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PROPRIETARY DRUG NAME[®]/GENERIC DRUG NAME: Geodon[®] / Ziprasidone hydrochloride

THERAPEUTIC AREA AND FDA APPROVED INDICATIONS: See USPI.

NATIONAL CLINICAL TRIAL NO.: NCT00145444

PROTOCOL NO: A1281006

PROTOCOL TITLE: A multi-center, double-blind, randomized trial of ziprasidone (80 - 160 mg) versus olanzapine (10 - 20 mg) in patients with recent-onset schizophrenia, schizoaffective and schizophreniform disorder.

Study Centers: Two study centers in The Netherlands and 2 in Belgium enrolled subjects.

Study Initiation and Completion Dates: 03 April 2002 to 17 October 2005

Phase of Development: Phase 3

Study Objectives: The *Primary Objective* of the study was to demonstrate effect on cognitive function of ziprasidone and olanzapine in the management of recent-onset psychosis, measured as the difference in efficacy in an 8-week period from the baseline visit to the end of week 8 visit.

Secondary Objectives:

- To demonstrate effect on cognitive function of ziprasidone and olanzapine in the management of recent-onset psychosis, measured as the difference in efficacy over a 24-week and one year period from baseline visit to the end of week 24 and week 52 visit
- To demonstrate effect of ziprasidone and olanzapine in the treatment of patients with recent-onset psychosis, measured in terms of response on the PANSS (Positive and Negative Symptom Scale) and the CGI (Clinical Global Impression) Improvement and Severity score
- To evaluate the effect on depressive symptoms of ziprasidone and olanzapine in the treatment of patients with recent-onset psychosis, measured in terms of response on the Calgary Depression Scale for Schizophrenia (CDSS)

- To evaluate safety and tolerability of ziprasidone and olanzapine in the treatment of patients with recent-onset psychosis, including prolactin levels
- To evaluate the effect of ziprasidone and olanzapine on quality of life and social functioning in the treatment of patients with recent-onset psychosis

METHODS

Study Design: This was a double-blind, randomized, double-dummy, parallel group, flexible dose, multicenter, 52-week study comparing cognitive function, effectiveness, safety and tolerability of the antipsychotic agents ziprasidone and olanzapine in patients with recent onset schizophrenia, schizoaffective disorder and schizophreniform disorder (referred to as “recent-onset psychosis”). Screening preceded randomization by a maximum of 10 days. Visits were at screening, baseline, end of day 3 (facultative) and weeks 1, 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48 and 52.

The total duration for the individual subject was between 52 weeks (plus a maximum of 10 days for screening) or if crossed-over 60 weeks (8 weeks plus 52 weeks and a maximum of 10 days for screening). Recruitment was continued for 30 months after randomization of the first subject or until a total number of 100 subjects had been randomized.

Non-response at week 8 was defined as failing to show a reduction of at least 20% on the PANSS.

Intolerance at week 8 was defined as a weight gain of > 4 kg increase from baseline, which was considered to be unacceptable by the subject, or a score of 5 on the modified patient preference scale (modified PPS) or a significant (> 3x upper limit of normal) elevation in hepatic transaminases or any other clinically significant laboratory abnormality.

Cross-over: Non-responders at week 8 week and subjects who discontinued medication due to side-effects or intolerability at week 8 were offered to a cross-over to the other treatment arm in a blinded fashion and continued treatment for another 52 weeks.

Drop outs: Subjects were considered to be drop-outs if they failed to complete a treatment period of 8 weeks for any reason and were not crossed over, or if they failed to complete an 8 week treatment period after cross-over.

Number of Subjects (Planned and Analyzed): A sample size of approximately 37 subjects per treatment arm was planned. An additional 30% enrollment (approximately 50 subjects per treatment arm overall) was recommended to offset the potential dropout rate.

A total of 81 subjects were screened, of which 74 were randomized, 39 to the ziprasidone arm and 35 to the olanzapine arm. All subjects randomized received at least one dose of study treatment and were members of the All Subjects Treated (AST) group. The Intent to Treat (ITT) group consisted of 56 subjects (ziprasidone 27, olanzapine 29). The Per Protocol (PP) group contained 52 subjects (ziprasidone 25, olanzapine 27).

Diagnosis and Main Criteria for Inclusion: Subjects were male or female out- or in-patients, aged 18-40 years who met the Diagnostic and Statistical Manual –Fourth Edition (DSM –IV) criteria for schizophrenia, schizoaffective disorder or schizophreniform disorder (295.xx, including 295.40) as confirmed on the basis of the Structured Clinical Interview for DSM IV, Text Revision (SCID). The duration of illness was ≤ 5 years (according to DSM-IV and onset first psychotic episode) and the Clinical Global Impression- Severity (CGI-S) score ≥ 4 (moderately ill). Subjects had to have a maximum exposure to antipsychotic treatment of ≤ 16 weeks.

Study Treatment:

- Ziprasidone HCl, 40 mg capsules
- Ziprasidone HCl, 60 mg capsules
- Ziprasidone HCl, 80 mg capsules
- Placebo for ziprasidone HCl, 40 mg capsules
- Placebo for ziprasidone HCl, 60 mg capsules
- Placebo for ziprasidone HCl, 80 mg capsules
- Olanzapine, 5 mg capsules
- Olanzapine, 10 mg capsules
- Placebo for olanzapine, 5 mg capsules
- Placebo for olanzapine, 10 mg capsules

Ziprasidone was started at 40 mg/day twice a day (BID) for 2 days (fixed), and was then adjusted to 40, 60 or 80 mg/day BID (flexible) from day 3 onwards. Flexible dosing (i.e., low, medium, high) was allowed at all subsequent visits up to week 52.

Olanzapine was started at 10 mg/day once a day (QD) for 2 days (fixed), and then adjusted to 10, 15 or 20 mg/day QD (flexible) from day 3 onwards. Flexible dosing (i.e., low, medium, high) was allowed at all subsequent visits up to week 52.

Medication was packed in a double-blind, double dummy fashion and was taken with food in the morning and evening.

Efficacy Evaluations: The *primary outcome measure* was the Dutch adaptation of the California Verbal Learning Test (CVLT) known as the “Verbale Leer en Geheugen Test” (VLGT). The VLGT was used to assess any differences in cognitive function between the two study arms. This measure was evaluated at baseline and at the week 8 or “early termination” visit. In the cross-over phase of this study, this evaluation was also performed at week 24 and at week 52 or “early termination.”

Secondary efficacy evaluations included:

- Positive and Negative Syndrome Scale (PANSS positive symptom subscale, PANSS negative symptom subscale, PANSS general psychopathology subscale, PANSS total): evaluated at baseline, weeks 4, 8, 12 24, 36 and 52 (or early termination)
- Clinical Global Impression – Severity (CGI-S): evaluated at all study visits

- Clinical Global Impression – Improvement (CGI-I): evaluated at all visits except at screening. The screening CGI-S value was to be the frame of reference for all subsequent CGI-I assessments
- The Calgary Depression Scale for Schizophrenia (CDSS): performed at baseline, weeks 4, 8, 12, 24, 36 and 52 (or early termination)

Other Evaluations: Additional neurocognitive tests included:

- Wisconsin Card Sorting Test
- Trails B
- Utrecht Latent Inhibition Task (only performed at W8 visit)
- Stroop Color Word Test
- Fluency
- Letter Fluency
- Category Fluency
- Continuous Performance Test-identical Pairs Version
- Test of Attentional Style (TAS)
- (Psycho) Motor Speed
- Finger Oscillation Test
- Trails A
- Wechsler Adult Intelligence Scale III (WAIS III): Digit Symbol – Coding
- California Verbal Learning Test (CVLT)
- Wechsler Memory Scale - Revised (WMS-R) Paired Associates
- WMS-R Visual reproduction with delayed Recall
- WAIS-III Letter-Number Sequencing
- Benton Judgment of Line Orientation Test

Additional Neurocognitive Assessments: General Cognitive Index: Premorbid general cognitive index as well as the current general cognitive index was measured at week 8. For subjects who crossed at week 8 visit, the additional battery of tests was performed 8 weeks after the cross-over (week 8 cross-over).

- Nederlandse leestest voor volwassenen (NLV, a Dutch reading test for adults)
- WAIS-III

If the condition of the subject did not allow the full neuropsychological evaluation, a core battery of tests was administered, consisting of: CVLT, Wisconsin Card Sorting test, Trails B, Stroop, Letter and Category-fluency, Continuous Performance test-identical pairs version, Finger Oscillation test and the WMS-R Visual reproduction.

These neurocognitive measures were performed at baseline, week 8, 24 and 52. An additional battery of tests to be used as possible covariates in analyzing the data of the core and additional battery was administered at week 8. For subjects who crossed at the week 8 visit, the additional battery of tests was performed 8 weeks after the cross-over (week 8 cross-over).

The Global Assessment of Functioning (GAF) was performed at baseline and week 52 (or early discontinuation).

The Drug Attitude Inventory (DAI) and the modified PPS were performed at baseline, weeks 4, 8, 24 and 52 (or early discontinuation).

The Heinrich Quality of Life Scale (QLS) and the Sexual Dysfunction Element of the Scandinavian Society of Psychopharmacology Committee of Clinical Investigations (UKU) were performed at baseline, weeks 8, 24 and 52 (or early discontinuation).

Safety Evaluations: Safety was assessed in this study using the St. Hans Rating Scale (SHRS) for extrapyramidal syndromes, the Barnes Akathisia Scale (BAS), the Abnormal Involuntary Movement Scale (AIMS), monitoring adverse events (AEs) at each study visit, collecting laboratory samples at specified intervals, electrocardiogram (ECG) collection and review, collection of vital signs data - including weight change - and physical examinations.

The SHRS, the BAS and the AIMS were performed at the baseline, week 4, and week 8 (or early termination) visits. During the cross-over phase, the SHRS and the BAS were performed at weeks 24, 36 and 52 (or early termination). The AIMS was performed at weeks 24 and 52 (or early termination).

Blood was drawn at baseline and week 8 (or early termination). For subjects who entered the cross-over phase, blood was also drawn at week 52 (or early termination). A pregnancy test was conducted for female subjects at screening and at week 52 (or early termination). All subjects had a urine drug screen at the screening visit.

Medical history was collected and a physical examination was performed at the screening visit. Brief physical examinations were performed on all scheduled visits thereafter. Blood pressure and pulse were recorded at screening, baseline, week 4 and week 8 (or early termination). At cross-over, blood pressure and pulse were recorded at weeks 12, 24, 36 and at week 52 (or early termination).

In addition, body height was recorded at screening. Body weights were measured at screening, baseline, week 4 and week 8 (or early termination). For cross-over subjects, weights were measured at weeks 12, 24, 36 and at week 52 (or early termination). Body Mass Index (BMI) was calculated based on the Quetelet Index. The body weights were carefully monitored to evaluate if a subject had gained ≥ 4 kg, which was one condition of “intolerance.”

An ECG was performed at screening, week 1 and week 52 (or early termination) for subjects who had entered cross-over.

Statistical Methods: For the purposes of this study, the all subjects treated (AST) population consisted of all randomized subjects who were known to have taken at least 1 dose of study drug. Safety analyses were performed on the AST group.

The intent-to-treat (ITT) group was defined as subjects in the AST group who had baseline and week 8 assessment of the primary efficacy variable (free long delay recall, measured

with the CVLT) or a premature study discontinuation assessment of the primary efficacy variable before week 8.

The per protocol (PP) population was defined as subjects in the ITT group who had no major protocol violations prior to week 8.

The primary analysis for the assessment of efficacy was performed on the ITT group. An additional analysis was performed on the PP group. An analysis of covariance (ANCOVA) model was used to test the effect of treatment at week 8 versus baseline. This analysis was limited to the period before cross-over, since after cross-over the treatment sequences were no longer randomized and statistical tests would have been invalid. Descriptive statistics and box-plots provided insights on the effect of cross-over and trends subsequent to week 8.

All statistical tests were carried out two-tailed, at the 5% level of significance. The Last Observation Carried Forward was the primary approach. The dependent variable in the ANCOVA analyses was the difference in the subject's score on the long delay recall test between baseline and week 8. A contrast was used to obtain an estimate and confidence interval for the effect of treatment at week 8 versus baseline. The subject's score at baseline included a covariate in order to control for the initial value. Other independent variables were the center where measurement took place and the dosage assigned to the subject at week 8.

For the key secondary endpoints (PANSS, CDSS, DAI and CGI-S), descriptive statistics were supplemented by a box-plot to graphically display trends in the data. An ANCOVA model was used to test the effect of treatment at week 8 versus baseline. This model was the same as for the primary efficacy analysis but was applied only to the ITT group. A special case was the DAI scale, which is dichotomous rather than interval measurement level. For this scale, a logistic regression model was estimated using PROC GENMOD.

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA), which resulted in a system organ class and a preferred term.

Laboratory data on hematology and biochemistry parameters were listed by subject and visit and out of normal range values were flagged. Frequency tables with number of subjects with abnormal laboratory data were presented as summary tables of median laboratory values and median changes to baseline.

At Week 8 the change from baseline in the subject's weight was analyzed using an ANCOVA model. Statistical analyses after cross-over was considered not to be informative because the groups were no longer randomized. Box plots and descriptive statistics on weight trends are presented after cross-over.

A summary table of QTc values from the ECG assessments was analyzed and changes were included for analysis. Vital signs were summarized at week 8 and for visits up to and including week 52.

RESULTS

Subject Disposition and Demography: Table S1, below, summarizes the disposition of all subjects.

Table S1. Frequency Table of Subject Disposition

	Ziprasidone n (%)	Olanzapine n (%)	Total n (%)
No. of subjects screened			81
No. of subjects randomized	39 (100.0)	35 (100.0)	74 (100.0)
No. in AST group	39 (100.0)	35 (100.0)	74 (100.0)
No. in ITT group	27 (69.2)	29 (82.9)	56 (75.7)
No. in PP group	25 (64.1)	27 (77.1)	52 (70.3)

In the study, 21 out of 74 subjects (28.4%) crossed over to the other treatment arm for reasons of non-response or intolerance. Based on that, for purposes of disposition, subjects were additionally broken out into four treatment sequences:

- Treatment Sequence A: Subjects receiving ziprasidone only
- Treatment Sequence B: Subjects receiving olanzapine only
- Treatment Sequence C: Subjects initially receiving ziprasidone, who subsequently crossed over to olanzapine
- Treatment Sequence D: Subjects initially receiving olanzapine, who subsequently crossed over to ziprasidone

Table S2 presents a frequency table of subjects who crossed over after 8 weeks of study.

Table S2. Subjects Who Crossed-over After 8 Weeks of Study (AST Group)

	Ziprasidone n (%)	Olanzapine n (%)	Total n (%)
No. of subjects continuing study	18 (46.2)	18 (51.4)	36 (48.6)
No. of subjects crossing over	10 (25.6)	11 (31.4)	21 (28.4)
Non-responder	10 (25.6)	11 (31.4)	21 (28.4)
Discontinuation due to intolerability	0	5 (14.3)	5 (6.8)
Total	39 (100)	35 (100)	74 (100)

The disposition of subjects per treatment arm during the different phases of the study is summarized in Table S3.

Table S3. Disposition of Subjects Across Treatment Arms

	Treatment sequence			
	A (Z-Z)	C (Z-O)	D (O-Z)	B (O-O)
Baseline	39			35
Drop-outs	-11			-6
Week 8	28			29
Cross-over	18	10	11	18
Drop-outs in cross-over group		-3	-6	
Week 8 post cross-over		7	5	
Drop-outs	-11	-3	-3	-12
Completed study	7	4	2	6

Z-Z = Received ziprasidone only

Z-O = Initially received ziprasidone, but crossed over to olanzapine

O-Z = Initially received olanzapine, but crossed over to ziprasidone

O-O = Received olanzapine only

The trial population consisted of 61 male and 13 female subjects, aged 18 – 39 years, with recent-onset schizophrenia, schizoaffective and schizophreniform disorder (according to DSM-IV) and with a CGI-S score ≥ 4 .

The frequency distribution of hospitalizations in the year preceding baseline was compared between groups. A total of 55 subjects (74.3%) had been hospitalized once for psychiatric reasons, 29 (74.4%) in the ziprasidone arm, 26 (74.3%) in the olanzapine arm. An additional 7 subjects (9.5%) had been hospitalized twice and one subject in the ziprasidone arm had been hospitalized more than 2 times. None of the subjects in the olanzapine arm had been hospitalized more than 2 times. Three subjects had been hospitalized for somatic reasons, 1 in the ziprasidone arm and 2 in the olanzapine arm. There were no remarkable differences between the arms in any of the other demographic parameters.

Efficacy Results

Primary Evaluation: The primary efficacy parameter was the free long delay recall, measured by the CVLT from baseline to endpoint (i.e. the week 8 visit or early termination). There was a small difference in mean CVLT score at baseline between the 2 treatment arms, a difference which had reduced at week 8. The mean CVLT score increased substantially for both treatment arms between baseline and week 8, however, the difference was not statistically significant ($p= 0.330$). Therefore, there were no treatment effects with respect to CVLT change from baseline to week 8.

The results of the long delay recall in the CVLT by treatment arm for the first 8 weeks of the study are summarized in Table S4.

Table S4. Summary Table of California Verbal Learning Test: Visits Up to Week 8 (ITT group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	8.8	3.13	3	9.0	14	27
	Olanzapine	9.2	4.00	0	10.0	15	29
Week 8	Ziprasidone	10.2	3.58	3	10.5	16	26
	Olanzapine	10.3	3.03	4	10.0	15	28

Secondary Evaluations: As this study contained a large number of secondary endpoints, seven of these measures were selected as key secondary endpoints and were analyzed in greater depth:

1. PANSS: positive symptom subscale
2. PANSS: negative symptom subscale
3. PANSS: general psychopathology subscale
4. PANSS: total
5. CGI-S
6. CDSS
7. DAI

The results of the Positive Symptom Subscale of PANSS during the first 8 weeks are summarized in Table S5.

Table S5. Summary Table of PANSS Positive Symptom Scale (ITT Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	21.6	5.33	9	21.0	34	27
	Olanzapine	21.9	3.76	14	22.0	29	28
Week 4	Ziprasidone	17.4	5.14	9	18.0	27	27
	Olanzapine	17.7	4.10	7	18.0	26	27
Week 8	Ziprasidone	14.7	5.07	7	14.5	27	26
	Olanzapine	14.8	3.96	7	15.0	21	27

The ANCOVA analysis on difference in PANSS Positive Symptom Subscale between 8 weeks and baseline confirms that the LS mean for the reduction from baseline to week 8 was statistically significant for both treatment arms ($p < 0.001$), but the difference between treatment arms was small and was not statistically significant ($p = 0.548$). From the 3 factors in the model (center, dosage, and baseline PANSS positive symptom value), only the baseline PANSS positive symptom score had a statistically significant effect ($p = 0.020$).

Table S6 summarizes the results of the Negative Symptom Subscale of PANSS during the first 8 weeks.

Table S6. Summary Table of the PANSS Negative Symptom Scale (ITT Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	19.3	5.57	8	20.0	29	27
	Olanzapine	18.9	5.73	9	18.0	33	28
Week 4	Ziprasidone	17.1	5.14	7	18.0	29	27
	Olanzapine	17.8	5.67	7	18.0	28	27
Week 8	Ziprasidone	16.6	5.73	9	16.0	36	26
	Olanzapine	16.8	4.85	7	17.0	27	27

The decrease in mean negative symptom scores during the first 8 weeks was less marked than was the case for the Positive Symptom Subscale. There were no large differences in mean negative symptom scores between treatment sequences in the post cross-over period.

Results of the PANSS: General Psychopathology Subscale are summarized in Table S7.

Table S7. Summary Table of the PANSS General Psychopathology Subscale (ITT Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	40.1	7.58	29	42.0	53	27
	Olanzapine	38.4	7.30	22	38.0	57	28
Week 4	Ziprasidone	35.1	7.56	24	34.0	51	27
	Olanzapine	33.3	9.22	16	33.0	51	27
Week 8	Ziprasidone	31.8	7.43	22	31.5	56	26
	Olanzapine	30.9	7.44	18	29.0	46	27

These results closely resemble those for the positive symptom subscale: steady decreases during the pre-cross-over period for both treatment arms, but with the differences in mean general psychopathology scores between treatment arms being small. ANCOVA analysis showed a significant decrease ($p < 0.001$) in general psychopathology scores between baseline and week 8 for both treatment arms, but no significant difference between the 2 arms.

The CGI-S score was included among the key secondary endpoints and was examined in greater depth. The CGI-I score was not a key secondary endpoint. Although the CGI-S and CGI-I scales are categorical values (measured on a scale from 1 to 7, with 0 = “not assessed”), they were treated as continuous variables in this analysis.

Results of CGI-S scores during the first 8 weeks are presented in Table S8.

Table S8. CGI-S Scores During the First 8 Weeks of Treatment (ITT Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	5	0.76	4	5	6	27
	Olanzapine	5	0.78	4	5	6	29
Week 4	Ziprasidone	4.5	0.75	3	4	6	27
	Olanzapine	4.3	1.01	2	4	6	29
Week 8	Ziprasidone	4	0.84	3	4	5	25
	Olanzapine	4	1.0	2	4	6	28

The mean CGI-S scores by treatment sequence for the entire period were initially fairly close together during the first 2 weeks of treatment. Subjects on treatment sequence D appeared to have relatively higher mean CGI-S scores between week 4 and week 20. The number of subjects in treatment sequence D declined during this period from 9 to only 2 between weeks 20 and week 52. After week 24, the mean CGI-S scores were fairly similar for the 4 treatment sequences, although treatment sequences A and B tended to have consistently lower values than treatment sequences C and D. ANCOVA analysis confirmed that there was a statistically significant ($p < 0.001$) decline in mean CGI-S scores between baseline and week 8 but that there was no significant difference in the rate of decline between the treatment arms ($p = 0.388$).

The results of the CDSS during the first 8 weeks are summarized in Table S9.

Table S9. The CDSS During the First 8 Weeks of Treatment (ITT Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	6.0	3.96	0	5.0	15	27
	Olanzapine	4.3	3.67	0	3.0	13	28
Week 4	Ziprasidone	5.0	3.62	0	5.0	12	26
	Olanzapine	3.9	3.71	0	2.5	13	28
Week 8	Ziprasidone	5.5	4.16	0	4.5	14	26
	Olanzapine	3.2	4.19	0	1.0	15	27

The ziprasidone arm had consistently higher mean scores during the first 8 weeks, and the mean CDSS score in the ziprasidone arm only decreased minimally between baseline and week 8, from 6.0 to 5.5 ($p = 0.723$), whereas the mean CDSS score in the olanzapine arm showed a more substantial decrease from 4.3 to 3.2 ($p = 0.024$). However, there was no statistically significant difference in the rate of decline between the 2 treatment arms ($p = 0.132$).

The mean CDSS levels for the entire period fluctuated in the post-cross-over period. These results are difficult to interpret due to subjects discontinuing treatment at various points in time.

The DAI scale consisted of ten TRUE/FALSE statements. The sum of the positive and negative scores was calculated. If this sum was positive, the subject was assigned a positive total final score (compliant). If the sum was zero or negative then the subject was assigned a negative total score (non-compliant). At week 8, the percentage of subjects with a positive

DAI final score was higher in the olanzapine arm (84.0%) than in the ziprasidone arm (65.2%).

Safety Results: The SHRS consists of 5 syndromes: akathisia (overall score 0-18): including subjective, objective, patient’s distress; dystonia (overall score 0-6): patient’s distress; parkinsonism (overall score 0-60): facial expression, bradykinesia, posture, arm swing, gait, tremor, rigidity, salivation, global, patient’s distress; passive dyskinesia (overall score 0-48): jaw, tongue, lips, face, head-neck, trunk, upper extremities, lower extremities; active dyskinesia (overall score 0-60): jaw, tongue, lips, face, head-neck, trunk, upper extremities, lower extremities, dyskinesia global and patient’s distress. Results of the 5 SHRS syndromes are summarized in Table S10.

Table S10. Summary Table for Results of SHRS Extrapyrimal Syndromes (AST Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Akathisia overall score							
Baseline	Ziprasidone	1.2	2.21	0	0.0	10	39
	Olanzapine	0.5	1.40	0	0.0	6	34
Week 4	Ziprasidone	1.0	2.04	0	0.0	10	29
	Olanzapine	0.5	1.29	0	0.0	6	31
Week 8	Ziprasidone	1.2	2.30	0	0.0	8	27
	Olanzapine	0.8	1.78	0	0.0	8	27
Dystonia patient distress score							
Baseline	Ziprasidone	0.0	0.00	0	0.0	0	39
	Olanzapine	0.0	0.00	0	0.0	0	34
Week 4	Ziprasidone	0.1	0.56	0	0.0	3	29
	Olanzapine	0.0	0.00	0	0.0	0	31
Week 8	Ziprasidone	0.0	0.19	0	0.0	1	27
	Olanzapine	0.0	0.00	0	0.0	0	27
Parkinsonism overall score							
Baseline	Ziprasidone	4.8	8.53	0	2.0	36	39
	Olanzapine	5.7	10.06	0	1.0	43	34
Week 4	Ziprasidone	4.3	7.20	0	2.0	31	29
	Olanzapine	5.1	6.97	0	3.0	31	30
Week 8	Ziprasidone	3.1	4.07	0	1.0	14	27
	Olanzapine	4.7	6.57	0	3.0	28	26
Passive dyskinesia overall score							
Baseline	Ziprasidone	0.2	0.66	0	0.0	3	39
	Olanzapine	0.1	0.56	0	0.0	3	34
Week 4	Ziprasidone	0.3	1.11	0	0.0	5	29
	Olanzapine	0.1	0.36	0	0.0	2	31
Week 8	Ziprasidone	0.1	0.77	0	0.0	4	27
	Olanzapine	0.3	1.00	0	0.0	4	27
Active dyskinesia overall score							
Baseline	Ziprasidone	0.4	1.23	0	0.0	6	39
	Olanzapine	0.4	1.25	0	0.0	6	34
Week 4	Ziprasidone	0.8	2.77	0	0.0	13	29
	Olanzapine	0.4	1.06	0	0.0	5	31
Week 8	Ziprasidone	0.5	1.63	0	0.0	7	27
	Olanzapine	1.0	2.99	0	0.0	13	27

Although there were isolated cases of extrapyramidal syndromes, the mean overall scores remained low.

The BAS consisted of 4 items:

- 1) Objective
- 2) Subjective 1: awareness of restlessness
- 3) Subjective 2: distress related to restlessness
- 4) Global clinical assessment of akathisia score

An overall akathisia rating score (range 0–14) was calculated as the sum of the 4 items. The overall akathisia rating score is summarized by treatment arm for the first 8 weeks in Table S11. The mean and median values were low; the maximum value was 8. On the whole, subjects had few or no symptoms of akathisia.

Table S11. Summary Table of the Overall Akathisia Rating Score (AST Group)

Visit	Treatment Group	Mean	Standard Deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	1.3	2.05	0	0.0	7	38
	Olanzapine	0.6	1.29	0	0.0	5	32
Week 4	Ziprasidone	1.1	2.01	0	0.0	8	27
	Olanzapine	0.6	1.48	0	0.0	7	31
Week 8	Ziprasidone	1.3	2.44	0	0.0	8	25
	Olanzapine	0.9	1.53	0	0.0	6	25

The AIMS consisted of 12 items relating to involuntary movements in different areas of the body:

- 1) Muscles of facial expression
- 2) Lips and perioral area
- 3) Jaw
- 4) Tongue
- 5) Upper Extremity
- 6) Lower Extremity
- 7) Neck, shoulders, hips
- 8) Severity of abnormal movements
- 9) Incapacitation due to abnormal movements
- 10) Subject awareness of abnormal movements
- 11) Current problems with teeth
- 12) Does subject usually wear dentures

The overall AIMS score was calculated as the sum of items 1 to 10. Table S12, below, summarizes the overall AIMS score by treatment arm for the first 8 weeks. The low mean overall AIMS score and the median value of 0.0 for all instances indicate that most subjects were not troubled by involuntary movements.

Table S12. Summary Table of the Overall AIMS Score (AST Group)

Visit	Treatment group	Mean	Standard deviation	Minimum	Median	Maximum	N
Baseline	Ziprasidone	0.9	2.45	0	0.0	12	39
	Olanzapine	0.3	1.04	0	0.0	5	34
Week 4	Ziprasidone	1.2	2.99	0	0.0	12	29
	Olanzapine	0.4	1.28	0	0.0	6	31
Week 8	Ziprasidone	0.6	1.95	0	0.0	9	27
	Olanzapine	1.1	2.80	0	0.0	11	27

There were no deaths in this study.

There were 15 subjects in this study who reported SAEs, 7 (14%) in the ziprasidone arm and 8 (17.8%) in the olanzapine arm. However, when relationship to treatment was considered, the number of subjects with SAEs were 2 (4%) for the ziprasidone group and 3 (6.7%) for the olanzapine group. The majority of the SAEs were related to worsening of the underlying disease. All SAEs are listed below in Table S13.

Table S13. Summary of Serious Adverse Events

Sex/ Age (years)	Treatment/ dose	Event term	Onset day ^a	Action taken
Male/20	Olanzapine, 15 mg	Psychotic disorder	8	Dose increased
	Olanzapine, 20 mg	Psychotic disorder	109	Treatment given
Male/23	Ziprasidone, 160 mg	Psychotic disorder	23	Permanently discontinued
Male/20	Ziprasidone, 120 mg	Anxiety	125	No action
Female/39	Ziprasidone, 160 mg	Psychotic disorder	15	Dose increased
Male/31	Ziprasidone, 160 mg	Psychotic disorder	29	No action
Male/24	Olanzapine, 10 mg	Depression*	111	No action
	Olanzapine, 10 mg	Suicidal ideation*	111	No action
Female/35	Olanzapine, 10 mg	Depression*	27	Permanently discontinued
Male/29	Olanzapine, 15 mg	Suicidal ideation	24	Unknown
Male/21	Olanzapine, 10 mg	Psychotic disorder	14	Dose increased
	Olanzapine, 10 mg	Suicidal ideation	14	Dose increased
Male/24	Olanzapine, 15 mg	Suicide attempt	49	No action
	Ziprasidone, 160 mg	Suicide attempt	44	No action
Male/21	Olanzapine, 10 mg	Mania*	2	Permanently discontinued
Male/25	Ziprasidone, 80 mg	Suicide attempt*	160	Unknown
Male/32	Olanzapine, 10 mg	Psychotic disorder	351	Permanently discontinued
Male/26	Post treatment	Psychotic disorder	31	Treatment given
Female/26	Ziprasidone, 80 mg	Suicidal ideation*	36	Dose increased
	Ziprasidone, 80 mg	Suicidal ideation*	51	Unknown

^aDay relative to first day of each treatment period; first day of each treatment period = day 1

*Event considered by investigator and sponsor to be related to study drug

Forty-six (92.0%) subjects in the ziprasidone group and 42 (93.3%) subjects in the olanzapine group reported treatment-emergent AEs. The most frequent treatment-emergent AEs (those occurring in $\geq 5\%$ subjects in either treatment group) are summarized in Table S14, below.

Table S14. Summary of Most Frequently Occurring ($\geq 5\%$ Subjects in Either Treatment Group) AEs (All Causality)

Adverse event (MedDRA preferred term):	Ziprasidone (n=50) n (%)	Olanzapine (n=45) n (%)
Sedation	19 (38.0)	15 (33.3)
Nausea	17 (34.0)	6 (13.3)
Akathisia	13 (26.0)	5 (11.1)
Headache	13 (26.0)	9 (20.0)
Dystonia	11 (22.0)	1 (2.2)
Tremor	10 (20.0)	8 (17.8)
Insomnia	9 (18.0)	9 (20.0)
Weight increased	9 (18.0)	23 (51.1)
Depression	7 (14.0)	6 (13.3)
Muscle rigidity	7 (14.0)	8 (17.8)
Dizziness	6 (12.0)	5 (11.1)
Fatigue	6 (12.0)	2 (4.4)
Parkinsonism	6 (12.0)	2 (4.4)
Salivary hypersecretion	6 (12.0)	2 (4.4)
Vomiting	6 (12.0)	3 (6.7)
Dyskinesia	5 (10.0)	4 (8.9)
Libido decreased	5 (10.0)	4 (8.9)
Psychotic disorder	5 (10.0)	4 (8.9)
Decreased appetite	4 (8.0)	1 (2.2)
Erectile dysfunction	4 (8.0)	1 (2.2)
Myalgia	4 (8.0)	0
Rhinitis	4 (8.0)	1 (2.2)
Anxiety	3 (6.0)	4 (8.9)
Back pain	3 (6.0)	3 (6.7)
Bradykinesia	3 (6.0)	0
Dry Mouth	3 (6.0)	2 (4.4)
Restlessness	3 (6.0)	0
Blood prolactin increased	1 (2.0)	4 (8.9)
Increased appetite	1 (2.0)	6 (13.3)
Alanine aminotransferase increased	0	4 (8.9)
Constipation	0	4 (8.9)
Contusion	0	3 (6.7)
Liver function test abnormal	0	3 (6.7)
Suicidal ideation	0	3 (6.7)

Note: Subjects were counted only once per treatment in each row.
 Includes data up to 6 days after last dose of study treatment.

During the first 8 weeks of the study, 8 subjects were discontinued from study treatment due to AEs, including 6 in the ziprasidone arm (weight increased, dystonia, drug eruption, hypersensitivity, and psychotic disorder [2 subjects]), and 2 in the olanzapine arm (weight increased, mania).

After 8 weeks, a total of 4 subjects discontinued treatment. One subject who received ziprasidone before and after 8 weeks discontinued the study due to an AE of oculogyration. One subject discontinued due to psychotic disorder after continuing treatment with olanzapine after 8 weeks. One subject discontinued due to an AE of depression after crossing over from ziprasidone to olanzapine. One subject discontinued due to nausea and decreased appetite after crossing over from olanzapine to ziprasidone.

The median laboratory values over time evaluated from screening to week 52 showed very similar results. There were, however, some values that changed. The cohort of subjects who continued on ziprasidone from baseline had a marked reduction (-67.5 ng/mL) in serum prolactin levels between screening and week 52. The triglyceride levels also were lower in the ziprasidone cohort after analysis. Cholesterol levels, however, were slightly higher in the ziprasidone arm. The other laboratory values were unremarkable.

A total of 17 subjects in the olanzapine arm reported clinically significant increases in body weight as compared to 2 subjects in the ziprasidone group during the first 8 weeks of the study. Two subjects in the ziprasidone arm reported weight decrease as AE during the same period. No subjects in the olanzapine group had weight decrease. During the first 8 weeks after cross-over 4 subjects in the Z-O group experienced clinically significant weight increases versus 2 subjects in the O-Z group.

In the first 8 weeks of the study, the mean weight in the olanzapine arm increased strongly whereas the mean weight in the ziprasidone arm remained stable. After cross-over the mean weight in treatment sequence C increased steadily, whereas mean weight in treatment sequence D remained stable. Interpretation of the results after cross-over must be treated with care due to small subject numbers as a result of discontinuations. The results of an analysis of variance model of change in weight between baseline and week indicated that the LS mean of the olanzapine arm was 7.4 kg higher at week 8 than at baseline ($p < 0.001$), the LS mean of the ziprasidone arm was 0.9 kg lower ($p = 0.445$). The difference in LS means between the two arms was -8.3, which was statistically significant ($p < 0.001$).

CONCLUSION

In this double-blind, active control, Phase 3 trial (protocol A1281006), the compounds in both treatment arms were shown to maintain good clinical effect on subjects suffering from schizophrenia. Both compounds showed good clinical effect in controlling symptoms associated with schizophrenia, schizoaffective or schizophreniform disorders. The effects on cognition were also comparable.

In this study, subjects with recent-onset schizophrenia, schizoaffective or schizophreniform disorder (duration of illness ≤ 5 years) were evaluated for cognitive function. Statistical analysis of performance with the CVLT illustrated that both compounds showed parity relating to cognitive function.

A low incidence of clinically significant weight gain showed that ziprasidone generally had a more favorable benefit-risk profile when compared to olanzapine in this study.