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PROPRIETARY DRUG NAME®/GENERIC DRUG NAME: Zeldox® / Geodon / Ziprasidone hydrochloride

PROTOCOL NO.: A1281147

PROTOCOL TITLE: A Multicenter, Randomized, Double-Blind, Parallel-Group Study, Comparing the Efficacy and Tolerability of Ziprasidone (Zeldox, Geodon) vs Olanzapine (Zyprexa) in the Treatment and Maintenance of Response in Patients With Acute Mania

Study Centers: A total of 47 centers in Europe took part in the study and 18 centers enrolled subjects; 9 in Italy, 3 in Germany, 4 in Spain, 2 in Turkey, and 1 in Greece.

Study Initiation Date and Final Completion Date: 14 November 2006 to 10 January 2008. The study was terminated prematurely.

Primary Completion Date: 30 July 2007.

Phase of Development: Phase 3b/4

Study Objective: The aim of this study was to compare the efficacy and tolerability of ziprasidone versus olanzapine in the treatment of acute mania. An open-label extension study would further evaluate the efficacy, safety, and tolerability of ziprasidone compared with olanzapine over a period of 6 months in subjects responding to acute treatment.

METHODS:

Study Design: This was a double-blind, parallel-group, comparative, multicenter, flexible dose study that was comprised of 3 phases as described below.

- Screening phase of at least 24 hours during which required assessments and wash out of existing psychoactive medication was completed.

- Double-blind acute assessment phase of up to 10 weeks during which eligible subjects received olanzapine or ziprasidone in a 1:1 randomization ratio. Subjects who met symptomatic remission criteria at Week 4, Week 6, or Week 10 would enter the open-label maintenance phase. Subjects who did not meet the remission criteria would be released from the study at Week 10.

- A 6-month open-label maintenance phase; subjects who entered this phase continued treatment with either olanzapine or ziprasidone. If, during the open-label phase, the subject had scores of Young Mania Rating Scale (YMRS) ≥15 and/or Montgomery Asberg Depression Scale (MADRS) ≥18, or they met the Diagnostic and Statistical

Manual Four (DSM-IV-TR) criteria for hypomania, the Investigator could modify the ziprasidone or olanzapine dose and add a benzodiazepine. The subject was assessed again after 2 weeks, and if there had been no improvement, the subject was either removed from the study or was given mood stabilizers. Subjects given mood stabilizers remained in the study for collection of safety data only. Subjects could be removed from the open-label maintenance phase at any time, if they met the criteria of DSM-IV-TR for manic episodes, and/or mixed episodes, and/or depressive episodes.

The schedule of activities for the study is presented in Table 1 and Table 2.

Table 1. Schedule of Activities – Double-Blind Phase

Visits	V1 (Screening)	V2 (Randomization)	V3	V4	V5	V6	V7[a]	V8[a]	V9[a]	V10[a]	V11[a]
Week	**-2**	**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**9**	**10**
Study Day	**-1 or Before**	**0**	**7**	**14**	**21**	**28**	**35**	**42**	**49**	**63**	**70**
Informed consent	X										
Pharmacogenomics sample[b]		X									
Randomization		X									
Inclusion/exclusion criteria	X	X									
Prior medication	X	X									
Medical history	X										
Physical examination	X					X[c]		X[c]			X
Vitals[d]	X	X	X			X		X[c]			X
ECG	X					X		X[c]			X
Clinical labs	X					X		X[c]			X
Serum T4 and TSH	X										
Urinalysis	X										
Urine drug screen	X					X[c]		X[c]			X
Pregnancy test (urine)[e]	X					X[c]		X[c]			X
Height and weight[f]	X					X		X[c]			X
Waist circumference	X					X		X[c]			X
Concurrent medication	X	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	X	X	X
MADRS		X	X	X	X	X	X	X	X	X	X
GAF		X				X		X[c]			X
CGI-BP		X	X	X	X	X	X	X	X	X	X
TSQM		X				X		X[c]			X
AIMS/BAS/SAS		X				X		X[c]			X
Q-LESQ		X				X		X[c]			X
Study medication dispensing		X	X	X	X	X	X	X	X	X	X

Table 1. Schedule of Activities – Double-Blind Phase

AIMS = Abnormal Involuntary Movement Scale; BAS = Barnes Akathisia Scale; CGI-BP = Clinical Global Impressions Scale for use in Bipolar Illness; ECG = ElectroCardioGraph; GAF = Global Assessment of Functioning; IEC = independent ethics committee; MADRS = Montgomery Asberg Depression Rating Scale; Q-LESQ = Quality of Life Enjoyment and Satisfaction Questionnaire; SAS = Simpson-Angus Scale; T4 = thyroxine; TSH = thyroid-stimulating hormone; TSQM = Treatment Satisfaction Questionnaire for Medication; V = visit; YMRS = Young Mania Rating Scale.

a. These assessments were only carried out on subjects remaining on the double-blind phase. Subjects who had entered the open-label phase followed an additional schedule of activities (Table 2).
b. Pharmacogenomics sample was only collected from those subjects who had given separate informed consent and was subject to IEC approval.
c. These tests were not to be performed on subjects continuing on the double-blind treatment phase.
d. Vitals were blood pressure and pulse rate.
e. Female subjects only. If the test was positive, a serum sample was sent away for analysis and confirmation.
f. Height and weight were measured to calculate Body Mass Index (BMI; body weight [kg] divided by square of height [m^2]).

Table 2. Schedule of Activities – Open-Label Maintenance Phase

Visits[a]	V1	V2	V3	V4	V5	V6	V7	V8 (End of Treatment)	V9 (End of Study)
Week of Open Label Phase	**2**	**4**	**6**	**8**	**12**	**16**	**20**	**24**	**28**
Study Day of Open Label Phase	**14**	**28**	**42**	**56**	**84**	**112**	**140**	**168**	**196**
Vitals	X		X	X	X	X	X	X	
Serum lithium level[b]		X	X	X	X	X	X	X	
Physical examination								X	
Height and weight								X	
ECG								X	
Waist circumference								X	
Clinical labs								X	
Pregnancy test (urine)[c]					X			X	
Adverse events	X	X	X	X	X	X	X	X	X
Concurrent medication	X	X	X	X	X	X	X	X	X
YMRS	X	X	X	X	X	X	X	X	
MADRS	X	X	X	X	X	X	X	X	
GAF								X	
CGI-BP	X	X	X	X	X	X	X	X	
TSQM								X	
AIMS/BAS/SAS								X	
Q-LESQ								X	
Study medication dispensing	X	X	X	X	X	X	X		

AIMS = Abnormal Involuntary Movement Scale; BAS = Barnes Akathisia Scale; CGI-BP = Clinical Global Impressions Scale for use in Bipolar Illness; ECG = ElectroCardioGraph; GAF = Global Assessment of Functioning; MADRS = Montgomery Asberg Depression Rating Scale; Q-LESQ = Quality of Life Enjoyment and Satisfaction Questionnaire; SAS = Simpson-Angus Scale; TSQM = Treatment Satisfaction Questionnaire for Medication; V = visit; YMRS = Young Mania Rating Scale.

a. Visits may be required between these visits (ie, after 2 weeks) for YMRS and MADRS assessment if mood stabilizers have been prescribed.

b. Lithium levels should be tested 4-7 days after starting lithium (only for subjects prescribed lithium) and repeated after dose increases or at the Investigator's discretion.

c. Female subjects only. If the test is positive, a serum sample should be sent away for analysis and confirmation.

Number of Subjects (Planned and Analyzed): A total of 352 subjects were planned for enrollment and a total of 29 subjects were assigned to treatment (15 in the ziprasidone group and 14 in the olanzapine group).

Of the 29 subjects; 15 were enrolled in Italy, 5 in Germany, 4 each in Spain and Turkey, and 1 in Greece.

Diagnosis and Main Criteria for Inclusion: Both male and female subjects aged 18 years to 65 years of age who were diagnosed with Bipolar I disorder, current episode manic (DSM-IV 296.4x) or mixed (DSM-IV296.6x) as determined by a structured clinical interview (Mini International Neuropsychiatric Interview) at Screening and who had a minimum score of 20 on the YMRS were included in the study. Subjects with a diagnosis of learning disability or organic brain syndrome and subjects who had a substance-induced psychotic disorder or behavioral disturbance thought to be due to substance abuse were excluded from the study.

Study Treatment: Ziprasidone and its matching placebo were supplied as hard gel capsules of either 40, 60 or 80 mg. Olanzapine and its matching placebo were supplied as film-coated tablets of either 5 or 10 mg. Study drugs were presented in blister cards, each containing sufficient medication for 1 week including spares.

Ziprasidone was initiated at a dosage of 80 mg/day (40 mg twice daily [BID]) on Day 1 and then was titrated to 120 mg/day (60 mg BID) from Day 3. From Day 7, the dosage was adjusted between 120 to 160 mg/day on the basis of clinical status at the Investigator's discretion. Olanzapine was started at 15 mg/day (15 mg once daily [QD]) on Day 1, and remained at this dosage until Day 7. The dosage was adjusted on the basis of clinical status up to 20 mg/day at the Investigator's discretion. This dosing regimen had been checked against the labels for consistency. Subjects might have also received placebo for ziprasidone or olanzapine during the double-blind phase.

During the open-label maintenance phase, olanzapine dosage was adjusted on the basis of clinical status between 10, 15, and 20 mg/day tablets at the Investigator's discretion. Ziprasidone dosage was adjusted on the basis of clinical status between 80, 120, and 160 mg/day capsules at the Investigator's discretion. Ziprasidone and olanzapine were used in compliance with local prescribing information.

Efficacy Endpoints:

Efficacy Endpoints:

Primary Endpoint: Mean reduction, after 4 weeks of treatment, in the YMRS score during the double blind phase.

Secondary Endpoints:

Double Blind Phase:

- Percentage of subjects with symptomatic remission (percentage of subjects with a YMRS score of ≤12 and MADRS ≤12 for at least 2 consecutive weeks) after 4, 6 and 10 weeks of treatment.

- Time to symptomatic remission.

- Percentage of subjects with clinical response (reduction of at least 50% in YMRS total score from Baseline) after 6 weeks of double-blind treatment.

- Change from Baseline in Clinical Global Impressions Scale for use in Bipolar Illness scores (CGI-BP).

- Change from Baseline in MADRS score.

- Change from Baseline in Global Assessment of Functioning Scale Scores.

Open Label Phase:

- Percentage of subjects with symptomatic relapse of mania during the maintenance phase (percentage of subjects with YMRS score ≥15 or, if it was not possible to perform the scale, for example if the subject was too ill, satisfaction of DSM IV-TR criteria for hypomania or for a manic or mixed episode).

- Percentage of subjects with symptomatic relapse of depression during the maintenance phase (percentage of subjects with MADRS ≥18, or if it was not possible to perform the scale, satisfaction of DSM IV-TR criteria for a depressive or mixed episode).

Study was terminated due to poor recruitment and no efficacy data were summarized due to very low sample size. Only safety data were summarized.

Safety Evaluations: Safety evaluations included clinical monitoring, assessment of adverse events (AEs), any abnormal objective test findings, vital signs (pulse, blood pressure), body mass index, 12-lead ECG monitoring, and assessments on Simpson-Angus Scale, Barnes Akathisia Scale, and Abnormal Involuntary Movement Scale.

Statistical Methods: Due to the small number of subjects enrolled in the study, no formal statistical analyses were performed for the efficacy endpoints. Safety data were summarized for all subjects who received at least 1 dose of study medication.

RESULTS:

Subject Disposition and Demography: A total of 29 subjects (15 in the ziprasidone group and 14 in the olanzapine group) were assigned to treatment and a total of 7 subjects completed treatment, (5 in the ziprasidone group and 2 in the olanzapine group). There were a total of 22 discontinuations, 10 of which were considered related to the study drug

(5 subjects in each group), and 12 of which were not considered related to the study drug (5 subjects in the ziprasidone group and 7 subjects in the olanzapine group).

Of 29 subjects randomized and treated in the study, all were analyzed for safety and 11/15 in the ziprasidone group and 14/14 in the olanzapine group had laboratory data analyzed in this study.

Subject disposition and subjects analyzed are summarized in Table 3.

Table 3. Subject Disposition and Subjects Analyzed

Number of Subjects	Ziprasidone	Olanzapine
Assigned to study treatment (n=29)		
Treated	15	14
Completed	5	2
Discontinued	10	12
Related to study drug	5	5
Adverse event	1	2
Lack of efficacy	3	3
Other	1	0
Not related to study drug	5	7
Adverse event	1	0
Other	1	4
Subject no longer willing to participate in study	2	2
Symptomatic deterioration	1	1
Analyzed for safety		
Adverse events	15	14
Laboratory data	11	14

Discontinuations occurring outside the lag period were attributed to the last study treatment received.
n = number of subjects.

A summary of subject demographics is presented in Table 4. Demographic characteristics were similar between the 2 treatment groups. Of the 29 subjects randomized and treated in this study, 14 subjects were male and 15 subjects were female. The mean age was 40.6 years in the ziprasidone group and 46.5 years in the olanzapine group. All subjects were White, with a mean weight of 77.7 kg in the ziprasidone group and 82.0 kg in the olanzapine group, and a mean height of 167.7 cm in the ziprasidone group and 169.2 cm in the olanzapine group.

Table 4. Demographic Characteristics

	Ziprasidone			Olanzapine		
	Male	**Female**	**Total**	**Male**	**Female**	**Total**
Number of subjects	5	10	15	9	5	14
Age (years)						
18-44	4	5	9	4	3	7
45-64	1	5	6	5	2	7
Mean	35.0	43.4	40.6	47.6	44.6	46.5
Range	20-48	23-59	20-59	22-64	32-57	22-64
Race						
White	5	10	15	9	5	14
Weight (kg)						
Mean	82.2	75.4	77.7	83.4	79.4	82.0
Range	69.0-100.0	55.0-92.0	55.0-100.0	62.0-105.2	52.0-121.0	52.0-121.0
Height (cm)						
Mean	174.2	164.5	167.7	172.4	163.5	169.2
Range	168.0-182.0	157.0-175.0	157.0-182.0	158.0-185.0	157.0-169.0	157.0-185.0

Safety Results: An overall summary of treatment-emergent AEs (TEAEs) is presented in Table 5.

Table 5. Summary of Treatment-Emergent Adverse Events (All Causalities)

	Ziprasidone n	**Olanzapine n**
Subjects evaluable for AEs	15	14
Number of AEs	16	36
Subjects with AEs	8	12
Subjects with SAEs	2	0
Subjects with severe AEs	4	1
Subjects discontinued due to AEs	2	2
Subjects with dose reduced or temporary discontinuation due to AEs	2	4

AEs and SAEs are not separated out. Included data up to 6 days after last dose of study drug.
Except for the number of adverse events subjects were counted only once per treatment in each row.
SAEs according to the Investigator's assessment.
MedDRA (v10.1) coding dictionary applied.
AEs = adverse events; MedDRA (v10.1) = Medical Dictionary for Regulatory Activities (version 10.1), n = number of subjects; SAEs = serious adverse events.

TEAEs (All Causalities): Table 6 presents TEAEs (all causalities) reported during the study. The most common TEAEs by body system in both treatment groups were nervous system disorders (4 subjects in each group) and psychiatric disorders (3 subjects in the ziprasidone group and 4 subjects in the olanzapine group). In the olanzapine group, other common TEAEs included gastrointestinal disorders, general disorders and administration site conditions, infections and infestations, and metabolism and nutrition disorders.

Table 6. Treatment-Emergent Adverse Events (All Causalities)

System Organ Class MedDRA (v10.1) Preferred Term	Ziprasidone (n=15)	Olanzapine (n=14)
Total preferred term events	16	36
Blood and lymphatic system disorders	0	1
Anaemia	0	1
Endocrine disorders	0	1
Hyperprolactinaemia	0	1
Eye disorders	1	0
Oculogyric crisis	1	0
Gastrointestinal disorders	1	4
Dry mouth	0	2
Flatulence	0	1
Gingivitis	0	1
Nausea	1	1
Vomiting	1	1
General disorders and administration site conditions	1	3
Disease progression	1	0
Fatigue	0	2
Pyrexia	0	1
Immune system disorders	0	1
Hypersensitivity	0	1
Infections and infestations	0	3
Nasopharyngitis	0	1
Pneumonia bacterial	0	1
Tonsillitis	0	1
Injury, poisoning and procedural complications	0	1
Joint dislocation	0	1
Investigations	1	1
Weight increased	1	1
Metabolism and nutrition disorders	0	3
Fluid retention	0	1
Hyperlipidaemia	0	1
Increased appetite	0	2
Nervous system disorders	4	4
Headache	1	1
Hypotonia	0	1
Somnolence	3	1
Tremor	1	3
Psychiatric disorders	3	4
Anxiety	1	1
Binge eating	0	1
Delusion	0	1
Depressed mood	1	0
Depression	0	1
Insomnia	2	0
Mania	1	0
Reproductive system and breast disorders	0	2
Breast enlargement	0	1
Sexual dysfunction	0	1
Respiratory, thoracic and mediastinal disorders	1	0
Laryngospasm	1	0
Skin and subcutaneous tissue disorders	0	2
Eczema	0	1
Hyperhidrosis	0	1
Surgical and medical procedures	0	1
Tooth extraction	0	1

Adverse events and serious adverse events are not separated out.
MedDRA (10.1) = Medical Dictionary for Regulatory Activities (version 10.1), n = number of subjects in each treatment group.

Severity of AEs: Most of the AEs were mild to moderate in intensity. Four TEAEs in the ziprasidone were considered severe in intensity and included the serious adverse events (SAEs) of oculogyric crisis and disease progression (worsening of disease under study), and the AEs of anxiety and mania. One TEAE of weight increased in the olanzapine group was considered severe in intensity.

SAEs: Two subjects in the ziprasidone group experienced SAEs, for which 1 subject was discontinued.

One subject experienced an SAE of worsening of disease under study that was ongoing from Day 22, which was not considered treatment-related and for which the subject was discontinued on Day 29. The SAE was considered severe in intensity, not related to the study drug, and no action was taken with the background drug. This subject also had an SAE of overdose on Day 30 after the study drug was discontinued. This event was considered by the Investigator to be not related to the study drug.

One subject experienced SAEs of severe oculogyric spasm and moderate laryngospasm on Day 2, which resolved on Day 3. These SAEs were considered related to the study drug and no action was taken with the study drug or the background drug. Treatment was given for the SAE of laryngospasm.

Death: No deaths were reported during the study.

Permanent Discontinuation From the Study Due to AEs: There were 4 discontinuations due to AEs, 3 of which were considered treatment-related (1 in the ziprasidone group and 2 in the olanzapine group) and 1 discontinuation in the ziprasidone group, due to an SAE, was not considered treatment-related.

The discontinuations due to AEs included 1 subject in the ziprasidone group who experienced severe anxiety (ongoing from Day 8) for which both the study drug and background drug were permanently discontinued. In the olanzapine group, 1 subject experienced severe increase in weight from Day 43 which resolved on Day 76, and 1 subject experienced moderate fatigue from Day 2 which resolved on Day 9. No action was taken with the background drug for either of these events.

Other Safety-Related Findings: Of the subjects with normal Baseline laboratory values, 5 subjects in the ziprasidone group and 9 subjects in the olanzapine group experienced laboratory abnormalities; however, none of these were considered clinically significant.

Efficacy analyses were not performed due to early termination of the study.

CONCLUSIONS: The objective of this study was to compare the efficacy and tolerability of ziprasidone versus olanzapine in the treatment of acute mania. This study was terminated early due to severe operational challenges due to difficulty in recruiting the target population. Due to the small number of subjects enrolled in the study, only listings were provided for the efficacy endpoints and no statistical analyses were performed. Ziprasidone therapy was generally well-tolerated with the majority of AEs being mild or moderate in severity, and

associated with the nervous system. The safety profiles of ziprasidone and olanzapine were similar, although there were limited data in this study.