2. SYNOPSIS

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** *Aclidinium bromide*	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: A Single Dose, Double-Blind, Double-Dummy, 3 Period Cross-Over, Placebo Controlled Clinical Trial To Assess the Rate of Onset of Action of Inhaled LAS34273 200 µg Compared to Placebo and Tiotropium 18 µg in Patients with Chronic Obstructive Pulmonary Disease (COPD).		
Investigators:		
Study centres:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 12 February 2007 Date study finalised (last patient last visit): 10 August 2007	**Phase of development:** III	
Objectives: The primary efficacy objective was to determine the rate of onset of bronchodilator action of inhaled LAS34273 (*aclidinium bromide)* compared to placebo. The secondary efficacy objectives were to: assess the rate of onset of action of inhaled LAS34273 (*aclidinium bromide)* compared to tiotropium 18 µg and to placebo. The safety and tolerability objective was to evaluate the safety and tolerability of single doses of LAS34273 (*aclidinium bromide*) in COPD patients.		
Methodology: This was a double-blind, double-dummy, three period cross-over, placebo controlled study with single doses of LAS34273 (*aclidinium bromide*) 200 µg, tiotropium 18 µg and placebo in male or female patients with COPD with stable airways obstruction. The study consisted of three periods, each of 1-day duration, separated by a washout period of 5 (minimum) to 7 (recommended) days. In each period, patients received one of the three treatments.		

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Number of patients (planned and analysed):
Planned: 108 randomised
Screened: 198
Randomised: 115
Completed study: 107
Evaluated for safety: 115
Evaluated for efficacy (ITT analysis): 115
Evaluated for efficacy (PP analysis): 97

Diagnosis and main criteria for inclusion:
Males and non-pregnant, non-lactating females aged ≥40 years, with stable COPD and with a post-salbutamol FEV_1 % of predicted ≥30% and <60% and FEV_1/FVC <70% and a smoking history of ≥10 pack-years.

Test product, dose and mode of administration, batch number, expiry date:
Name: LAS34273 (rINN: *aclidinium bromide*).
Administration route: Inhalation by Novolizer multidose dry powder inhaler.
Dosage form: *Aclidinium bromide* formulated as an inhalation powder.
Dose and regimen: 200 µg single dose (1 puff) in the morning between 08:00 and 10:00 hours.
Batch number: 6B001. Expiry date: 01/2009.

Duration of treatment:
1 day (single dose).

Reference therapy, dose and mode of administration, batch number, expiry date:
Name: Placebo to LAS34273 (rINN: *aclidinium bromide*)
Administration route: Inhalation by Novolizer multidose dry powder inhaler
Dosage form: Placebo (lactose) formulated as an inhalation powder.
Dose and regimen: Single dose (1 puff) in the morning between 08:00 and 10:00 hours..
Batch number: 6A001. Expiry date: 01/2009.

Name: Tiotropium (active comparator).
Administration route: Inhalation by HandiHaler® dry powder inhaler.
Dosage form: Dry powder in hard gelatine capsule form inserted in a HandiHaler®.
Dose and regimen: 18 µg (tiotropium bromide monohydrate 22.5 µg) single dose (1 puff) in the morning between 08:00 and 10:00 hours.
Batch number: 057F0093. Expiry date: 11/2007.

Name: Placebo to tiotropium.
Administration route: Inhalation by HandiHaler® dry powder inhaler.
Dosage form: Dry powder (lactose) in hard gelatine capsule form inserted in a HandiHaler®.
Dose and regimen: Single dose (1 puff) in the morning between 08:00 and 10:00 hours.
Batch number: 042F0063. Expiry date: 11/2007.

Criteria for evaluation:
Efficacy:
The primary variable was the percentage of patients achieving a FEV_1 increase from baseline equal to or greater than 10% at 30 minutes.
The main secondary variables were the normalised area under the curve $(AUC)_{0\text{-}3\ h}$ of FEV_1 and change from baseline in FEV_1 at 30 min.
The additional efficacy variables were:

- Percentage of patients achieving a FEV_1 increase from baseline equal to or greater than 10% at 10, 20, 45, 60, 120 and 180 minutes after dosing.
- Percentage of patients achieving a FEV_1 increase from baseline equal to or greater than 12% at 10, 20, 30, 45, 60, 120 and 180 minutes after dosing.

- Percentage of patients achieving a FEV_1 increase from baseline equal to or greater than 15% at 10, 20, 30, 45, 60, 120 and 180 minutes after dosing.
- Change from baseline in FEV_1 at 10, 20, 45, 60, 120 and 180 minutes after dosing.
- Change from baseline in FVC and $FEF_{25-75\%}$ at 10, 20, 30, 45, 60, 120 and 180 minutes after dosing.
- Change from baseline in IC at 30, 60 and 180 minutes after dosing.
- Maximal changes from baseline in FEV_1, FVC, $FEF_{25-75\%}$ and IC.
- Time to maximal change in FEV_1, FVC, $FEF_{25-75\%}$ and IC.
- Normalised $AUC_{0-30min}$ and $AUC_{0-1\ h}$ of FEV_1, FVC and $FEF_{25-75\%}$, normalised $AUC_{0-3\ h}$ of FVC and IC.
- Change from baseline in perception of dyspnoea assessed with a VAS at 10, 20, 30, 45, 60, 120, and 180 minutes after dosing.

Safety:
Adverse events, vital signs, 12-lead ECGs, clinical laboratory evaluations, pregnancy tests, and physical examination.

Statistical methods:
The primary efficacy variable was dichotomised into success and failure and the new binary variable analysed using a logistic regression model for cross-over designs including sequence, period, treatment and country as factors and baseline as a covariate. The statistical significance of the logistic regression coefficients (β's) was tested using Wald's test. The odds ratios (OR) between treatments and their 95% confidence intervals (CI) were estimated using the coefficients and the corresponding standard errors derived from the logistic regression model. The secondary efficacy variables of percentage of patients achieving a FEV_1 increase from baseline equal to or greater than 12% and 15% at all timepoints post-dose were also analysed using this methodology.
The main secondary and additional efficacy variables were analysed using an Analysis of Covariance (ANCOVA) model for cross-over designs including sequence, subject, period, treatment and country as factors and baseline as a covariate. The time to change in the secondary efficacy variables were descriptively analysed and a comparison between treatments was performed using the Wilcoxon Signed-Rank test.

SUMMARY

Efficacy Results:

Primary Efficacy Variable:
Approximately 50% of patients on *aclidinium bromide* achieved an increase in FEV_1 from baseline ≥10% at 30 minutes post-dose, compared to 14% of patients following placebo, with this difference being statistically significant ($p < 0.0001$). Similar results were obtained with tiotropium. There was no statistically significant difference between *aclidinium bromide* and tiotropium treatment in the primary efficacy variable.

Main Secondary Efficacy Variables:
Normalised $AUC_{0-3\ h}$ of FEV_1: The normalised $AUC_{0-3\ h}$ of FEV_1 was statistically significantly (0.13 L) higher following *aclidinium bromide* compared to placebo ($p < 0.0001$). Bronchodilator response following *aclidinium bromide*, in terms of $AUC_{0-3\ h}$ of FEV_1, was comparable to tiotropium.

Change from baseline in FEV_1 at 30 minutes: The mean baseline FEV_1 values for each treatment group were similar. At 30 minutes post-dose, the mean change from baseline following *aclidinium bromide* was statistically significantly superior (122 mL [12% relative increase]) compared to placebo 27 mL [3% relative increase]). The mean change from baseline in FEV_1 at 30 minutes following *aclidinium bromide* was comparable to tiotropium.

Additional Efficacy Variables:
The success rate of patients experiencing a FEV_1 increase from baseline ≥10% increased over time from 10 minutes to 3 hours post-dose following *aclidinium bromide* and tiotropium administration whereas for placebo, the success rate remained similar. There were no statistical differences in the percentage of patients with improving FEV_1 ≥10% between both active treatments, although the differences increased from 3.9% at 10 minutes up to 9.7% at 3 hours post-dose, favouring the *aclidinium bromide* group.

Results for the percentage of patients experiencing a FEV_1 increase from baseline ≥12% generally reflected those for the 10% threshold. A maximal difference between both active treatments was

observed at 10 minutes post-dose (5.8% more patients improving after *aclidinium bromide* inhalation than after tiotropium) although this was not statistically different. The difference between *aclidinium bromide* and placebo reached statistical significance at all timepoints, while after tiotropium administration, the difference versus placebo did not reach statistical significance at 10 minutes post-dose.

The percentage of patients experiencing a FEV_1 increase from baseline ≥15% was higher after *aclidinium bromide* and tiotropium compared to placebo at all timepoints. However, the difference between both active treatments and placebo did not reach statistical significance at 10 minutes post-dose. There was no statistically significant difference between *aclidinium bromide* and tiotropium in any timepoint.

The mean absolute change from baseline in FEV_1 increased over time for *aclidinium bromide* and tiotropium from 77 and 69 mL respectively (corresponding to 7.5% and 7.1% relative increase) at 10 minutes post-dose to 211 and 185 mL respectively (corresponding to 20.0% and 17.8% relative increase) at 3 hours post-dose. Changes were statistically significant at all timepoints relative to placebo administration, and there was no statistically significant difference between *aclidinium bromide* and tiotropium treatments in the absolute and relative changes from baseline at any timepoint.

Similar changes from baseline were observed for FVC as for the changes from baseline in FEV_1, with a statistically significant improvement observed following *aclidinium bromide* compared to placebo at 10 minutes post-dose (134 mL, $p < 0.0001$); and a statistically significant increase observed following tiotropium compared to placebo at the same timepoint (100 mL, $p = 0.002$). The maximal improvement in FVC compared to placebo was observed at 2 hours post-dose (*aclidinium bromide*: 321 mL or 12.8% improvement, $p < 0.0001$; tiotropium: 268 mL or 10.2% improvement, $p < 0.0001$). There was no statistically significant difference between *aclidinium bromide* and tiotropium treatments in the absolute and relative change from baseline in FVC at any timepoint.

The absolute and relative changes from baseline in $FEF_{25-75\%}$ were statistically significantly higher (from 16 L/s or 4.4% to 61 L/s or 14.9% following *aclidinium bromide*, and from 18 L/s or 5.3% to 48 L/s or 13.6% following tiotropium) compared to placebo at all timepoints with the exception of 10 minutes post-dose, when the difference did not reach statistical significance. There was no statistically significant difference between *aclidinium bromide* and tiotropium treatments in the absolute and relative change from baseline in $FEF_{25-75\%}$ at any time-point post-dose.

The absolute change from baseline in IC following *aclidinium bromide* ranged from 219 to 305 mL (relative changes of 12% and 17%) at 30 minutes and 3 hours post-dose, respectively, and from 186 to 261 mL (relative changes of 10% and 14.7%) at 30 minutes and 3 hours after tiotropium administration, respectively. When compared to placebo, both active treatments showed a statistically significant improvement in IC from 30 minutes post-dose (the first time-point where IC was measured). There was no statistically significant difference between *aclidinium bromide* and tiotropium treatments in the changes from baseline in IC at 30, 60, and 180 minutes post-dose.

The mean maximal change from baseline in FEV_1 data was slightly higher after *aclidinium bromide* (245 mL) than after tiotropium (230 mL), with both treatments being statistically superior to placebo (differences of 129 mL and 115 mL respectively). For FVC, mean maximal changes of 559 mL after *aclidinium bromide* and 551 mL after tiotropium were statistically significantly higher than following placebo (302 mL). Similar results were observed for $FEF_{25-75\%}$. For IC, mean maximal changes of 370 mL after *aclidinium bromide* and 325 mL after tiotropium were statistically significantly higher than following placebo (175 mL). There were no statistically significant differences between *aclidinium bromide* and tiotropium treatments in the maximal change from baseline in FEV_1, FVC and $FEF_{25-75\%}$.

A maximal change in FEV_1 ≥10%, 12%, and 15% was achieved earlier following *aclidinium bromide* compared to placebo, and following tiotropium compared to placebo, although the difference between both active treatments versus placebo reached statistical significance ($p < 0.05$) for the maximal change in FEV_1 ≥10% only. There were no statistically significant differences in the time to maximal change in FEV_1 ≥10%, 12%, and 15% following *aclidinium bromide* compared to tiotropium.

For both active treatments, normalised $AUC_{0-30min}$ and $AUC_{0-1\ h}$ of FEV_1, FVC and $FEF_{25-75\%}$, and normalised $AUC_{0-3\ h}$ of FVC and IC were all statistically significantly higher ($p < 0.0001$ for *aclidinium*

bromide and ≤0.01 for tiotropium) compared to placebo. There were no statistically significant differences in these normalised parameters following *aclidinium bromide* compared to tiotropium.

Following *aclidinium bromide* administration, there was an improvement from baseline in perception of dyspnoea assessed with a VAS at all timepoints compared to placebo, with the difference reaching statistical significance at 10, 60, and 120 minutes ($p < 0.05$) and at 180 minutes post-dose ($p < 0.0001$). The most improvement was observed at 180 minutes post-dose. Following tiotropium administration, there was a statistically significant increase from baseline in the perception of dyspnoea all timepoints compared to placebo ($p < 0.05$ [10 and 120 minutes post-dose]; $p < 0.01$ [60 and 180 minutes post-dose]). There was no statistically significant difference in the perception of dyspnoea between *aclidinium bromide* and tiotropium treatments.

Subgroup Analyses

These subgroup analyses are described in the protocol and expanded in the Statistical Analysis Plan (SAP). The success rate, assessed by a FEV_1 increase from baseline ≥10% at 30 minutes post-dose, was lower in women (39.4%) compared to men (54.0%) following *aclidinium bromide* administration, and lower when BMI ≥25 kg/m^2 (43.6%) compared to BMI<25 kg/m^2 (55.6%). No statistical tests were performed for these comparisons. A similar success rate was observed for *aclidinium bromide* treatment by age group (<65 years versus ≥65 years) and by smoking status (current versus ex-smoker). Similarly, following tiotropium administration, the success rate was lower in women compared to men, with values of 42.4% and 55.8%, respectively and also for ex-smokers (45.9%) compared to current smokers (59.2%). The success rate following tiotropium administration was similar for the two age groups and BMI category.

In addition, the percentage of patients with an improvement of FEV_1 ≥10% at 30 minutes post-dose was higher in the responders group (patients with an increase in FEV_1 higher than 12% and 200 mL after salbutamol administration) than in the non-responders group (patients with an increase in FEV_1 lower or equal than 12% and 200 mL after salbutamol administration) for both active treatments. However, the percentage of response was similar in both groups (responders and non-responders) in the placebo arm.

Safety Results:

Single inhaled doses of *aclidinium bromide* 200 µg, tiotropium 18 µg and placebo were safe and well tolerated, with a similar and low incidence of AEs observed following each treatment. All drug-related AEs reported following *aclidinium bromide* 200 µg were mild in intensity.

There were no deaths during the study. There were two serious AEs (SAEs) that led to discontinuation: hospitalisation due to COPD exacerbation and brain infarction respectively, both of which were reported following tiotropium administration and were considered to be unrelated to the study drug. Three further patients were withdrawn from the study, due to COPD exacerbation/coughing and wheezing, following placebo (2 patients) or *aclidinium bromide* (1 patient) respectively.

The Systems Organ Class (SOC) with the most frequently reported Treatment-Emergent Adverse Events (TEAEs) were the nervous system disorders due to headache, and respiratory, thoracic and mediastinal disorders.

There were no clinically important changes in serum biochemistry, haematology, or urinalysis data, and no clinically significant physical examination findings or vital signs assessments during the study. There were no clinically relevant ECG findings during the study, with the exception of a report of atrial flutter experienced by a single patient who discontinued from the study following tiotropium 18 µg.

CONCLUSIONS:

DATE OF REPORT:

29 February 2008.