Synopsis – Study 12396A

Title of Study A randomised, double-blind, parallel-group, active-controlled, flexible-dose study exploring the efficacy and safety of 12 weeks treatment with Lu 31-130 in patients with schizophrenia
Investigators 21 investigators at 21 centres in 9 countries *Signatory investigator* – Michael Davidson, Professor, MD, Department of Psychiatry, Tel Aviv University, Tel Aviv, Israel
Study Centres 21 centres – 6 in the Czech Republic, 3 in France, 1 in Hong Kong, 2 in Indonesia, 2 in Israel, 2 in the Philippines, 1 in Poland, 2 in Spain, 2 in Thailand
Publications None (as of the date of this report)
Study Period *First patient first visit* – 29 August 2008 *Last patient last visit* – 27 October 2009
Objectives • to explore the efficacy of flexible doses of zicronapine (5 or 7 mg/day) compared to olanzapine (10 or 15 mg/day) following 12 weeks of treatment by means of change in Positive and Negative Syndrome Scale (PANSS) total score in patients with schizophrenia • to explore the effect of flexible doses of zicronapine (5 or 7 mg/day) on neurocognitive performance compared to olanzapine (10 or 15 mg/day) using the Brief Assessment of Cognition in Schizophrenia (BACS) battery • to explore the effect of flexible doses of zicronapine (5 or 7 mg/day) on depressive symptoms compared to olanzapine (10 or 15 mg/day) using the Calgary Depression Scale for Schizophrenia (CDSS) • to explore the effect of flexible doses of zicronapine (5 or 7 mg/day) on body weight compared to olanzapine (10 or 15 mg/day) • to explore the effect of flexible doses of zicronapine (5 or 7 mg/day) on body mass index (BMI), waist circumference, and laboratory variables including serum concentrations of total cholesterol, LDL-cholesterol, VLDL-cholesterol, HDL-cholesterol, triglycerides, HbA_{1c} [not assessed post-baseline], and fasting glucose compared to olanzapine (10 or 15 mg/day) • to explore the effect of flexible doses of zicronapine (5 or 7 mg/day) on the serum concentrations of ALT and AST compared to olanzapine (10 or 15 mg/day)

Methodology

- This was an exploratory, multi-national, multi-centre, randomised, double-blind, parallel-group, active-comparator (olanzapine), flexible-dose study.
- The patients were recruited by psychiatrists from in- and out-patient clinics.
- The study was composed of four sequential periods:
  - a screening period of at most 4 weeks
  - a 3-week double-blind, fixed-dose period
  - a 9-week double-blind, flexible-dose period
  - a 4-week follow-up period, with a safety assessment scheduled 1 week after last investigational medicinal product (IMP) intake, and a telephone call scheduled 4 weeks after last IMP intake
- For compliance and safety reasons, it was required that the patients be hospitalised from Screening Visit 2 until at least 2 weeks after the Baseline Visit.
- Efficacy and safety data were collected at weekly intervals throughout the Treatment Period (the 3-week fixed-dose period plus the 9-week flexible-dose period).
- At predetermined time points, blood samples were drawn for drug concentration analysis of zicronapine and its major metabolite Lu AA22774. The pharmacokinetic data are to be reported separately.

Number of Patients Planned and Analysed

- Initially, 120 patients were planned for enrolment, however, to evaluate the results from this study concomitantly with the results from another recently finalised phase II study, Study 11613A, the study was terminated.
- Patient disposition is tabulated below:

	Zicronapine		Olanzapine		Total	
	n	(%)	n	(%)	n	(%)
Patients randomised	47		46		93	
Patients treated (all-patients-treated set [APTS]):	47		46		93	
Patients completed	38	(80.9)	38	(82.6)	76	(81.7)
Patients withdrawn	9	(19.1)	8	(17.4)	17	(18.3)
Primary reason for withdrawal:						
Adverse event(s)	5	(10.6)	3	(6.5)	8	(8.6)
Protocol violation	0	(0.0)	1	(2.2)	1	(1.1)
Withdrawal of consent	4	(8.5)	4	(8.7)	8	(8.6)
Analysis sets:						
APTS	47		46		93	
Full-analysis set (FAS)	47		46		93	
Per-protocol set (PPS)	33		38		71	

n = number of patients

Diagnosis and Main Inclusion Criteria

Patients with a primary diagnosis of schizophrenia according to DSM-IV-TR™ criteria, who:

- had a PANSS total score ≥70 and ≤120 at Screening Visit 2 and at Baseline
- had a Clinical Global Impression – Severity of Illness (CGI-S) score ≥4 (*moderately ill*) at Screening 1, at Screening 2, and at Baseline
- had a score ≤4 (*moderate*) on the following PANSS items: P7 (*hostility*) and G8 (*uncooperativeness*)
- were ≥18 and ≤65 years of age
- were willing to be hospitalised from Screening 2 until at least 2 weeks after Baseline

Investigational Medicinal Product, Doses and Mode of Administration, Batch Numbers

Zicronapine (Lu 31-130) – 5 mg/day for the first 3 weeks, then 5 or 7 mg/day; encapsulated tablets, orally; batch Nos. PD1651/R197-08, PD1760/R239-08 (5 mg encapsulated tablet); PD1696/R198-08, PD1761/R240-08, PD1761/R274-08 (7 mg encapsulated tablet)

Duration of Treatment 12 weeks
Reference Therapy, Doses and Mode of Administration, Batch Numbers *Olanzapine* – 10 mg/day for the first 3 weeks, then 10 or 15 mg/day; encapsulated tablets, orally; batch Nos. A456618/R199-08, A456618/R241-08 (10 mg encapsulated tablet); A408052/R200-08, A513966/R242-08 (15 mg encapsulated tablet)
Efficacy Assessments • PANSS total score • PANSS Positive Symptoms subscale score • PANSS Negative Symptoms subscale score • PANSS General Psychopathology subscale score • PANSS Cognition subscale score • PANSS Depression subscale score • Proportion of patients with a ≥20%, ≥30%, ≥40%, or ≥50% reduction in PANSS total score from Baseline (PANSS responders) • CGI-S score • Clinical Global Impression – Global Improvement (CGI-I) score • CDSS total score • BACS individual test scores
Safety Assessments Adverse events (AEs), clinical safety laboratory tests, abnormal movement rating scales (Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BAS], Abnormal Involuntary Movements Scale [AIMS]), vital signs, weight, BMI, waist circumference, physical and neurological examinations, and electrocardiograms (ECGs)

Statistical Methodology

- The following analysis sets were used:
  - *all-patients-treated set* (APTS) – all randomised patients who took at least one dose of IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had a valid baseline assessment and at least one valid post-baseline assessment of the PANSS total score
- *per-protocol set* (PPS) – all patients in the FAS who:
  - had no major protocol deviations
  - received IMP up to and including the Week 8 visit
  - had at least one valid assessment of the PANSS total score at or after the Week 8 visit
  - did not take disallowed concomitant medication judged to interfere with the treatment response during the Treatment Period
  - had a compliance rate of at least 80% until completion or withdrawal
- All efficacy analyses were conducted on the FAS and all safety analyses were conducted on the APTS. Unless otherwise specified, efficacy analyses were done using both the last observation carried forward (LOCF) and the observed cases (OC) principles of data imputation.
- *Efficacy analyses* – The changes from baseline to each visit were analysed using a two-sided analysis of covariance (ANCOVA) at the 5% level of significance using treatment group and centre as factors and the baseline score as a covariate for the following variables: PANSS total score, PANSS positive subscale score, PANSS negative subscale score, PANSS general psychopathology subscale score, PANSS depressive subscale score, PANSS cognitive subscale score, and CGI-S score. The CGI-I score was analysed using a similar ANCOVA model with the baseline CGI-S score as a covariate. The PANSS responder rates were analysed using the χ^2 test.
- *Safety analyses* – The incidences of individual adverse events occurring in ≥5% of the patients and the incidence of overall withdrawal were compared between groups using Fisher's exact test. The changes from baseline to each assessment in the abnormal movement rating scales, based on the SAS, BAS, and AIMS scores, were summarised using descriptive techniques. Treatment group differences in SAS, BAS, and AIMS scores were analysed using ANCOVA with treatment and centre as factors and the baseline total score as a covariate, and the shifts in SAS status were tabulated. Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, BMI, waist circumference, and ECG parameters were summarised using descriptive statistics. Changes in weight, BMI, and waist circumference were analysed using ANCOVA to assess treatment differences. Values outside the reference range, as well as potentially clinically significant (PCS) values, were flagged and tabulated.

Demography of Study Population

- There were no clinically significant differences between the zicronapine group and the olanzapine group with respect to age, sex, or race in the APTS. In both treatment groups, the ratio of men to women was approximately 2:1, the mean age was approximately 37 years (no patient was over 63 years), and there were approximately equal proportions of Caucasians and Asians (53% and 47%, respectively).
- The mean baseline PANSS total score was 92 in the zicronapine group and 95 in the olanzapine group, indicating that the patients had *moderate to severe* schizophrenia.

Efficacy Results

- The efficacy results are summarised below:

Efficacy variable	Zicronapine			Olanzapine		
	n	Mean	(SE)[a]	n	Mean	(SE)[a]
PANSS total score						
Baseline	47	91.5	(12.1)	46	95.1	(11.6)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-18.4	(2.8)	46	-20.8	(2.8)
Δ Week 12 (FAS, OC, ANCOVA)	38	-25.0	(2.8)	38	-27.0	(2.8)
Δ Week 12 (PPS, LOCF, ANCOVA)	33	-22.3	(3.3)	38	-26.3	(2.9)
PANSS Positive Symptoms subscale score						
Baseline	47	20.1	(4.6)	46	21.0	(5.0)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-3.8	(0.9)	46	-5.5	(0.9)
PANSS Negative Symptoms subscale score						
Baseline	47	25.8	(6.6)	46	27.7	(5.3)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-5.8	(0.8)	46	-5.2	(0.8)
PANSS General Psychopathology subscale score						
Baseline	47	45.6	(7.3)	46	46.4	(6.7)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-9.0	(1.4)	46	-10.1	(1.4)
PANSS Cognitive subscale score						
Baseline	47	23.7	(4.4)	46	25.1	(4.5)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-4.4	(0.8)	46	-4.9	(0.8)
PANSS Depression subscale score						
Baseline	47	16.2	(3.8)	46	15.6	(4.4)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-4.6	(0.5)	46	-4.5	(0.5)
CGI-S score						
Baseline	47	4.6	(0.7)	46	4.9	(0.6)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-1.0	(0.2)	46	-1.1	(0.2)
CGI-I score						
Week 12 (FAS, LOCF, ANCOVA)	47	3.0	(0.2)	46	2.8	(0.2)
CDSS total score						
Baseline	47	3.2	(3.9)	46	2.3	(3.1)
Δ Week 12 (FAS, LOCF, ANCOVA)	47	-1.4	(0.3)	46	-1.3	(0.2)
Responders at Week 12 (FAS, LOCF, χ^2)[b]:						
≥20% reduction in PANSS total score	47	27	(57.5%)	46	29	(63.0%)
≥30% reduction in PANSS total score	47	16	(34.0%)	46	16	(34.8%)
≥40% reduction in PANSS total score	47	10	(21.3%)	46	10	(21.7%)
≥50% reduction in PANSS total score	47	7	(14.9%)	46	4	(8.7%)

a Baseline values are mean (SD) scores
b Responder values are number of responders (% of responders)

- Overall, the analyses using LOCF or OC showed similar improvements from baseline in PANSS total score throughout the Treatment Period (comprising the 3-week fixed-dose period and the 9-week flexible-dose period) in both treatment groups. There was a statistically significant difference at Week 1 in favour of zicronapine.
- For the PANSS subscale scores, the analyses using LOCF also showed similar improvements from baseline in PANSS Positive Symptoms subscale score, PANSS Negative Symptoms subscale score, PANSS General Psychopathology subscale score, PANSS Cognitive subscale score, and PANSS Depression subscale score throughout the Treatment Period for both treatment groups. There was a statistically significant difference in the first 2 weeks for the PANSS Negative Symptoms subscale score, PANSS General Psychopathology subscale score, and PANSS Cognitive subscale score in favour of zicronapine. Similar results were seen for the OC.
- Overall, there was an increase with time in the proportion of responders in both treatment groups based on a ≥20%, ≥30%, ≥40%, or ≥50% reduction in PANSS total score. However, none of the responder rate analyses showed any statistically significant differences between the two treatment groups.

Efficacy Results (continued)

- For the CGI-S score, the analyses using LOCF showed similar improvements from baseline for the two treatment groups throughout the Treatment Period, with no statistically significant differences between the two treatment groups at any timepoint. Similar results were seen for the OC.
- For the CGI-I score, the analyses using LOCF showed similar improvements for the two treatment groups throughout the Treatment Period, with no statistically significant differences between the two treatment groups at any timepoint. Similar results were seen for the OC.
- For the CDSS total score, the analyses using LOCF or OC showed similar improvements from baseline throughout the Treatment Period, with no statistically significant differences between the two treatment groups at any timepoint.
- There were minor fluctuations in the mean BACS individual test scores over time in both treatment groups. However, due to the low number of patients who completed the BACS test, no statistical analysis was performed.

Safety Results

- The adverse event incidence is summarised below:

	Zicronapine		Olanzapine	
	n	(%)	n	(%)
Patients treated	47		46	
Patients who died	0	(0.0)	0	(0.0)
Patients with serious AEs (SAEs)	3	(6.4)	4	(8.7)
Patients with AEs	34	(72.3)	37	(80.4)
Total number of AEs	109		102	

n = number of patients; % = percentage of patients within treatment group

- During the study, 66% of the patients in the zicronapine group and 78% of the patients in the olanzapine group had treatment-emergent adverse events (TEAE).
- In either treatment group, the TEAEs with an incidence ≥10% were:
  - weight increased – zicronapine (23%); olanzapine (17%)
  - insomnia – zicronapine (13%); olanzapine (9%)
  - agitation – zicronapine (11%); olanzapine (2%)
- The majority of the TEAEs considered *probably* or *possibly related* to IMP in each treatment group were *mild* or *moderate*.
- No deaths occurred during the study. A total of 7 patients had SAEs during the study (3 patients in the zicronapine group and 4 patients in the olanzapine group). In both treatment groups, the majority of SAEs were *related* to worsening of the underlying disease (system organ class [SOC]: *psychiatric disorders*). There were no other apparent trends regarding SAEs between or within the treatment groups.
- A total of 8 patients withdrew due to adverse events: 5 patients in the zicronapine group and 3 patients in the olanzapine group. The only adverse event leading to withdrawal in >1 patient was psychotic disorder (2 patients in each treatment group). In 2 of the 4 patients with psychotic disorder, the event occurred on Day 0 (pre-treatment) and in 1 patient the event occurred on Day 2.
- Changes in clinical laboratory tests from baseline to Week 12 were small and similar between the treatment groups for the majority of the tests, and the majority of the mean post-baseline laboratory values at the scheduled assessments were within the reference ranges.
- There were no apparent trends in the proportion of PCS clinical safety laboratory values between the two treatment groups, apart from the proportion of PCS high triglycerides values, which was lower in the zicronapine group than in the olanzapine group, and the proportion of PCS high CK values, which was higher in the zicronapine group than in the olanzapine group.
- Treatment with zicronapine did not result in an increased frequency of PCS elevated values of transaminases in the zicronapine group relative to the olanzapine group.

Safety Results (continued)

- The baseline scores for SAS, BAS, and AIMS were low in both treatment groups, and overall, during the study, small fluctuations were seen. The mean changes from baseline to Week 12 in SAS, BAS, and AIMS scores were small and similar between the two treatment groups (LOCF and OC).
- Weight, BMI, and waist circumference increased in both treatment groups throughout the study. The mean increase from baseline was smaller in the zicronapine group than in the olanzapine group at all timepoints. The adjusted mean weight increase from baseline to Week 12 was 1.6 kg for the zicronapine-treated patients *versus* 3.4 kg for the olanzapine-treated patients. For the BMI, the adjusted mean increase at Week 12 was 0.72 kg/m^2 for the zicronapine-treated patients *versus* 1.24 kg/m^2 for the olanzapine-treated patients, and for the waist circumference, the adjusted mean increase at Week 12 was 2.23 cm for the zicronapine-treated patients *versus* 3.35 cm for the olanzapine-treated patients. None of the differences were statistically significant (OC).
- The QT_c interval increased in both treatment groups. The mean increase in QT_{cB} interval from baseline to Week 12 was 12.6 ms in the zicronapine group and 6.4 ms in the olanzapine group. The mean increase in QT_{cF} interval from baseline to Week 12 was 10.2 ms in the zicronapine group and 5.9 ms in the olanzapine group. For QT_{cB} and/or QT_{cF}, 5 patients in the zicronapine group and 1 patient in the olanzapine group had PCS high values. Of these, 1 patient in the zicronapine group had a QT_{cB} >500 ms, whereas the remaining 5 patients all had a QT_{cB} and QT_{cF} ≤500 ms but an increase in QT_{cB} and/or QT_{cF} from baseline >60 ms.
- There were no clinically relevant differences between or within treatment groups in vital signs or physical or neurological examinations.

Conclusions

- The results of this exploratory study suggests that zicronapine at flexible doses of 5 or 7 mg/day is efficacious in the treatment of patients with moderate to severe schizophrenia and comparable to olanzapine at flexible doses of 10 or 15 mg/day. There were similar improvements in PANSS total score, as well as in PANSS subscale scores, and in CGI-I, CGI-S, and CDSS scores during the 12-week Treatment Period in both treatment groups.
- The safety data for zicronapine and olanzapine were similar with respect to the total incidence of adverse events, SAEs, and withdrawals due adverse events.
- Treatment with either zicronapine or olanzapine resulted in a mean weight, BMI, and waist circumference increase, however, the increase in the zicronapine group was approximately half that observed in the olanzapine group, and the corresponding increase in mean waist circumference in the zicronapine groups was approximately two-thirds that in the olanzapine group.
- Treatment with either zicronapine or olanzapine resulted in small fluctuations in lipid and fasting glucose values, however, none of these changes were considered to be clinically relevant.
- Treatment with zicronapine did not result in an increased incidence of PCS high values of transaminases in the zicronapine group relative to the olanzapine group.
- The QT_c interval increased in both treatment groups, with a higher mean increase in QT_{cF} in the zicronapine group than in the olanzapine group.
- Overall, the safety and tolerability of zicronapine and olanzapine were comparable and no safety issues were raised in this study.

Date of the Report

20 October 2010

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