Synopsis – Study 11918A

Title of Study

Randomised, double-blind, parallel-group, placebo-controlled, duloxetine-referenced, dose-finding study of Lu AA24530 in Major Depressive Disorder

Investigators

73 investigators at 73 centres in 17 countries
Signatory investigator – Lars Häggström, MD, Häggström Brain & Body AB, Haverdal, Sweden

Study Centres

73 centres – 4 in Australia, 3 in Austria, 2 in Belgium, 6 in Canada, 5 in the Czech Republic, 6 in Finland, 6 in France, 6 in India, 3 in Lithuania, 3 in Malaysia, 3 in Norway, 3 in the Philippines, 5 in the Russian Federation, 2 in Serbia, 3 in the Republic of Korea, 6 in Sweden, and 7 in Ukraine

Publications

None (as of the date of this report)

Study Period

First patient first visit – 8 October 2007

Last patient last visit – 13 March 2009

Objectives

- *Primary objectives*:
  - to compare the efficacy of three doses of Lu AA24530 to that of placebo in terms of the change from baseline in MADRS total score after 6 weeks of treatment
  - to establish a dose level to be investigated in further studies
- *Secondary objectives*:
  - to compare the efficacy of Lu AA24530 to that of placebo in terms of the proportion of patients with response after 6 weeks of treatment
  - to compare the efficacy of Lu AA24530 to that of placebo in terms of the proportion of patients in remission after 6 weeks of treatment
  - to compare the efficacy of Lu AA24530 to that of placebo in terms of the proportion of patients with a response after 14 days of treatment that is maintained or further improved after 6 weeks of treatment
  - to compare the efficacy of Lu AA24530 to that of placebo in terms of the change from baseline in MADRS total score during the course of the study
  - to assess the safety and tolerability of Lu AA24530
  - *Additionally:*
  - to conduct exploratory analyses of the population pharmacokinetics of Lu AA24530 and its metabolite Lu AA37208 in depressed patients and to evaluate any relationship between exposure and efficacy, tolerability, and safety
  - to evaluate the efficacy of Lu AA24530 in the subpopulations of patients with major depressive disorder (MDD) with melancholic features and with atypical features
  - to evaluate the effect of Lu AA24530 on pain
  - to evaluate the effect of Lu AA24530 on cognitive deficits
  - to evaluate the effect of Lu AA24530 on health-related quality of life
  - to conduct exploratory analyses of biomarkers to better understand the pathophysiology of MDD and the treatment response
  - to explore associations between biological parameters (mRNA levels, genetic variants, or endogenous metabolite levels) and clinical features such as disease symptoms, treatment response or potential adverse events

Objectives – continued

- The population pharmacokinetic (the first bullet of the additional *Secondary Objectives*) and exploratory biomarker results (the last two bullets of the additional *Secondary Objectives*) will be reported separately.

Methodology

- This was a multi-national, multi-centre, randomised, double-blind, parallel-group, placebo-controlled, active-referenced (duloxetine), fixed-dose study. The patients were in- or outpatients from psychiatric clinics.
- The study consisted of the following periods:
  - *Screening Period* – the patients were characterised as extensive or poor metabolisers based on the cytochrome P450 subtype CYP2D6.
  - *6-week Treatment Period* (Weeks 1 to 6) – extensive metabolisers were randomised 13:13:16:13:13 to receive fixed doses of Lu AA24530 5, 10, or 20 mg/day, duloxetine 60 mg/day, or placebo; poor metabolisers did not receive the 20 mg Lu AA24530 dose, but were randomised 1:1:1:1 to the remaining four treatment groups.
  - *Taper Period* – patients who completed the 6-week Treatment Period entered a 1-week, double-blind Taper Period; patients randomised to Lu AA24530 20 mg/day received Lu AA24530 10 mg/day; patients randomised to Lu AA24530 10 mg/day received Lu AA24530 5 mg/day; patients randomised to Lu AA24530 5 mg/day, or placebo, received placebo; patients randomised to duloxetine 60 mg/day received duloxetine 30 mg/day. Taper IMP was also offered to patients who withdrew.
  - *Safety Follow-up Period* – patients who completed the Taper Period entered a 3-week Safety Follow-up Period; patients who withdrew entered a 4-week Safety Follow-up Period after the last dose of IMP.
- Efficacy was assessed at each visit in the 6-week Treatment Period; safety and tolerability were assessed at each visit.
- At predetermined time points, blood samples were drawn for drug concentration analysis of Lu AA24530 and its major metabolite Lu AA37208.

Number of Patients Planned and Analysed

- 625 patients were planned for enrolment: 125 in each treatment group
- Patient disposition is tabulated below:

	AA24350_5		AA24350_10		AA24350_20		Duloxetine		Placebo		Total	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients randomised	136		138		107		133		138		652	
Patients treated (all-patients-treated set [APTS]):	135		136		107		133		136		647	
Patients completed	112	(83)	112	(82)	85	(79)	106	(80)	109	(80)	524	(81)
Patients withdrawn	23	(17)	24	(18)	22	(21)	27	(20)	27	(20)	123	(19)
Primary reason for withdrawal:												
Adverse event(s)	11	(8.1)	6	(4.4)	11	(10.3)	9	(6.8)	8	(5.9)	45	(7.0)
Lack of efficacy	5	(3.7)	3	(2.2)	2	(1.9)	4	(3.0)	4	(2.9)	18	(2.8)
Other	7		15		9		14		15		60	
Analysis sets:												
APTS	135		136		107		133		136		647	
Full-analysis set (FAS)	133		133		102		132		136		636	
Per-protocol set (PPS)	112		120		88		109		117		546	

Diagnosis and Main Inclusion Criteria

In- and outpatients with a primary diagnosis of Major Depressive Episode (MDE) according to DSM-IV-TR™ criteria, who:

- had a MADRS total score ≥26 at screening and at baseline
- were ≥18 and ≤65 years of age

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

Lu AA24530 – 5, 10, or 20 mg/day; encapsulated capsules, orally; batch Nos. PD1661/E04914-003E (5 mg), PD1661/E05341-003E (5 mg), PD1661/E05341-014E (5 mg), PD1662/E04914-004E (10 mg), PD1662/E05341-004E (10 mg), and PD1662/E05341-015E (10 mg)

Duration of Treatment

6 weeks of double-blind treatment, 1 week of double-blind taper

Reference Therapy, Dose and Mode of Administration, Batch Numbers

Duloxetine (Cymbalta®[duloxetine HCl]) – 60 mg/day; encapsulated capsules, orally; batch Nos. A269594/E04914-002E (30 mg), A307472/E05331-007E (30 mg), A475528/E05341-028E (30 mg), A262430/E04914-001E (60 mg), A375294/E05331-006E (60 mg), and A425927/E05341-013E (60 mg)

Placebo-capsules, orally; batch Nos. E04914-005E, E04879-001E, and E05341-016E

Efficacy Assessments

- *Primary variable*:
  - Montgomery-Åsberg Depression Rating Scale (MADRS) total score
- *Secondary variables*:
  - MADRS single item and total scores
  - Hamilton Rating Scale for Depression 23-item ($HAM\text{-}D_{23}$) including the Bech-Rafaelson Melancholia Scale (MES) total score ($HAM\text{-}D\text{-}MES_{23}$) single item and total scores
  - Hamilton Depression Scale – 17 items ($HAM\text{-}D_{17}$) total score
  - Bech-Rafaelson Melancholia Scale (MES) total score
  - Clinical Global Impression – Severity (CGI-S) score
  - Clinical Global Impression – Improvement (CGI-I) score
  - proportion of patients with a response to treatment (defined as a ≥50% reduction from baseline in MADRS total score, a ≥50% reduction from baseline in $HAM\text{-}D_{17}$ total score, or a CGI-I score ≤2)
  - proportion of patients who achieved remission (defined as a MADRS total score ≤10, a $HAM\text{-}D_{17}$ total score ≤7, or a CGI-S score ≤2)
  - proportion of patients with sustained MADRS response to treatment (defined as a MADRS response at Week 2 that once achieved was maintained to Week 6)
  - Medical Outcomes Study (MOS) 36-item Health Survey (SF-36) Acute Version subscale scores
  - Pain Intensity Numeric Rating Scale (NRS) subscale (back pain, shoulder pain, headache, overall pain) scores
  - Rey Auditory Verbal Learning Test (RAVLT) scores
  - Digit Symbol Substitution Test (DSST) scores
  - Digit Span Backward (DS-B) score
  - Stroop Colour Naming Test (STROOP) scores

Safety Assessments

Adverse events (AEs), clinical safety laboratory tests, vital signs, weight, body mass index (BMI), lean body mass (LBM), and electrocardiograms (ECGs)

Statistical Methodology

- For the statistical analyses, the following periods were defined:
  - Screening Period – from screening to randomisation
  - Entire Study Period – from randomisation to the last visit/contact
  - 6-week Treatment Period – the 6-week double-blind treatment period with either Lu AA24530, duloxetine, or placebo (Weeks 1 to 6)
  - Taper Period – the 1-week double-blind down-taper period with either Lu AA24530, duloxetine, or placebo
  - Safety Follow-up Period – the 3-week period after the Taper Period
- 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 IMP
  - *full-analysis set* (FAS) – all patients in the APTS who had at least one valid post-baseline assessment of the MADRS total score
  - *extensive metabolisers set* (EMS) – all patients in the FAS who were phenotyped (inferred metabolic status) as intermediate (IM), extensive (EM), or ultra-extensive (UM) metabolisers
  - *per-protocol set* (PPS) – all patients in the FAS who did not violate important inclusion or exclusion criteria, who received IMP up until the Week 3 visit, who had at least one assessment of the MADRS total score following 3 weeks of double-blind treatment, who did not start taking disallowed concomitant medication continuously before the Week 3 visit, who did not have a drug holiday during treatment for more than 6 consecutive days, and who were not unblinded or partially unblinded during the study
- The primary efficacy analysis was an analysis of covariance (ANCOVA) of the change from baseline to Week 6 in MADRS total score (FAS, last observation carried forward [LOCF]), with treatment and centre as fixed factors and the baseline MADRS score as a covariate. Three hypotheses were identified as being part of the primary analysis:
  - no difference between 5 mg Lu AA24530 and placebo at Week 6
  - no difference between 10 mg Lu AA24530 and placebo at Week 6
  - no difference between 20 mg Lu AA24530 and placebo at Week 6
- For each of the three doses of Lu AA24530, the MADRS total score, as well as key secondary efficacy variables, were analysed hierarchically (FAS, LOCF) *versus* placebo at a Bonferoni-adjusted significance level of 0.05/3 = 0.0167:
  - MADRS total score, change from baseline (primary analysis, ANCOVA)
  - MADRS response (logistic regression)
  - CGI-I score (ANCOVA)
  - MADRS remission (logistic regression)
  - SF-36 social functioning score, change from baseline (ANCOVA)
  - SF-36 mental health score, change from baseline (ANCOVA)
  - SF-36 vitality score, change from baseline (ANCOVA)
- In this testing strategy, the analysis proceeded as long as there was a statistically significant difference *versus* placebo in the preceding step for the Lu AA24530 dose analysed. All statistical tests not included in the testing strategy were performed at a 5% level of significance.
- The primary efficacy analysis was repeated on the FAS using observed cases (OC).
- The robustness of the primary efficacy analysis was evaluated using the PPS (LOCF and OC). To evaluate the influence of withdrawals before the first efficacy assessment, the primary efficacy analysis was repeated on the APTS (LOCF, where the baseline MADRS score was carried forward for patients not in the FAS).

Statistical Methodology – continued

- The primary efficacy analysis was repeated on OC data, using a mixed model for repeated measurements (MMRM).
- The influence of covariates, such as centre, country, baseline efficacy scores, sex, baseline weight, BMI, LBM, age, first episode of major depression, withdrawn/completed, and phenotype was investigated within the ANCOVA model by adding main terms for covariates as well as interaction terms with treatment.
- The primary efficacy analysis was repeated on the EMS. To further investigate the influence of inferred metabolic status, the primary efficacy analysis was repeated on the FAS (LOCF) with treatment, centre, and inferred metabolic status as fixed factors (as well as an interaction term between treatment and inferred metabolic status) and the baseline MADRS score as a covariate.
- The change from baseline to each visit in all the secondary efficacy variables, except response, remission, and CGI-I was analysed using an ANCOVA, adjusting for baseline score, centre, and treatment, using both OC and LOCF data.
- Response and remission were analysed per visit using a logistic regression analysis adjusting for baseline score, centre, and treatment, using both OC and LOCF data. Response and remission were also analysed per visit using Fisher's exact test. Sustained response was analysed in the same way.
- The CGI-S and CGI-I scores were also analysed at the last visit (OC and LOCF) using the Cochran-Mantel-Haenszel test and stratifying by centre.
- Selected efficacy analyses were repeated for the subgroups of patients with MDE with melancholic features.
- The change from baseline to each visit in SF-36 subscale scores was analysed as described for the MADRS total scores (FAS, OC and LOCF).
- The change from baseline to each visit in pain scores (back pain, shoulder pain, headache, overall pain) was analysed as described for the MADRS total scores (FAS, OC and LOCF). In addition, the pain scores were analysed at the last visit (LOCF, OC) using the Cochran-Mantel-Haenszel test and stratifying by centre. The ANCOVA analyses were repeated for the subgroup of patients with a pain score >0 at baseline.
- The change from baseline to each visit in cognitive parameters (DSST, DS-B, RAVLT, and STROOP) were analysed as described for the MADRS total scores (FAS, OC and LOCF).
- On an exploratory basis, and based on both system organ class (SOC) and preferred term, the incidences of individual adverse events were compared between groups using Fisher's exact test.
- The time to first event (preferred term) was analysed using Kaplan-Meier plots, log-rank tests, and the Cox model for certain adverse events (nausea, diarrhoea, and vomiting).
- Logistic regression and Fisher's exact test were used to compare the incidences of withdrawals for all reasons, withdrawals due to adverse events, and withdrawals due to lack of efficacy between treatment groups.
- The relation between withdrawals and treatment was analysed using time-to event methods for the time to withdrawal.

Demography of Study Population

- Approximately 60% of the patients in each treatment group were women. The mean age of the patients was 44 years, ranging from 19 to 65 years, and the majority (77% to 83%) were Caucasian/Hispanic.
- At baseline, there were no clinically relevant differences between the treatment groups in height, weight, BMI, LBM, waist circumference, or physical examination findings for men or women.
- The majority of the patients (82% to 91%) in each treatment group were CYP2D6 extensive metabolisers.
- Approximately two-thirds of the patients in each treatment group had had a previous MDE. The mean duration of the current MDE was 7 months. Approximately three-quarters of the patients had an MDE with current melancholic features.
- At baseline, the mean MADRS total score indicated that the patients had *moderate* to *severe* MDD and the mean CGI-S score indicated that the patients were *mildly* to *severely* ill. The mean HAM-D_{17} total score was in line with the MADRS and CGI-S scores with respect to severity of depression.
- At baseline, there were no clinically relevant differences in efficacy scores between the treatment groups.

Efficacy Results

- In the testing strategy, using a Bonferroni-corrected level of significance of 0.0167, all three doses of Lu AA24530 were statistically significantly superior to placebo in the mean change from baseline in MADRS total score at Week 6 (LOCF). The mean treatment differences to placebo were 3.2 (AA24530_5), 5.3 (AA24530_10), and 4.4 points (AA24530_20). Duloxetine was also statistically significantly superior to placebo in the mean change from baseline in MADRS total score at Week 6, with a mean treatment difference to placebo of 6.1 points.
- Similar results were obtained from the analyses based on OC. However, at Week 6, there was a slightly smaller separation between AA24530_10 and placebo (4.1 points). For duloxetine, the treatment difference to placebo was 7.3 points.
- Repeating the primary efficacy analysis on the PPS, EMS, APTS, and APRS did not change the conclusions.
- AA24530_10 was statistically significantly ($p < 0.0167$) superior to placebo for all the other endpoints in the testing strategy and AA24530_20 was statistically significantly ($p < 0.0167$) superior to placebo in the proportion of MADRS responders, in the mean CGI-I score, in the proportion of MADRS remitters at Week 6, and SF-36 social functioning score.
- All active treatments were statistically significantly superior to placebo at Week 6 (LOCF and OC) in the secondary efficacy analyses of the HAM-D-MES$_{23}$, HAM-D$_{17}$, and MES total scores and the CGI-S and CGI-I scores.
- At Week 6, the proportion of responders was statistically significantly ($p < 0.05$) higher in all active treatment groups, than in the placebo group, except the AA24530_5 group. The proportions were slightly higher in the OC analysis.
- At Week 6, the proportion of remitters was also statistically significantly ($p < 0.05$) higher in all active treatment groups than in the placebo group, except the AA24530_5 group based on the CGI-S criterion. The proportions were slightly higher in the OC analysis.
- A statistically significantly larger proportion of patients in the AA24530_5 (11%), AA24530_20 (15%), and duloxetine groups (12%) than in the placebo group (4%) achieved sustained MADRS response. In the AA24530_10 group, 11% of the patients achieved sustained MADRS response ($p = 0.065$).
- Based on the MADRS and the MES, exploratory subgroup analyses showed that all three doses of Lu AA24530 were statistically significantly superior to placebo in patients with MDE with melancholic features.
- Overall, patients in the active treatment groups had an improvement in their quality of life, as assessed using the SF-36 subscale scores at Week 6. At Week 6 (LOCF), AA24530_10 and duloxetine were statistically significantly ($p < 0.05$) superior to placebo on all but one of the subscales (physical functioning). AA24530_5 and AA24530_20 were each statistically significantly ($p < 0.05$) superior to placebo on two subscales each: role-physical and social functioning (AA24530_5) and social functioning and mental health (AA24530_20).
- For SF-36 item 2 (health transition), AA24530_10 and duloxetine were statistically significantly superior to placebo at Week 6 in the LOCF analysis.
- In the evaluation of the effect of Lu AA24530 on pain, AA24530_20 and duloxetine had a statistically significant ($p < 0.05$) effect on shoulder pain at Week 6 (LOCF and OC), both in all patients in the FAS and in the subgroup of patients with baseline shoulder pain.
- The assessments of cognition showed that patients in all treatment groups improved over time on the DSST, which measures psychomotor speed, the DS-B, which measures the patient's ability to retain auditory information and to manipulate remembered items in working memory, the RAVLT, which measures episodic memory, and the STROOP, which measures the patient's selected attention. At Week 6, a consistent statistically significant ($p < 0.05$) difference to placebo was seen for Lu AA24530 on the majority of the RAVLT parameters.

Safety Results

- The adverse event incidence for the Entire Study Period (from randomisation to last visit/contact) is summarised below:

	AA24530_5		AA24530_10		AA24530_20		Duloxetine		Placebo	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Patients treated	135		136		107		133		136	
Patients who died	1	(0.7)								
Patients with serious AEs (SAEs)	3	(2.2)	2	(1.5)			1	(0.8)	1	(0.7)
Patients with AEs	90	(67)	95	(70)	88	(82)	97	(73)	80	(59)
Total number of AEs	255		265		226		292		176	

- During the Entire Study Period, the incidences of adverse events in the Lu AA24530 groups increased with dose from 67% in the AA24530_5 group to 82% in the AA24530_20 group. In the duloxetine and placebo groups, the incidence of adverse events was 73% and 59%, respectively.
- During the Entire Study Period, 1 patient died: a patient in the AA24530_5 group died after an alcohol intoxication and mirtazapine overdose.
- Seven patients had SAEs. None of the patients in the AA24530_20 group had SAEs. There were no apparent trends with respect to overall incidences, or distribution across SOCs or adverse events and none of the SAEs occurred in more than 1 patient in any of the treatment groups.
- The proportion of patients who withdrew due to adverse events was low, and there were no statistically significant differences between the treatment groups in the proportion of patients with adverse events leading to withdrawal. The lowest proportion of patients who withdrew due to adverse events was in the AA24530_10 group. All patients in the active treatment groups who withdrew due to adverse events did so during the 6-week Treatment Period.
- During the 6-week Treatment Period, the adverse events with an incidence >10% in any of the active treatment groups comprised nausea and headache, and in the duloxetine group also somnolence. The only adverse event in any of the Lu AA24530 groups with an incidence >10%, and for which the incidence was statistically significantly higher than that in the placebo group, was nausea (all Lu AA24530 groups). The incidence of nausea increased with the dose of Lu AA24530.
- In all the treatment groups, the majority of patients with adverse events in the 6-week Treatment Period had *mild* adverse events. The incidence of *severe* adverse events was highest (9%) in the AA24530_20 group. The incidences of *severe* adverse events in the AA24530_5, AA24530_10, and duloxetine groups were comparable to that in the placebo group.
- Two patients had suicidal ideations and were withdrawn from the study: 1 patient in the AA24530_5 group and 1 patient in the AA24530_20 group.
- The adverse events with an incidence between 5 and 10% in any of the active treatment groups for which the incidence was statistically significantly higher than that in the placebo group comprised diarrhoea (AA2450_20 group), vomiting (AA2450_20 group), somnolence (AA2450_5, AA2450_10, and duloxetine groups), and hyperhidrosis (duloxetine group).
- For all treatment groups, the vast majority of nausea events had an onset within the first 4 days of treatment. At least half of the nausea events had a duration of less than 14 days in all treatment groups.
- The incidence of adverse events related to liver and kidney function during the 6-week Treatment Period was low in all treatment groups and comparable between the Lu AA24530 groups and placebo.
- The incidence of adverse events was low during the Taper Period; the incidence was highest in the AA24530_20 group and lowest in the AA24530_10 group. Headache was the only adverse event with an incidence ≥2% (≥2 patients) in the Taper Period in all the Lu AA24530 groups.
- The proportion of patients with adverse events during the Safety Follow-up Period was low and none of the patients in the Lu AA24530 groups had adverse events during this period.
- There were no clinically relevant changes in mean clinical safety laboratory values, vital signs, weight, or ECG values, and the incidences of PCS values were low.

Conclusions

- The primary efficacy analysis showed that daily doses of 5, 10, or 20 mg Lu AA24530 were statistically significantly superior to placebo in mean change from baseline in MADRS total score at Week 6 in patients with Major Depressive Disorder (MDD).
- AA24530_10 was statistically significantly superior to placebo on all other endpoints in the testing strategy and AA24530_20 was statistically significantly ($p < 0.0167$) superior to placebo in the proportion of MADRS responders, in mean CGI-I score, and in the proportion of MADRS remitters at Week 6.
- Treatment with 5, 10, or 20 mg/day Lu AA24530 for 6 weeks is safe and well tolerated in patients with MDD. However, there was a trend towards less tolerability of the 20 mg/day dose, which, like the 5 mg/day and 10 mg/day doses, was given without dose escalation from the first day of treatment.
- All three doses of Lu AA24530 were statistically significantly superior to placebo at Week 6 in secondary efficacy analyses of the MADRS, HAM-D-MES_{23}, HAM-D_{17}, MES, CGI-S, and CGI-I. The superior efficacy of Lu AA24530 over placebo was seen both in the LOCF and in the OC analyses.
- The proportion of patients who responded to treatment after 6 weeks was statistically significantly higher in the AA42530_10 and AA24530_20 groups than in the placebo group.
- The proportion of patients in remission after 6 weeks was statistically significantly higher in the AA42530_5, AA24530_10, and AA24530_20 groups than in the placebo group, based on the MADRS and HAM-D_{17}.
- A statistically significantly larger proportion of patients in the AA24530_5 and AA24530_20 groups than in the placebo group achieved sustained MADRS response.
- All three doses of Lu AA24530 were effective in patients with MDE with melancholic features.
- AA24530_ 20 had a statistically significant effect on shoulder pain at Week 6, both in all patients in the FAS and in the subgroup of patients with baseline shoulder pain.
- The cognitive deficits, as measured by the DSST, the DS-B, the RAVLT, and the STROOP, improved over time with all three doses of Lu AA24530. At Week 6, a consistent statistically significant difference to placebo was seen for AA24530_10 on the majority of the RAVLT parameters, and for AA24530_5 and AA24530_20 on selected RAVLT parameters.
- AA24530_10 improved health-related quality of life, as measured using the SF-36. AA24530_5 and AA24530_20 improved social functioning (both), role physical (AA24530_5), and mental health (AA24530_20).
- Based on the results of this study, Lu AA24530 10 mg/day and 20 mg/day seem to be the target dose range for further evaluation of the clinical effects of Lu AA24530.

Date of the Report

25 March 2010

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