2. SYNOPSIS

<table>
<tr><td>Name of Sponsor / Company:
AstraZeneca

Name of Finished Product:
N.A.

Name of Active Ingredients:
LAS100977</td><td>Individual Study Table Referring to Part of the Dossier

Volume:

Page:</td><td>(For National Authority Use only)</td></tr>
<tr><td colspan="3">Title of Study: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, 4-WAY CROSSOVER CLINICAL TRIAL TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE DOSES OF LAS100977 ADMINISTERED BY INHALATION TO STABLE ASTHMA PATIENTS</td></tr>
<tr><td colspan="3">Investigators:</td></tr>
<tr><td colspan="3">Study centres:</td></tr>
<tr><td colspan="3">Publication (reference):
None</td></tr>
<tr><td colspan="2">Studied period (years):
Date study initiated (first screening): 04 November 2008
Date study finalised (last patient last visit): 02 March 2009</td><td>Phase of development: IIa</td></tr>
<tr><td colspan="3">Objectives:
a) To assess the efficacy of three single doses of LAS100977 administered by inhalation to patients with stable persistent asthma.

b) To evaluate the safety and tolerability of three single doses of LAS100977 after single administration to patients with stable persistent asthma.

c) To assess pharmacokinetics of three doses of LAS100977 after single administration to patients with stable persistent asthma.</td></tr>
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Methodology:
This was a phase IIa, randomised, double-blind, placebo-controlled, 4-way crossover clinical study. Within a run-in period of 14 days maximum before the first IMP administration, patients underwent a screening assessment and their usual asthma therapy, apart from inhaled corticosteroids, was withdrawn. Twenty-eight male asthma patients were randomly assigned in a 1:1:1:1 ratio to one of four treatment sequences; seven patients per sequence. Each treatment sequence consisted of four treatment periods. Four treatments; LAS100977 0.625 µg, 1.25 µg and 5 µg, and placebo were tested; with one treatment administered per treatment period, and a washout period for at least one week between each treatment period (see below).

	Treatment Period 1	**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**
Sequence 1 (n=7)	LAS100977 0.625 µg	PLACEBO	LAS100977 1.25 µg	LAS100977 5 µg
Sequence 2 (n=7)	LAS100977 1.25 µg	LAS100977 5 µg	LAS100977 0.625 µg	PLACEBO
Sequence 3 (n=7)	LAS100977 5 µg	LAS100977 1.25 µg	PLACEBO	LAS100977 0.625 µg
Sequence 4 (n=7)	PLACEBO	LAS100977 0.625 µg	LAS100977 5 µg	LAS100977 1.25 µg

Number of patients (planned and analysed):

Planned:	28
Screened:	38
Randomised:	28
Completed study:	26
Evaluated for efficacy:	26
Evaluated for pharmacokinetics:	26
Evaluated for safety:	28

Diagnosis and main criteria for inclusion:
- Adult male patients aged 18-70 years (both included)
- With a clinical diagnosis of persistent asthma (according to GINA guidelines 2007 update) for at least 6 months prior to screening
- Maintained on a stable dose of inhaled corticosteroids together with either a short or a long-acting β2-agonist over the previous 6 weeks prior to screening
- Screening FEV_1 value of 60% < FEV_1 ≤ 85% of the predicted normal value (based on European Community for Steel and Coal predicted values Quanjer et al. 1993 for calculation purposes) after a washout of at least 6 hours for short-acting β2-agonists and 72 hours for long-acting β2-agonists if applicable, FEV_1 reversibility ≥ 12% and an absolute increase of at least 200 ml over baseline value within 30 minutes after inhalation of 400 µg (four inhalations) of salbutamol via a metered dose inhaler using a spacer, pre-dose FEV_1 value of first treatment period within the range of 80-120% of the FEV_1 measured at screening prior to salbutamol inhalation [i.e. within the interval: 0.8 x pre-salbutamol FEV_1 (screening) – 1.2 x pre-salbutamol FEV_1 (screening)].
- Normal values or non-clinically relevant abnormalities in the results of the physical examination, laboratory tests and 12-lead ECG; QT and QTcB lower than 500 milliseconds and lower than or equal to 450 milliseconds, respectively, in the ECGs performed at screening and before the first IMP administration.

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Test product , dose and mode of administration, batch number, expiry date:

Name: LAS100977

Administration route: Oral inhalation

Dosage form: Dry powder (hard capsule) for inhalation delivered through a rechargeable cyclohaler

Dose and regimen: A single dose of 0.625 µg, 1.25 µg and 5 µg on Day 1 of the study period

Dose	Batch number	Expiry date
LAS100977 0.625 µg	085F0142	03/2009
LAS100977 1.25 µg	084F0140	03/2009
LAS100977 5 µg	076F0125	03/2009

Duration of treatment:

The total duration of the study for each patient was approximately 7 weeks, including screening (up to 14 days before first IMP administration on Day 1 of the treatment period), post-IMP administration assessments, and follow-up evaluation (7 days after last IMP administration).

Reference therapy, dose and mode of administration, batch number, expiry date:

Name: LAS100977 Placebo

Administration route: Oral inhalation

Dosage form: Dry powder for inhalation (hard capsule) delivered through a rechargeable cyclohaler

Dose and regimen: Placebo

Batch number: 074F0121

Expiry date: 03/2009

Criteria for evaluation:

Efficacy

Lung function tests (spirometry): Forced Expiratory Volume in first second (FEV_1), Forced Vital Capacity (FVC), Peak Expiratory Flow (PEF) and Forced Mid-Expiratory Flow (FEF_{25-75}) were the parameters determined at Pre-dose and 5 min, 15 min, 30 min, 1h, 2h, 3h, 4h, 6h, 8h, 12h, 14h, 23h, 24h, 36h and 48h after morning IMP inhalation on Day 1.

Safety and Tolerability

Adverse events, physical examination, vital signs (blood pressure and pulse rate), 12-lead ECG, routine haematology, coagulation (screening only), blood chemistry, with serum potassium and blood glucose, urinalysis, alcohol breath/urine test, anti-viral serology test (Hepatitis B surface antigen or HBc, HIV and Hepatitis C antibodies), and screening for illicit drugs (cannabis, amphetamines, barbiturates, benzodiazepines, cocaine and opiates).

Pharmacokinetics

Blood and urine samples for LAS100977 pharmacokinetic analysis were drawn at different timepoints after study drug administration. Area under the concentration-time curve from zero to time t [AUC(0-t)], maximum plasma concentration (C_{max}), time to reach maximum plasma concentration (t_{max}), total body clearance from plasma (CL/f), mean residence time (MRT), amount of unchanged drug excreted in urine (Ae) and renal clearance (CL_R) were determined. If the terminal disposition phase was observed, the smallest (terminal) elimination rate constant (λ_z), the elimination half-life ($t_{1/2}$), the apparent volume of distribution during the terminal phase (V_z/f), the area under the concentration-time curve from zero to infinity (AUC) were estimated. See Section 9.5.5.1 for PK definitions.

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Statistical methods:

Efficacy
The analyses of all the efficacy variables were performed on the Per Protocol (PP) Population. The primary efficacy variable (change from pre-dose in trough FEV_1 at Day 1), was analysed by means of an Analysis of Covariance (ANCOVA) models for crossover designs. Secondary efficacy variables (change from pre-dose in trough FVC, PEF and FEF_{25-75}, AUC 0-6, AUC 0-12, AUC 0-24, AUC 0-36, AUC 0-48, AUC 12-24 and change from pre-dose in FEV_1, FVC, PEF and FEF_{25-75} at each time point), were analysed according to the nature of variable, by means of ANCOVA models or descriptive statistics.

Safety and Tolerability
All safety and tolerability outcomes were analysed using the Safety Population. Safety and tolerability data (AEs, vital signs, laboratory parameters, ECG and physical examination), were analysed by means of the appropriate descriptive statistics across treatment groups.

Pharmacokinetics
All analyses of the pharmacokinetic parameters were performed on the PP Population. Pharmacokinetic parameters of the LAS100977 were analysed by appropriate descriptive statistics and graphs for each dose group.

Analysis of Other Variables
The following analyses were carried out for the safety population: The number, and percentage of patient withdrawals and reasons of withdrawal, and the number and percentage of patients taking previous, concomitant and rescue medications. These were described using descriptive statistics. And individual listings were also performed.

SUMMARY – STUDY RESULTS

Efficacy Results:

- LAS100977 after single inhaled morning dose administration of 0.625 µg, 1.25 µg and 5 µg using a dry powder formulation delivered by a Cyclohaler® device, induced a relevant and over time maintained bronchodilatory effect in stable asthma male patients. Adjusted mean [Standard Error (SE)] increases from pre-dose in trough FEV_1 when compared to placebo, were 0.281 (0.048) L, 0.296 (0.067) L and 0.516 (0.049) L across the ascending dose range of LAS100977 (0.625 µg, 1.25 µg and 5 µg doses respectively). These increases in trough FEV_1 were all clinically and statistically significant.
- A statistically significant ($p<0.001$) dose related difference in change from pre-dose in trough FEV_1 was observed between the LAS100977 5 µg and both lower dose levels, but not between the 0.625 µg and 1.25 µg dose levels. A dose-related response was therefore demonstrated in this trial.
- Adjusted mean (SE) increases in FEV_1 from pre-dose at 5 minutes when compared to placebo were 0.087 (0.047) L, 0.068 (0.056) L and 0.338 (0.051) L for 0.625 µg, 1.25 µg and 5 µg, respectively. For this timepoint only the 5 µg dose produced a statistically significant ($p<0.001$) and clinically relevant effect. From the 15 minutes timepoint until 24 hours, all LAS100977 doses compared to placebo showed statistically significant ($p<0.001$) and clinically relevant increases from pre-dose FEV_1 [with the exception of the 1.25 µg dose at 23 h ($p<0.05$)].
- Adjusted mean (SE) increases from pre-dose in normalized AUC_{0-12} of FEV_1 when compared to placebo were 0.355 (0.046) L, 0.361 (0.055) L and 0.528 (0.050) L for 0.625 µg, 1.25 µg and 5 µg, respectively. These increases in normalized AUC_{0-12} of FEV_1 were all clinically and statistically significant ($p<0.0001$).
- Adjusted mean (SE) changes from pre-dose in peak FEV_1 after LAS100977 0.625 µg, 1.25 µg and 5 µg doses when compared to placebo were 0.364 (0.047) L, 0.347 (0.068) L, and 0.497 (0.056) L, respectively. The median time to reach peak FEV_1 was 3 hours for the three LAS100977 doses tested (180 min for LAS100977 0.625 µg and 1.25 µg and 182 min for LAS100977 5 µg).

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- All doses of LAS100977 showed a relevant bronchodilatory effect which was observed over 24 hours post-dose for LAS100977 0.625 µg, until 36 hours post-dose for LAS100977 1.25 µg and until the last timepoint assessed (48 hours post-dose) for LAS100977 5µg. Adjusted mean (SE) increases from pre-dose at these timepoints compared to placebo were 0.274 (0.052) L, 0.152 (0.060) L and 0.139 (0.060) L for LAS100977 0.625 µg, 1.25 µg and 5 µg, respectively. Adjusted mean (SE) increases from pre-dose at the 24 hour timepoint compared to placebo were 0.274 (0.052) L, 0.286 (0.062) L and 0.487 (0.046) L and at the 48 hour timepoint 0.019 (0.071) L, 0.000 (0.085) L and 0.139 (0.060) L for LAS100977 0.625 µg, 1.25 µg and 5 µg respectively.
- The adjusted mean changes from pre-dose in trough FVC, PEF and FEF_{25-75} and normalized AUCs of FEV_1 confirmed the bronchodilatory effect observed after administration of LAS100977 0.625 µg, 1.25 µg and 5 µg. These increased changes were all statistically significant compared with placebo treatment, except for trough FVC after LAS100977 1.25 µg.
- Significant adjusted mean changes from pre-dose in PEF and FEF_{25-75} versus placebo were observed until 36 hours after LAS100977 0.625 µg and 1.25 µg and until 48 hours after LAS100977 5 µg. The effects on FVC were less well sustained and were significantly different to placebo until about 14 to 24 hours after dosing.

Pharmacokinetic Results:

- Generally there were no quantifiable plasma concentrations observed in subjects following 0.625 and 1.25 µg inhalation doses of LAS100977. Relatively low exposure and sparse quantifiable concentrations of LAS100977 were observed in subjects receiving 5 µg LAS100977.
- The absorption of LAS100977 was rapid with a median t_{max} of 0.75 to 0.77 hours. Following C_{max}, plasma concentration decreased in a monophasic manner with an apparent terminal elimination half-life of approximately 4 hours.
- The percentage of the LAS100977 inhaled dose excreted into urine as unchanged compound was very low, with mean values ranging from 0.7 to 1.3% of administered dose over the 0.625 to 5 µg dose range.

Safety and Tolerability Results:

- Single inhaled morning doses of LAS100977 0.625, 1.25 and 5 µg showed an overall good safety and tolerability profile in male patients with mild to moderate stable asthma. A dose-response relationship could not be observed in any of the different safety and tolerability outcomes evaluated.
- Overall, 14 (50%) of the 28 patients who participated in the trial reported 33 TEAEs. Most of these TEAEs were considered by the investigator to be either of mild (20 events) or moderate (10 events) intensity, while 3 were severe. The percentage of patients who experienced at least one TEAE was 25%, 22% and 27% in the LAS100977 0.625 µg, 1.25 µg and 5 µg treatment groups, respectively, and 11% after placebo treatment. The number of TEAEs per treatment group was higher after LAS100977 0.625 µg, 1.25 µg and 5 µg doses (11, 7 and 12 events, respectively) than after placebo treatment (3 events). However, the number of TEAEs considered to be related to the study drug did not relevantly increase with ascending LAS100977 doses; 1 TEAE each after LAS100977 0.625 µg and 1.25 µg and 2 TEAEs after LAS100977 5 µg, compared with none related TEAE following placebo treatment. The TEAEs were headache (2 events), fatigue and diarrhoea.
- The most frequently reported TEAEs were headache (8 events in 6 patients: 3 events in 3 patients in the LAS100977 0.625 µg group, 2 events in 2 patients in the LAS100977 1.25 µg group and 3 events in 3 patients in the LAS100977 5 µg group), followed by nasopharyngitis (5 events in 5 patients: 2 events in 2 patients in the placebo group, 1 event in 1 patient in the LAS100977 0.625 µg group, and 2 events in 2 patients in the LAS100977 5 µg group), and productive cough (3 events in 1 patient: 1 event in 1 patient in the LAS100977 0.625 µg group and 2 events in 1 patient in the LAS100977 5 µg group).
- No SAEs and no deaths occurred during the clinical study. One patient was withdrawn due to an adverse event (lower respiratory infection), that was considered to be not related to the study drug.
- There was no evidence of a clinically relevant effect on any safety laboratory parameter and no

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laboratory results constituted a TEAE.

- There was also no evidence of clinically meaningful effects on serum potassium or on blood glucose after the inhalation of any LAS100977 doses.
- No clinically relevant changes in systolic and diastolic blood pressure were observed in any group and no relevant findings in the physical examinations were detected.
- No clinically meaningful changes in pulse or heart rate apparently related to LAS100977 treatment became evident. Minor changes observed across the observation period were not consistently different from fluctuations seen following placebo treatment.
- None of the ECG parameters showed clinically relevant changes over time and there were no clinically meaningful differences between treatments, including placebo. No QTcB and QTcF values > 450 ms and no QTcF changes from pre-dose ≥ 60 ms were observed in any of the study groups. Increases in QTcB ≥ 30 ms were observed in a total of 17 patients in all treatment groups including placebo, whereas QTcF ≥ 30 ms were determined only in a total of 4 patients for LAS100977 1.25 µg and 5 µg doses. As this was not a thorough QTc study, caution should be taken in interpreting these data.
- No findings of clinical relevance were found in the rest of the 12-lead ECG parameters assessed.

CONCLUSIONS:

DATE OF REPORT:
16 November 2010

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