2. SYNOPSIS

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: A PHASE IIa, RANDOMISED, DOUBLE-BLIND, MULTIPLE DOSE, PLACEBO CONTROLLED, 3 PERIOD CROSS-OVER, ASCENDING DOSE CLINICAL TRIAL TO ASSESS THE EFFICACY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF THREE DIFFERENT DOSES OF LAS100977, ADMINISTERED BY INHALATION DURING 7 DAYS TO STABLE ASTHMA PATIENTS		
Investigators:		
Study centres:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 11 September 2008 Date study finalised (last patient last visit): 8 December 2008	**Phase of development:** IIa	
Objectives: a) To assess the efficacy of three doses of LAS100977 administered once daily over 7 days by inhalation to patients with stable persistent asthma. b) To evaluate the safety and tolerability of three doses of LAS100977 after 7 days of administration to patients with stable persistent asthma. c) To assess explorative pharmacokinetics of three doses of LAS100977 administered once daily over 7 days by inhalation to patients with stable persistent asthma.		
Methodology: This was a phase IIa, randomised, double-blind, multiple dose, placebo controlled, 3 period cross-over sequential, dose-ascending clinical study. Within a period of 14 days before the first IMP administration, a screening assessment took place and the usual asthma therapy of patients was withdrawn, (except corticosteroid therapy). Twenty male asthma patients were included in the study. They were randomly assigned to 1 of 4 possible treatment sequences according to a randomisation schedule in a (1:1:1:1) ratio:		

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

	Treatment Period 1	**Treatment Period 2**	**Treatment Period 3**
Sequence 1	LAS100977 2.5μg	LAS100977 5 μg	Placebo
Sequence 2	LAS100977 2.5 μg	Placebo	LAS100977 10 μg
Sequence 3	Placebo	LAS100977 5 μg	LAS100977 10 μg
Sequence 4	LAS100977 2.5 μg	LAS100977 5μg	LAS100977 10 μg

During each treatment period, 15 patients received 2.5 µg LAS100977, 5 µg LAS100977 or 10 µg LAS100977 and 5 patients received placebo. The duration of each treatment in each treatment period was 7 days and consecutive periods were separated by a washout phase of 7-21 days.
Patients underwent serial study evaluations on Days 1 and 7 of each period. Escalation to the next dose level occurred only when the safety and tolerability of the previous dose level had been fully evaluated (blinded assessment) and when the investigator and sponsor agreed that escalation was appropriate.
All doses of LAS100977 and placebo were administered in the morning as dry powder delivered from hard capsules inhaled through a rechargeable device (Cyclohaler).
Seven days after inhalation of the last treatment, a follow-up evaluation was performed. Throughout the treatment and washout periods, rescue therapy (100 µg/puff of salbutamol pMDI) was permitted on an as-needed basis but should be avoided within 6 hours prior to any pulmonary function test performed for the study.

Number of patients (planned and analysed):

Planned:	20 patients
Screened:	28 patients
Randomised:	20 patients
Completed treatment phase:	19 patients
Completed study:	19 patients
Evaluated for efficacy:	19 patients (PP population)
Evaluated for pharmacokinetics:	19 patients (PP population)
Evaluated for safety:	20 patients (Safety population)

Diagnosis and main criteria for inclusion:

- Adult male patients aged 18-70 years (inclusive).
- Clinical diagnosis of persistent asthma (according to GINA guidelines 2007 update) for at least 6 months prior to screening.
- Maintenance on a stable dose of inhaled corticosteroids together with either a short or a long-acting β_2-agonist over the previous 6 weeks prior to screening.
- Screening FEV_1 value of 60% < FEV_1 ≤ 85% of the predicted normal value after a washout of at least 6 hours for short-acting β_2-agonists and 72 hours for long-acting β_2-agonists, if applicable.
- FEV_1 reversibility ≥ 12% and an absolute increase of at least 200 mL over baseline value within 30 min after inhalation of 400 µg (four inhalations) of salbutamol via a metered dose inhaler.
- 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 QTc [calculated according to Bazett's formulae ($QTc=QT[msec] / RR[sec]^{1/2}$)] 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.

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

- Ability to communicate adequately with the investigator and comply with the protocol requirements, instructions and protocol-stated restrictions.
- Ability to use an inhaler device and perform spirometries.
- Eligibility and ability to participate in the study and consent to do so in writing after the purpose and nature of the investigation have been explained.

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

Name:	LAS100977
Administration route:	Oral inhalation
Dosage form:	Dry powder for inhalation delivered through a rechargeable Cyclohaler
Dose and regimen:	Once-daily doses of 2.5 µg, 5 µg and 10 µg for 7 days
Batch numbers:	LAS100977 2.5 µg: 080F0132 LAS100977 5.0 µg: 076F0125
Expiry date:	LAS100977 2.5 µg: 12/2008 LAS100977 5.0 µg: 12/2008

Duration of treatment:

The total duration of the clinical study for each patient was between 8 and 12 weeks, including screening (up to 14 days before first IMP administration), post-IMP administration assessments on Day 1, Day 4 and Day 7 of each treatment period (the duration of each treatment in each treatment period was 7 days), washout periods from 7 to 21 days 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 (lactose) delivered through a rechargeable Cyclohaler
Dose and regimen:	Placebo
Batch number:	074F0121
Expiry date:	12/2008

Criteria for evaluation:

Efficacy:

At each treatment period, the efficacy of different doses of LAS100977 and placebo was assessed by pulmonary function tests (spirometry) at different time points during each treatment period: up to 24 hours after morning IMP inhalation on Day 1 and up to 36 hours after Day 7 administration; in addition a pre-dose spirometry was performed on Day 4. Spirometers were used to measure forced vital capacity (FVC), forced expiratory volume in first second (FEV_1), peak expiratory flow (PEF), and forced mid-expiratory flow (FEF_{25-75}), and met American Thoracic Society (ATS) and European Respiratory Society (ERS) recommendations for accuracy and precision.

Safety and tolerability:

Adverse events, vital signs (blood pressure and pulse), physical examination, 12-lead electrocardiogram (ECG), and laboratory tests (haematology, biochemistry, and urinalysis), were assessed at the different established time points of each treatment period. Drug screening (cannabinoids, amphetamines, barbiturates, benzodiazepines, cocaine and opiates), alcohol breath/urine tests, serology tests (Hepatitis B surface antigen, Hepatitis C antibodies, and Human immunodeficiency virus [HIV]) and coagulation test were assessed at screening.

Pharmacokinetics:

Blood samples for LAS100977 pharmacokinetic analysis were drawn at different time points after study drug administration on Day 1 and Day 7 of treatment. Area under the concentration-time curve from zero to the last quantificable point on Day 1 [AUC(0-t)] and on Day 7 of treatment [$AUC(0\text{-}t)^{SS}$], area under the plasma concentration time-curve from time zero to infinity (AUC) on Day 1, area under the plasma

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

concentration time curve from time 0 up to 8 hours post-dose on Day 1 [AUC(0-8)] and on Day 7 of treatment [$AUC(0\text{-}8)^{SS}$], maximum plasma concentration on Day 1 (C_{max}) and on Day 7 (C_{max}^{SS}), minimum plasma concentration on Day 1 (C_{min}) and on Day 7 (C_{min}^{SS}), time to reach maximum plasma concentration (t_{max}), total body clearance from plasma (CL/f), accumulation factor based on AUC(0-8) (R_{AUC}), based on C_{max} (R_{Cmax}) and based on C_{min} (R_{Cmin}), were determined.
If the terminal disposition phase was observed, the smallest (terminal) elimination rate constant (λ_z), the elimination half-life ($t_{½}$), the apparent volume of distribution during the terminal phase (V_z/f), the area under the concentration-time curve from zero to infinity (AUC) and the mean residence time (MRT), were estimated.

Statistical methods:
The primary efficacy variable was analysed by means of Analysis of Covariance (ANCOVA) model for crossover designs. Secondary efficacy variables were analysed, according to the nature of variable, by means of ANCOVA models or descriptive statistics.

Safety and tolerability data, number of withdrawals and concomitant medications were analysed by means of the appropriate descriptive statistics across treatment groups.

For each dose, full descriptive statistics were given for all pharmacokinetic parameters of LAS100977. The relationship between the administered dose and area under the plasma concentration time curve from time zero to last sampling time [AUC(0-t)] or Maximum plasma concentration (C_{max}) on Day 1 and $AUC(0\text{-}t)^{ss}$ or C_{max}^{ss} on Day 7 were analysed by means of regression models.

SUMMARY – CONCLUSIONS

Efficacy Results:
Multiple inhaled morning doses of LAS100977 2.5 µg, 5 µg and 10 µg induced a clinically relevant bronchodilatory effect in terms of an adjusted mean (standard error [SE]) increase from pre-dose (Day 1) in trough FEV_1 after 7 days of treatment, which was 0.334 (0.095) L, 0.365 (0.097) L and 0.294 (0.100) L greater than that following placebo administration ($p<0.05$), respectively. No dose-relationship was observed between the three tested LAS100977 doses on Day 7.

The bronchodilatory effects of the first single inhaled morning doses of LAS100977 2.5 µg, 5 µg and 10 µg were slightly more pronounced than those on Day 7 as indicated by an adjusted mean (SE) increases in trough FEV_1 of 0.444 (0.084) L, 0.500 (0.089) L and 0.520 (0.098) L relative to pre-dose (Day 1) and placebo ($p<0.001$) on Day 1, respectively. There was no statistically significant difference between the three tested LAS100977 doses on Day 1.

The adjusted mean increases from pre-dose (Day 1) in FEV_1 after dosing LAS100977 2.5 µg, 5 µg and 10 µg versus placebo were considered clinically relevant and statistically significant at all time points on Day 1 ($p<0.001$), except for the 5 min time point with the dose of 2.5 µg (adjusted mean increase [SE] of 0.159 [0.047] L versus placebo with a $p<0.05$), and at almost all time points on Day 7 ($p<0.05$), except for 36 hours post-dose after LAS100977 10 µg (adjusted mean increase [SE] of 0.113 [0.082] L versus placebo with a $p>0.05$) and after 5 µg (adjusted mean [SE] increase of 0.173 [0.075] L versus placebo with a $p<0.05$).

Adjusted mean (SE) increases from pre-dose (Day 1) in peak FEV_1 after LAS100977 2.5 µg, 5 µg and 10 µg doses relative to placebo amounted to 0.482 (0.063) L, 0.548 (0.069) L and 0.565 (0.082) L on Day 1 (all $p<0.001$) and to 0.364 (0.072) L, 0.403 (0.084) L and 0.375 (0.101) L on Day 7 (all $p<0.01$), respectively. All these increases were clinically relevant and statistically significant.

The peak FEV_1 values following active and placebo dosing on Day 1 were reached at a median time of 180 min (3 hours) post-dose. At Day 7, the majority of patients reached their peak FEV_1 within 2 and 4 hours post-dose.

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Normalised AUC of FEV_1 showed adjusted mean increases from pre-dose (Day 1) of 0.567 to 0.774 L on Day 1 and of 0.356 to 0.593 L on Day 7. On both Day 1 and Day 7, the strongest effect on the FEV_1 AUC parameters within each LAS100977 dose group was seen for AUC_{0-6} followed by AUC_{0-12}, AUC_{0-24} and AUC_{12-24}.

The adjusted mean increase from pre-dose (Day 1) in FEV_1 AUC_{0-36} on Day 7 ranged from 0.390 to 0.484 L across the LAS100977 doses, which was only slightly lower than the corresponding increase in normalised AUC_{0-24} (0.428 to 0.517 L), thus indicating a sustained bronchodilator effect beyond 24 hours on Day 7 for all LAS100977 doses.

At pre-dose Day 4, there was a statistically significant adjusted mean increase from pre-dose (Day 1) in FEV_1 of 0.446 to 0.458 L after 3 days of administration of LAS100977 2.5 µg, 5 µg and 10 µg, ($p<0.05$ to <0.001 for comparison vs. placebo). These values were close to the increase observed with the trough FEV_1 at Day 1 (from 0.521 to 0.598 L).

The other secondary efficacy variables including change from pre-dose (Day 1) in trough FVC, PEF and FEF_{25-75} on Day 1 and Day 7, change from pre-dose (Day 1) in FVC, PEF and FEF_{25-75} at each time point on Day 1 and Day 7, and at pre-dose Day 4, as well as normalised FVC AUC_{0-6}, AUC_{0-12}, AUC_{0-24}, AUC_{0-36} and AUC_{12-36} values showed a similar behaviour to that of FEV_1, thus generally supporting the results for the different FEV_1 variables and the sustained bronchodilatory effect of LAS100977. However, the effect of LAS100977 doses on FVC was less pronounced than that on FEV_1 at both Day 1 and Day 7 and statistically significant differences between active and placebo were less frequently achieved, in particular on Day 7. In contrast, almost all comparisons of LAS100977 2.5 µg, 5 µg and 10 µg vs. placebo, respectively, for the different PEF and FEF_{25-75} variables were statistically significant ($p<0.05$) at both Day 1 and Day 7.

Pharmakokinetic Results:

Relatively low exposure and sparse quantifiable concentrations of LAS100097 were observed following once daily inhalation of 2.5 µg LAS1000977, however plasma concentrations were profiled well at the 5 and 10 µg LAS100977 dose levels.

Median t_{max} ranged from 0.533 to 0.750 hours post-dose at each dose level, on both Days 1 and 7.

Plasma concentrations of LAS100977 appeared to decline in a mono-phasic manner with an apparent terminal elimination half-life ranging from 3.0 to 6.5 hours on Day 1 and 4.8 to 12.4 hours on Day 7. The increase of the apparent terminal elimination half-life on Day 7 may be considered to be the result of plasma concentrations being quantifiable for a longer period of time, revealing more the true terminal elimination phase.

Accumulation of LAS100977 in plasma was approximately 1.6-fold following 7 days of dosing based upon mean C_{max}. Based on AUC(0-8), mean accumulation ranged from 2.2 to 9.9 fold at the 2.5 and 10 µg dose levels, however this is most likely an artefact of the low concentrations observed on Day 1, most notably at the 2.5 and 5 µg dose levels.

Systemic exposure, as measured by C_{max} appeared to increase in an approximately dose-proportional manner over the dose range 2.5 to 10 µg on Days 1 and 7. AUC(0-8) appeared to increase in a supra-porportional manner between 2.5 and 5 µg dose level and in a dose-proportional manner between the 5 and 10 µg doses on both Days 1 and 7. The non-linearity observed between the 2.5 and 5 µg dose levels may be due to the lack of quantifiable concentrations at the lowest dose level.

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Safety and Tolerability Results:

Single and multiple (up to 7 days) inhaled morning doses of LAS100977 2.5, 5 and 10 µg showed an overall good safety and tolerability profile in male patients with stable asthma. A dose-response relationship was observed after repeated dosing in some of the different safety and tolerability outcomes evaluated, such as pulse rate, heart rate, and the occurrence of tremor and nervousness.

Overall, 15 (75%) patients reported 56 TEAEs. Most of these TEAEs were considered by the investigator to be either of mild (28) or moderate (23) intensity, while 5 were severe. The incidence of patients with at least one TEAE was 40%, 57% and 50% in the LAS100977 2.5 µg, 5 µg and 10 µg treatment groups, respectively, and 47% after placebo treatment. The number of TEAEs per treatment group was only slightly higher after LAS100977 2.5 µg, 5 µg and 10 µg doses (14, 13 and 17 events, respectively) than after placebo treatment (12 events). However, the number of TEAEs considered to be related to IMP increased with the LAS100977 dose administered, this was from 5 and 6 TEAEs after LAS100977 2.5 µg and 5 µg, respectively, to 15 TEAEs after LAS100977 10 µg, compared with 2 related TEAEs following placebo treatment.

One half of the TEAEs (28 events) were judged by the investigator as being related to the inhaled IMPs, most of which occurred after LAS100977 10 µg (15 events), followed by LAS100977 5 µg and 2.5 µg (6 events and 5 events, respectively) and placebo (2 events). The most frequently reported TEAEs were headache (15 events occurring in 11 patients: 5 events in each the LAS100977 2.5 µg and 10 µg groups and the placebo group), followed by tremor (8 events occurring in 7 patients: 2 events in the LAS100977 5 µg group and 6 in the 10 µg group), migraine (6 events occurring in 4 patients: 4 events in the LAS100977 5 µg group, 1 in the 10 µg group and 1 in the placebo group), dyspnoea (5 events occurring in 5 patients: 3 events in the LAS100977 2.5 µg group, 1 in the 5 µg group and 1 in the placebo group), nervousness (3 events occurring in 3 patients, all in the LAS100977 10 µg group), somnolence (3 events occurring 1 patient of the LAS100977 5 µg group) and nasopharyngitis (3 events occurring in 2 patients: 2 events in the placebo group, and 1 event in the LAS100977 2.5 µg group). Most events of tremor and nervousness started from the second day of administration and lasted from 5 to 8 days. The events of nervousness ocurred between 3 hours and 3 days after first dosing and lasted for 4 to 6 days. None of these events led to patient's discontinuation.

No SAEs and no deaths occurred during the clinical study. One patient was withdrawn due to a TEAE (acute bronchitis), that was considered to be not related to IMP.

There was no evidence of a clinically relevant effect on any safety laboratory parameter and no 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, on Day 1 or Day 7.

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.

Pulse rate was increased from pre-dose Day 1 after multiple dosing of LAS100977 doses on Day 7 compared to placebo. This augmentation in pulse rate values was dose-dependent, and reached values of up to 7.3, 8.8 and 12.6 bpm at 36, 8 and 6 hours after dosing with LAS100977 2.5 µg, 5 µg and 10 µg, respectively, compared with up to 4.1 bpm at 36 hours after placebo treatment.

Similar increases from pre-dose Day 1 were obtained for heart rate from the 12-lead ECG on Day 7 compared to placebo: The mean increase in heart rate was dose-dependent until 36 hours post-dose (except for the time point of 4 hours) and reached a maximum value of 10.7 bpm at 6 hours after dosing LAS100977 10 µg and 6.1 and 7.5 bpm at 36 and 8 hours after dosing 2.5 µg and 5 µg, respectively. By comparison, the mean increase in the placebo group reached a maximum of 4.1 bpm at 36 hours post-

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** LAS100977	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

dose.

A tendency towards a small prolongation in QTcF interval was observed on Day 7, after active treatment when compared to placebo. A slight and in part dose-dependent prolongation from pre-dose Day 1 in QTcB values was observed following multiple dosing of LAS100977 on Day 7. Nevertheless, a cautious analysis and evaluation of these data should be performed as the trial was not specifically designed for a thorough QT assessment.

No findings of clinical relevance were found in the rest of the 12-lead ECG parameters assessed.

The lowest dose of 2.5 µg LAS100977 inhaled once in the morning for 7 days showed a similar safety and tolerability profile to that of placebo treatment.

Conclusions:

DATE OF REPORT:
11 November 2010 (final)

#

#

#