Synopsis – Study 11613A

Title of Study A double-blind, randomised, parallel-group, placebo-controlled study of the safety, tolerability, and efficacy following sequential dose regimens of Lu 31-130 to patients with schizophrenia
Investigators 35 investigators at 33 centres in 11 countries *Signatory investigator* – Hans-Jürgen Möller, Prof. Dr. med., Ludwig-Maximilians-Universität München/ Medizinische Klinik – Innenstadt, Klinik und Poliklinik für Psychiatrie und Psychotherapie, Munich, Germany
Study Centres 33 centres – 2 in Germany, 3 in Indonesia, 5 in India, 4 in Korea, 2 in Malaysia, 1 in the Philippines, 1 in Poland, 5 in Russia, 2 in Slovakia, 1 in Taiwan, 7 in Ukraine
Publications None (as of the date of this report)
Study Period *First patient first visit* – 5 March 2007 *Last patient last visit* – 22 October 2009
Objectives • To assess the safety and tolerability of daily doses (3, 5, 7, 10, and 14 mg/day) of zicronapine administered for 8 weeks to patients with schizophrenia • To identify and quantify the frequency of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) abnormalities (increases) • To evaluate the efficacy of zicronapine in patients with schizophrenia (change from baseline to endpoint [Week 8] in Positive and Negative Syndrome Scale [PANSS] total score, PANSS subscale scores, Clinical Global Impression – Severity of Illness [CGI-S] score, and Clinical Global Impression – Global Improvement [CGI-I] score) • To investigate the pharmacokinetic (PK) properties of zicronapine and the metabolite Lu AA22774 following daily oral doses of zicronapine to patients with schizophrenia (to be reported separately)
Methodology • This was an interventional, multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, fixed-ascending-dose study. • The study included five study parts – Parts A, B, C, D, and E – with fixed doses of zicronapine 3, 5, 7, 10, and 14 mg/day, respectively, *versus* placebo (Part E was not initiated). Enrolment of patients into Parts A, B, C, and D was sequential and continuous. Patients enrolled in each study part were new patients who had not been enrolled in a previous study part. A Data Monitoring Committee (DMC) gave advice regarding the safety of continuing with each of Parts B, C, and D based on accumulated safety and tolerability data from patients in the study. • Patients in each study part entered a 3- to 14-day Screening Period, during which current antipsychotic medication was discontinued at least 3 days before baseline. At baseline, patients were randomised to zicronapine or placebo (ratio of 2:1) for an 8-week Treatment Period. For each patient, the total study duration was approximately 14 weeks from baseline to the end of follow-up. The patients had to remain hospitalised for the first 2 weeks of the Treatment Period. • Efficacy and safety data were collected weekly throughout the Treatment Period. • At predetermined time points, blood samples were obtained for drug concentration analysis of zicronapine and its major metabolite Lu AA22774.

Methodology (continued)

- A Safety Follow-up Visit was scheduled for 1 week after completion of the Treatment Period or after withdrawal from the study. A telephone interview was scheduled for 30 days after the Treatment Period or after withdrawal from the study to collect data on ongoing and new serious adverse events (SAEs).
- Patients with potentially clinically significant (PCS) AST or ALT values (≥3× the upper limit of the reference range [ULN]) had additional monitoring during the study and the Safety Follow-up was extended from 30 days to 3 months or until the AST and ALT values were within the reference ranges or the reason for the increase had been identified.

Number of Patients Planned and Analysed

- 300 patients were planned for enrolment:
  - Part A: 50 in the zicronapine (ZIC_3) group and 25 in the placebo (PBO_A) group
  - Part B: 50 in the zicronapine (ZIC_5) group and 25 in the placebo (PBO_B) group
  - Part C: 40 in the zicronapine (ZIC_7) group and 20 in the placebo (PBO_C) group
  - Part D: 30 in the zicronapine (ZIC_10) group and 15 in the placebo (PBO_D) group
  - Part E: 30 in the zicronapine (ZIC_14) group and 15 in the placebo (PBO_E) group (not initiated)
- Patient disposition is tabulated below:

	Part A n (%)		Part B n (%)		Part C n (%)		Part D n (%)		Total n (%)
	ZIC_3	PBO_A	ZIC_5	PBO_B	ZIC_7	PBO_C	ZIC_10	PBO_D	
Patients randomised	55	25	55	25	40	22	39	19	280
Patients treated (all-patients-treated set [APTS]):	55 (100)	25 (100)	55 (100)	25 (100)	40 (100)	22 (100)	39 (100)	19 (100)	280 (100)
Patients completed	35 (64)	16 (64)	39 (71)	20 (80)	30 (75)	9 (41)	29 (74)	11 (58)	189 (68)
Patients withdrawn	20 (36)	9 (36)	16 (29)	5 (20)	10 (25)	13 (59)	10 (26)	8 (42)	91 (32)
Primary reason for withdrawal:									
Adverse event(s)	7 (13)	1 (4)	4 (7)	2 (8)	4 (10)	5 (23)	5 (13)	4 (21)	32 (11)
Lack of efficacy	11 (20)	6 (24)	10 (18)	2 (8)	4 (10)	1 (5)	1 (3)	2 (11)	37 (13)
Other	2 (4)	2 (8)	2 (4)	1 (4)	2 (5)	7 (32)	4 (10)	2 (11)	22 (8)
Analysis sets:									
APTS	55 (100)	25 (100)	55 (100)	25 (100)	40 (100)	22 (100)	39 (100)	19 (100)	280 (100)
FAS	55 (100)	25 (100)	54 (98)	25 (100)	40 (100)	21 (95)	39 (100)	19 (100)	278 (99)
PPS	39 (71)	19 (76)	40 (73)	22 (88)	34 (85)	13 (59)	29 (74)	14 (74)	210 (75)

Diagnosis and Main Inclusion Criteria Patients with a primary diagnosis of schizophrenia according to the DSM-IV-TR™ criteria, who: • were ≥18 and ≤65 years of age • had a PANSS total score ≥60 at screening and baseline • had a CGI-S score ≤4 at screening and baseline • did not experience an acute exacerbation requiring hospitalisation within 6 months before screening • did not experience an acute exacerbation requiring change in medication (with respect to compound and dose) within 4 weeks before screening • had a score ≤4 (*moderate*) on PANSS items P7 (*hostility*) and G8 (*uncooperativeness*) at screening and baseline • was willing to be hospitalised full time, starting from the Screening Visit until 2 weeks after baseline
Investigational Medicinal Product, Doses and Mode of Administration, Batch Numbers *Zicronapine* – 3, 5, 7, or 10 mg/day; tablets, orally: • Part A – 3 mg tablets; batch No. PD1636 • Part B – 5 mg tablets; batch No. PD1651 • Part C – 7 mg tablets; batch No. PD1696 • Part D – 5 mg tablets; batch No. PD1793
Duration of Treatment 8 weeks
Reference Therapy, Mode of Administration, Batch Numbers *Placebo* – tablets, orally; batch Nos. PD1635, PD1792
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 • CGI-S score • CGI-I score
Safety Assessments Adverse events (AEs), clinical safety laboratory tests, vital signs and body temperature, weight, BMI, mean waist circumference (WCM), electrocardiograms (ECGs), physical and neurological examinations, abnormal movement rating scale (Simpson-Angus Scale [SAS], Barnes Akathisia Scale [BAS], Abnormal Involuntary Movements Scale [AIMS]) scores

Statistical Methodology

- 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 investigational medicinal product (IMP)
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline efficacy assessment
  - *per-protocol set* (PPS) – all patients in the FAS who:
    - did not have any major protocol violations, including violations of selection criteria
    - received IMP until at least Week 4 and had at least one efficacy assessment following 4 weeks of IMP
    - did not take disallowed concomitant medication judged to interfere with the treatment response during the treatment period
- All efficacy analyses were exploratory and based on the FAS and, unless otherwise specified, done using both last observation carried forward (LOCF) and observed cases (OC) principles of data imputation.
- All safety analyses were based on the APTS.
- The efficacy analyses were performed by *treatment group* and, for PANSS total score, by *part and treatment group* also. The safety analyses were performed by *treatment group* and, for selected variables, by *part and treatment group* also. *Treatment group* and *part and treatment group* were defined as:
  - *treatment group* – ZIC_3, ZIC_5, ZIC_7, ZIC_10, PBO groups (where the PBO group comprised the PBO_A, PBO_B, PBO_C, and PBO_D groups)
  - *part and treatment group* – ZIC_3, ZIC_5, ZIC_7, ZIC_10, PBO_A, PBO_B, PBO_C, PBO_D groups
- *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 country as factors and the baseline score as a covariate for the following variables: 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, 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 time course of improvement in all the efficacy variables was analysed using a mixed model for repeated measurements (MMRM), including country as well as a baseline-score-and-time-interaction term as systematic effects, based on a 'Missing at Random' assumption and OC only. The effect at each time point (week number) for each treatment was allowed to vary freely and an unstructured covariance matrix was assumed.
  The potential influence of covariates on the ANCOVA model was investigated; the following covariates were tested (at the 5% significance level) for main effect and interaction with treatment effect: centre, country, sex, age, race, weight, body mass index (BMI) and BMI category (<20, ≥ 20 and ≤ 25, $>25\,kg/m^2$), WCM, number of prior episodes of schizophrenia, and SAS, BAS, AIMS, and CGI-S scores at baseline.
  Due to the sequential study design with dose escalation, differences between study parts were observed with respect to the study centres involved, sex distribution, race distribution, and mean baseline PANSS total score. To investigate the impact of study part, Parts A to D were analysed separately using the ANCOVA model. The influence of study part was further examined using an MMRM analysis of change from baseline to each week in PANSS total score, in which centre as well as a mean-baseline-PANSS-total-score-and-time-interaction term were included as systematic effects and study part as well as study-part-and-time-interaction were included as random effects.
- *Safety analyses* – The incidences of individual adverse events with an incidence ≥5% in any treatment group, and the incidences of overall withdrawal were compared between treatment groups using Fisher's exact test. Absolute values and changes from baseline in clinical safety laboratory tests, vital signs, weight, BMI, WCM, and ECG parameters were summarised using descriptive statistics. Values outside the reference range, as well as PCS values, were flagged and tabulated. The changes from baseline to each assessment in 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 country as factors and baseline scores as covariates. Shifts in SAS status were also tabulated.

Demography of Study Population

• The baseline values are presented by *treatment group* below:

			ZIC_3 n (%)	ZIC_5 n (%)	ZIC_7 n (%)	ZIC_10 n (%)	PBO n (%)
Patients treated			55 (100)	55 (100)	40 (100)	39 (100)	91 (100)
Sex	Men		52 (95)	38 (69)	31 (78)	33 (85)	70 (77)
	Women		3 (5)	17 (31)	9 (22)	6 (15)	21 (23)
Race	Caucasian		40 (73)	26 (47)	15 (38)	24 (62)	52 (57)
	Asian		15 (27)	28 (51)	25 (62)	15 (38)	39 (43)
	Other		0 (0)	1 (2)	0 (0)	0 (0)	0 (0)
Metabolic status	CYP2D6	EM	54 (98)	48 (87)	37 (92)	37 (95)	0 (0)
		PM	1 (2)	4 (7)	0 (0)	0 (0)	0 (0)
		und.	0 (0)	3 (5)	3 (8)	2 (5)	91 (100)
	CYP2C19	EM	51 (93)	46 (84)	36 (90)	37 (95)	0 (0)
		PM	4 (7)	6 (11)	1 (2)	0 (0)	0 (0)
		und.	0 (0)	3 (5)	3 (8)	2 (5)	91 (100)
Mean age (years)			40.5	35.8	37.6	39.5	37.9
Mean height (cm)			172	166	167	171	169
Mean weight (kg)			67.7	65.7	65.0	69.2	66.5
Mean BMI (kg/m^2)			22.9	23.6	23.0	23.6	23.3
Mean WCM (cm)			83.7	82.4	82.4	85.7	83.9
PANSS total score			76.5	78.5	80.0	81.3	77.9
CGI-S score			3.7	3.7	3.8	3.7	3.7

EM = extensive metaboliser, PM = poor metaboliser, und. = undetermined, WCM = mean waist circumference

• Overall, the ratio of men to women was 4 to 1, but the distribution varied across treatment groups. In the ZIC_3 group, 95% of the patients were men, because women were excluded from the study until the implementation of Protocol Amendment SA04.

• The mean PANSS total score at baseline was indicative of a patient population with *moderately severe* symptoms of schizophrenia and the mean CGI-S score at baseline was indicative of a patient population that was *moderately ill*.

Efficacy Results

- All analyses of efficacy were exploratory.
- The efficacy results are presented below (mean change from baseline to Week 8 [FAS, LOCF, ANCOVA] unless otherwise indicated):

Variable (Score [SE])	Treatment Group				
	ZIC_3	ZIC_5	ZIC_7	ZIC_10	PBO
PANSS total	0.7 (2.7)	-1.7 (2.5)	-7.8 (2.9)	-9.4 (3.1)	-0.5 (2.2)
PANSS total (PPS)	-6.8 (2.7)	-9.9 (2.5)	-10.2 (2.6)	-12.6 (3.0)	-8.6 (2.1)
PANSS Positive Symptoms subscale	0.9 (0.9)	0.2 (0.9)	-1.2 (1.0)	-2.1 (1.1)	-0.1 (0.7)
PANSS Negative Symptoms subscale	-1.5 (0.7)	-1.9 (0.6)	-3.6 (0.8)	-4.2 (0.8)	-1.6 (0.6)
PANSS General Psychopathology subscale	0.8 (1.4)	-0.1 (1.3)	-3.1 (1.5)	-3.0 (1.6)	1.1 (1.1)
PANSS Cognition subscale	-0.7 (0.7)	-0.3 (0.6)	-1.7 (0.7)	-2.1 (0.8)	0.0 (0.5)
PANSS Depression subscale	-0.1 (0.6)	-0.3 (0.5)	-2.0 (0.6)	-1.4 (0.6)	0.0 (0.4)
CGI-S	0.2 (0.1)	0.0 (0.1)	-0.1 (0.2)	-0.4 (0.2)	0.1 (0.1)
CGI-I (adjusted mean score at Week 8)	4.0 (0.2)	3.8 (0.2)	3.6 (0.2)	3.1 (0.2)	4.0 (0.2)

SE = standard error

- The PANSS total score decreased (improved) more from baseline to Week 8 in the ZIC_7 and ZIC_10 groups than in the PBO group, regardless of the analysis or data imputation method. These differences were statistically significant in the ANCOVA using LOCF and in the MMRM analysis.
- All the PANSS subscale scores decreased more from baseline to Week 8 in the ZIC_7 and ZIC_10 groups than in the PBO group, regardless of the analysis or data imputation method.
- The CGI score indicated that the ZIC_10 group had improved more than the PBO group at Week 8.

Safety Results

- The adverse event incidence is summarised below:

	ZIC_3		ZIC_5		ZIC_7		ZIC_10		PBO	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	55	(100)	55	(100)	40	(100)	39	(100)	91	(100)
Patients who died	0	(0)	0	(0)	0	(0)	0	(0)	0	(0)
Patients with SAEs	0	(0)	2	(4)	1	(2)	1	(3)	4	(4)
Patients with AEs	32	(58)	33	(60)	24	(60)	28	(72)	57	(63)
Patients with pre-treatment AEs	2	(4)	9	(16)	5	(12)	11	(28)	22	(24)
Patients with treatment-emergent AEs	31	(56)	30	(54)	24	(60)	27	(69)	55	(60)

- During the study, 69% of the patients in the ZIC_10 group had treatment-emergent adverse events (TEAEs), whereas 54% to 60% of the patients in the other treatment groups had TEAEs. *Insomnia* was the TEAE with the highest incidence (from 13% to 31%). The incidence of *agitation* was highest in the PBO group and decreased with zicronapine dose; the incidence of *schizophrenia* was higher in the ZIC_3 group than in the other treatment groups. The incidence of *weight increased* increased with zicronapine dose and *atrioventricular block* occurred exclusively in the ZIC_7 and ZIC_10 groups.
- For the majority of patients in each treatment group who had *related* TEAEs, the events were *mild* or *moderate*.
- There were no deaths in the study. A total of 8 patients had treatment-emergent SAEs: 2 in the ZIC_5 group, 1 in each of the ZIC_7 and ZIC_10 groups, and 4 in the PBO group. There were no apparent trends regarding SAEs between or within treatment groups.
- Approximately 10% of the patients in each treatment group withdrew due to adverse events. The adverse events leading to withdrawal in >1 patient in any treatment group were related to the underlying disease (*schizophrenia*, *agitation*, and *psychotic disorder*) and occurred primarily in the ZIC_3 and PBO groups.
- For the safety laboratory tests, the proportion of patients with PCS values varied across treatment groups with no obvious trends.
- There were no clinically relevant differences between treatment groups with respect to absolute values or changes from baseline in vital signs.
- The mean weight increased in all treatment groups from baseline to Week 8 with a minimal increase (0.3 kg) in the PBO group and greater increases (0.9 to 1.6 kg) with increasing zicronapine dose. Likewise, the mean BMI increased least in the PBO group and most in the ZIC_10 group. For the WCM, the same trend was observed. The proportions of patients who had PCS weight, BMI, or WCM increases also increased with increasing zicronapine dose with the greatest proportion of patients with PCS values in the ZIC_7 and ZIC_10 groups.
- There were no relevant mean changes in body temperature in any of the treatment groups.
- There was a tendency for the mean QT_{cF} to increase from baseline to last assessment in all treatment groups with a trend for greater changes with higher doses of zicronapine. The mean change from baseline to Week 8 in QT_{cF} was 10.9 ms in the ZIC_10 group and -1.5 ms in the PBO group (the mean change from baseline to last assessment was 7.9 and 4.0 ms, respectively). Three patients had a PCS prolongation of the QT_{cB} interval: 2 in the ZIC_3 group and 1 in the ZIC_10 group, but none of the patients in this study had PCS QT_{cF} values.
- There were no clinically relevant differences between treatment groups in physical and neurological status at Week 8.
- Abnormal movement rating scale SAS, BAS, and AIMS scores showed that the patients had few symptoms of abnormal movement in all treatment groups.

Conclusions

- The results of this exploratory study suggest that zicronapine at doses of 7 mg/day or 10 mg/day is efficacious in the treatment of stable patients with *moderately severe* schizophrenia. There were improvements in PANSS total score and in PANSS subscale scores, as well as in CGI-I and CGI-S scores during the 8-week treatment period for both doses.
- Overall, the safety data for the zicronapine groups with respect to the total incidence of adverse events, SAEs, and withdrawals due adverse events were comparable to those for the placebo group.
- The incidence of PCS high values of transaminases was similar in the zicronapine and placebo groups.
- Treatment with zicronapine resulted in mean increases in weight, BMI, and waist circumference.
- Treatment with zicronapine resulted in small fluctuations in mean fasting lipid and glucose values. However, none of these changes were considered clinically relevant.
- The QT_{cF} increased in all zicronapine groups, with a greater mean increase in QT_{cF} at the higher doses.
- Overall, zicronapine was safe and well tolerated.

Date of the Report

15 December 2010

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