## 2 SYNOPSIS

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| **Name of Sponsor / Company:**<br>AstraZeneca<br><br>**Name of Finished Product:**<br>N.A.<br><br>**Name of Active Ingredients:**<br>LAS100977 | **Individual Study Table Referring to Part of the Dossier**<br><br>**Volume:**<br><br>**Page:** | **(For National Authority Use only)** |
| **Title of Study:** A PHASE IIA, RANDOMISED, SINGLE DOSE, DOUBLE-BLIND, DOUBLE-DUMMY, 6 WAY COMPLETE CROSS-OVER, PLACEBO CONTROLLED CLINICAL TRIAL TO ASSESS THE EFFICACY, SAFETY AND TOLERABILITY OF 4 DOSES OF LAS100977 QD COMPARED TO PLACEBO AND AN ACTIVE COMPARATOR IN PATIENTS WITH PERSISTENT ASTHMA | | |
| **Investigators:** | | |
| **Study centres:** | | |
| **Publication (reference):**<br>None | | |
| **Studied period (years):**<br>Date study initiated (first screening): 10 August 2011<br>Date study finalised (last patient last visit ): 23 January 2012 | **Phase of development:** IIa | |

**Objectives:**

- To evaluate the pharmacodynamics of single doses of inhaled LAS100977 0.313, 0.625, 1.25 and 2.5 µg once daily (QD) administered via the Genuair® inhaler in patients with persistent asthma.
- To assess the safety and tolerability of the LAS100977 doses in the same target population.

**Methodology:**

This was a phase IIa, randomised, double-blind, double-dummy, 6 way cross-over, single dose administration, multicentre clinical study.

After signature of the Informed Consent Form, patients were allowed to continue with their usual inhaled corticosteroid (ICS) therapy, but all other asthma therapies were withdrawn. Patients were allowed to use salbutamol as reliever medication throughout the duration of the study. After washout from prior and prohibited therapies, a Screening Visit took place, 12 to 16 days before randomisation. After the Screening evaluation, eligible patients entered into a 12 to 16 day run-in period to assess their clinical stability. At the end of the run-in period, those patients still fulfilling the inclusion/exclusion criteria were assigned to one of the 6 treatment sequences according to a William's design for cross over studies and using a balanced 1:1:1:1:1:1 randomisation ratio.

The study consisted of 6 periods of single treatment days separated by a washout period of 7 to 14 days. A follow-up phone contact was performed 14 (±2) days after last investigational medicinal product (IMP) administration (or after premature discontinuation) to monitor patients' safety. The total duration of the study for each patient was approximately 10 to 16 weeks, including screening, post-IMP administration assessments, and last follow-up contact.

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**Methodology (continued):**
The end of the study was the date of the last patient last visit, including the follow-up phone call (or visit, if needed). However, patients completing the 6 treatment periods were considered completers, even in the absence of completing the follow up phone call (or visit).

**Number of subjects (planned and analysed):**
Planned: Approximately 84 patients were planned to be screened to achieve a total number of 54 randomised patients.
Screened: 115 patients
Randomised: 62 patients
Completed study: 58 patients
Evaluated for safety: 62 patients
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 62 patients
Evaluated for efficacy (Per Protocol [PP] analysis): 61 patients

**Diagnosis and main criteria for inclusion**:

- Adult male and non-pregnant, non-lactating female patients aged 18-70 years (both included)
- Clinical diagnosis of persistent asthma (according to Global Initiative for Asthma [GINA] guidelines 2009 update) for at least 6 months prior to screening.
- Screening Forced Expiratory Volume in the first second ($FEV_1$) value of $60\% < FEV_1 \leq 85\%$ (pre-salbutamol) of the predicted normal value after a washout of at least 6 hours for short-acting $\beta_2$-agonists and 48 hours for long-acting $\beta_2$-agonists, when applicable.
- $FEV_1$ reversibility ≥12% and an absolute increase of at least 200 mL over baseline value after inhalation of 400 µg (4 inhalations) of salbutamol via a metered dose inhaler at least in one of the 2 pulmonary function tests performed (between 10-15 min and at 30 min).
- Pre-dose $FEV_1$ value of the first treatment period within the range of ± 20% of the $FEV_1$ measured at screening prior to salbutamol inhalation.
- Patients on a stable dose and regimen (i.e., a minimum of 4 weeks prior to screening) of background ICS with up to the equivalent of 1600 µg/day of beclometasone dipropionate. Patients continued with the same ICS dose throughout the study.
- No prior exposure to LAS100977.

**Test product, dose and mode of administration, batch number, expiry date:**
Name: LAS100977
Administration route: Oral inhalation
Dosage form: Dry powder for inhalation administered via Genuair®
Dose and regimen: 1 puff of 0.313 µg in the morning (09:00 ± 1 hour)
Batch number: K20-181-L38 Expiry date: July 2012

Name: LAS100977
Administration route: Oral inhalation
Dosage form: Dry powder for inhalation administered via Genuair®
Dose and regimen: 1 puff of 0.625 µg in the morning (09:00 ± 1 hour)
Batch number: K20-175-L36 Expiry date: July 2012

Name: LAS100977
Administration route: Oral inhalation
Dosage form: Dry powder for inhalation administered via Genuair®
Dose and regimen: 1 puff of 1.25 µg in the morning (09:00 ± 1 hour)
Batch number: K20-177-L39 Expiry date: July 2012

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**Test product, dose and mode of administration, batch number, expiry date (continued):**
Name: LAS100977
Administration route: Oral inhalation
Dosage form: Dry powder for inhalation administered via Genuair®
Dose and regimen: 1 puff of 2.5 µg in the morning (09:00 ± 1 hour)
Batch number: K20-167-L37 Expiry date: July 2012

**Duration of treatment:**
The planned treatment duration was 6 days of treatment for each patient (a single day of treatment for 6 treatment periods).

**Reference therapy, dose and mode of administration, batch number, expiry date:**
Name: Salbutamol
Administration route: Oral inhalation
Dosage form: Pressurised inhalation suspension administered via Ventolin Evohaler®
Dose and regimen: 400 µg (4 puffs of 100 µg) in the morning (09:00 ± 1 hour)
Batch number: 8735-L45 Expiry date: January 2013

Name: Placebo to LAS100977
Administration route: Oral inhalation
Dosage form: Dry powder for inhalation administered via Genuair®
Dose and regimen: 1 puff of placebo in the morning (09:00 ± 1 hour)
Batch number: K20-126-L35 Expiry date: July 2012

Name: Placebo to Salbutamol
Administration route: Oral inhalation
Dosage form: Pressurised inhalation suspension administered via Ventolin Evohaler®
Dose and regimen: 1 puff Of salbutamol placebo in the morning (09:00 ± 1 hour)
Batch number: S11E01I-L46 Expiry date: January 2013

**Criteria for evaluation:**

**Efficacy:**
Primary Efficacy Variable:
- Change from baseline to peak $FEV_1$ on Day 1.

Secondary Efficacy Variables:
- Percentage (relative) change from baseline to peak $FEV_1$ on Day 1.
- Percentage (relative) change in $FEV_1$ from baseline at each specific time point on Day 1 and Day 2.
- Peak $FEV_1$ and Forced Vital Capacity (FVC) on Day 1.
- Change from baseline to trough $FEV_1$ and FVC on Day 2.
- Change from baseline in the $FEV_1$ and FVC at each specific time point on Day 1 and Day 2.
- $FEV_1$ and FVC at each specific time point on Day 1 and Day 2.
- Change from baseline in normalised $FEV_1$ and FVC area under the curve (AUC) over the 24-hour period immediately after morning IMP administration ($AUC_{0-24}$) on Day 1 and Day 2.
- Change from baseline in normalised $FEV_1$ and FVC AUC over the 6-hour period immediately after morning IMP administration ($AUC_{0-6}$) on Day 1.
- Change from baseline in normalised $FEV_1$ and FVC AUC over the 12-hour period immediately after morning IMP administration ($AUC_{0-12}$) on Day 1.

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**Criteria for evaluation (continued):**

Secondary Efficacy Variables (continued):

- Change from baseline to peak FVC on Day 1.
- Time to peak $FEV_1$ and FVC on Day 1.

Additional Exploratory Efficacy Variables:

- Percentage of patients with an increase from baseline to peak $FEV_1$ ≥12% and ≥200 mL on Day 1.
- Percentage of patients with an increase from baseline in $FEV_1$ ≥12% and ≥200 mL at each specific time point of Day 1 and Day 2.
- Percentage of patients with an increase from baseline to peak $FEV_1$ greater than or equal to the upper 95% CI of placebo (measured in % and mL) on Day 1.
- Percentage of patients with an increase from baseline in $FEV_1$ greater than or equal to the upper 95% CI of placebo (measured in % and mL) at each specific time point of Day 1 and Day 2.

**Safety and tolerability:**

Safety and tolerability assessments included eliciting of adverse events (AEs) and serious AEs (SAEs), the monitoring of blood pressure, 12-lead electrocardiogram (ECG) parameters, clinical laboratory assessments (haematology, blood chemistry, urinalysis, serum potassium and blood glucose) and physical examinations. Pregnancy tests were performed in female patients of childbearing potential.

**Statistical methods:**

The analysis of all efficacy variables was performed on the ITT population (defined as all randomised patients who took at least 1 dose of IMP and have at least a baseline and 1 post-dose value of $FEV_1$ of at least 1 treatment period).

All statistical comparisons for primary endpoint comparing active treatments versus placebo were two-sided hypothesis tests, and the significance level was set at 0.05. All confidence intervals (CIs) were two-sided at the 95% confidence level. Due to the exploratory (learning phase) nature of this study, Type I error rate was not adjusted for multiple treatment comparisons.

The primary and secondary efficacy variables (except for 'time to peak $FEV_1$ and FVC at Day 1') were analysed by means of an Analysis of Covariance (ANCOVA) model for cross-over designs with sequence, treatment and period as fixed effect factors, patient within sequence as a random effect, and baseline $FEV_1$ or FVC value (as appropriate) at each period as a covariate. All between groups comparisons were performed using the appropriate contrast in the ANCOVA model. Between groups Least Squares (LS) means and 95% confidence intervals (CIs) were given for all pairwise comparisons.

Time to peak $FEV_1$ and FVC at Day 1 was analysed using descriptive statistics.

Additional exploratory analyses of between-groups comparisons for active treatments versus placebo for the percentage of patients with an increase from baseline to peak $FEV_1$ ≥12%, ≥200 mL, ≥ (upper 95% CI of that from placebo) % and ≥ (upper 95% CI of placebo) mL on Day 1 and at each specific time point on Day 1 and Day 2 were conducted using the McNemar's test.

Safety outcomes were summarised for the safety population by means of descriptive statistics.

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**SUMMARY – CONCLUSIONS**

**Efficacy Results:**

Primary efficacy variable: Change from baseline to peak $FEV_1$ at Day 1

Before IMP administration in each treatment period, mean baseline $FEV_1$ values were similar across all treatments. Following single dose IMP administration, all doses of LAS100977 showed a statistically significantly greater improvement from baseline in LS mean peak $FEV_1$ (LS mean differences 0.274 L to 0.405 L; p<0.0001) compared to placebo at Day 1.

| Treatment (A) | Treatment (B) | Change from Baseline to Peak $FEV_1$ (L) | | | |
|---|---|---|---|---|---|
| | | LSMD (SE) (A – B) | 95% CI for the Difference | | p-value |
| | | | Lower | Upper | |
| **Primary Treatment Comparisons** | | | | | |
| LAS100977 2.5 µg | Placebo | 0.405 (0.027) | 0.353 | 0.458 | <0.0001 |
| LAS100977 1.25 µg | Placebo | 0.371 (0.027) | 0.318 | 0.424 | <0.0001 |
| LAS100977 0.625 µg | Placebo | 0.322 (0.027) | 0.269 | 0.375 | <0.0001 |
| LAS100977 0.313 µg | Placebo | 0.274 (0.027) | 0.221 | 0.327 | <0.0001 |
| **Secondary Treatment Comparison** | | | | | |
| Salbutamol 400 µg | Placebo | 0.353 (0.027) | 0.299 | 0.406 | <0.0001 |

Study M/100977/202
ANCOVA=analysis of covariance; CI=confidence interval; $FEV_1$=Forced Expiratory Volume in the first second; ITT=Intention-to-Treat; LSMD=least squares mean difference; SE=standard error.
LSMD and p-value obtained from an ANCOVA model for cross-over designs with change from baseline in peak $FEV_1$ at Day 1 of treatment as response, sequence, treatment and period as fixed effect factors, patient within sequence as a random effect and baseline peak $FEV_1$ at each period as a covariate.
Source: Appendix 16.5, Table 14.4.1.3

LAS100977 2.5 µg showed statistically significantly greater improvement from baseline in mean peak $FEV_1$ compared to LAS100977 0.625 µg (0.084 L; p=0.0020) and LAS100977 0.313 µg (0.131 L; p<0.0001). LAS100977 1.25 µg also showed statistically significantly greater improvement from baseline in mean peak $FEV_1$ compared to LAS100977 0.313 µg (0.096 L; p=0.0004).

Salbutamol 400 µg showed statistically significantly greater improvement in mean peak $FEV_1$ compared to placebo (0.353 L; p<0.0001) and LAS100977 0.313 µg (0.078 L; p=0.0040) for the ITT population. There were no other statistically significant differences in mean changes from baseline to peak $FEV_1$ between salbutamol and the rest of the LAS100977 doses. Similar results were observed when these analyses were performed in the PP population.

The effect of all doses of LAS100977 and of salbutamol 400 µg on the LS mean change from baseline to peak $FEV_1$ at Day 1 was considered to be clinically relevant, as the magnitude of the superiority over placebo exceeded 0.200 L (200 mL) in all cases. The effect of all doses of LAS100977 was considered to be clinically similar to the effect observed following salbutamol 400 µg.

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**Efficacy Results (continued):**

Secondary efficacy variables: Endpoints based on $FEV_1$

*Change from baseline to trough $FEV_1$ at Day 2:* All doses of LAS100977 showed a statistically significantly greater increase from baseline in LS mean trough $FEV_1$ at Day 2 compared to both placebo and salbutamol 400 µg, which was considered to be c linically relevant, as the magnitude of the superiority exceeded 0.200 L (200 mL) in all cases.

*Change from baseline in normalised $FEV_1$ $AUC_{0-6}$, $AUC_{0-12}$ and $AUC_{0-24}$ at Day 1:* For all doses of LAS100977, mean increases from baseline in normalised $FEV_1$ $AUC_{0-6}$, $AUC_{0-12}$ and $AUC_{0-24}$ were statistically significantly greater than both placebo and salbutamol, with the exception of 0.313 µg versus salbutamol for $AUC_{0-6}$.

The results of the statistical analyses of the changes from baseline in the secondary $FEV_1$ variables are summarised in the following table:

| $FEV_1$ Variable (L) | Comparison | LS Mean Differences in Changes from Baseline (p-value) | | | |
|---|---|---|---|---|---|
| | | LAS100977 0.313 µg (N=60) | LAS100977 0.625 µg (N=60) | LAS100977 1.25 µg (N=60) | LAS100977 2.5 µg (N=61) |
| Trough at Day 2 | vs. Placebo | 0.219 (<0.0001) | 0.259 (<0.0001) | 0.332 (<0.0001) | 0.400 (<0.0001) |
| | vs. Salbutamol | 0.241 (<0.0001) | 0.281 (<0.0001) | 0.354 (<0.0001) | 0.422 (<0.0001) |
| Normalised $AUC_{0-6}$ at Day 1 | vs. Placebo | 0.266 (<0.0001) | 0.315 (<0.0001) | 0.373 (<0.0001) | 0.409 (<0.0001) |
| | vs. Salbutamol | 0.007 (0.7890) | 0.056 (0.0336) | 0.114 (<0.0001) | 0.150 (<0.0001) |
| Normalised $AUC_{0-12}$ at Day 1 | vs. Placebo | 0.285 (<0.0001) | 0.330 (<0.0001) | 0.392 (<0.0001) | 0.433 (<0.0001) |
| | vs. Salbutamol | 0.128 (<0.0001) | 0.174 (<0.0001) | 0.235 (<0.0001) | 0.276 (<0.0001) |
| Normalised $AUC_{0-24}$ at Day 1 | vs. Placebo | 0.275 (<0.0001) | 0.314 (<0.0001) | 0.383 (<0.0001) | 0.440 (<0.0001) |
| | vs. Salbutamol | 0.182 (<0.0001) | 0.221 (<0.0001) | 0.290 (<0.0001) | 0.347 (<0.0001) |

Study M/1009977/202
$AUC_{0-6}$=area under the curve over the 6-h period immediately after morning IMP administration; $AUC_{0-12}$=area under the curve over the 12-h period immediately after morning IMP administration; $AUC_{0-24}$=area under the curve over the 24-h period immediately after morning IMP administration; $FEV_1$=Forced Expiratory Volume in the first second; IMP=investigational medicinal product; ITT=Intention-to-Treat; LS mean=least squares mean; N=number of patients in the ITT population.
Analyses were performed on the ITT population. For placebo, N=59; for salbutamol, N=58.
LS mean differences and p-values obtained from an analysis of covariance model for cross-over designs with change from baseline in $FEV_1$ variable as response, sequence, treatment and period as fixed effect factors, patient within sequence as a random effect and the corresponding baseline value at each period as a covariate.
Source: Appendix 16.5, Tables 14.4.3.3, 14.4.7.3, 14.4.14.3, 14.4.15.3 and 14.4.16.3

*Time to peak $FEV_1$ at Day 1:* For all doses of LAS100977, the median time to peak $FEV_1$ at Day 1 was 3.0 hours post-dose. The median time to peak $FEV_1$ at Day 1 was 2.0 hours post-dose for placebo and 1.0 hour post-dose for salbutamol 400 µg.

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**Efficacy Results (continued):**

*Changes from baseline in $FEV_1$ at specific time points on Day 1 and Day 2:* During the observation period, all doses of LAS100977 showed statistically significantly greater increases compared to placebo at all time points from the first assessment at 15 minutes post-dose to 36 hours post-dose (0.109 L to 0.497 L; p<0.0001 to p=0.0100) and from 4 to 36 hours post-dose compared to salbutamol (0.108 L to 0.442 L; p<0.0001 to p=0.0106). From 8 hours post-dose, changes from baseline in $FEV_1$ following salbutamol were not statistically significantly different to those observed following placebo.

Exploratory efficacy variables: Endpoints based on $FEV_1$

*Percentage of patients with an increase from baseline to peak $FEV_1$ ≥12% and ≥200 mL on Day 1:* The percentage of patients showing an increase from baseline to peak $FEV_1$ ≥12% and ≥200 mL following all doses of LAS100977 (71.67% to 88.52%) and salbutamol (77.59%) was statistically significantly higher (p<0.0001) than following placebo (18.64%), based on the McNemar's test.

*Percentage of patients with an increase from baseline to peak $FEV_1$ ≥ (upper 95% CI of placebo) % and ≥ (upper 95% CI of placebo) mL on Day 1:* Based on the McNemar's test, all doses of LAS100977 (73.33% to 83.61%) and salbutamol 400 µg (77.59%) showed a statistically significantly greater percentage of patients (p<0.0001) with an increase to peak $FEV_1$ ≥ the upper 95% CI of placebo compared to placebo (15.25%).

Secondary efficacy variables: Endpoints based on FVC

*Change from baseline to peak FVC at Day 1:* All doses of LAS100977 showed a statistically significantly greater improvement from baseline in LS mean peak FVC (0.095 L to 0.158 L; p<0.0001 to p=0.0010) compared to placebo at Day 1. There were no statistically significant differences in changes in LS mean peak $FEV_1$ between any of the LAS100977 doses and salbutamol 400 µg (-0.045 L to 0.018 L).

*Change from baseline to trough FVC at Day 2:* All doses of LAS100977 showed a statistically significantly greater improvement in LS mean trough FVC compared to placebo and salbutamol 400 µg (0.077 L to 0.185 L; p<0.0001 to p=0.0435) at Day 2.

*Change from baseline in normalised FVC $AUC_{0-6}$, $AUC_{0-12}$ and $AUC_{0-24}$ at Day 1:* All doses of LAS100977 showed statistically significantly greater improvements from baseline in LS mean normalised FVC $AUC_{0-6}$, $AUC_{0-12}$ and $AUC_{0-24}$ compared to placebo (0.092 L to 0.175 L; p<0.0001 to p=0.0012) at Day 1. Compared to salbutamol, the dose levels of LAS100977 generally showed statistically significantly greater improvements from baseline for mean normalised FVC $AUC_{0-12}$ and $AUC_{0-24}$ (0.057 L to 0.138 L; p<0.0001 to p=0.0261) but not for normalised FVC $AUC_{0-6}$.

*Time to peak FVC at Day 1:* Across all doses of LAS100977, the median time to peak FVC at Day 1 was 1.5 hours (0.313 µg) to 2.0 hours (0.625, 1.25 and 2.5 µg) post-dose. The median time to peak FVC at Day 1 was 2.0 hours post-dose for placebo and 1.0 hours post-dose for salbutamol 400 µg.

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**Efficacy Results (continued):**

*Changes from baseline in FVC at specific time points on Day 1 and Day 2:* All doses of LAS100977 showed a statistically significantly greater improvement in LS mean FVC compared to placebo at all time points on Days 1 and 2 (0.073 L to 0.222 L; p<0.0001 to p=0.0460), except for LAS100977 0.625 µg versus placebo at 12, 23 and 36 hours post-dose (0.029 L to 0.060 L), which were not statistically significant.

**Safety and Tolerability Results:**

Adverse events:

Overall, 51 (82.3%) of the 62 patients who participated in the study reported 144 treatment-emergent AEs (TEAEs). The majority of these TEAEs were considered by the investigator to be of either mild (106 events) or moderate (33 events) intensity, while 5 were considered to be severe. The percentage of patients who experienced at least one TEAE was 30.0%, 26.7%, 30.0% and 37.7% following LAS100977 0.313 µg, 0.625 µg, 1.25 µg and 2.5 µg, respectively, compared to 27.1% following placebo and 20.7% following salbutamol 400 µg. It should be noted that the percentage of patients with at least one IMP-related TEAE was <10% for each dose level of LAS100977 and that these values were similar to those observed following placebo (3.4%) and salbutamol 400 µg (5.2%). However, with increasing dose of LAS100977, a very slight increase in the number of patients with at least one IMP-related TEAE was observed (1.7%, 3.3%, 5.0% and 9.8% of patients following LAS100977 0.313 µg, 0.625 µg, 1.25 µg and 2.5 µg, respectively).

No SAEs or deaths occurred during the clinical study and no patients were withdrawn from it due to a TEAE.

The most frequently reported TEAEs were headache (47 events in 26 patients), nasopharyngitis (18 events in 17 patients), chest discomfort (6 events in 5 patients), wheezing (6 events in 4 patients) and atrioventricular block first degree (7 events in 1 patient). Of these, 8 events of headache in 6 patients (1 event in 1 patient following each of LAS100977 0.313 µg, LAS100977 0.625 µg and LAS100977 2.5 µg, 2 events in 2 patients following LAS100977 1.25 µg and 3 events in 3 patients following salbutamol 400 µg) were considered to be related to the study drug or active comparator, while none of the events of nasopharyngitis, chest discomfort, wheezing or atrioventricular block first degree were considered to be related to the active treatments.

Safety laboratory results:

No clinically relevant changes versus screening were observed in haematology, biochemistry and urinalysis parameters at the end of the study and no safety laboratory results constituted a TEAE. No clinically relevant changes versus pre-dose and versus placebo were observed in serum potassium and blood glucose over time following any dose of LAS100977, and no LAS100977 dose-related or treatment-related trends were identified.

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**Safety and Tolerability Results (continued):**

Vital signs (blood pressure):

No clinically relevant changes versus pre-dose and versus placebo were observed in systolic and diastolic blood pressure over time following any dose of LAS100977 or salbutamol, and no LAS100977 dose-related or treatment-related trends were identified.

12-lead ECGs:

No clinically relevant changes versus pre-dose and versus placebo were observed in ECG parameters, including heart rate, over time following any dose of LAS100977 or salbutamol, and no LAS100977 dose-related or treatment-related trends were identified. QTcB (QT interval corrected using Bazett's formula) and QTcF (QT interval corrected using Fridericia's formula) changes from baseline >60 msec were observed in very few patients, but no overall clinically relevant differences were identified between treatments, including placebo, and no LAS100977 dose response was observed. As this was not a thorough QT study, interpretation of QTcB and QTcF data should be made with caution.

**CONCLUSIONS:**

**DATE OF REPORT:**
08 November 2012