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Clinical Study Report: M/101057/01

PHASE I, RANDOMIZED, SINGLE-BLIND, PLACEBO-CONTROLLED, MONOCENTER STUDY TO EVALUATE THE SAFETY, TOLERABILITY AND PHARMACOKINETICS OF THE ADENOSINE A_{2B} RECEPTOR ANTAGONIST LAS101057 FOLLOWING ORAL ADMINISTRATION OF SINGLE AND MULTIPLE ASCENDING DOSES IN HEALTHY MALE SUBJECTS

Investigational Product(s): LAS101057

Indication: Asthma

Study Design: Single-blind, randomized, placebo-controlled, monocenter

Name of Sponsor: Laboratorios Almirall, S.A.

Protocol Identification: M/101057/01

Study Initiation Date: 08 March 2007

Study Completion Date: 12 October 2007

Development Phase: Phase 1

Investigators(s):

Sponsor signatory:

Authors:

Date of Report: 24 April 2008

The study was performed in compliance with Good Clinical Practice (GCP), including the archiving of essential documents.

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LAS101057

Signature Page

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2 SYNOPSIS

Name of Sponsor/Company: Laboratorios Almirall, S.A. **Name of Drug Product:** LAS101057 **Name of Drug Substance:** Adenosine A_{2B} receptor antagonist	Individual Study Table Referring to Clinical Part of the Dossier Volume: Page:	*(For National Authority Use only)*
Title of Study: Phase 1, randomized, single-blind, placebo-controlled, monocenter study to evaluate the safety, tolerability and pharmacokinetics of the adenosine A_{2B} receptor antagonist LS101057 following oral administration of single and multiple ascending doses in healthy male subjects.		
Investigator(s): Xendo Drug Development B.V. University Medical Center Groningen-Biotech Center Hanzeplein 1, Entrance 53 9713 GZ Groningen The Netherlands [redacted]		
Study Centre: Xendo Drug Development B.V. University Medical Center Groningen-Biotech Center Hanzeplein 1, Entrance 53 9713 GZ Groningen The Netherlands		**Publication (reference):** Not applicable
Study Period (years): 08 March 2007-12 October 2007		**Phase of Development:** Phase 1:
Objectives: Primary objectives: • To evaluate safety and tolerability of LAS101057 administered orally as single and multiple doses in healthy male subjects. • To evaluate the pharmacokinetics of LAS101057 administered orally as single and multiple doses, and its main metabolites in healthy male subjects. Secondary objective: • To assess the effect of a high-fat, high-calorie meal on the bioavailability of LAS101057 administered as an oral tablet.		
Methodology:		

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Single-dose escalation
Single doses of LAS101057 at 6 ascending dose steps were to be administered orally in the morning to healthy male subjects under fasting conditions: 5, 10, 25, 50, 100, and 200 mg. The starting dose of 5 mg was selected by applying the FDA guidance to the relevant data obtained from preclinical pharmacology, toxicology, safety pharmacology and drug metabolism studies. Twenty-four (24) subjects, divided into two groups (A and B), were to be included. Each group comprised 12 subjects. According to a 3:1:1:1 randomization ratio and specific treatment sequences, 6 subjects were to receive 3 ascending doses of LAS101057, and another 6 subjects were to receive 2 ascending doses of LAS101057 and 1 dose of matching placebo in 3 consecutive treatment periods. The treatment periods were separated by a washout period of at least 7 days. In each period, 10 subjects received LAS101057 and 2 placebo. Subjects in group A were to receive doses of 5, 25 and 100 mg. The corresponding doses in group B were 10, 50 and 200 mg. Furthermore, to dose escalate in a controlled way, within each dose step, subjects were divided into 2 subgroups of 4 (including one placebo) and 8 subjects (including one placebo) respectively, in which dosing was staggered by approximately 48 h. The decision on escalating the dose was based on the clinical assessment of the safety and tolerability of the preceding doses. Based on these assessments, intermediate doses (15 or 75 mg) as well as doses lower than 5 mg (1 or 2 mg) were to be considered.

Interaction with food
The effect of a high-fat, high-calorie meal (American breakfast) on the bioavailability of LAS101057 was to be evaluated after a single oral tablet. Dose selection was to be based on the results obtained from the first 4 dose steps of the single-dose escalation phase. Following an overnight fast of at least 10 h, 10 healthy male subjects were to receive LAS101057 either in the fasted or fed state, according to a 1:1 randomization ratio and a 2-period crossover design. Treatment phases were to be separated by a washout period of at least 7 days. In each period, subjects were to be divided into 2 subgroups of 6 and 4 subjects, in which dosing was to be staggered by approximately 48 h.

Multiple-dose escalation
Following the completion of the single dose escalation, multiple doses of LAS101057 at 3 ascending dose steps were to be administered orally to healthy male subjects under fasting conditions. Dose selection was to be based on the results (interim safety report and pharmacokinetic data) obtained from the single-dose escalation

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phase. Exposure was not to be higher than that observed in the single-dose escalation phase. LAS101057 was to be administered as a single daily dose in the morning for 7 consecutive days. Ten subjects were to be randomized to each dose level at a 4:1 active:placebo randomization ratio, of which 8 were to receive active treatment and 2 matching placebo. Dose escalation was to be staggered by approximately 7 days and was to be based on the clinical assessment of the safety and tolerability of the preceding doses.

If the pharmacokinetic profile obtained during the single dose escalation phase did not suggest compatibility with once-daily dosing, subjects were to receive twice-daily (b.i.d.) or three-times-daily (t.i.d.) administrations separated by 12 or 8 hours, respectively.

Number of Subjects (Planned and Analyzed):
Number of subjects planned: 64 (24 subjects for the single dose escalation phase, 30 subjects for the multiple dose escalation phase and 10 additional subjects for the assessment of food interaction)
Number of subjects analyzed: 22

Diagnosis and Main Criteria for Inclusion:

Inclusion criteria:

- Caucasian male aged between 18 and 55 years (both included)
- Body Mass Index (BMI: weight in kg/height in m^2) in the range of 18.5 to 29.9 kg/m^2 (both included) at screening
- Systolic blood pressure between 100 and 140 mmHg and diastolic blood pressure between 60 and 90 mmHg (both included) at screening
- Heart rate between 45 and 90 bpm (both included) at screening
- Oral body temperature between 35.5 and 37.5 °C (both included) at screening
- Non-smoker or smoker of less than 5 cigarettes daily
- Normal values or non-clinically relevant abnormalities in the results of the physical examination and laboratory tests at screening as judged by the medical investigator
- Normal values or non-clinically relevant abnormalities in 12-lead Electrocardiogram (ECG) at screening as judged by the medical investigator
- Ability to communicate adequately with investigators and comply with protocol requirements, including overnight stays, blood and urine sample collections as defined in the protocol

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- Ability to understand and willingness to sign the informed consent form
- No objection received from the subject's general practitioner regarding his participation in the trial

Exclusion criteria

- Presence or history of clinically significant ECG abnormalities, cardiovascular, renal, hepatic, respiratory, gastrointestinal, haematological, neurological, genitourinary, autoimmune, endocrine, metabolic, ophthalmologic or psychiatric disorder (treated or not)
- QT values higher than 500 msec or QTcB values higher than 450 msec at screening
- History of severe allergy (anaphylaxis, angioneurotic oedema), any type of clinically relevant chronic seasonal allergy (e.g. allergic rhinitis, urticaria) or asthma
- Respiratory infection within the 2 preceding weeks of first IMP administration
- Existence of any surgical or medical condition which, in the judgement of the investigator, might interfere with the absorption, distribution, metabolism or excretion of the IMP
- History of drug hypersensitivity reactions or hypersensitivity to drugs chemically related to the IMP
- History or any current evidence of alcohol or drug abuse
- Positive laboratory test for urine drug screening (amphetamines, barbiturates, benzodiazepines, cocaine, marijuana, methadone, methamphetamine, morphine, phencyclidine, tricyclic antidepressants)
- Consumption of more than 50 g or 4 units of alcohol per day, or more than 6 cups per day of caffeine or xanthine-containing beverages
- Positive laboratory test for Hepatitis B surface antigen (HbsAg), anti-HBc IgM, anti-HIV, or anti-HCV antibodies
- Administration of any prescribed or over the counter drug within 2 weeks prior to the first IMP administration, with the exception of paracetamol (acetaminophen), which is allowed up to 72 hours prior to the administration of the first dose
- Administration of an immunosuppressive drug within 3 months prior to first IMP administration
- Participation in other clinical trials testing any investigational or commercially

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available drugs within 90 days of first IMP administration

- Participation in more than 4 clinical trials testing any investigational or commercially available drugs within the 10 preceding months of first IMP administration
- Donation of blood or loss of more than 250 ml blood within 1 month prior to first IMP administration
- Donation of more than 1.5 liters of blood within the 10 preceding months of first IMP administration

Test Product, Dose and Mode of Administration, Batch Number:
Product: Adenosine A_{2B} receptor antagonist LAS101057
Dose: 5, 10, 25, 50, 100 or 200 mg
Dosage form: 1, 5, 25 and 100 mg coated tablets
Administration route: oral
Frequency and mode of administration: Once-daily as single or multiple doses for 7 consecutive days (alternative b.i.d. or t.i.d. schedules were considered based on pharmacokinetics data obtained in the single dose escalation phase)
Batch Numbers: LAS101057 1mg - 049F0079
LAS101057 5mg - 050F0083
LAS101057 25mg - 052F0084
LAS101057 100mg - 053F0089

Duration of Treatment:
Single-dose escalation: Three single ascending dose administrations of LAS101057 or two single ascending dose of LAS101057 and one of placebo, with a wash-out of at least 7 days between treatments.

Interaction with food: Two single-dose treatment periods of LAS101057 administration for each subject, with a wash-out of at least 7 days between treatments.

Multiple-dose escalation: Administration of one dose of LAS101057 or placebo once daily for 7 consecutive days for each subject.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Product: Placebo
Dose: Placebo
Dosage form: Matching placebo tablets
Administration route: oral

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Frequency and mode of administration: Once-daily as single or multiple doses for 7 consecutive days (alternative b.i.d. or t.i.d. schedules were considered based on pharmacokinetics data obtained in the single dose escalation phase)

Batch Number: LAS101057 Placebo 1-5mg A - 044F0074
LAS101057 Placebo 25mg A - 045F0075
LAS101057 Placebo 100mg A - 047F0076

Criteria for Evaluation:

Baseline assessments:

1. Medical history and demographic data at screening.
2. Serology tests at screening.
3. Drug screening at screening and Day -1 of each IMP administration.
4. Alcohol breath test at screening and Day -1 of each IMP administration.

Safety:

1. Averse events (both intensity and relationship to the IMP) were volunteered by the subject, elicited by investigator questioning, or detected by physical examination, laboratory tests or other means throughout the trial.
2. Vital signs (heart rate, systolic and diastolic blood pressure) at multiple time points throughout the trial. Oral body temperature was measured at screening, pre-dose of each IMP administration and at the follow-up visit.
3. 12-lead ECG (supine, after 5 minutes of rest) at multiple time points during the trial.
4. Clinical laboratory tests (routine hematology, coagulation, clinical chemistry, hormonal analysis, urinalysis) at multiple time points throughout the study.
5. Physical examination at multiple time points during the trial.
6. Electrocardiographic telemetry monitoring (1 h before dosing until 24 h after IMP administration in the single-dose escalation and food interaction study; 1 h before dosing and 2 h after expected t_{max} on Day 1, 4 and 7 of the multiple-dose escalation study).

Pharmacokinetics:

Blood samples for the measurement of LAS101057 plasma concentrations were taken throughout the trial. For the single-dose escalation and food interaction study the following parameters were to be calculated: $AUC_{0-\infty}$, AUC_{0-t}, C_{max}, t_{max}, $t_{1/2}$, λ_z, MRT, CL/F and V_z/F.

For the multiple-dose escalation study, multiple samples were to be taken on Day 1

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and the following parameters were to be calculated: AUC_{0-t}, $AUC_{0-\infty}$, C_{max}, C_{min}, t_{max}, $t_{1/2}$ and λ_z. On Days 2 to 6, one blood sample was to be taken pre-dose and at the expected t_{max}. The following parameters were to be calculated: C_{min} and C_{max}. On Day 7 multiple blood samples were to be taken, on Day 8 two samples were taken and both on Day 9 and Day 10 one sample was taken. The following parameters were to be calculated: $AUC_{0-\tau}^{ss}$, C_{max}^{ss}, C_{min}^{ss}, C_{av}^{ss}, t_{max}, $t_{1/2}$, λ_z, CL/F, Vz/F, R and FI.
In subjects in whom an unexpected pharmacokinetic profile was obtained, genotyping for CYP2C19 was to be carried out to assess if the observed variability could be due to CYP2C19 poor metabolizer condition.

Urine samples were to be collected at multiple time points during the single dose escalation phase pre-dose and in quantitative fractions after IMP administration in each period in the single dose escalation phase. Parameters to be calculated were: Ae and CL_R.

Statistical Methods:
For each phase of the trial, the safety and tolerability variables and the pharmacokinetic parameters were to be analyzed by means of descriptive statistics. Furthermore, the dose proportionality of AUC and C_{max} in the single-dose escalation phase and the dose proportionality of AUC^{ss} and C_{max}^{ss} in the multiple-dose escalation phase were to be tested by appropriate regression models for exploratory purposes. In addition, for each dose in the multiple-dose escalation phase, the comparisons of all pharmacokinetic parameters were to be performed between days of treatment in order to establish a possible time effect. Finally, the effect of food was to be studied by means of an analysis of variance (ANOVA) model for cross-over designs on the log-transformed AUC and C_{max} parameters.

Summary and Conclusions:

Only the first two periods of Group A and the first period of Group B of the single-dose escalation part of the study were performed (5 mg, 10 mg and 25 mg of LAS101057).

Pharmacokinetic results:

Evaluation of PK parameters showed that LAS101057 was metabolized rapidly, with a mean $t_{1/2}$ of 1.58 ± 0.55 hr after administration of 5 mg of the study drug, 1.60 ± 0.48 hr after administration of 10 mg LAS101057 and 2.59 ± 0.75 hr after the highest dose of 25 mg LAS101057.

Furthermore, AUC_{0-t} and the $AUC_{0-\infty}$ of the metabolites LAS101238 and LAS101560 were higher than for the parent compound LAS101057. After the highest dose of 25

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mg LAS101057, AUC_{0-t} and $AUC_{0-\infty}$ of the unchanged form were 359.1 ± 98.03 hr·ng/mL and 362.7 ± 98.08 hr·ng/mL, respectively. For LAS101238, AUC_{0-t} was 2682 ± 591.6 hr·ng/mL and $AUC_{0-\infty}$ was 2726 ± 623.6 hr·ng/mL. For the metabolite LAS101560, AUC_{0-t} and $AUC_{0-\infty}$ were 640.3 ± 106.9 hr·ng/mL and 646.1 ± 106.9 hr·ng/mL, respectively.

These findings are in contrast with the findings obtained in preclinical studies with laboratory animals, in which plasma AUCs of the metabolites were all below the AUCs of the unchanged compound.

Safety Results:

Evaluation of the safety and tolerability of LAS101057 showed that 4 out of 8 subjects reported 7 AEs after receiving 5 mg of LAS101057, 6 out of 10 subjects reported 13 AEs after the middle dose of 10 mg LAS101057 and 5 out of 7 subjects reported 8 AEs after administration of 25 mg of LAS101057.

Abdominal pain, diarrhoea and somnolence were only reported after administration of LAS101057 and not after treatment with placebo. All reports of abdominal pain (1 subject after 5 mg of LAS101057, 1 subject after 10 mg and 1 subject after treatment with 25 mg) and all reports of diarrhoea (1 subject treated with 5 mg of the study drug and 1 subject treated with 10 mg of LAS101057) were considered to be related to treatment with LAS101057. For somnolence, the report of 1 subject treated with 10 mg LAS101057 and the report by 1 subject treated with 25 mg LAS101057 were considered to be related to the study drug. One (1) report of somnolence by a subject in the 10 mg group was considered not related to the treatment.

A total of 7 episodes of headache were reported by 6 subjects. One (1) episode of headache reported by 1 subject after administration of 5 mg LAS101057 and 1 episode reported by 1 subject after treatment with 10 mg LAS101057 were considered to be related to the study medication. Both episodes were of mild intensity. All other episode of headache, among which were 1 episode of severe intensity and 1 episode of moderate intensity, were considered to be not related to treatment with LAS101057.

Laboratory findings, vital signs, physical examination, ECGs and electrocardiographic telemetry did not reveal any clinically relevant findings.

Conclusions:

LAS101057 was safe and well tolerated in this study. However, the PK data showed a high clearance of the active parent compound LAS101057, while a marked and

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sustained occurrence of the metabolites LAS101238 and LAS101560 led to exposures higher than that of the parent compound. These unexpected and unfavorable results made the sponsor decide to prematurely terminate this study. Date of Report: 24 April 2008		