2.0 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 RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP, 6-WEEK CLINICAL STUDY TO ASSESS THE EFFECT OF INHALED ACLIDINIUM BROMIDE (LAS34273) 200 µg ON EXERCISE ENDURANCE AND LUNG HYPERINFLATION IN PATIENTS WITH MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		
Investigators: [redacted]		
Study centers: [redacted]		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 27 July 2007 Date of completion of the Study (last patient last visit): 18 Dec 2008		Phase of development: III

Objectives:

The objectives of the study were:

1. The primary objective of this study was to examine the effect of inhaled aclidinium bromide 200 µg on exercise endurance in patients with moderate-to-severe COPD.
2. The secondary objective of the study was to determine the effect of inhaled aclidinium bromide 200 µg on reducing resting and dynamic lung hyperinflation in patients with moderate-to-severe COPD.
3. An additional objective of the study was to evaluate the safety and tolerability of aclidinium bromide 200 µg administered by inhalation (with the Novolizer) once-daily for 6 weeks in patients with moderate-to-severe COPD.

Methodology:

This clinical study was conducted as a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group study comparing the repeated once-daily administration of aclidinium bromide 200 µg by inhalation with placebo in patients diagnosed with moderate-to-severe stable COPD.

The study consisted of a 2-week run-in period designed to assess the stability of patients' disease, to familiarize patients with testing procedures and to establish each patient's baseline characteristics. The run-in period was followed by 6 weeks of double-blind treatment. At the end of the run-in period, patients meeting the entry criteria for this study were randomized (1:1) to either aclidinium bromide 200 µg or

placebo. The date of the last patient visit was a follow-up telephone contact 1 week after the last dose of study drug.

Number of subjects (planned and analyzed):

Planned: 296 randomized in a 1:1 ratio, aclidinium bromide 200 µg:placebo

Screened: 587 patients

Randomized: 181 (86 patients to aclidinium bromide 200 µg and 95 patients to placebo)

Completed study: 159 (87.8%) (aclidinium bromide 200 µg: 81 [94.2%]; placebo: 78 [82.1%])

Evaluated for safety: 181 (100%) (aclidinium bromide 200 µg: 86 [100%]; placebo: 95 [100%])

Evaluated for efficacy (Intention-to-Treat [ITT] population): 180 (99.4%) (aclidinium bromide 200 µg: 86 [100.0%]; placebo: 94 [98.9%])

Evaluated for efficacy (Per Protocol [PP] population): 169 (93.4%) (aclidinium bromide 200 µg: 81 [94.2%]; placebo: 88 [92.6%])

Diagnosis and main criteria for inclusion:

Males and non-pregnant, non-lactating females aged ≥40 years, who were current or former cigarette smokers (with a ≥10 pack-year history), with a clinical diagnosis of stable moderate-to-severe COPD, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines, stable airway obstruction and who consented to participate were eligible for the study. The patient's forced expiratory volume in one second (FEV_1) at Visit 1 measured between 30-45 minutes post inhalation of 400 µg of salbutamol had to be ≥30% and <80% of the predicted normal value, the pre-dose FEV_1 at Visit 4 had to be within the range of 80 to 120% (inclusive) of the FEV_1 measured at Visit 1 prior to salbutamol inhalation and the post-salbutamol FEV_1/forced vital capacity (FVC) at Visit 1 had to be <70%. Functional residual capacity (FRC) at Visit 1 had to be ≥120% of the predicted value. Patients with a history or current diagnosis of asthma were excluded as were patients who had experienced a COPD exacerbation within 3 months of the Visit 1.

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

Name: Aclidinium bromide

Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Novolizer).

Dosage form: Dry powder for inhalation.

Dose and regimen: 200 µg (1 inhalation) once-daily in the morning

Batch number: 6B001

Expiry date: Jan 2009

Duration of treatment:

6-week treatment period. The total duration of the study for each patient was approximately 9 weeks including the screening and follow-up visits.

Reference therapy, dose and mode of administration, batch number, expiry date:

Name: Placebo to aclidinium bromide

Administration route: Oral inhalation by Almirall multidose dry powder inhaler (Novolizer).

Dosage form: Dry powder for inhalation.

Dose and regimen: 1 inhalation once-daily in the morning

Batch number: K1-22

Expiry date: Jan 2009

Criteria for evaluation:

Efficacy:

Efficacy was assessed by endurance time, pulmonary function tests (FEV_1, FVC, inspiratory capacity [IC], vital capacity [VC]), Body Plethysmography (FRC, total lung capacity [TLC] and residual volume [RV]),

measurement of disease-specific health status using the Chronic Respiratory Questionnaire – Self Administered Standardized (CRQ-SAS), evaluation of dyspnea using the Baseline and Transition Dyspnea Indexes (BDI/TDI), and rescue medication usage.

Safety:

Safety assessments included eliciting of adverse events (AEs) and serious AEs (SAE), the monitoring of hematology, blood biochemistry and urine values, physical examinations including blood pressure measurement and recording of 12-lead electrocardiograms (ECGs). Pregnancy tests were performed in females of child-bearing potential.

Statistical methods:

Analysis of the primary efficacy variable, the change from baseline (Day -5) in endurance time (ET) at Week 6 on therapy was analyzed using an Analysis of Covariance (ANCOVA) model. The number of patients in some centers was small, so centers were gathered into countries, and "centre" was replaced by "country" as a factor into the model of all statistical analysis where this factor had been adjusted. The final decision on this issue was addressed during the Blind Data Review Meeting (BDRM) which was held before breaking the blind. The primary treatment comparison between aclidinium bromide 200 µg and placebo was carried out by means of contrasts on the treatment factor. The treatment effect was estimated by means of Least Square (LS) mean and its standard error (SE) and 95% confidence interval (CI). The treatment difference between aclidinium bromide 200 µg and placebo was estimated by differences between LS means and their SE and 95% CI. Additionally, the evolution of ET for each treatment group over time was displayed in graphs showing the LS mean and SE at each visit.

For the primary variable, missing data for patients who withdrew due to COPD exacerbations was imputed using the Worst Observation Carried Forward of all ETs (WOCF), while ETs that were missing for other reasons were imputed using the Last Observation Carried Forward (LOCF) method based on the last visit available. Missing TDI dimension scores were imputed by carrying forward the value observed on the last prior visit available (LOCF). For pulmonary function tests missing values due to a premature discontinuation or patients who missed specific trial visits were imputed by carrying forward the last value observed at each specific time point (time-matched LOCF). For all the remaining efficacy variables, missing data was handled according to the Observed approach.

There were four secondary efficacy variables defined in the study: the change from baseline in trough FEV_1 at Week 6, the change from baseline in trough IC at Week 6, the change from baseline in trough FRC at Week 6 and the change from baseline in trough IC/TLC at Week 6.

SUMMARY – CONCLUSIONS

Efficacy Results:

Endurance Time:

- The study results show that the primary efficacy variable, change from baseline in ET at Week 6, increased by an adjusted mean of 116.44 sec compared with placebo; this treatment difference being statistically significant (p=0.0042).
- Results of the sensitivity analysis with the PP population confirmed the results of the primary analysis, with an adjusted mean treatment difference of 126.75 sec in favor of aclidinium bromide 200 µg (p=0.0028).
- Changes observed on Day 1 or following 3 weeks of treatment were similar, with statistically significant treatment differences of an adjusted mean of 142.98 sec (p=0.0002) and 125.96 sec (p=0.0007), respectively, in favor of aclidinium bromide 200 µg.

Resting lung function

Treatment with aclidinium bromide 200 µg led to an improvement in resting lung function, characterized by the following:

- Changes in lung function at the end of the dosing interval (trough)
  - A significant increase in trough FEV_1, trough IC, trough IC/TLC and trough FVC, with adjusted mean treatment differences of 0.101 L, 0.102 L, 0.017, and 0.219 L, respectively, following 6 weeks of treatment (p-value ranging from 0.037 to <0.0001). Similar changes were observed after 3 weeks of treatment. Increases in trough VC, with adjusted mean treatment differences of 0.135 L and 0.121 L after 3 and 6 weeks of treatment were also observed, but statistical significance was only reached at the 3-week time point (p=0.0298).
  - A decrease in trough FRC and trough RV, with adjusted mean treatment differences of -0.062 L and -0.055 L, respectively, following 6 weeks of treatment. These differences did not however reach statistical significance. Similar changes were observed after 3 weeks of treatment. No relevant changes in trough TLC were observed.

- Changes in lung function at 2h post-dose administration:
  - A significant increase in FEV1, FVC, IC, VC and IC/TLC, with adjusted mean treatment differences of 0.261 L, 0.448 L, 0.303 L, 0.319 L and 0.046 L, respectively, after 6 weeks of treatment ($p \leq 0.0002$). Similar changes were observed on Day 1 and after 3 weeks of treatment.
  - A significant decrease in FRC and RV, with adjusted mean treatment differences of 0.282 L and 0.324 L, respectively, following 6 weeks of treatment (p=0.0011 and p=0.0015, respectively). Similar changes were observed on Day 1 and after 3 weeks of treatment. Small decreases in TLC were also observed, with statistically significant differences at earlier time points (Day 1 p=0.0318 and Week 3 p=0.0046).

Exertional dyspnea and leg discomfort

- The likelihood for a patient to stop the exercise test because of discomfort with breathing was significantly lower (less than half) in the aclidinium bromide 200 µg group than for placebo after 6 weeks of treatment (p=0.0208).
- Treatment with aclidinium bromide 200 µg led to an improvement in exertional dyspnea at isotime, with a statistically significant decrease compared to placebo of more than 1 Borg unit on Day 1 and Week 3 and of an adjusted mean 0.704 Borg unit after 6 weeks of treatment (p=0.0129).
- Treatment with aclidinium bromide 200 µg also led to an improvement in leg discomfort at isotime, with statistically significant reduction in leg discomfort of an adjusted mean of -0.853 Borg unit at isotime on Day 1 (p=0.0015) and 0.603 (p=0.0215) at Week 3, but not at Week 6.
- No differences between aclidinium bromide 200 µg and placebo were observed at rest for exertional dyspnea or leg discomfort.
- At peak exercise, statistically significant differences were observed between treatment groups only for leg discomfort at Week 6 (LS mean=0.636; p=0.0157).

Operating lung volumes

- There was no evidence of a treatment difference in change from baseline in IC following 6 weeks of treatment, either at rest, isotime or end of exercise. Statistically significant ($p \leq 0.0001$) treatment differences of more than adjusted mean 0.200 L were observed at rest at earlier time points.
- Adjusted mean exercise induced changes in IRV measured at rest increased at all time points, particularly in the aclidinium bromide 200 µg group; and statistically significant treatment differences in favor of aclidinium bromide 200 µg were observed at Day 1 (LS mean=0.241 [p=0.0006]) and Week 3 (LS mean=0.232 [p=0.0004]). The treatment difference observed at Week 6 was of a smaller magnitude (LS mean=0.124), and not statistically significant (p=0.1124).
- Treatment with aclidinium bromide 200 µg led to a decrease in IRV during exercise at isotime and peak time, with adjusted mean treatment differences of -0.053 L and -0.064 L, respectively. Neither of these differences reached statistically significance.

Ventilatory responses to exercise

- Treatment with aclidinium bromide 200 µg led to a statistically significant decrease in resting VT, with an adjusted mean treatment difference of -0.077 L (p=0.0301), and to a significant increase in VT both at isotime and peak time (0.111 L and 0.098 L, respectively, p<0.0001 and p=0.0007) after 6 weeks of treatment.
- A small decrease in fR was also observed at isotime (LS mean=-0.989 breath per min) and at peak (LS mean=-0.291 breath per min) relative to placebo. These treatment differences were however not statistically significant.
- There was no evidence of a treatment effect for any of the other parameters examined (V'E, V'O2, V'CO2).

Dyspnea status, use of rescue medication, and chronic respiratory questionnaire (CRQ-SAS)

- Treatment with aclidinium bromide 200 µg led to a clinically and statistically significant improvement in dyspnea status since the first time point assessed (3 weeks), with an adjusted mean TDI treatment difference of 1.713 units (p=0.0004) at Week 6. Statistically significant changes were observed for each of the three TDI dimensions.
- Treatment with aclidinium bromide 200 µg led to a reduction in the use of daily rescue medication, with an adjusted mean treatment difference of -0.14 puffs after 6 weeks of treatment. This difference was not statistically significant.
- There was no evidence of a treatment difference in any of the dimension of the CRQ-SAS.

Conclusions

- Aclidinium bromide 200 µg significantly improved symptom-limited exercise ET during cycle ergometry at 75% of maximal work capacity by 116 sec.
- Aclidinium bromide 200 µg provided statistically and clinically significant bronchodilation as measured by the trough FEV1 during the 6-week treatment period (LS mean=101 mL improvement).
- Aclidinium bromide 200 µg improved lung hyperinflation at rest, with a significant improvement in trough IC (LS mean=102 mL improvement) and a positive trend in FRC.

Aclidinium bromide 200 µg provided a clinically significant improvement in chronic activity-related dyspnea (TDI >1 unit vs placebo) and on exercise-related dyspnea (LS mean=-0.7 Borg units at isotime vs placebo).

Safety Results:

Inhaled treatment with aclidinium bromide 200 µg was well-tolerated with a safety profile similar to that observed with placebo after 6 weeks treatment. Adverse events observed in each treatment group were generally events expected in COPD patients.

In total, treatment-emergent AEs (TEAEs) were reported in 93 patients (51.38%): 49 patients (56.98%) treated with aclidinium bromide 200 µg, and 44 patients (46.32%) treated with placebo. The types of AEs reported were generally similar across all treatment groups.

The TEAEs reported by ≥3.0% of patients in either treatment group were: cough (5.8% in aclidinium bromide 200 µg vs 3.2% in placebo), upper respiratory tract infection (5.8% vs 2.1%), nasopharyngitis (4.7% vs 2.1%), back pain (3.5% vs 3.2%), pharyngolaryngeal pain (3.5% vs 1.1%), dyspepsia (3.5% vs 1.1%), headache (5.8% vs 7.4%), COPD exacerbation (2.3% vs 7.4%), urinary tract infection (2.3% vs 4.2%), dyspnea (1.2% vs 3.2%) and sinus congestion (0.0% vs 4.2%). Cough, upper respiratory tract infection, nasopharyngitis, back pain, pharyngolaryngeal pain and dyspepsia were all reported by more patients in the aclidinium bromide 200 µg group compared with the placebo group, while headache, COPD exacerbation, urinary tract infection, dyspnea and sinus congestion were reported by more patients

in the placebo group compared with the aclidinium bromide 200 µg group

The majority of TEAEs were of mild or moderate intensity in both treatment groups TEAEs of severe intensity were experienced by 9.3% of patients treated with aclidinium bromide 200 µg and 7.4% of patients treated with placebo. No clear differences were observed between the two treatment groups. The majority of TEAEs were considered by the Investigator to be not related to Investigational Medicinal Product (IMP) for both treatment groups. Cough was the only treatment-related TEAE to be reported by two patients (aclidinium bromide 200 µg group). All other treatment-related TEAEs were reported by one patient in either treatment group.

Few patients discontinued the study due to TEAEs and mainly in the placebo treatment group. All TEAEs leading to discontinuation were respiratory events, mainly COPD exacerbations which according to the protocol led to study discontinuation. The other reasons were dyspnea , pneumonia, bronchitis and upper respiratory tract infection.

Overall, five patients experienced five treatment-emergent SAEs. None were fatal. Two SAEs were reported by patients in the aclidinium bromide 200 µg group (both gastrointestinal in nature; one ileitis and a diverticulum) compared with three patients in the placebo group (two patients with respiratory events, a COPD exacerbation and bronchitis and the third patient with a bladder transitional cell carcinoma). None of the SAEs were reported to be related to IMP. Bronchitis and COPD exacerbation, reported by patients in the placebo group, both led to permanent discontinuation from the study. All patients recovered from the SAEs.

Overall, 11 patients had a TEAE that led to premature discontinuation from the study, all were respiratory events. The number of patients who experienced a TEAE that led to discontinuation was higher in the placebo group (8.4%) compared to the aclidinium bromide 200 µg group (3.5%). COPD exacerbation was the most frequently reported TEAE leading to discontinuation overall, and the incidence was higher in the placebo group (6.3%) compared with the aclidinium bromide 200 µg group (2.3%).

There were no cardiac-related TEAEs reported during this study compared with 5.5% of patients and 7.2% of patients in Study M/34273/30 and M/34273/31, respectively. This is most likely due to the fact that patients with contraindications to clinical exercise testing were to be excluded from this study (Exclusion criterion #20), but this did not apply to patients in Studies M/34273/30 and M/34273/31.

Few patients experienced potential anticholinergic TEAEs. Two patients reported constipation (one in the aclidinium bromide 200 µg group and one in the placebo group), one patient in the placebo group reported dry mouth and six patients reported urinary tract infection (two patients in the aclidinium bromide 200 µg group and four patients in the placebo group).

Laboratory tests and vital signs data were in general similar to placebo and did not reveal any safety signals as well as the ECG findings with few patients with outlier values in the ECG recording.

CONCLUSIONS:

[redacted]

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DATE OF REPORT:
06 Oct 2009