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, DOUBLE-DUMMY, PLACEBO AND ACTIVE COMPARATOR CONTROLLED, 5-WAY CROSSOVER CLINICAL TRIAL TO ASSESS THE ACTIVITY, SAFETY, TOLERABILITY AND PHARMACOKINETICS OF SINGLE DOSES OF LAS100977 ADMINISTERED BY INHALATION TO ASTHMA PATIENTS.		
_____ **Investigators:**		
Study centres:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 7 November 2007 Date study finalized (last patient last visit): 19 January 2008	**Phase of development:** IIa	
Objectives: a) To assess the activity of single doses of LAS100977 administered by inhalation to patients with persistent asthma. b) To evaluate the safety, tolerability and pharmacokinetics of single doses of LAS100977 after single administration to patients with persistent asthma.		

Methodology:
This was a Phase IIa, randomized, double-blind, double-dummy, placebo and active comparator (salmeterol) controlled, 5-way crossover clinical study. During a run-in period (also screening) of maximum 14 days, the usual asthma therapy of the patients was withdrawn (except the corticosteroid treatment).
Overall, 25 eligible, male asthma patients were included and randomly assigned to one of five possible treatment sequences according to a William's designs for crossover clinical studies and with a balanced (1:1:1:1:1) randomization.
During each treatment period, patients received one of the five treatments that were to be tested (LAS100977 5 μg qd, LAS100977 10 μg qd, LAS100977 25 μg qd, salmeterol 50 μg bid, and placebo). The LAS100977 doses were administered in the morning as dry powder delivered from hard capsules inhaled through a rechargeable device (Cyclohaler). Salmeterol was inhaled in the morning and in the evening through a multi-dose dry powder inhaler (Accuhaler®). Corresponding placebo treatments were administered by the Cyclohaler and the Accuhaler® devices. The duration of each treatment period was 36 hours. Between two consecutive treatment periods, there was a washout phase of at least 7 days (up to 21 days).
During washout periods, patients' usual asthma therapy with β_2-adrenergic agents and corticosteroids, as well as asthma rescue medication, was permitted. Specific washout periods were defined for each concomitant treatment including rescue medication prior to the next visit. Throughout treatment periods, only corticosteroids and asthma rescue treatment (100 μg/puff of salbutamol pMDI) was allowed. Patients were provided with a paper diary card to record dose and administration time of the concomitant and rescue medication taken.
At least 7 days (up to 14 days) after the last investigational medicinal product (IMP) administration a follow-up evaluation took place.

Number of patients (planned and analyzed):

Planned:	25 patients
Screened:	33 patients
Randomized:	25 patients
Completed treatment phase:	25 patients
Completed study:	24 patients
Evaluated for activity:	24 patients (PP population)
Evaluated for pharmacokinetics:	25 patients
Evaluated for safety:	25 patients (Safety population)

Diagnosis and main criteria for inclusion:
Male patients aged between 18 and 70 years of age, limits inclusive, with persistent asthma (GINA guidelines) for at least 6 months prior to the start of the study. Maintenance on a stable dose of inhaled corticosteroids over the previous 6 weeks, either together with a short- or a long-acting ß$_2$-agonist. 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 ß$_2$-agonists and 72 hours for long-acting ß$_2$-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. No other relevant pulmonary disease or history of thoracic surgery. Normal values or not-clinically relevant abnormalities in the results of the physical examination, laboratory tests and electrocardiogram recording.

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

Name:	LAS100977
Administration route:	Oral inhalation
Dosage form:	Dry powder for inhalation delivered from hard capsules through a rechargeable Cyclohaler
Dose and regimen:	Single doses of 5 μg, 10 μg and 25 μg
Batch numbers:	065F0111 (5 μg) and 067F0110 (25 μg)
Expiry date:	March 2008

Duration of treatment:
The total duration of the clinical study for each patient was approximately 7 weeks, including previous Screening (up to 14 days before first morning IMP administration), post-IMP administration assessments, and follow-up visit (7 days after last morning IMP administration).

Reference therapy, dose and mode of administration, batch number, expiry date:	
Name:	Salmeterol
Administration route:	Oral inhalation
Dosage form:	Dry powder for inhalation delivered through a multi-dose inhaler (Accuhaler®)
Dose and regimen:	Single dose of 50 µg twice daily
Batch number:	E04893-007I01
Expiry date:	April 2009
Name:	LAS100977 Placebo
Administration route:	Oral inhalation
Dosage form:	Dry powder for inhalation (lactose) delivered from hard capsules through a rechargeable Cyclohaler
Dose and regimen:	Placebo
Batch number:	065F0106
Expiry date:	March 2008
Name:	Salmeterol Placebo
Administration route:	Oral inhalation
Dosage form:	Powder for inhalation (lactose) delivered through a multi-dose inhaler (Accuhaler®)
Dose and regimen:	Placebo
Batch number:	E04893-006I01
Expiry date:	April 2009

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Criteria for evaluation:

Activity:
Lung function tests (spirometries and body plethysmographies) were performed at different timepoints during each treatment period, in order to assess the pulmonary effect of LAS100977. For spirometry, forced expiratory volume in first second (FEV_1), forced vital capacity (FVC), peak expiratory flow (PEF) and forced expiratory flow (FEF_{25-75}) were determined. For body plethysmography, specific airway conductance (sGaw) and airway resistance (Raw) were measured.

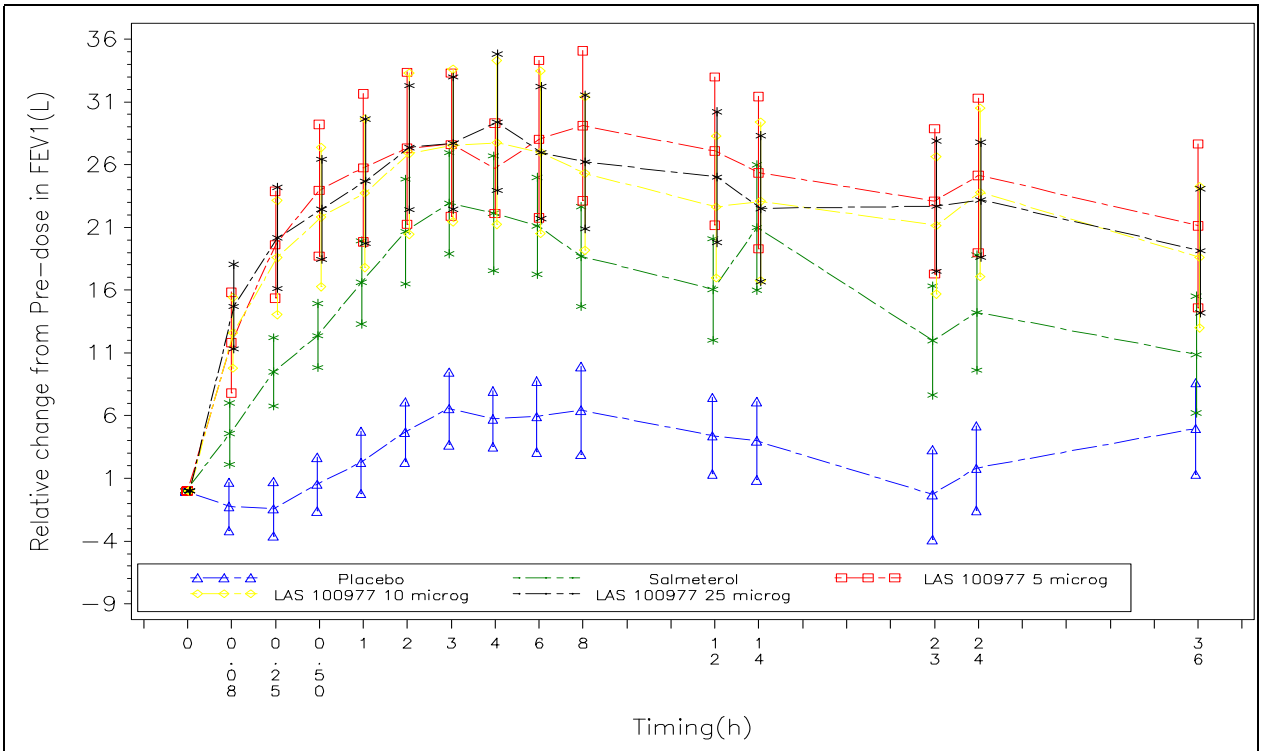
Safety and tolerability:
Adverse events, 12-lead electrocardiogram (ECG), vital signs (blood pressure and pulse), laboratory tests (hematology, coagulation, biochemistry, and urinalysis), physical examination were assessed at the different established timepoints during the 36-hour period of each treatment phase. Drug screening (cannabinoids, amphetamines, barbiturates, benzodiazepines, cocaine, and opiates), alcohol breath test and serology test (Hepatitis B core antibodies, Hepatitis B surface antigen, Hepatitis C virus antibodies, and Human immunodeficiency virus [HIV]) were assessed at screening.

Pharmacokinetics:
AUC(0-t), C_{max}, t_{max}, CL/f and MRT were determined. If the terminal disposition phase was well 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) and the area under the concentration-time curve from zero to infinity (AUC) were estimated.

Statistical methods:
The analysis of all the activity variables and the pharmacokinetic parameters was performed on the Per Protocol (PP) population. All safety outcomes were analyzed using the Safety population.
All variables of activity were analyzed using Analysis of Covariance (ANCOVA) models for crossover designs.
Safety and tolerability data, number of withdrawals and concomitant medication were summarized by means of the appropriate descriptive statistics across treatment groups.
For each dose and sampling time, full descriptive statistics was given for all pharmacokinetic parameters of LAS 100977. The relationship between the dose of IMP used and AUC(0-t) or C_{max} were explored by means of a regression model.

Results:

Activity:
The FEV_1 time profiles following inhalation of placebo, salmeterol 50 µg bid, and LAS100977 5 µg, 10 µg and 25 µg are shown in the following plot:



LAS100977 at single inhaled morning doses of 5 µg, 10 µg and 25 µg induced a marked bronchodilatory effect that was sustained over time and well preserved until the end of the treatment period, that is 36 hours after morning IMP dosing. FEV_1 increases were observed at all timepoints of assessment, and were statistically significantly greater than placebo ($p<0.0001$) and salmeterol 50 µg bid ($p<0.05$), and clinically relevant. No dose-relationship was observed between LAS100977 tested doses.

At the very first time point of assessment (5 minutes after dosing), an adjusted mean FEV_1 increase versus pre-dose of 0.338 L, 0.367 L and 0.434 L was estimated for the doses of LAS100977 5 µg, 10 µg and 25 µg, respectively, whereas salmeterol 50 µg bid and placebo showed a difference from pre-dose of 0.135 L and –0.032 L, respectively. The FEV_1 increases observed after the administration of LAS100977 doses were statistically significantly greater than placebo ($p<0.0001$) and salmeterol 50 µg bid ($p<0.001$), and clinically relevant.

LAS 100977 doses of 5 µg, 10 µg and 25 µg showed a change from pre-dose in peak FEV_1 of 0.813 L, 0.813 L and 0.843 L, respectively. Salmeterol 50 µg bid and placebo exhibited a much lower response in the same variable, with values of 0.668 L and 0.224 L, respectively. For the 3 LAS100977 doses, the peak was reached between 137 and 158 minutes after dosing, whereas for salmeterol 50 µg bid and placebo, 145 and 134 minutes after inhalation, respectively.

After 1 day of treatment, adjusted mean trough FEV_1 values increased 0.636 L, 0.660 L and 0.689 L versus pre-dose after the inhalation of LAS 100977 5 µg, 10 µg and 25 µg doses, respectively, 0.333 L versus pre-dose after the inhalation of salmeterol 50 µg bid, and 0.024 L versus pre-dose after the inhalation of placebo. These increases were statistically significant and clinically relevant for the 4 active treatments.

When compared to placebo, the adjusted mean change from pre-dose in trough FEV_1 after the inhalation of LAS100977 5 µg, 10 µg and 25 µg doses was 0.612 L, 0.636 L and 0.665 L, respectively, favouring the 3 active treatments, whereas after the inhalation of salmeterol 50 µg bid, 0.309 L, also favouring the active treatment. All these values were statistically significant ($p<0.0001$) and clinically relevant as well.

When compared to salmeterol 50 µg bid, the adjusted mean change from pre-dose in trough FEV_1 after the inhalation of LAS100977 5 µg, 10 µg and 25 µg doses was 0.303 L, 0.327 L and 0.356 L, respectively, favouring the 3 LAS100977 doses. These values were statistically significant ($p<0.0001$) and clinically relevant, too.

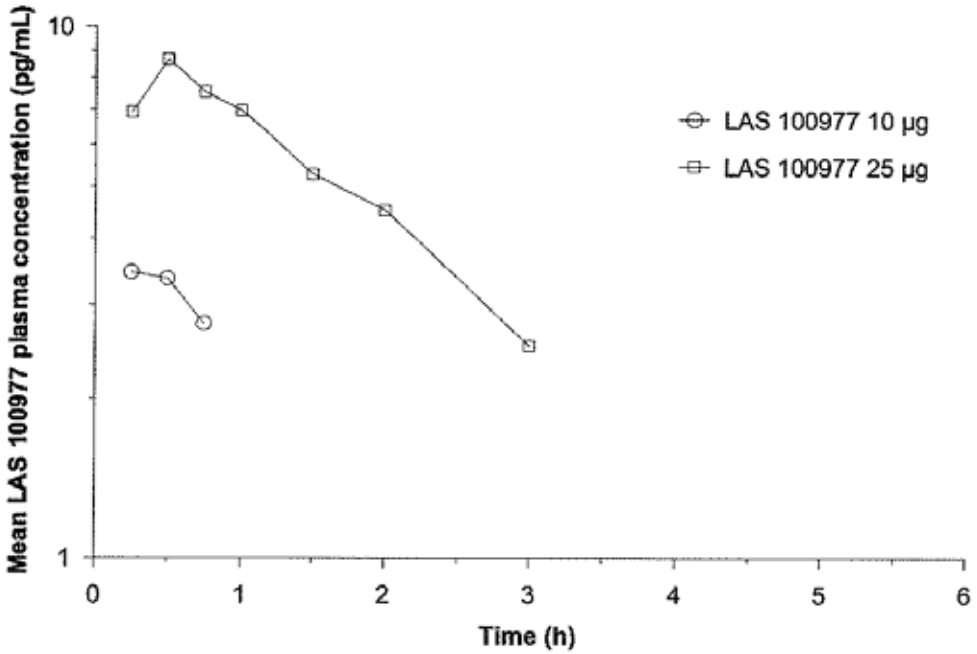
The effect of the three LAS100977 doses on the change from pre-dose in trough FEV_1 was statistically and clinically not distinguishable from each other.

Secondary activity variables (change from pre-dose in trough FVC, PEF and FEF_{25-75}, change from pre-dose in FVC, PEF and FEF_{25-75} at each time-point, normalised FEV_1, FVC, PEF and FEF_{25-75} AUC0-6, AUC0-12, AUC0-24, AUC0-36 and AUC12-36, peak FEV_1, FVC, PEF and FEF_{25-75}, etc..) supported the results of the different FEV_1 variables. Again, the bronchodilatory effects were sustained over time, well

preserved until the end of the observation period, and statistically significantly greater than placebo and salmeterol, as well as clinically relevant.
Body plethysmography confirmed the bronchodilatory effects of LAS100977 from 1 until 36 hours after IMP inhalation. sGaw and Raw were markedly improved after LAS100977 doses and after salmeterol, but not after placebo. Maximum mean effects were seen 2 to 6 hours after inhalation.

Safety and tolerability:
Overall, 21 (84%) of the 25 patients who participated in the study reported 66 treatment-emergent adverse events (TEAEs). Most of them were either mild or moderate in intensity, and 4 were severe. The number of TEAEs and of patients experiencing a TEAE increased with increasing doses of LAS100977. The percentage of patients who had at least one AE was 20%, 36% and 68% in the LAS100977 5 µg, 10 µg and 25 µg treatment groups, respectively, whereas in the placebo and salmeterol 50 µg bid groups, the percentage was 16% and 8%, respectively. The majority of TEAEs (40) was judged by the investigator as related to the inhaled IMPs, and occurred in 15 (60%) of the 25 patients who took part in the trial. The most frequent drug-related TEAEs were tremor (17 episodes occurring in 10 patients), restlessness (8 episodes occurring in 6 patients) and nervousness (4 episodes occurring in 4 patients), all reported after 10 µg or 25 µg of LAS100977.
One treatment-emergent serious adverse event (SAE), spinal ostheoarthritis, occurred in one patient in the LAS100977 10 µg treatment period. The event required surgery and was judged by the investigator as not related to the IMP.
No patients were withdrawn from the study due to AEs, and no deaths occurred. All AEs were resolved by the end of the study.
There was no evidence of a clinically relevant effect on any safety laboratory parameter and no laboratory results constituted a TEAE.
After the inhalation of all LAS100977 doses a trend towards a slight decrease versus pre-dose in serum potassium and a slight increase vs pre-dose in blood glucose was observed; as could be expected from the long-lasting pharmacological action of the compound, the effect on potassium was still present at the 36-hour time point. The effect on glucose, however, was not observed at the timepoints of 24 and 36 hours post-dose. Salmeterol also caused a slight decrease in potassium and a slight increase in glucose, which was less pronounced than those seen for LAS100977.
No clinically relevant changes from pre-dose and from placebo were observed for LAS100977 doses and salmeterol in systolic and diastolic blood pressure.
Pulse and heart rate were increased after the two highest doses of LAS 100977 compared with placebo, salmeterol and the low dose of LAS 100977. A LAS100977 dose-related increase that persisted at 36 hours after dosing was observed between the 3 LAS100977 doses. At 24 hours after IMP inhalation, however, the values of all treatments were similar to those determined at pre-dose, except for the dose of LAS100977 25 µg, that showed an increase of around 7 beats per minute.
No clinically relevant increases in QTc Fridericia were determined in any of the 5 treatments tested. With the two highest doses of LAS 100977 (10 µg and 25 µg), however, a slight prolongation in the QTc Bazett, that was maximum between 6 and 8 hours after morning dosing, was observed. Nevertheless, a cautious analysis and evaluation of these data should be performed since the study was not specifically designed for a thorough QT assessment.
No abnormal findings of clinical relevance were found in the rest of the 12-lead ECG parameters.
The lowest dose of 5 µg LAS 100977 inhaled once in the morning proved to be as safe and tolerable as placebo or salmeterol.

Pharmacokinetics:
The PK of LAS 100977 at doses 5 µg, 10 µg and 25 µg were studied in plasma up to 24 hours post-dose. The following mean profiles were observed:



The following PK parameters were derived from the profiles:

Parameter	LAS 100977 10 µg	LAS 100977 25 µg
C_{max} (pg/mL)	3.79 ± 2.15	9.21 ± 3.92
t_{max} (h)	0.50 (0.23-1.98) [a]	0.52 (0.08-1.03)
AUC(0-t) (h.pg/mL)	4.38 ± 3.96	20.1 ± 12.8
$t_{1/2}$ (h)	5.92 ± 1.58 [b]	4.75 ± 4.11 [c]
MRT(0-t)(h)	0.820 ± 0.360 [a]	1.68 ± 0.712

Values are arithmetic means ± SD, except t_{max}: median (range).
n = 25, except [a] n = 21, [b] n=2 and [c] n=11

Almost all profiles had concentrations below quantifiable concentration in the lowest dose (5 µg), except for two patients. The median time to peak was around 30 minutes for both highest doses. Peak concentration was 3.79 pg/mL for 10 µg dose and 9.21 pg/mL for 25 µg dose. Half life estimation could not be performed on most of profiles and is around 5 to 6 hours. Values of AUC(0-t) and MRT(0-t) have to be considered with caution because several profiles have BLOQ values concentrations between two quantifiables data points. Inter-subject variability was moderate to high (27 to 90%).

Conclusions:

DATE OF REPORT:

06 November 2009