2. SYNOPSIS

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

Title of Study:

A double-blind, randomised, placebo-controlled, 4-way cross-over Phase I study to investigate the pharmacokinetics, pharmacodynamics and safety of escalating single doses of E-52862 in young healthy male and female subjects

Principal Investigator:

U K

Study Centre(s): Richmond Pharmacology Ltd

St George's University of London, Cranmer Terrace, Tooting, London, SW17 0RE, UK

Croydon University Hospital, Woodcroft Wing, 530 London Road, Croydon, CR7 7YE, UK

Publication (reference):

Studied Period:	**Phase of Development:**
25.06.10 (date of first enrolment) 12.08.10 (date of last follow up)	PHASE I

Objectives:

Primary

- To assess the safety and tolerability of single ascending 500 mg, 600 mg and 800 mg doses of E-52862

Secondary

- To describe the cardiovascular safety profile, including rhythm and conduction abnormalities, categorical QT/QTc interval data and qualitative and quantitative ECG variations from baseline
- To describe and compare the number and the rates of adverse events under each treatment
- To describe the pharmacokinetic profiles (PK) of E-52862 and metabolites in the study population
- To describe dose response relationship, using a battery of cognitive tests

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

Methodology:

Double-blind, randomised, cross-over, escalating single dose, single centre study

Number of Subjects (Planned and Analysed):

32 healthy subjects were randomised with 31 of them completing all periods of the study. Of these subjects, 17 were male and 15 were female.

Main Criteria for Inclusion:

Subjects were included if they were male or female, Caucasian, 18-35 years (inclusive) of age, ,with a body mass index of 18-25kg/m^2 (inclusive), using an effective contraceptive method (or were abstinent), judged to be healthy from a medical history, physical examination, routine laboratory investigations and screening ECG assessments.

All subjects included in the study had to meet the ECG screening baseline selection criteria and had to be signed off for inclusion by a cardiologist.

Test Product, Dose and Mode of Administration, Batch Number:

A single oral dose of 500 mg E-52862.HCl, expressed as free base

A single oral dose of 600 mg E-52862.HCl, expressed as free base

A single oral dose of 800 mg E-52862.HCl, expressed as free base

Supplied as:

100 mg capsules (batch number 802235)

200 mg capsules (batch number 802237)

300 mg capsules (batch number 802238)

Duration of Treatment:

A single oral dose of each study treatment per study period

Reference Therapy, Dose and Mode of Administration, Batch Number:

A single oral dose of placebo matching E-52862

Supplied as placebo capsules (batch number 802236)

Criteria for Evaluation:

ECG analysis:

All ECG recordings were examined for qualitative ECG variations, including morphological variations of the P wave, T wave, occurrence of a U wave, occurrence of ventricular arrhythmia and quantitative

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

ECG variations including relative and absolute variations of mean QTc interval, relative and absolute variation of P and PR interval, relative and absolute variations of QRS interval.

Hotler ECG analysis included quantitative and qualitative descriptions of the assessment periods and a comparison to all off treatment assessments.

The baseline ECG recordings were taken on Day -1, at the beginning of each treatment period and were treatment and period specific. Baseline ECG values were scheduled to match the "on-treatment" ECG sampling time-points following administration of study medication on Day 1. All recordings were in triplicate and were compliant with RPL's SOPs for the current recording of ECG (in thorough QT/QTc studies). Mean and median QT/QTc values were calculated for each time-point (triplicate ECG) for subsequent analyses.

Different QT corrections were applied and the most accurate heart rate correction was used to define the primary outcome of the study. This was chosen under blinding conditions by the statisticians based on ECG data from screening and Day -1 of each period ("off-treatment" ECG recordings) from one of the following formulae: (1) Individual correction (QTcI) (linear and nonlinear models); (2) Population correction (QTcP) (linear and nonlinear models); (3) Fridericia's correction; (4) Bazett's correction.

The primary baseline corrections were calculated using averaged QTc baseline values (the mean of all median triplicate readings recorded for each time-point on the baseline Day -1). This single value ($QTc^{baselineAV}$) was used to calculate ΔQTc for each study period. The effect on QTc was calculated as the placebo subtracted time matched difference as:

$\Delta\Delta QTc = (QTc^{active} - QTc^{baselineAV}) - (QTc^{placebo} - QTc^{baselineAV})$ calculated for each of the 12 post-dose ECG time-points.

Cognitive tests

Computerised battery tests were performed including:

- Groton maze learning task (executive function)
- One card learning task (working memory and learning)
- Detection task (simple reaction time/psychomotor function)
- Identification task (choice reaction time)
- Sustained vigilance test (repeat of the detection task)
- VAS

Pharmacokinetic analysis

Blood for analysis of E-52862 levels in plasma was collected at specified times for each period. All PK samples were taken after the corresponding ECG recordings.

Safety analysis

Emergent adverse events were recorded and laboratory investigations, physical and vital signs examinations performed. Interim safety reports were generated between each study period to assess the available data before continuation to the next period.

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

Statistical Methods:

Descriptive analyses were performed to appropriately qualify and quantify the finding from all ECG assessments. Summary statistics (n, arithmetic mean, median, minimum, and maximum) for all primary and secondary parameters were calculated by treatment and time.

The analysis of QT interval changes observed on the cross-over part of the study used the most appropriate heart rate correction (QTcI/QTcF/QTcB) and was based on the change from average baseline. A linear mixed model with sequence, period, sex, time and time by treatment interaction as fixed effects, and baseline as covariate were adapted, with subject as a random effect. Two-sided 90% confidence intervals (CIs) for the difference between each dose of E-52862 and placebo were derived.

Baseline constituted the averaged baseline reference period used for the calculation of the baseline composite. The baselines were period specific in order to provide information on any possible carryover effects. Baseline ECG was scheduled to match the on-treatment clock time-points for each treatment period.

Categorical analyses were performed to determine the number of subjects per treatment regimen and time who had an increase from baseline QTc greater than or equal to 30 msec and greater than or equal to 60 msec. Individual subjects who had a QTc value greater than or equal to 450 msec, greater than or equal to 480 msec and greater than or equal to 500 msec were summarised for each treatment regimen by gender.

Scatter plots of QT and QTc against RR were produced for all data to visualise the best correction formula. Plots of the differences with 90% CIs between all doses of E-52862 and placebo over time were produced for all analyses to describe the concentration and effect relationship.

Cognitive tests

Baseline cognitive testing was performed on Day -1 of each treatment period.

A linear mixed model was used to compare the treatment effect on cognitive test. The model had treatment, sequence, period, sex, time and time by treatment interaction as fixed effects, baseline cognitive test as covariate, and subject as random effect. Two-sided 95 % CIs for the difference between each dose of E-52862 and placebo at each time-point were derived.

Pharmacokinetic analysis

The following endpoints were determined for E-52862 and its metabolites. They were derived by non-compartmental analysis of the plasma concentration-time data (C_{max}, AUC, and $t_{½}$ values were assumed to be log-normally distributed):

- Maximum concentration (C_{max}).
- Time to reach maximum plasma concentration (t_{max}).
- Half-life ($t_{½}$).
- Area under the plasma concentration-time curve from zero to time t of the last measured concentration above the limit of quantification (AUC_{0-t}).

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

- Area under the plasma concentration-time curve from zero to infinity ($AUC_{0-\infty}$).

PK parameters were analysed descriptively:

AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, $t_{½}$, and t_{max} were summarised with arithmetic mean, geometric mean, minimum, median, maximum, SD, standard error, CVb(%), and 95% confidence limits of the means for each dose group. The dose proportionality of pharmacokinetic parameters was evaluated using a linear regression model on a log transformed parameter.

Safety analysis

All emergent adverse events, laboratory investigations, physical and vital signs examinations (including pulse rate and blood pressure) were included in the descriptive safety analysis.

SUMMARY – CONCLUSIONS:

Safety Results:

The safety findings of this study demonstrate that all three dose groups and placebo were well tolerated. Overall, there were no serious adverse events in this study and the majority of reported AEs were of mild intensity. However, one subject was withdrawn from the study due to telemetry findings of atrial fibrillation with an episode of vasovagal syncope during cannulation before active study medication was administered. In total, 116 post-dose treatment AEs were reported by 25 subjects; while 21 pre-dose AEs were reported by 11 subjects. The greatest number of adverse events reported was in the highest dose (800 mg) group with 15 subjects experiencing 50 adverse events, the majority being classified into two MedDRA System Organ Classes, the nervous system and psychiatric disorders. Seventeen (17) subjects experienced 42 adverse events for the 600 mg dose group, while 12 subjects reported 17 adverse events in 500 mg group. Six subjects experienced seven adverse events when receiving placebo. The most commonly reported AEs after E-52862 administration were: from Nervous System Disorders, headache (12 events), postural dizziness (9 events) and dizziness (7 events); and from Psychiatric Disorders, euphoric mood (6 events), dissociation (5 events) and abnormal thinking (5 events). It should be noted that seven of the psychiatric and three of the CNS AEs were reported retrospectively at a later stage and there were no clinical indications of these events during the day of dosing and no obvious concerns during monitoring. All subjects performed and completed their tasks including their cognitive function tests. There were no clinically significant changes in haematology, biochemistry or urinalysis parameters and physical examination during the study.

The results of the QTc analysis comparing the QTcI difference between E-52862 and placebo demonstrated that a single dose of 500 mg E-52862, 600 mg E-52862, and 800 mg E-52862 has no QTc prolonging effect. The largest time-matched QTcI difference between 500 mg E-52862 and placebo was 1.44 msec, between 600 mg E-52862 and placebo was -0.39 msec, and between 800 mg E-52862 and placebo was 1.32 msec. The categorical analyses show that the majority of subjects had either slight decreases or increases from baseline in QTcI which were <30 msec for all of the three dose levels. There were no increases from baseline in QTcI which were greater than 60 msec at any of the measurement time-points for any of the dose levels. All of the subjects had all their QTcI values ≤500 msec at all three dose levels. Mean HR was found to slightly increase at approximately 25 minutes post-dose for all three dose levels ranging from 6.20 to 8.42 bpm. A parallel decrease was

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

observed in mean PR interval values. No changes were observed in QRS interval or vital signs. No clinically relevant changes were found. The majority of subjects had normal telemetry findings during the study. Two subjects showed increases in HR at rest, one of them on 600 mg and 800 mg, reaching a maximum of 150 bpm, and the other subject with the highest dose of 800 mg with HR values up to 174bpm, in both cases always with a regular rhythm.

It was difficult to establish a clear plasma concentration threshold at which cardiovascular and neuropsychiatric AEs are likely to occur. However, the threshold of a plasma concentration of around 3500-5000 ng/mL was observed when the majority of cardiovascular and neuropsychiatric AEs began to occur.

Pharmacodynamic Results:

The cognitive findings of the study indicate that after 2 hours of dosing with E-52862, there was some slowing of responses for simple reaction time (Detection task) and choice reaction time (Identification task), but this slowing of responses recovered by the 24 hour post-dose assessment. There was no effect of any dose of E-52862 on visual memory or executive function, attention or somnolence at any assessment.

In addition, subjective ratings of mood indicated that at 2 hours post-dose, when subjects had been administered E-52862, they rated themselves as more drowsy, dreamy, incompetent and mentally slow than when they had been administered placebo. The negative ratings of mood were largest at the 800 mg dose. These differences were not present at the 24 hours assessment. Taken together this shows that there was no lasting effect after 24 hours of E-52862 administration at 500 mg, 600 mg or 800 mg.

Pharmacokinetic Results:

Mean C_{max} increased dose dependently with values of 3938.50 ng/mL, 4357.94 ng/mL, and 5580.12 ng/mL for the 500 mg, 600 mg and 800 mg dose levels, respectively. Exposure in terms of $AUC_{0-\infty}$ increased with dose reaching 85754.70 ng·hr/mL (500 mg), 112069.7 ng·hr/mL (600 mg), and 155911.0 ng·hr/mL (800 mg). The maximum individual exposure observed in the study was 194037.7 ng·hr/mL with the 800 mg dose. The metabolites showed lower levels of exposure compared to E-52862 in terms of AUC parameters. E-52862 was found to be approximately proportional in relation to dose for C_{max} and AUC parameters.

CONCLUSIONS :

- E-52862 at doses up to 800 mg was safe and well tolerated by the subjects.
- In total, 116 post-dose treatment AEs were reported by 25 subjects.
- The greatest number of adverse events reported was in the 800 mg group with 15 subjects experiencing 50 adverse events, the majority being involved with the nervous system and psychiatric disorders. Seventeen (17) subjects experienced 42 adverse events in the 600 mg dose group and 12 subjects reported 17 adverse events in 500 mg group. Six subjects experienced seven adverse events when receiving placebo.
- The most commonly reported AEs after E-52862 administration were: from Nervous System

Name of Sponsor: Laboratorios del Dr. Esteve S.A.	**Individual Study Table Referring to Part of the Dossier** **Volume:** **N/A** **Page:** **N/A**	(For National Authority Use only)
Name of Finished Product: E-52862 (as E-52862.HCl)		
Name of Active Ingredient:		

Disorders, headache (12 events), postural dizziness (9 events) and dizziness (7 events); and from Psychiatric Disorders, euphoric mood (6 events), dissociation (5 events) and abnormal thinking (5 events).

- Seven of the psychiatric and three of the CNS AEs were reported retrospectively at a later stage and there were no clinical indications of these events during the day of dosing and no obvious concerns during monitoring. All subjects performed and completed their tasks including their cognitive function tests.
- No deaths, serious adverse events were reported.
- The majority of reported AEs were of mild intensity. One subject was withdrawn due to safety issues (telemetry findings) before active study medication was administered.
- No clinically significant findings in laboratory parameters and physical examination were observed.
- It was difficult to establish a clear plasma concentration threshold at which cardiovascular and neuropsychiatric AEs are likely to occur. However, the threshold of a plasma concentration of around 3500-5000 ng/mL was observed when the majority of cardiovascular and neuropsychiatric AEs began to occur.
- The results of the QTc analysis comparing the QTcI difference between E-52862 and placebo demonstrated that a single dose of 500 mg E-52862, 600 mg E-52862, and 800 mg E-52862 has no QTc prolonging effect.
- Mean HR was found to slightly increase in all three dose levels ranging from 6.20 to 8.42 bpm. A parallel decrease was observed in mean PR interval values. No changes were observed in QRS interval or vital signs. The majority of subjects had normal telemetry findings during the study.
- Cognitive findings of the study indicate that after 2 hours of dosing with E-52862, there was some slowing of responses for simple reaction time (Detection task) and choice reaction time (Identification task), but this slowing of responses recovered by the 24 hour post-dose assessment. There was no effect of any dose of E-52862 on visual memory or executive function, attention or somnolence at any assessment. The magnitude of this effect is about 50% of the effect of a glass of wine or fatigue after 24 hours wakefulness for reaction time and 75% for attention.
- Mean C_{max} increased dose dependently with values of 3938.50 ng/mL, 4357.94 ng/mL, and 5580.12 ng/mL for the 500 mg, 600 mg and 800 mg dose levels, respectively.
- Exposure in terms of AUC0-∞ increased with dose reaching 85754.70 ng·hr/mL (500 mg), 112069.7 ng·hr/mL (600 mg), and 155911.0 ng·hr/mL (800 mg).
- The maximum individual exposure observed in the study was 194037.7 ng·hr/mL with the 800 mg dose.
- The metabolites showed lower levels of exposure compared to E-52862 in terms of AUC parameters.
- E-52862 was found to be approximately dose proportional in relation to dose for C_{max} and AUC parameters.

Date of the Report: **28 April 2011**