2 SYNOPSIS

Name of Sponsor/Company: AstraZeneca Name of Finished Product: N.A. Name of Active Ingredients: LAS100977 (LABA) named Abediterol	Individual Study Table Referring to Part of the Dossier Volume: 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 STRENGTHS OF LAS100977 QD COMPARED TO PLACEBO AND AN ACTIVE COMPARATOR IN PATIENTS WITH STABLE MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		
Investigators: .		
Study sites: .		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 22 August 2011 Date study finalised (last patient last visit): 27 December 2011	Phase of development: IIa	
Objectives: • To evaluate the pharmacodynamics (bronchodilation) of single doses of inhaled LAS100977 0.625, 2.5, 5 and 10 µg once daily (QD) in COPD patients. • To assess the safety and tolerability of the LAS100977 doses in the same target population. • To assess the pharmacokinetics (PK) of LAS100977 in a sub-set of study patients.		

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Methodology:
This was a phase IIa, randomised, double-blind, double-dummy, 6-way cross-over, placebo controlled, single dose administration, multicentre clinical study to assess the efficacy, safety and tolerability (and PK in a sub-set of patients) of LAS100977 0.625, 2.5, 5 and 10 µg administered QD by inhalation from the Genuair® device. There was also an active comparator, indacaterol 150 µg administered QD by inhalation from the Onbrez Breezhaler® device.

After signature of the Informed Consent Form (ICF), patients were withdrawn from their usual COPD therapy in accordance with the study protocol, prior to the Screening Visit. Patients could use inhaled short-acting β_2-agonists (SABAs) as reliever medication throughout the whole duration of the study. After washout from prior and prohibited therapies, a Screening Visit took place, 14 (±2) days before randomisation. After the screening evaluation, eligible patients entered into a 14 (±2) day run-in period to assess patients' 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 treatment periods of 1 treatment day each separated by a washout period of 7 to 14 days. A minimum of 7 days between treatment periods was required. Each treatment period corresponded to one study visit (Visit 1 to Visit 6) and the duration of each visit was 36 hours. A follow-up phone contact was performed 14 (±2) days after the last investigational medicinal product (IMP) administration (Visit 6) to monitor patients' safety. Patients completing the 6 treatment periods were considered completers, even in the absence of completing the follow-up contact.

Blood samples for PK determinations were drawn at each treatment period in the sub-set of patients participating in the PK assessments.

Number of patients (planned and analysed):
Planned: Approximately 92 patients were planned to be screened to achieve the goal of 60 randomised patients and 48 completers (8 patients on each of the 6 treatment sequences).
Screened: 87 patients
Randomised: 70 patients (20 patients participated in the PK sub study)
Completed study: 63 patients
Evaluated for safety: 70 patients
Evaluated for efficacy (Intention-to-Treat [ITT] analysis): 70 patients
Evaluated for efficacy (Per-Protocol [PP] analysis): 69 patients

Diagnosis and main criteria for inclusion:
- Adult male and non-pregnant, non-lactating female patients aged ≥ 40 years with stable moderate to severe COPD (as defined by the Global Initiative for Chronic Obstructive Lung Disease [GOLD] guidelines).
- Post-salbutamol forced expiratory volume in 1 second (FEV_1) ≥ 30% and < 80% of predicted normal value and post-salbutamol FEV_1/forced vital capacity (FVC) at screening < 70%.
- 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)].
- Current or ex-cigarette smokers of ≥ 10 pack-years.
- Patients with no history or current diagnosis of asthma.

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- No signs of a COPD exacerbation within 6 weeks prior to the Screening Visit.
- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities.
- No other relevant pulmonary disease or history of thoracic surgery.

Test product, dose and mode of administration, batch number, expiry date:
Name: LAS100977
Administration route: Oral inhalation by Genuair® inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 0.625 µg LAS100977 at approximately 09:00 (± 1h).
Batch number: K20-175-L32 Expiry date: July 2012

Name: LAS100977
Administration route: Oral inhalation by Genuair® inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 2.5 µg LAS100977 at approximately 09:00 (± 1h).
Batch number: K20-167-L33 Expiry date: July 2012

Name: LAS100977
Administration route: Oral inhalation by Genuair® inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 5 µg LAS100977 at approximately 09:00 (± 1h).
Batch number: K20-179-L40 Expiry date: July 2012

Name: LAS100977
Administration route: Oral inhalation by Genuair® inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of 10 µg LAS100977 at approximately 09:00 (± 1h).
Batch number: K20-182-L41 Expiry date: July 2012

Duration of treatment:
The planned treatment duration for this study was 6 days (one per treatment period x 6 treatment periods).

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Indacaterol
Administration route: Oral inhalation by Onbrez Breezhaler® inhaler
Dosage form: Dry powder in a hard gelatine capsule
Dose and regimen: 1 puff (150 µg indacaterol) at approximately 09:00 (± 1h).
Batch number: S0031-L44 Expiry date: September 2012

Name: Placebo to LAS100977
Administration route: Oral inhalation by Genuair® inhaler
Dosage form: Dry powder
Dose and regimen: 1 puff of placebo at approximately 09:00 (± 1h).
Batch number: K20-126-L31 Expiry date: July 2012

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Name: Placebo to indacaterol
Administration route: Oral inhalation by Onbrez Breezhaler® inhaler
Dosage form: Dry powder in a hard gelatine capsule
Dose and regimen: 1 puff of placebo at approximately 09:00 (± 1h).
Batch number: 108F0227-L42 Expiry date: September 2012

Criteria for evaluation:

Efficacy:
Primary Efficacy Variable:
- Change from baseline to trough FEV_1 on Day 2.

Secondary Efficacy Variables:
- Change from baseline to trough FVC at Day 2.
- Change from baseline in normalised FEV_1 and FVC area under the curve over the 12-h period immediately after IMP administration (AUC_{0-12}) at Day 1.
- Change from baseline in normalised FEV_1 and FVC area under the curve over the 24-h period immediately after IMP administration (AUC_{0-24}) at Day 1.
- Change from baseline in normalised FEV_1 and FVC area under the curve over the 12-h night-time period (AUC_{12-24}) at Day 1.
- Change from baseline in FEV_1 and FVC at each scheduled time point at Day 1 and Day 2.
- Absolute FEV_1 and FVC values at each scheduled time point at Day 1 and Day 2.
- Change from baseline in inspiratory capacity (IC) at each scheduled time point at Day 1 and Day 2.
- Absolute IC values at each scheduled time point at Day 1 and Day 2.
- Change from baseline to the peak FEV_1 and FVC at Day 1.
- Time to peak FEV_1 and FVC at Day 1.

Safety and Tolerability:
Safety and tolerability assessments included eliciting of adverse events (AEs) and serious AEs (SAE), the monitoring of haematology, blood biochemistry and urinalysis values, the monitoring of glucose and potassium values, blood pressure measurement, recording of 12-lead electrocardiograms (ECGs), and physical examinations. Pregnancy tests were performed in females of childbearing potential.

Pharmacokinetic parameters:
In a sub-set of 20 patients participating in the study, the following PK parameters of the 4 doses of LAS100977 were determined in plasma for each IMP:
- $AUC_{(0-t)}$ = area under the plasma concentration versus time curve from zero to the last quantifiable time point
- AUC = area under the plasma concentration versus time curve from zero to infinity
- C_{max} = maximum plasma concentration
- t_{max} = time to reach maximum plasma concentration
- λ_z = smallest (terminal) elimination rate constant
- $t_{½}$ = terminal elimination half-life
- λ_1 = largest (fastest) elimination rate constant
- $t_{½}$ λ_1 = elimination half-life associated with the largest disposition rate constant
- CL/f = total body clearance from plasma
- V_z/f = apparent volume of distribution during the terminal phase

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- MRT = mean residence time

If the terminal disposition phase was well observed, λ_z, $t_{½}$, V_z/f and AUC were estimated.

PK parameters of LAS100977 were analysed by appropriate descriptive statistics and graphs for each dose group. PK evaluation and statistical analyses were carried out by the Almirall Drug Metabolism and Pharmacokinetics Department following the specific PK protocol and results were presented in a separate report.

Statistical methods:
The analysis of all the efficacy variables were performed using the ITT population (i.e., patients who took at least 1 dose of IMP and had at least a baseline and 1 post-dose value of FEV_1 from at least 1 treatment period). In addition, the primary efficacy variable was also analysed using the PP population to assess the robustness of the findings from the ITT population. All demographic and baseline characteristics, safety outcomes and other variables were analysed using the Safety population.

All statistical comparisons were 2-sided hypothesis tests and the significance level was set at 0.05. Due to the exploratory nature of this study there was no multiplicity adjustment.

The primary and secondary efficacy variables, except for time to peak FEV_1 and FVC, 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 the corresponding baseline value of each period as a covariate.

All between-group comparisons were tested using the appropriate contrast in the ANCOVA model. Between-groups least squares (LS) means and 95% confidence intervals (CI) were given for all pairwise comparisons.

Time to peak FEV_1 was analysed descriptively.

Safety outcomes (AEs, SAEs, laboratory parameters, blood pressure and 12-lead ECGs) were summarised for the Safety population by descriptive statistics across treatment groups.

Dose-proportionality analysis of the 4 dose levels of LAS100977 was performed on the PP population. The analysis of dose proportionality for $AUC_{(0-t)}$ and C_{max} parameters at Day 1 was performed by means of a fixed effect model which was carried out in an exploratory manner.

SUMMARY – CONCLUSIONS

Efficacy Results:
<u>Primary efficacy variable: Change from baseline to trough FEV_1 at Day 2</u>

Before IMP administration in each treatment period, mean baseline FEV_1 values were similar across all treatments. Following single dose IMP administration, the LS mean change from baseline to trough FEV_1 at Day 2 showed a dose response of 0.066 L, 0.168 L, 0.198 L and 0.223 L for LAS100977 0.625 µg, 2.5 µg, 5 µg and 10 µg, respectively, -0.035 L for placebo and 0.076 L for indacaterol 150 µg.

<u>All doses of LAS100977 showed a statistically significantly greater improvement from baseline in</u>

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LS mean trough FEV_1 ($p<0.0001$) compared to placebo at Day 2. LAS100977 10 µg showed statistically significantly greater improvement in mean trough FEV_1 compared to LAS100977 2.5 µg (least squares mean difference [LSMD] of 0.056 L; p 0.0064) and 0.625 µg (LSMD of 0.157 L; $p<0.0001$). LAS100977 5 µg and LAS100977 2.5 µg also showed statistically significantly greater improvement in mean trough FEV_1 compared to LAS100977 0.625 µg (LSMD of 0.132 L and 0.101 L, respectively; $p<0.0001$ for both).

With the exception of LAS100977 0.625 µg, all other LAS100977 doses (2.5 µg, 5 µg and 10 µg) showed statistically significant greater improvement in mean trough FEV_1 compared to indacaterol 150 µg (LSMD of 0.092 L, 0.122 L and 0.148 L, respectively; $p<0.0001$ for all three dose levels). Indacaterol 150 µg also showed statistically significant greater improvement in mean trough FEV_1 compared to placebo (LSMD of 0.111 L; $p<0.0001$).

Treatment (A)			95% CI for the Difference		
			Lower	Upper	
~~Primary Treatment Comparisons~~					
~~LAS100977 10 µg~~	~~Placebo~~	~~0.259 (0.020)~~	~~0.219~~	~~0.298~~	~~<0.0001~~
~~LAS100977 5 µg~~	~~Placebo~~	~~0.233 (0.020)~~	~~0.194~~	~~0.273~~	~~<0.0001~~
~~LAS100977 2.5 µg~~	~~Placebo~~	~~0.203 (0.020)~~	~~0.164~~	~~0.242~~	~~<0.0001~~
~~LAS100977 0.625 µg~~	~~Placebo~~	~~0.102 (0.020)~~	~~0.062~~	~~0.141~~	~~<0.0001~~
~~Additional Treatment Comparisons~~					
~~Indacaterol 150 µg~~	~~Placebo~~	~~0.111 (0.020)~~	~~0.072~~	~~0.150~~	~~<0.0001~~

~~Study M/100977/25~~

Secondary efficacy variables: Endpoints based on FEV_1

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	vs. Indacaterol	0.019 (0.3350)	0.089 (<0.0001)	0.091 (<0.0001)	0.119 (<0.0001)

Study M/100977/25
AUC_{0-12}=area under the curve over the 12-h period immediately after morning IMP administration; AUC_{12-24}=area under the curve over the 12-h night-time 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 1 second; IMP=investigational medicinal product; ITT=Intention-to-Treat; LS mean=least squares mean; N= ITT population size of treatment group.
Analyses were performed on the ITT population. For placebo, N=68; for indacaterol, N=68.
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 group 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 14.4.4.3, 14.4.5.3, 14.4.6.3, and 14.4.16.3.

Change from Baseline in Normalised FEV_1 AUC_{0-12}, AUC_{12-24} and AUC_{0-24} at Day 1:
A statistically significantly greater improvement in LS mean normalised FEV_1 AUC_{0-12}, AUC_{12-24} and AUC_{0-24} compared to placebo (LSMD ranging from 0.131 L to 0.290 L; $p < 0.0001$) was seen at Day 1 for all doses of LAS100977. With the exception of 0.625 µg, all doses of LAS100977 also showed a statistically significantly greater improvement in LS mean normalised FEV_1 AUC_{0-12}, AUC_{12-24} and AUC_{0-24} compared to indacaterol 150 µg (LSMD ranging from 0.095 L to 0.157 L; all with $p < 0.0001$).

Change from Baseline to Peak FEV_1 at Day 1:
All doses of LAS100977 showed a statistically significantly greater LS mean change from baseline to peak FEV_1 (LSMD ranging from 0.185 L to 0.285 L; $p < 0.0001$) compared to placebo at Day 1. LAS100977 10 µg showed statistically significantly greater mean peak FEV_1 compared to LAS100977 0.625 µg (LSMD of 0.100 L; $p < 0.0001$). LAS100977 2.5 µg and 5 µg also showed statistically significantly greater mean peak FEV_1 compared to LAS100977 0.625 µg (LSMD of 0.070 L and 0.072 L, respectively; $p = 0.0004$ and $p = 0.0002$, respectively). LAS100977 2.5 µg, 5 µg and 10 µg showed statistically significant greater mean peak FEV_1 compared to indacaterol 150 µg (LSMD of 0.089 L, 0.091 L and 0.119 L, respectively; $p < 0.0001$ for all three dose levels). Indacaterol 150 µg showed statistically significantly greater mean peak FEV_1 compared to placebo (LSMD of 0.166 L; $p < 0.0001$).

Absolute FEV_1 values and Change from Baseline in FEV_1 at Specific Time Points at Day 1 and Day 2:
The greatest LS mean change from baseline in FEV_1 occurred between 4 to 6 hours post-dose across all doses of LAS100977, but occurred slightly earlier for placebo and indacaterol 150 µg 1 to 3 hours post-dose. All doses of LAS100977 showed a statistically significantly greater improvement in LS mean FEV_1 compared to placebo at all-time points on Days 1 and 2 ($p < 0.0001$ to $p = 0.0114$).

Absolute Inspiratory Capacity (IC) values and Change from Baseline in IC at each scheduled time point at Day 1 and Day 2: All doses of LAS100977 showed a statistically significantly greater improvement in mean IC values compared to placebo at Day 1, 4 hours post-dose (all p-values <0.0001) and at Day 2, 24 hours post-dose (p-values <0.0001 to 0.0004).

<u>Secondary efficacy variables: Endpoints based on FVC</u>

Analysis of FVC parameters showed similar results to FEV_1 parameters, with LAS100977 showing statistically significantly greater improvement in trough FVC compared to placebo ($p < 0.0001$ to $p = 0.0002$), statistically significantly greater improvement in LS mean normalised FVC AUC_{0-12}, AUC_{12-24} and AUC_{0-24} ($p < 0.0001$) compared to placebo, statistically significantly greater improvement in LS mean peak FVC ($p < 0.0001$ to $p = 0.0110$) compared to placebo at Day 1. The greatest LS mean change from baseline in FVC occurred between 4 to 6 hours post dose for LAS100977 0.625 µg and 2.5 µg, slightly

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later for the higher doses at 14 hours post-dose.

Safety and Tolerability Results:

Adverse events:

Overall, 32 (45.7%) of the 70 patients who participated in the study reported 57 TEAEs. The majority of these TEAEs were considered by the investigator to be of either mild (37 events) or moderate (17 events) intensity, while 3 were considered to be severe. The percentage of patients who experienced at least one TEAE was 10.4%, 7.6%, 9.1% and 13.4% following LAS100977 0.625 µg, 2.5 µg, 5 µg and 10 µg, respectively, compared to 13.2% following placebo and 14.7% following indacaterol 150 µg. The percentage of patients with at least one IMP-related TEAE was <5% for each LAS100977 dose level and was similar to the percentages observed with placebo (2.9%) and indacaterol 150 µg (2.9%).

With increasing doses of LAS100977 there were no relevant differences in the overall number of patients with at least one IMP-related TEAE, with 1.5% of patients experiencing at least one IMP-related TEAE following LAS100977 0.625 µg and 3.0% of patients following LAS100977 2.5 µg, LAS100977 5 µg and LAS100977 10 µg. The most frequently reported TEAEs were nasopharyngitis (15 events in 14 patients; 20.0%) and headache (8 events in 7 patients; 10%), and the most frequently reported IMP-related TEAE was headache (2 events in 2 patients; 2.9%).

No deaths occurred during the study. Two patients experienced treatment-emergent SAEs which were considered not related to IMP: 1 patient following LAS100977 5 µg (COPD exacerbation) and 1 patient following LAS100977 10 µg (dizziness). The COPD exacerbation led to discontinuation from the study. Three patients were discontinued from the study due to TEAEs: 1 patient following LAS100977 0.625 µg (nasopharyngitis), 1 patient following LAS100977 5 µg (COPD exacerbation) and 1 patient following indacaterol 150 µg (dyspnoea).

Safety laboratory results:

No clinically relevant changes in haematology, biochemistry and urinalysis parameters were observed 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.

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 indacaterol. Also no LAS100977 dose-related or treatment-related trends were evident.

12-lead ECGs:

No clinically relevant changes from pre-dose and from placebo were identified for LAS100977 doses and indacaterol in ECG parameters, including heart rate, over time, and no LAS100977 dose-related or treatment-related trends were evident. No QTcF changes from baseline >60 msec and no QTcF >500 msec were observed in any treatment group. The number of patients with QTcF >480 msec and

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of male subjects with QTcF >450 msec was very low, with no differences or trends observed between treatment groups, including placebo and indacaterol. As this was not a thorough QT study, interpretation of QTcB and QTcF data should be made with caution.

Pharmacokinetic Results:

Maximum plasma concentrations of LAS100977 were reached between 0.5 to 1.5 hours following dosing with similar values for t_{max} across all doses. After reaching C_{max}, plasma LAS100977 concentrations declined in a bi-exponential manner describing two well-defined disposition phases, the fastest phase with mean associated half-life values ($t_{½}\lambda_1$) of about 3 hours and the slowest (terminal) phase with mean associated half-life values ($t_{½}$) between 15 to 27.5 hours. There were no relevant trends in the estimated $t_{1½}\lambda_1$ or $t_{½}$ values, with the exception of $t_{½}$ at the low 0.625 µg dose, which was longer in comparison to the higher 2.5, 5 or 10 µg doses. However, it should be noted that limited concentration data were available for the low dose at the latest kinetic time points and that $t_{½}$ could be only estimated in five patients. It should also be noted that in all cases the $t_{½}$ and $t_1\lambda_1$ values reported were calculated over a period of time of less than two half-lives. Similarly to $t_{½}\lambda_1$ and $t_{½}$, there was no apparent trend in the values obtained for CL/f and V_z/f across all administered doses, overall suggesting a linear PK behaviour of LAS100977 within the range of LAS100977 doses studied. Analysis of the C_{max} and $AUC_{(0-t)}$ values of LAS100977 showed that these parameters increased proportionally with administered dose within the range of 0.625 to 10 µg LAS100977.

CONCLUSIONS:

DATE OF REPORT:
17 January 2013