings at some time points. At Day 14 there was a stastically significant difference between the paliperidone ER and placebo groups in BAS ratings of subjective distress related to restlessness, due to an increased incidence of 'mild' subjective distress in the paliperidone ER group, however there were no statistically significant differences between treatment groups for the distribution of BAS scores at Monotherapy Endpoint. At Study Endpoint (but not Day 42), there was a significant difference in the BAS objective condition score between the paliperidone ER+ and placebo+ groups, reflecting more paliperidone ER+ subjects with ratings of 'mild' and to a lesser extent, 'moderate/severe'. Statistically significant differences were noted between the paliperidone ER and quetiapine groups, favoring quetiapine, in shifts from Baseline in BAS objective condition score (Day 14, Monotherapy Endpoint), BAS objective condition score (Day 42), and shifts from Baseline in the BAS subjective distress related to restlessness score (Day 42 and Study Endpoint), however neither group differed significantly from placebo in any of these comparisons.

UKU sleepiness/sedation scale score results showed significant increases in sedation relative to Baseline for the paliperidone ER and quetiapine groups during the Monotherapy phase however significant differences relative to placebo were noted only at Day 7 for the paliperidone group, compared with Days 3, 5, 7, 9, 14, and Monotherapy Endpoint LOCF for the quetiapine group. At Day 5 and Day 14 a significant difference was observed between the quetiapine and paliperidone ER groups indicating greater sedation with quetiapine. No significant differences were observed in UKU sleepiness/sedation scale scores at Day 42 or Study Endpoint. Increases in sedation were noted in the quetiapine+ group relative to placebo at Days 21 and 28, and between the paliperidoneER+ and placebo+ group at Day 28.

OUTCOME RESEARCH RESULTS:

There was no significant difference in hospital length of stay (LOS) during the study between the paliperidone ER+ and quetiapine+ groups. Compared to placebo+, both the paliperidone ER+ and quetiapine+ groups had significantly shorter lengths of hospital stay.

Paliperidone ER+ was associated with a lower rate and cost of polypharmacy than quetiapine+.

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CONCLUSION:

The results of this study demonstrate that in schizophrenia patients with a recent acute exacerbation requiring hospitalization:

- Paliperidone ER monotherapy produced rapid and significant improvements in symptoms and overall clinical status as well as satisfaction with study medication compared to quetiapine and placebo.
- Beginning as early as Day 5 and through the Monotherapy Endpoint, subjects treated with paliperidone ER were significantly more improved than those treated with quetiapine or placebo.
- Quetiapine treatment was similar to placebo on measures of symptoms and satisfaction with study medication.
- The benefits of paliperidone ER persisted on nearly all measures when used in conjunction with additional psychotropics, most of which were antipsychotics.
- Paliperidone ER and quetiapine were safe and generally well-tolerated when used as monotherapy or in conjunction with additional psychotropic medications. No unexpected TEAEs were noted for subjects treated with paliperidone ER or quetiapine. The safety findings were consistent with the known side effects for these drugs. No additional safety concerns were raised by the data in this study.
- Paliperidone ER was associated with lower rates of all-cause discontinuation than quetiapine and placebo.
- Paliperidone ER was associated with a lower rate and cost of polypharmacy than quetiapine.

Date of the report: 18 January 2008

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