# Synopsis – Study 13639A

| |
|---|
| **Title of Study**<br>A 6-month, randomised, double-blind, parallel-group, risperidone-controlled, fixed-dose study evaluating the safety and efficacy of zicronapine in patients with schizophrenia |
| **Investigators**<br>23 investigators at 23 sites in 5 countries<br>*Signatory investigator* – Pierre-Michel Llorca, MD, PhD, CHU Gabriel Montpied CMP, Clermont-Ferrand, France |
| **Study Sites**<br>23 sites – 8 in Czech Republic, 4 in Estonia, 1 in Finland, 4 in France, 6 in Poland |
| **Publications**<br>None (as of the date of this report) |
| **Study Period**<br>*First patient first visit* – 7 April 2011<br>*Last patient last visit* – 9 October 2012 |
| **Objectives**<br>• *Primary objective*:<br>– to assess the effect of zicronapine *versus* risperidone on metabolic parameters comprising body weight, body mass index (BMI), waist circumference, levels of fasting blood lipids and glucose during 6 months of treatment<br>• *Secondary objectives*:<br>– Safety objectives:<br>• to assess the overall safety and tolerability of zicronapine *versus* risperidone during 6 months of treatment<br>• to assess the potential of zicronapine *versus* risperidone to induce extrapyramidal symptoms using change from baseline to each assessment in the Simpson Angus Scale (SAS), Barnes Akathisia Rating Scale (BARS), and Abnormal Involuntary Movement Scale (AIMS) total scores<br>• to assess the effect of zicronapine *versus* risperidone on serum prolactin levels<br>• to assess the effect of zicronapine on suicidal ideation and behaviour using the Columbia Suicide-Severity Rating Scale (C-SSRS)<br>• to assess the effect of zicronapine *versus* risperidone on electrocardiogram (ECG) parameters<br>– Efficacy objectives:<br>• to assess the efficacy of zicronapine *versus* risperidone following 6 months of treatment using change from baseline in the Positive and Negative Syndrome Scale (PANSS) total score<br>• to assess the efficacy of zicronapine *versus* risperidone using change from baseline to each assessment in the PANSS total score and PANSS subscale scores (Positive Symptoms, Negative Symptoms, and General Psychopathology)<br>• to assess the efficacy of zicronapine *versus* risperidone by comparing the proportions of responders (using two definitions of response: ≥20% and ≥50% decrease from baseline in PANSS total score)<br>• to assess the efficacy of zicronapine *versus* risperidone on global improvement using change from baseline to each assessment in the Clinical Global Impression – Severity of Illness (CGI-S) score<br>• to assess the effect of zicronapine *versus* risperidone on personal and social functioning using the Personal and Social Performance Scale (PSP)<br>• to assess the effect of zicronapine *versus* risperidone on functioning using the Global Assessment of Functioning scale (GAF) |

**Objectives (continued)**

- to assess the effect of zicronapine *versus* risperidone on quality of life using the disease specific Schizophrenia Quality of Life scale (S-QoL)
- to assess the effect of zicronapine *versus* risperidone on the patients' satisfaction with treatment using the Medication Satisfaction Questionnaire (MSQ)

– Other objectives:

- to assess the pharmacokinetic properties of zicronapine and its major metabolite Lu AA22774 in patients with schizophrenia
- to explore biological parameters (including gene expression profiling, metabolomics, and genetic biomarker analysis) that may be associated with schizophrenia, the effect of treatment, and/or the treatment response

**Methodology**

- This was an interventional, multi-national, multi-site, randomised, double-blind, parallel-group, active-comparator, fixed-dose study.
- The study included the following periods:
  – Screening Period: period of up to 4 weeks between the Screening and Baseline Visits
  – Treatment Period: 6-month period between the Baseline and Completion Visits. The patients were randomised (1:1) at the Baseline Visit to receive either zicronapine 7.5 mg/day or risperidone 5 mg/day. The patient's previous antipsychotic medication and investigational medicinal product (IMP) were cross-tapered during the first week of this period.
  – Safety Follow-up Period: 8-week period after the Completion or Withdrawal Visit
- Efficacy and safety data were collected at weekly intervals during the first month of the Treatment Period, bi-weekly during the second month, and monthly thereafter until the Completion Visit.
- Safety Follow-up Visits were scheduled for 1, 4, and 8 weeks after completion of the study or after withdrawal from the study.
- Blood samples for drug concentration analysis of zicronapine and its major metabolite Lu AA22774 were collected at Weeks 8 and 24.

**Diagnosis and Main Inclusion Criteria**

Outpatients with a primary diagnosis of schizophrenia according to Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR™) criteria, who:

- had a PANSS total score ≥60 and ≤100 at screening and at baseline
- were ≥18 and ≤65 years of age

**Investigational Medicinal Products, Doses and Mode of Administration, Batch Numbers**

*zicronapine* – 5 mg/day; encapsulated tablets, orally; batch No. E07940-036E

*zicronapine* – 7.5 mg/day; encapsulated tablets, orally; batch No. E07940-037E

**Duration of Treatment**

6 months

**Reference Therapies, Doses and Mode of Administration, Batch Numbers**

*risperidone* – 2 mg/day; encapsulated tablets, orally; batch No. E07940-038E

*risperidone* – 4 mg/day; encapsulated tablets, orally; batch No. E07940-039E

*risperidone* – 5 mg/day; encapsulated tablets, orally; batch Nos. E07940-040E and E07940-055E

**Pharmacokinetic Assessments**

The analysis of pharmacokinetic parameters will be reported separately.

**Efficacy Assessments**

- Efficacy
  - PANSS total score
  - PANSS Positive Symptoms subscale score
  - PANSS Negative Symptoms subscale score
  - PANSS General Psychopathology subscale score
  - CGI-S score
- Health Outcome Assessments
  - Personal and Social Performance Scale (PSP) score
  - GAF score
  - Schizophrenia Quality of Life scale (S-QoL) score
  - S-QoL Subscale (Psychological Well-being, Self-esteem, Family Relationships, Relationships with Friends, Resilience, Physical Well-being, Autonomy, Sentimental Life) scores
  - MSQ score

**Safety Assessments**

- Metabolic parameters
  - weight
  - BMI
  - waist circumference
  - metabolic clinical laboratory parameters (fasting triglycerides, fasting total cholesterol, fasting low-density lipoprotein (LDL) cholesterol, fasting high density lipoprotein (HDL) cholesterol, fasting blood glucose, HbA1c)
- Adverse events (AEs)
- SAS score
- BARS score
- AIMS score
- Serum prolactin levels and other clinical safety laboratory tests
- C-SSRS score
- ECGs
- Vital signs

**Statistical Methodology**

- All analyses were exploratory with no adjustments for multiplicity.
- The following analysis sets were used:
  - *all-patients-randomised set* (APRS) – all randomised patients
  - *all-patients-treated set* (APTS) – all patients in the APRS who took at least one dose of double-blind IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline efficacy assessment
- Tabulation of disposition summary was based on the APRS, all withdrawal and safety analyses were based on the APTS, and efficacy analyses were based on the FAS.
- Disposition, exposure, demographics, and baseline characteristics (including safety and efficacy parameter values) were summarised by treatment group using counts and percentages or descriptive statistics and time-to-withdrawal (for any reason) analyses are presented using Nelson-Aalen plots of the cumulative hazard functions for withdrawal.
- The statistical tests of the efficacy endpoints were 2-sided tests with a 5% significance level. Descriptive statistics for all efficacy endpoints are presented by treatment group and visit using observed cases (OC) and, in addition, Week 24 data are presented using last observation carried forward (LOCF).

**Statistical Methodology (continued)**

- The comparisons of efficacy between treatments were based on estimates from a mixed model for repeated measurements (MMRM) including site, week, treatment-by-week, and baseline score-by-week as fixed effects and baseline score as covariate. An unstructured covariance structure was used to model the within-patient errors and the estimation method was a restricted-maximum-likelihood-based approach. The analysis was based on the "missing at random" assumption and performed using OC data.
- The robustness of the MMRM analysis results was assessed by performing supportive analysis of covariance (ANCOVA) with treatment and centre as fixed factors and score at baseline as covariate to estimate the mean change from baseline to Week 24 (OC and LOCF). The potential influence of sex as a covariate was investigated within the MMRM model by adding main terms for sex and interaction terms with treatment to the model.
- The PANSS and MSQ responder analyses (OC and LOCF) compared the response between the treatment groups using logistic regression (LREG) with treatment and site (country) as factors and the baseline score (only for PANSS responder analysis) as a covariate and presented odds ratios (zicronapine *versus* risperidone) with associated 95% confidence intervals. For time-points where no response was observed in one of the treatment groups, Fisher's exact test was used to compare the treatment groups.
- The changes from baseline in metabolic parameters, SAS, BARS (including both total and global scores), and AIMS (including global judgement scores), and $QT_{cF}$ interval were analysed using the same MMRM model that was used for the efficacy comparisons with the same model assumptions. For the other safety parameters, the absolute values and changes from baseline are presented using descriptive statistics.
- The proportion of patients meeting a potentially clinically significant (PCS) criterion (Tables 185 and 186) are presented by each, last, and any assessment (that is, any post-baseline assessment during the study) for metabolic parameter, vital sign, ECG parameter, and clinical laboratory liver values (alanine aminotransferase [ALAT], aspartate aminotransferase [ASAT], and bilirubin). These proportions were compared between the treatment groups at last and any assessment using Fisher's exact test. For weight and BMI, the odds ratio (zicronapine *versus* risperidone) with associated 95% confidence intervals for having a PCS value at last and any assessment were quantified using LREG with treatment and centre as factors and the baseline score as covariate. For other clinical laboratory parameters (all excluding ALAT, ASAT, and bilirubin), the proportion of patients meeting a PCS criterion are presented by each and last assessment. The proportion of patients with values ouside the reference range at each, last, and any assessment were included for vital signs and ECG parameters, and at each and last assessment for clinical laboratory parameters (including metabolic laboratory and liver parameters).
- The proportion of patients in the BMI categories *underweight*, *normal weight*, *overweight*, and *obese* (Table 187) are presented at each and last assessment. The proportions of patients who shifted (up or down) BMI category from baseline to last assessment was compared between treatment groups using Fisher's exact test. The proportion of patients in the lipid and blood glucose categories *low*, *normal*, *high*, and *borderline* (Table 188), were presented as for the BMI categories.
- The incidences of all adverse events were tabulated by primary system organ class (SOC) and preferred term. The incidences of *related* adverse events (*probably* and *possibly related*) were also summarised by preferred term and intensity.
- All adverse events were included in the data listings but, with the exception of an overview summary of all adverse events, only treatment-emergent adverse events (TEAEs), treatment-emergent serious adverse events (SAEs), and TEAEs leading to withdrawal were summarised.
- The incidence of TEAEs occurring in at least 5% of the patients in either treatment group were compared between the treatment groups using Fisher's exact test.
- C-SSRS data were coded and summarised by treatment and visit using the Columbia Classification Algorithm for Suicide Assessment (C-CASA) categories. The C-CASA categories were derived from the C-SSRS as outlined in Table 189. The number and percentage of patients in the C-CASA categories were summarised for the lifetime evaluation, at baseline, and overall during the study.

**Number of Patients Planned and Analysed**

- 160 patients were planned for enrolment: 80 in the zicronapine group and 80 in the risperidone group
- Patient disposition is tabulated below:

| | Risp 5 mg/day | | Zic 7.5 mg/day | | Total | |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | n | (%) |
| **Patients randomised** | 82 | | 78 | | 160 | |
| **Patients treated (all-patients-treated set [APTS]):** | 82 | | 78 | | 160 | |
| Patients completed | 47 | (57) | 44 | (56) | 91 | (57) |
| Patients withdrawn | 35 | (43) | 34 | (44) | 69 | (43) |
| **Primary reason for withdrawal:** | | | | | | |
| Adverse event(s) | 20 | (24) | 21 | (27) | 41 | (26) |
| Lack of efficacy | 3 | (4) | 6 | (8) | 9 | (6) |
| Withdrawal of consent | 8 | (10) | 4 | (5) | 12 | (8) |
| Other | 4 | (5) | 3 | (4) | 7 | (4) |
| **Analysis sets:** | | | | | | |
| APTS | 82 | | 78 | | 160 | |
| Full-analysis set (FAS) | 80 | | 78 | | 158 | |

Cross-reference: Tables 1 and 2
Withdrawals by all reasons are summarised in Table 3 and listed in Listing 1.

- Overall, the proportion of patients who withdrew from the study was similar in the two treatment groups; however, a greater proportion of the patients in the zicronapine group had lack of efficacy as the primary reason for withdrawal and a greater proportion of patients in the risperidone group had withdrawal of consent as the primary reason for withdrawal (Table 2 and Figures 1 and 2).

**Exposure**

- The median exposure to IMP was 24 weeks in both treatment groups and the total exposure was 25 patient-years in the zicronapine group and 26 patient-years in the risperidone group (Table 4). Compliance with IMP was >95% for >95% of the patients in each treatment group.

**Demography of Study Population**

- Patient demographics and key efficacy and safety values are summarised below.

| | | Risp | | Zic | | Total | |
|---|---|---|---|---|---|---|---|
| | | n | (%) | n | (%) | n | (%) |
| Patients randomised (APTS) | | 82 | (100) | 78 | (100) | 160 | (100) |
| Sex | Men | 45 | (55) | 38 | (49) | 83 | (52) |
| | Women | 37 | (45) | 40 | (51) | 77 | (48) |
| Race | White | 81 | (99) | 78 | (100) | 159 | (99) |
| | Other | 1 | (1) | 0 | (0) | 1 | (1) |
| Mean age (years) | | 42.9 | | 41.8 | | 42.4 | |
| Mean height (cm) | | 173 | | 172 | | 172 | |
| Mean weight (kg) | | 82.1 | | 82.1 | | 82.1 | |
| Mean BMI ($kg/m^2$) | | 27.5 | | 27.7 | | 27.6 | |
| Mean waist circumference (cm) | | 97 | | 96 | | 97 | |
| Mean triglycerides, fasting (mmol/L) | | 1.9 | | 1.6 | | 1.8 | |
| Mean cholesterol, fasting (mmol/L) | | 5.1 | | 5.2 | | 5.2 | |
| Mean LDL-cholesterol, fasting (mmol/L) | | 2.9 | | 3.1 | | 3.0 | |
| Mean HDL-cholesterol, fasting (mmol/L) | | 1.4 | | 1.3 | | 1.4 | |
| Mean glucose, fasting (mmol/L) | | 5.7 | | 5.3 | | 5.5 | |
| Mean HbA1c (%) | | 5.7 | | 5.6 | | 5.6 | |
| PANSS total score (FAS) | | 80 | | 80 | | 80 | |
| CGI-S score (FAS) | | 4.4 | | 4.4 | | 4.4 | |

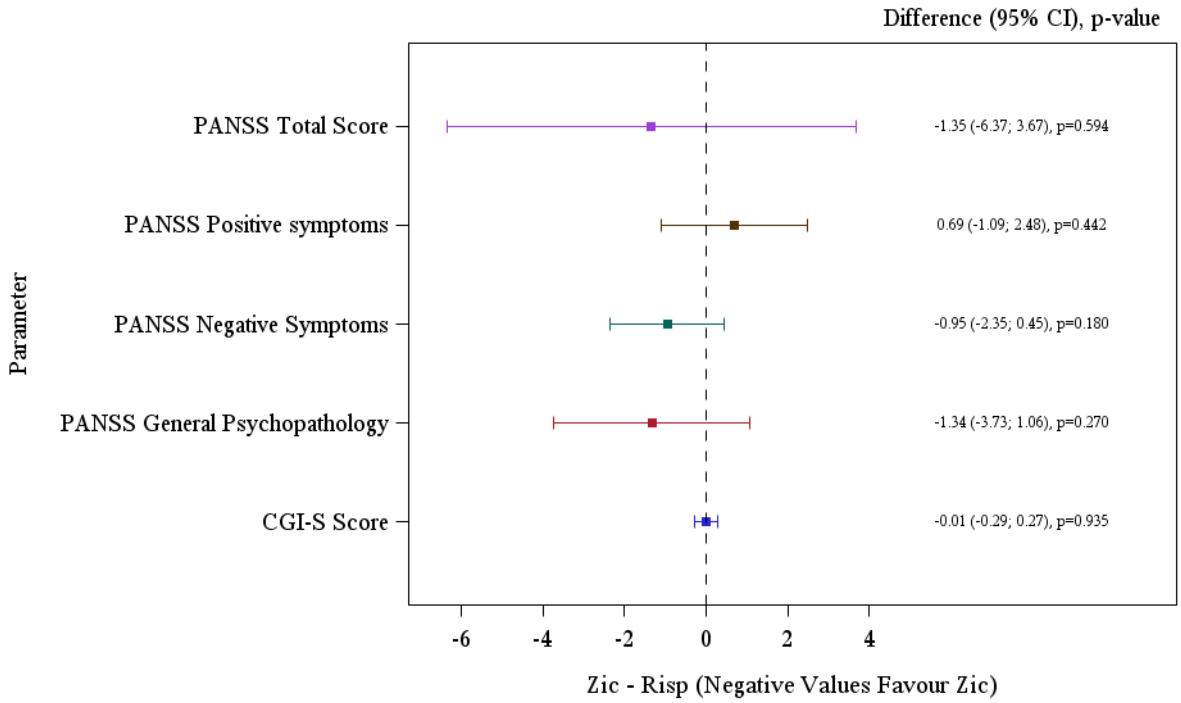
Cross-reference: Tables 5 to 8

**Demography of Study Population (continued)**

- The baseline demographics were similar in the two treatment groups, except for the ratio of men to women which was higher in the risperidone group.
- The mean baseline PANSS total score was 80 and the mean baseline CGI-S score was 4.4 in both treatment groups indicating that the patients were *moderately* to *markedly ill.*
- The mean baseline weight, BMI, mean waist circumference (MWC), and metabolic parameters were similar in the two treatment groups. The baseline metabolic parameters by category (*low, normal*, *borderline*, *high*) and baseline BMI by category (*underweight*, *normal weight*, *overweight*, *obese*) were similar in the two treatment groups except for the proportion of patients with *high* fasting triglycerides values which was smaller in the zicronapine group (12%) than in the risperidone group (24%) (Table 9).
- The mean baseline AIMS, BARS, and SAS scores were similar in the treatment groups and indicated that the majority of patients had none or minimal signs (median score ≤1) of drug-induced abnormal involuntary movements or other signs of parkinsonism (Table 10).
- The mean baseline health outcome assessment scores were similar in the two treatment groups (Table 11).
- The medical, neurological, and psychiatric history was similar in the treatment groups, except that a smaller proportion of the patients had *metabolism and nutrition disorders* in the zicronapine group (33%) than in the risperidone group (44%) (Table 12). All of these patients, except 2 in the risperidone group, had *metabolism and nutrition disorders* ongoing at baseline (Table 13). Most of the difference between the treatment groups in the proportion of patients with *metabolism and nutrition disorders* ongoing at baseline was due to medical histories of hypercholesterolaemia (2 patients in the zicronapine group and 8 patients in the risperidone group) and type 2 diabetes mellitus (1 patient in the zicronapine group and 4 patients in the risperidone group).
- The lifetime C-SSRS (C-CASA) scores shows that in each treatment group, approximately 85% of the patients had no history of suicidal ideation or behaviour and 9% had had suicidal ideation (Table 14). In total, 4 patients in the zicronapine group (5%) and 2 patients in the risperidone group (2%) had had a non-fatal suicide attempt. The baseline assessment shows that 4 patients in the zicronapine group (5%) and 2 patients in the risperidone group (2%) had a non-suicidal self-injurious behaviour between screening and baseline and 1 patient in the zicronapine group (1%) and 4 patients in the risperidone group (5%) had suicidal ideation between screening and baseline (Table 15).
- Medication stopped before first dose of IMP (Table 16), concomitant medication stopped after first dose of IMP (Table 18), concomitant medication started during the treatment period (Table 17), or medication started after the last dose of IMP (Table 19) were similar in the treatment groups. As the dose of the previous antipsychotic medication was changed during the cross-tritration period (first week of the treatment period), a large proportion of patients in each treatment group were recorded as “starting” antipsychotic medications during the treatment period, and consequently, antipsychotics (psycholeptics) were the most common medications taken in both treatment groups. Antipsychotics were disallowed after Day 7 (Table 184).

**Efficacy Results**

- The difference (zicronapine minus risperidone) between the treatment groups in the mean change (MMRM) from baseline in PANSS total and subscale scores is shown below with associated 95% confidence interval (CI):




Estimates from MMRM analyses
13639A FINAL ForestPlotsEfficacy01 08JUL2013:16:49:13 SADs Build Number: 159

| Efficacy Parameter | Risp 5mg/day n | Risp 5mg/day score | Zic 7.5mg/day n | Zic 7.5mg/day score | Difference score | Difference 95% CI [min; max] |
|---|---|---|---|---|---|---|
| **PANSS total** | | | | | | |
| Baseline | 80 | 79.7 | 78 | 80.0 | | |
| ΔWeek 24 (MMRM) | 48 | -10.9 | 45 | -12.3 | -1.3 | [-6.4; 3.7] |
| **PANSS Positive Symptoms** | | | | | | |
| Baseline | 80 | 17.0 | 78 | 16.9 | | |
| ΔWeek 24 (MMRM) | 48 | -2.9 | 45 | -2.2 | 0.7 | [-1.1; 2.5] |
| **PANSS Negative Symptoms** | | | | | | |
| Baseline | 80 | 23.8 | 78 | 24.0 | | |
| ΔWeek 24 (MMRM) | 48 | -3.6 | 45 | -4.5 | -1.0 | [-2.4; 0.4] |
| **PANSS General Psycopathology** | | | | | | |
| Baseline | 80 | 38.8 | 78 | 39.1 | | |
| ΔWeek 24 (MMRM) | 48 | -4.9 | 45 | -6.2 | -1.3 | [-3.7; 1.1] |
| **CGI-S** | | | | | | |
| Baseline | 80 | 4.4 | 78 | 4.4 | | |
| ΔWeek 24 (MMRM) | 48 | -0.6 | 45 | -0.6 | -0.0 | [-0.3; 0.3] |

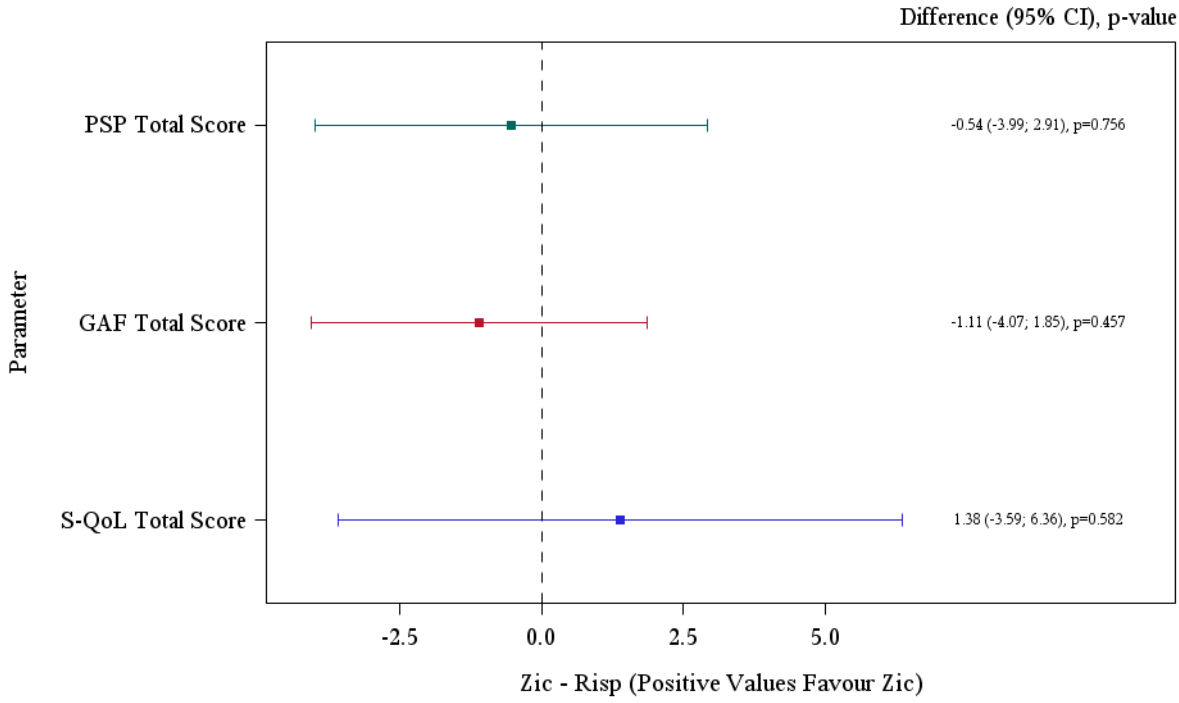
Cross-reference: Tables 20 to 29

- The mean change from baseline in PANSS total score showed a general decrease that was similar in the treatment groups throughout the study, except at Week 1, at which, the decrease from baseline was statistically significantly greater in the zicronapine group (Figure 3).
- The mean change from baseline in PANSS Positive Symptoms subscale score showed a general decrease that was similar in the treatment groups throughout the study (Figure 4).

**Efficacy Results (continued)**

- The mean change from baseline in PANSS Negative Symptoms subscale score showed a decrease that was similar in the treatment groups throughout the study except at Weeks 1 and 2, at which, the decrease from baseline was statistically significantly greater in the zicronapine group (Figure 5).
- The mean change from baseline in PANSS General Psychopathology subscale score showed a decrease that was similar in the treatment groups throughout the study (Figure 6).
- The mean change from baseline in CGI-S score showed a decrease that was similar in the treatment groups throughout the study (Figure 7).
- The ANCOVAs (using either OC or LOCF) of the change from baseline to Week 24 supported each of the corresponding MMRM analyses for all the efficacy parameters (Tables 30 to 34)
- The additional MMRM analysis with sex added to the model showed that the difference between the treatment groups in sex ratio did not impact the results of the MMRM analysis for any of the efficacy parameters (Tables 35 to 39).
- The PANSS responder analyses showed that, for all three criteria for response, similar proportions of patients in each treatment group responded to treatment (Tables 40 to 42 and Figures 8 to 10).

- The difference (zicronapine minus risperidone) between the treatment groups in the mean change (MMRM) from baseline in PSP, GAF, and S-QoL total scores is shown below with associated 95% CI:




Estimates from MMRM analyses
13639A FINAL ForestPlotsEfficacy03 08JUL2013:16:49:19 SADs Build Number: 159

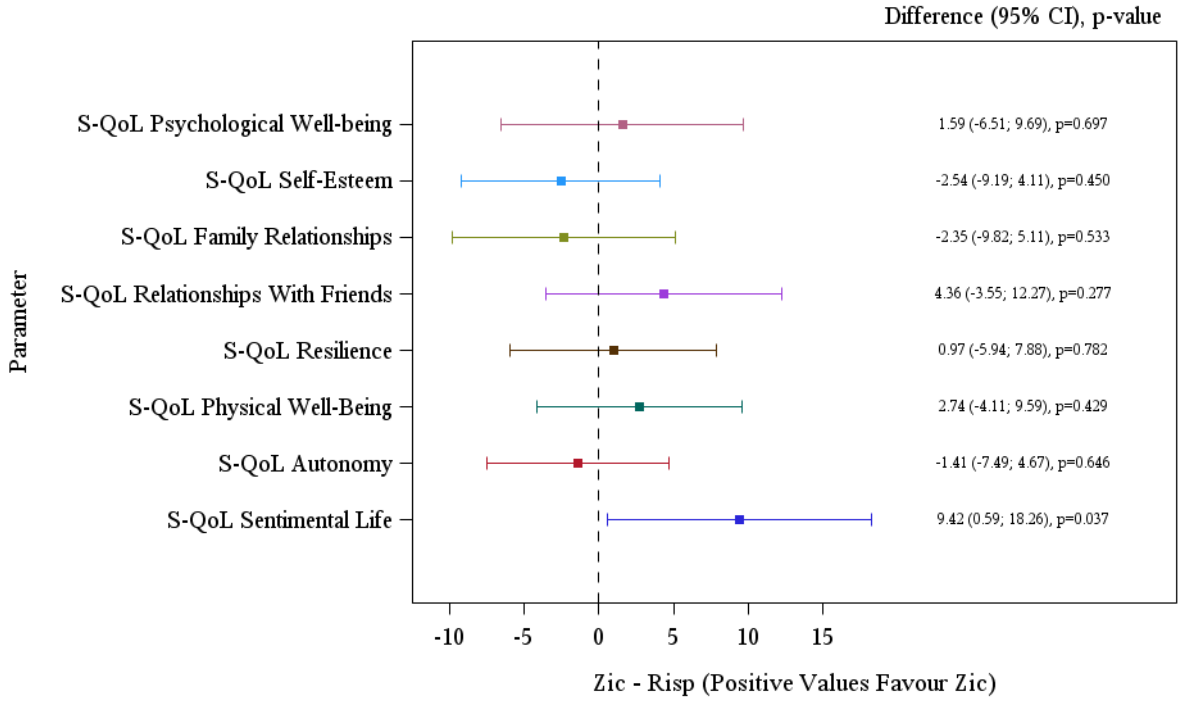
| Efficacy Parameter | Risp 5mg/day n | Risp 5mg/day score | Zic 7.5mg/day n | Zic 7.5mg/day score | Difference score | Difference 95% CI [min; max] |
|---|---|---|---|---|---|---|
| **PSP total** | | | | | | |
| Baseline | 80 | 51.1 | 78 | 53.0 | | |
| ΔWeek 24 (MMRM) | 51 | 4.0 | 47 | 3.5 | -0.5 | [-4.0; 2.9] |
| **GAF total** | | | | | | |
| Baseline | 80 | 49.9 | 78 | 51.1 | | |
| ΔWeek 24 (MMRM) | 51 | 5.0 | 47 | 3.9 | -1.1 | [-4.1; 1.8] |
| **S-QoL total** | | | | | | |
| Baseline | 78 | 44.1 | 78 | 48.6 | | |
| ΔWeek 24 (MMRM) | 50 | 1.8 | 47 | 3.2 | 1.4 | [-6.3; 6.4] |

Cross-reference: Tables 43 to 48

- The mean change from baseline in PSP, GAF, and S-Qol total scores was similar in the treatment groups.

**Health Outcome Results (continued)**

- The difference (zicronapine minus risperidone) between the treatment groups in the mean change (MMRM) from baseline in S-QoL Subscale scores is shown below with associated 95% CI:



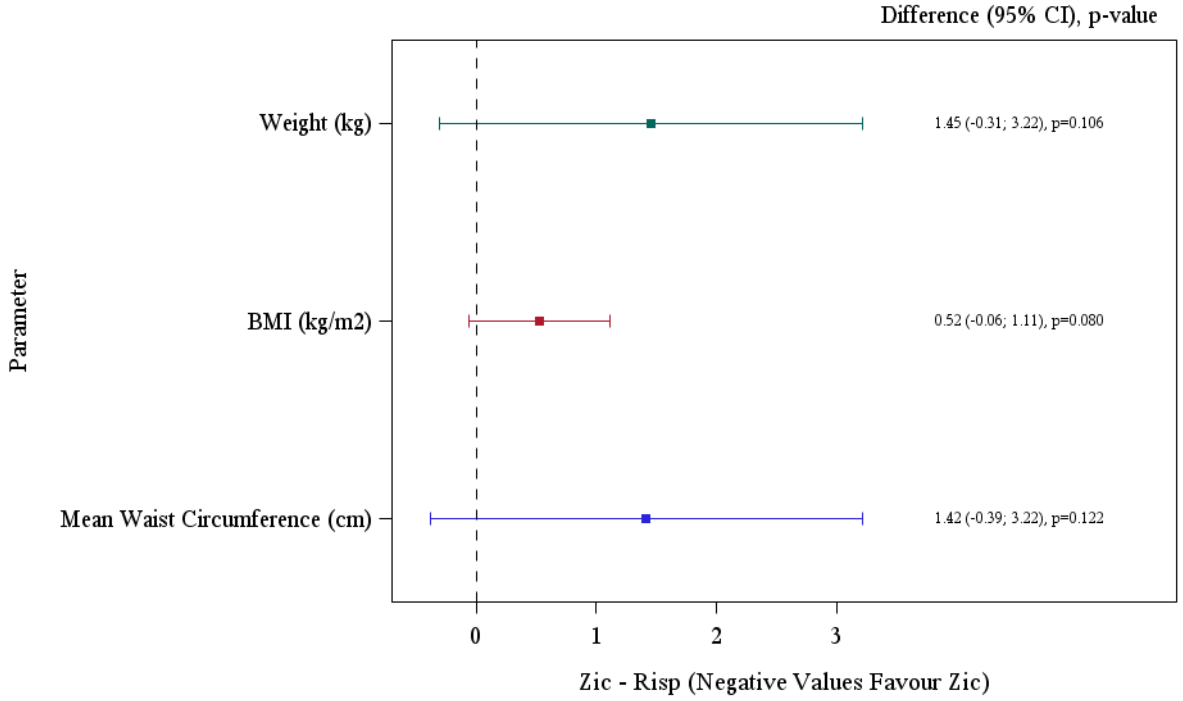

Estimates from MMRM analyses
13639A FINAL ForestPlotsEfficacy04 08JUL2013:16:49:22 SADs Build Number: 159

- Each of the mean changes from baseline in the S-QoL subscale scores were similar in the treatment groups, except for Sentimental Life, for which, the increase from baseline to Week 24 was statistically significantly greater in the zicronapine group than in the risperidone group (Tables 49 to 64).
- The ANCOVA (using OC or LOCF) of the change from baseline to Week 24 supported the MMRM analysis of the change from baseline in PSP, GAF, and S-Qol total scores and S-QoL Subscale scores (Tables 65 to 75).
- The additional MMRM analyses with sex added to the model showed that the difference between the treatment groups in sex ratio did not impact the results of the health outcome assessment MMRM analyses (Tables 76 to 86).
- The proportion of patients who responded to treatment as assessed by the MSQ ranged from 58% to 82% and was similar in the treatment groups (Table 87 and Figure 11).

**Safety Results**

***Metabolic Parameters***

- The difference (zicronapine minus risperidone) between the treatment groups in the mean change (MMRM) from baseline in weight, BMI, and MWC is shown below with associated 95% CI:




Estimates from MMRM analyses
13639A FINAL ForestPlotsMetabolic01 08JUL2013:16:49:25 SADs Build Number: 159

| Metabolic Parameter | Risp 5mg/day n | Risp 5mg/day score | Zic 7.5mg/day n | Zic 7.5mg/day score | Difference score | Difference 95% CI [min; max] |
|---|---|---|---|---|---|---|
| **Weight (kg)** | | | | | | |
| Baseline | 80 | 82.8 | 75 | 83.1 | | |
| ΔWeek 24 (MMRM) | 48 | 0.7 | 45 | 2.2 | 1.4 | [-0.3; 3.2] |
| **BMI (kg/m$^2$)** | | | | | | |
| Baseline | 80 | 27.8 | 75 | 27.9 | | |
| ΔWeek 24 (MMRM) | 48 | 0.2 | 45 | 0.7 | 0.5 | [-0.1; 1.1] |
| **MWC (cm)** | | | | | | |
| Baseline | 80 | 96.7 | 75 | 96.7 | | |
| ΔWeek 24 (MMRM) | 48 | -0.2 | 45 | 1.2 | 1.4 | [-0.4; 3.2] |

Cross-reference: Tables 88 to 93

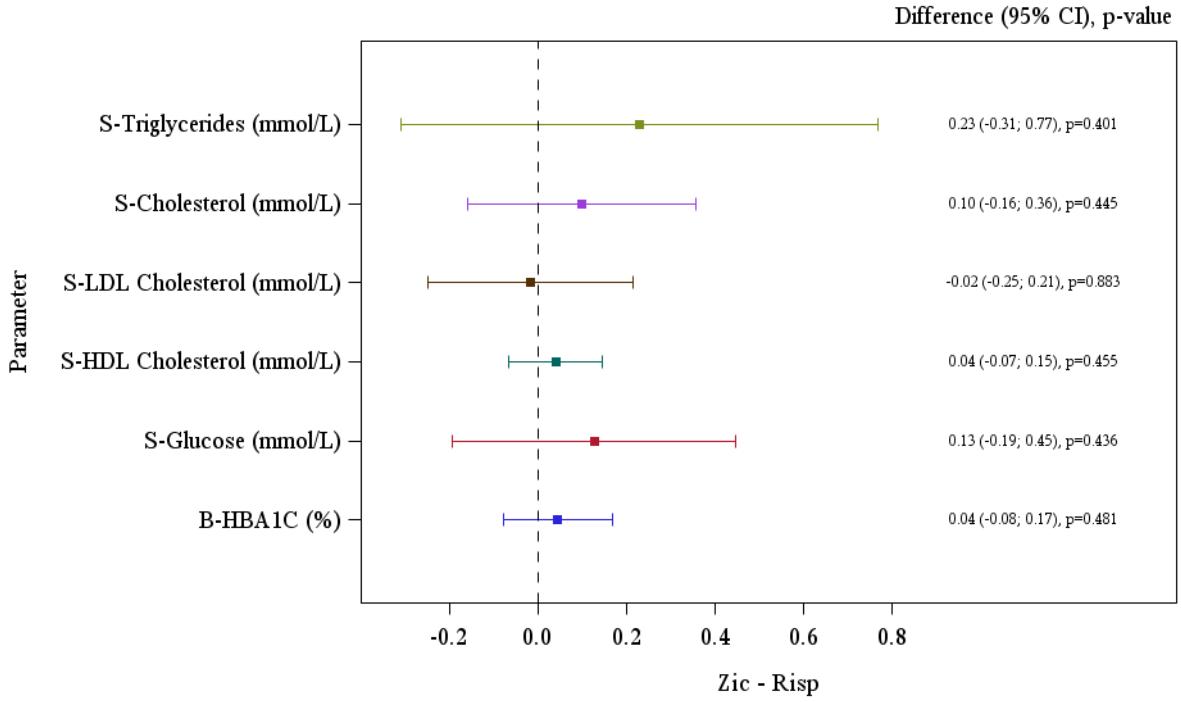
- Overall, the mean weight (and BMI) increased during the study in both treatment groups (Figures 12 and 13) and although the increase was higher in the zicronapine group, the difference between the treatment groups at Week 24 (1.4kg [0.5kg/m$^2$]) was not statistically significant.
- Overall, the mean MWC increased in the zicronapine group and was unchanged in the risperidone group (Figure 14). The difference between the treatment groups at Week 24 (1.4cm) was not statistically significant.

**Safety Results (continued)**

- The proportion of patients who had PCS changes in weight, BMI, and MWC values are summarised by visit (including last visit and any visit) in Tables 94, 95, and 96, respectively. The proportion of patients with a PCS increase in weight (and BMI) at Week 24 was higher in the in the zicronapine group (29%) than in the risperidone group (10%) and the proportion of patients with a PCS increase in MWC was similar in the treatment groups (Figures 15, 16, and 17). The LREG analysis of the proportion of patients with a PCS increase in weight (and BMI) showed that there was a statistically significant difference between the treatment groups at last visit (21% in the zicronapine group and 8% in the risperidone group) and at any visit (22% in the zicronapine group and 10% in the risperidone group) (Tables 97 and 98).
- The proportion of patients who shifted to a higher BMI category from baseline to last assessment was higher in the zicronapine group (14%) than in the risperidone group (8%) (Table 99). Approximately one-half of the patients in each treatment group who shifted to a higher BMI category from baseline to last assessment shifted from *normal weight* to *overweight* and the other half shifted from *overweight* to *obese* (Table 100).
- The ANCOVA (using OC or LOCF) of the change from baseline to Week 24 supported the MMRM analysis of change from baseline in weight, BMI, and MWC (Tables 101 to 103).
- The additional MMRM analyses with sex added to the model showed that the difference between the treatment groups in sex ratio did not impact the results of MMRM analyses of change from baseline in weight, BMI, or MWC (Tables 104, 105, and 106, respectively).

**Safety Results (continued)**

- The difference (zicronapine minus risperidone) between the treatment groups in the mean change (MMRM) from baseline in fasting metabolic laboratory parameters is shown below with associated 95% CI:




Estimates from MMRM analyses
13639A FINAL ForestPlotsMetabolic03 08JUL2013:16:49:28 SADs Build Number: 159

| Metabolic Parameter | Risp 5mg/day n | Risp 5mg/day score | Zic 7.5mg/day n | Zic 7.5mg/day score | Difference score | Difference 95% CI [min; max] |
|---|---|---|---|---|---|---|
| **Triglycerides (mmol/L)** | | | | | | |
| Baseline | 80 | 1.9 | 77 | 1.6 | | |
| ΔWeek 24 (MMRM) | 45 | -0.3 | 42 | -0.1 | 0.2 | [-0.3; 0.7] |
| **Cholesterol (mmol/L)** | | | | | | |
| Baseline | 80 | 5.1 | 77 | 5.2 | | |
| ΔWeek 24 (MMRM) | 45 | -0.2 | 42 | -0.1 | 0.1 | [-0.2; 0.4] |
| **LDL cholesterol (mmol/L)** | | | | | | |
| Baseline | 80 | 2.9 | 77 | 3.1 | | |
| ΔWeek 24 (MMRM) | 45 | -0.1 | 42 | -0.1 | 0.0 | [-0.2; 0.2] |
| **HDL cholesterol (mmol/L)** | | | | | | |
| Baseline | 80 | 1.4 | 77 | 1.3 | | |
| ΔWeek 24 (MMRM) | 45 | 0.0 | 42 | 0.0 | 0.0 | [-0.1; 0.2] |
| **Glucose (mmol/L)** | | | | | | |
| Baseline | 82 | 5.7 | 78 | 5.3 | | |
| ΔWeek 24 (MMRM) | 45 | 0.0 | 42 | 0.1 | 0.1 | [-0.2; 0.4] |
| **HbA1c (%)** | | | | | | |
| Baseline | 80 | 5.7 | 77 | 5.6 | | |
| ΔWeek 24 (MMRM) | 45 | 0.0 | 44 | 0.0 | 0.0 | [-0.1; 0.2] |

Cross-reference: Tables 107 to 118

- Overall, the mean changes in metabolic laboratory parameters during the study were small and clinically insignificant in both treatment groups (Figures 18 to 23).

**Safety Results (continued)**

- The proportion of patients who had PCS metabolic laboratory parameter values are summarised by visit (including last visit and any visit) in Tables 119 to 124. The proportion of patients with a PCS value was similar in the treatment groups for all metabolic laboratory parameters (Figures 24 to 29).
- The proportion of patients who shifted to a higher triglyceride category from baseline to last assessment was higher in the zicronapine group (12%) than in the risperidone group (6%), and the proportion of patients who shifted to a lower glucose category was lower in the zicronapine group (9%) than in the risperidone group (20%) (Table 125). For one-third (3 patients) of the patients who shifted to a higher triglyceride category from baseline to last assessment, the shifts were over two categories from *normal* to *high* (Table 126).
- The ANCOVA of the change from baseline to Week 24 supported the MMRM analysis of change from baseline in the metabolic laboratory parameters whether using OC or the LOCF method of imputing missing data (Tables 127 to 132).
- The additional MMRM analysis with sex added to the model showed that the difference between the treatment groups in sex ratios did not impact the MMRM analyses of change from baseline in metabolic laboratory parameters (Tables 133 to 137).
- All assessments for each metabolic parameter for which a patient had a PCS value are listed for all patients who had PCS metabolic parameter values in Listing 2, and all adverse events in these patients are listed in Listing 3.

***Adverse Events***

- The adverse event incidence is summarised below:

| | Risp | | Zic | |
|---|---|---|---|---|
| | n | (%) | n | (%) |
| Patients treated | 82 | | 78 | |
| Patients who died | 0 | (0.0) | 0 | (0.0) |
| Patients with serious AEs (SAEs) | 5 | (6.1) | 10 | (12.8) |
| Patients with AEs leading to withdrawal | 20 | (24.4) | 21 | (26.9) |
| Patients with AEs | 62 | (75.6) | 62 | (79.5) |
| Total number of AEs | 247 | | 217 | |

Cross-reference: Table 138

- All pre-treatment adverse events are in Listing 4 and all TEAEs are in Listing 5. There were no pre-treatment SAEs (Listing 4).
- The proportion of patients with TEAEs was approximately 77% in both treatment groups.

**Safety Results (continued)**

- The most common (≥5% of patients in either treatment group) are summarised below:

| Preferred Term (MedDRA Version 15) | Risp n | Risp (%) | Zic n | Zic (%) |
|---|---|---|---|---|
| Patients treated | 82 | | 78 | |
| Weight Increased | 7 | (8.5) | 14 | (17.9) |
| Anxiety | 9 | (11.0) | 11 | (14.1) |
| Insomnia | 14 | (17.1) | 10 | (12.8) |
| Schizophrenia | 5 | (6.1) | 7 | (9.0) |
| Irritability | 4 | (4.9) | 6 | (7.7) |
| Somnolence | 13 | (15.9) | 6 | (7.7) |
| Hypercholesterolaemia | 2 | (2.4) | 5 | (6.4) |
| Headache | 6 | (7.3) | 5 | (6.4) |
| Postural Orthostatic Tachycardia Syndrome | 6 | (7.3) | 5 | (6.4) |
| Nausea | 3 | (3.7) | 5 | (6.4) |
| Hypomania | 2 | (2.4) | 4 | (5.1) |
| Agitation | 2 | (2.4) | 4 | (5.1) |
| Diarrhoea | 4 | (4.9) | 4 | (5.1) |
| Nasopharyngitis | 6 | (7.3) | 4 | (5.1) |
| Tremor | 5 | (6.1) | 3 | (3.8) |
| Akathisia | 10 | (12.2) | 2 | (2.6) |
| Dizziness | 5 | (6.1) | 2 | (2.6) |
| Asthenia | 6 | (7.3) | 2 | (2.6) |

All TEAEs are summarised by preferred term in Table 139

Cross reference: Table 140

- The most common (incidence >10%) adverse events in the zicronapine group were weight increased, anxiety, and insomnia, and in the risperidone group the most common adverse events were insomnia, somnolence, akathisia, and anxiety.
- The SOCs with the highest incidence (>20%) of adverse events in either treatment group were (zicronapine *versus* risperidone): *psychiatric disorders* (54% *versus* 39%), *nervous system disorders* (27% *versus* 44%), and *investigations* (24% *versus* 15%) (Table 141). The higher incidence of *psychiatric disorders* in the zicronapine group reflected a general difference across preferred terms within this SOC. This pattern was also reflected in the reasons for withdrawal: more patients in the zicronapine group [17 patients] than in the risperidone group [9 patients] had lack of efficacy as a reason for withdrawal. The higher incidence of *investigations* in the zicronapine group was mainly due weight increased (9% *versus* 18%), and the higher incidence of *nervous system disorders* in the risperidone group was mainly due to the adverse events somnolence (8% *versus* 16%) and akathisia (3% *versus* 12%).
- The incidence of treatment-emergent SAEs was higher in the zicronapine group (13%) than in the risperidone group (6%) (Table 142). The vast majority of patients who had SAEs had SAEs in the SOC *psychiatric disorders* (9 of 10 in the zicronapine group and 4 of 5 in the risperidone group) (Table 143). All treatment-emergent SAEs are listed in Listing 6 (for further details, see *Narratives of Serious Adverse Events*).
- Approximately 25% of the patients in each treatment group had adverse events leading to withdrawal (Table 144). Schizophrenia (preferred term) was the only adverse event leading to withdrawal in >2 patients in both treatment groups (6 in the zicronapine group and 3 in the risperidone group) and psychiatric disorders was the SOC with the highest incidence of adverse events leading to withdrawal in both treatment groups (23% *versus* 15%) (Table 145). All adverse events leading to withdrawal are listed in Listing 7.
- The incidence of *severe* TEAEs (approximately 12%) was similar in the treatment groups (Table 146). The incidence of *moderate* TEAEs was higher in the zicronapine group (51%) than in the risperidone group (34%), whereas the incidence of *mild* TEAEs was lower in the zicronapine group (15%) than in the risperidone group (29%). The incidence of TEAEs within each intensity category was similar in the treatment groups for TEAEs considered *related* to IMP by the investigator (approximately 25% had *mild*, *related* TEAEs, 35% had *moderate*, *related* TEAEs, and 8% had *severe*, *related* TEAEs) (Table 147).

**Safety Results (continued)**

***SAS, BARS, and AIMS***

- The mean SAS total score (Table 148) and adjusted mean change from baseline in SAS total score (Table 149) showed a decrease in the zicronapine group (-0.90 points at Week 24) and no clinically significant change in the risperidone group (-0.39 points at Week 24) (Figure 31).
- The mean BARS total and global scores (Tables 150 and 151, respectively) and adjusted mean change from baseline in BARS total score (Tables 152 and 153) showed no clinically relevant change in either of the treatments groups (Figures 32 and 33).
- The mean AIMS total score (Table 154) and adjusted mean change from baseline in AIMS total score (Table 155) showed a decrease in the zicronapine group (-0.37 points at Week 24) and no clinically relevant change in the risperidone group (-0.04 points at Week 24) (Figure 34). The mean AIMS Global Judgement scores (Tables 156 to 160) and adjusted mean change from baseline in AIMS Global Judgement scores (Table 157 to 161) showed similar changes in Incapacitation-due-to-Abnormal-Movement score in the treatment groups, and a decrease in the zicronapine group *versus* no change in the risperidone group for Severity-of-Abnormal-Movement score and Patient's-Awareness-of-Abnormal-Movement score (Figures 35 to 37).

***Serum Prolactin Levels and Other Clinical Safety Laboratory Parameters***

- The prolactin values are summarised by each and last assessment in Table 162 and the change from baseline to each and last assessment are summarised in Table 163. All the mean prolactin values were within the reference range at each assessment. The mean changes from baseline to each assessment showed a decrease of approximately 30% of the baseline value in the zicronapine group and an increase of approximately 300% of the baseline value in the risperidone group.
- The clinical safety laboratory values are summarised by each and last assessment in Table 164 and the change from baseline to each and last assessment are summarised in Table 165 (non-fasting metabolic laboratory paramter values [including values of unknown fasting status] and changes from baseline are summarised in Tables 166 and 167). All the mean clinical safety laboratory values were within the reference ranges at each assessment. The mean changes from baseline to each assessment were clinically insignificant and similar in the treatment groups for all the clinical safety laboratory parameters.
- The proportion of patients who had PCS or out-of-reference-range clinical safety laboratory values are summarised by each and last assessment in Table 168. The proportion of patients with a PCS clinical safety laboratory parameter value was small (<5%) and similar in the treatment groups for all clinical safety laboratory parameters except for prolactin. At each sceduled assessment, the proportion of patients with a PCS high prolactin value was <3% in the zicronapine group and 34% to 39% in the risperidone group, and the proportion of patients with a prolactin value above the reference range was 4% to 9% in the zicronapine group and 81% to 84% in the risperidone group. There was a higher proportion of patients with ALAT values above the reference range at each assessment in the zicronapine group but the values were generally not clinically relevant. The comparisons of proportions of patients with PCS liver parameter values using Fisher's exact test showed no statistically significant difference between the treatment groups (Table 169).
- The urinalysis parameters are summarised in Table 170. The majority (>75%) of results were negative whith no relevant chamge during the study.
- All assessments for each safety laboratory parameter for which a patient had a PCS value are listed for all patients who had PCS safety laboratory parameter values in Listing 8, and all adverse events in these patients are listed in Listing 9.

***C-SSRS (C-CASA)***

- During the study, 1 patient in the zicronapine group had a non-fatal suicide attempt and 4 patients in each treatment group had suicidal ideation. Four patients in the zicronapine group and 2 patients in the risperidone group had non-suicidal self-injurious behaviour (Table 171).

**Safety Results (continued)**

***ECGs***

- The ECG parameter values are summarised by each and last assessment in Table 172 and the change from baseline to each and last assessment are summarised in Table 173. All the mean ECG parameter values were within the reference ranges at each assessment. The mean changes from baseline to each assessment were clinically insignificant and similar in the treatment groups for all the ECG parameters.
- The MMRM analysis of mean change from baseline in $QT_{cF}$ interval showed no clinically significant difference between the zicronapine and risperidone groups (-0.8 and -1.9 ms at Week 24, respectively) (Table 174 and Figure 38). The proportion of patients who had a change in $QT_{cF}$ interval >30 ms and >60 ms and a $QT_{cF}$ interval >450 ms, >480 ms, and >500 ms were similar in the treatment groups for each criterion at each assessment (including last visit and any visit) (Table 175).
- The proportion of patients who had PCS ECG parameter values are summarised by assessment (including last and any assessment) in Table 176. The proportion of patients with a PCS ECG parameter value was similar in the treatment groups for all ECG parameters.
- The proportion of patients who had ECG parameter values outside the reference range are summarised by each and last assessment in Table 177 and by any visit in Table 178. The proportions were generally low and there were no relevant differences between the treatment groups.
- All assessments for each ECG parameter for which a patient had a PCS value are listed for all patients who had a PCS ECG parameter value in Listing 10, and all adverse events in these patients are listed in Listing 11.

***Vital Signs***

- The vital sign values are summarised by each and last visit in Table 179 and the change from baseline to each and last visit are summarised in Table 180. All the mean vital sign values were within the reference ranges at each assessment. The mean changes from baseline to each visit were clinically insignificant and similar in the treatment groups for all the vital signs parameters except for minor differences between the treatment groups in supine diastolic and systolic blood pressure and supine pulse rate:
  - The supine diastolic blood pressure generally increased 1 to 4 mmgHg in the zicronapine group whereas it decreased 1 to 4 mmHg in the risperidone group (the difference between the treatment groups ranged from 1 to 7 mmgHg).
  - The supine systolic blood pressure generally increased 1 to 5 mmHg in the zicronapine group whereas it generally decreased 1 to 3 mmHg in the risperidone group (the difference between the treatment groups ranged from 1 to 7 mmHg).
  - The supine pulse rate generally decreased 1 to 3 bpm in the zicronapine group whereas it increased 1 to 6 beats per minute (bpm) in the risperidone group (the difference between the treatment groups ranged from 3 to 7 bpm).
- The proportion of patients who had PCS vital sign values are summarised by assessment (including last visit and any visit) in Table 181. The proportion of patients with a PCS vital sign value was similar in the treatment groups for all parameters except for PCS high orthostatic pulse rate which was generally lower in the zicronapine group (31% at any visit) than in the risperidone group (45% at any visit). The proportion of patients who had vital sign values outside the reference range are summarised by each and last visit in Table 182 and by any visit in Table 183. The proportion of patients with an orthostatic pulse rate above the reference range was generally lower in the zicronapine group (21% at last visit) than in the risperidone group (28% at last visit). The proportion of patients with supine pulse rate above the reference at any visit was also lower in the zicronapine group (8%) than in the risperidone group (16%) whereas for supine systolic blood pressure, a lower proportion of patients in the zicronapine group had values below the reference range at any visit (21% *versus* 31%) and a higher proportion of patients in the zicronapine group had values above the reference range at any visit (29% *versus* 21%).
- All assessments for each vital sign parameter for which a patient had a PCS value are listed for all patients who had PCS vital sign values in Listing 12, and all adverse events in these patients are listed in Listing 13.

**Conclusions**

- This study showed that zicronapine was safe and well tolerated.
- The weight (and BMI) increased during the study in both the zicronapine and risperidone group (2.2 and 0.7 kg, respectively). The mean waist circumference increased 1.2 cm in the zicronapine group and decreased 0.2 cm in the risperidone group.
- The overall incidence of adverse events was similar in the treatment groups but the pattern of adverse events differed. The most common (>10%) adverse events in the zicronapine group were weight increased (18%), anxiety (14%), and insomnia (13%), and the most common adverse events in the risperidone group were insomnia (17%), somnolence (16%), akathisia (12%), and anxiety (11%).
- The mean changes from baseline during the study in fasting metabolic laboratory parameter (blood lipids and glucose, and HbA1c), and ECG parameter values were small and clinically insignificant in both treatment groups. The prolactin values decreased approximately 30% below the baseline level in the zicronapine group and increased approximately 300% above the baseline level in the risperidone group.
- Zicronapine and risperidone treatments did not induce extrapyramidal side effects as assessed using SAS, BARS, or AIMS, or suicidality as assessed using C-SSRS and applying the C-CASA.
- Overall, there were similar improvements in the efficacy and health outcome parameters in the treatment groups.

**Date of the Report**

9 July 2013

This study was conducted in compliance with the principles of *Good Clinical Practice*.