2.0 SYNOPSIS

Name of Sponsor/Company AstraZeneca	Individual Study Table Referring to Part of the Dossier	*(For National Authority Use Only)*
Name of Finished Product Aclidinium bromide	**Volume:**	
Name of Active Ingredient (3R)-3-[(hydroxy)di(thiophen-2-yl)acetyloxy]-1-(3-phenoxypropyl)-1λ5-azabicyclo[2.2.2]octan-1-ylium bromide	**Page:**	
Study Number: LAS-MD-35		
Title of Study: A Long-term, Randomized, Double-blind Study of the Safety, Tolerability and Efficacy of Aclidinium Bromide at Two Dosage Levels When Administered to Patients With Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication (reference): Not applicable		
Study Period First Patient First Visit: 23 November 2009 Last Patient Last Visit/Early Termination: 28 April 2011	**Development Phase:** 3	
Objectives 1. To assess the long-term safety and tolerability of inhaled aclidinium bromide 200 µg or 400 µg administered twice a day (BID), once in the morning and once in the evening, via a multidose dry-powder inhaler in patients with moderate to severe, stable chronic obstructive pulmonary disease (COPD) 2. To assess the long-term efficacy, health-related quality-of-life benefits, and COPD symptoms improvement of inhaled aclidinium bromide 200 µg or 400 µg administered BID, once in the morning and once in the evening, via a multidose dry-powder inhaler in patients with moderate to severe, stable COPD		
Study Design: This was a long-term, randomized, double-blind, multicenter, parallel-group study of inhaled aclidinium bromide 200 µg or 400 µg administered BID via a multidose dry-powder inhaler in patients with moderate to severe, stable COPD. The study consisted of a 2-week run-in period designed to assess the stability of patients' disease and establish each patient's baseline characteristics. The run-in period was followed by a 52-week double-blind treatment period. Patients meeting the entry criteria for this study were randomized in a 1:1 ratio to either aclidinium bromide 200 µg or aclidinium bromide 400 µg BID. Two weeks following the last dose of investigational product, a follow-up phone call with the investigative study center (or an in-person visit if deemed necessary by the Investigator) took place. Due to the filing of a New Drug Application for this product, there was a data cut-off prior to completion of the study. Predefined team members were unblinded at the time of the data cut-off.		
Diagnosis and Main Criteria for Inclusion: Male or female outpatients, of at least 40 years of age, who had a diagnosis of moderate to severe, stable COPD as defined by criteria of the Global Initiative for Chronic Obstructive Lung Disease (post–salbutamol/albuterol forced expiratory volume in 1 second [FEV_1] ≥ 30% to < 80% of predicted, FEV_1/forced vital capacity [FVC] < 70% predicted) and a smoking history of 10 pack-years or more. Patients who had a history or presence of asthma, respiratory tract infection, a COPD exacerbation in the 6 weeks before Visit 1 (3 months if the exacerbation resulted in hospitalization), clinically relevant respiratory or cardiovascular conditions including clinically significant electrocardiographic or laboratory abnormalities could not participate in the study.		
Investigational Product, Dose and Mode of Administration, Lot Number: Aclidinium bromide 200 µg or 400 µg administered BID, once in the morning and once in the evening, via a multidose dry-powder inhaler. Lot numbers: DPI038 for aclidinium bromide 200 µg; DPI047 and DPI048 for aclidinium bromide 400 µg. Expiration date: Inhaler devices did not have an expiration date as they formed part of ongoing stability studies.		
Reference Therapy, Dose and Mode of Administration, Lot Number: Placebo devices for training on the treatment inhaler were provided separately to the study centers. Lot number: DPI022 for placebo training devices. Expiration date: Inhaler devices did not have an expiration date as they formed part of ongoing stability studies.		
Duration of Treatment: 52-week treatment period.		

Criteria for Evaluation

Efficacy

Primary: Change from baseline in morning predose (trough) FEV_1 at Week 52.

Secondary: Change from baseline in peak FEV_1 at Week 52.

Additional: Pulmonary function tests (FEV_1, FVC), at peak, trough, and by time point and the area under the curve from time 0 to 3 hours postdose ($AUC_{(0\text{-}3h)}$); health-related quality-of-life (St. George's Respiratory Questionnaire [SGRQ]) and EuroQol quality-of-life questionnaire [EQ-5D]); and rescue medication use.

Safety

Adverse event (AE) recording (including COPD exacerbations), clinical laboratory measures, vital sign parameters, and electrocardiograms (ECGs).

Statistical Methods

Demographics and Other Baseline Characteristics: Demographic parameters and other baseline characteristics were summarized by treatment group (aclidinium bromide 200 µg and aclidinium bromide 400 µg) and overall for the Safety and Intent-to-Treat (ITT) populations. No statistical tests were performed.

Efficacy: Efficacy analyses were based on the ITT Population using both last-observation-carried-forward (LOCF) and observed cases (OC) approach. The primary efficacy parameter (change from baseline in morning predose [trough] FEV_1 at Week 52) was analyzed by means of an analysis-of-covariance model with treatment group and sex as factors and baseline FEV_1 and age as covariates.

Safety: All safety parameters were analyzed descriptively. Safety analyses were based on the Safety Population.

SUMMARY OF RESULTS

Disposition: From the total of 605 patients randomized, 602 patients (99.5%) received at least 1 dose of double-blind treatment and were included in the Safety Population. Of these patients, 600 (99.2%) had at least 1 postbaseline FEV_1 assessment and qualified for the ITT Population. All patients in the ITT Population were included in the efficacy analyses. The percentages of patients who discontinued prematurely in the aclidinium bromide 200-µg (42.6%) and aclidinium bromide 400-µg (44.7%) treatment groups were comparable.

Patient Populations:

Populations	***AB 200 µg***	***AB 400 µg***	***Total***
Screened Population, N	—	—	1334
Randomized Population, N	312	293	605
Safety Population, n (%)	311 (99.7)	291 (99.3)	602 (99.5)
ITT Population, n (%)	310 (99.4)	290 (99.0)	600 (99.2)

The Screened Population consisted of all patients who signed a written informed consent form and received a patient identification number. The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group in the study. The Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product. The ITT Population consisted of all patients in the Safety Population who had a baseline and at least 1 postbaseline assessment of FEV_1.

AB = aclidinium bromide; ITT = intent-to-treat, N = number of patients in the study population; n = number of patients in the specified category.

Demographics and Other Baseline Characteristics: The treatment groups were generally comparable with respect to the demographic characteristics. Patients in the aclidinium bromide 400-µg group had a higher percentage of COPD exacerbations in the previous year (21.3%) compared with patients in the aclidinium bromide 200-µg group (17.0%). Patients in the aclidinium bromide 400-µg group also had lower prebronchodilator values (1.354 L) compared with the aclidinium bromide 200-µg group (1.407 L).

Bronchodilation Results:

Primary Endpoint: At the end of 52 weeks of treatment, the adjusted mean change from baseline in morning predose (trough) FEV_1 was 0.034 L in the aclidinium bromide 200-µg group and 0.072 L in the aclidinium bromide 400-µg group. Both doses of aclidinium bromide showed improvement in bronchodilation from baseline; however, aclidinium bromide 400 µg showed a numerically greater response than aclidinium bromide 200 µg (LOCF).

Secondary Endpoint: At the end of 52 weeks of treatment, the adjusted mean change from baseline in peak FEV_1 was 0.185 L in the aclidinium bromide 200-µg group and 0.214 L in the aclidinium bromide 400 µg group. Both doses of aclidinium bromide showed improvement in peak FEV_1 from baseline; however, aclidinium bromide 400 µg showed a numerically greater response (LOCF).

Additional Efficacy Parameters: For change in trough FEV_1, peak FEV_1, FEV_1 normalized $AUC_{(0\text{-}3h)}$, trough FVC, peak FVC, and FVC normalized $AUC_{(0\text{-}3h)}$, both doses of aclidinium bromide showed improvement from baseline and maintained improvement in treatment effects from Weeks 1 up to 52, and aclidinium bromide 400 µg showed a numerically greater response than aclidinium bromide 200 µg (LOCF and OC).

Health Status Variables:
SGRQ: Both doses of aclidinium bromide provided clinically significant improvements in quality-of-life as measured by SGRQ total scores from baseline to Week 52 (–5.29 and –5.16 for the aclidinium bromide 200-µg and 400µg groups, respectively). Throughout the study, a higher percentage of patients in the aclidinium bromide 400-µg group achieved a clinically meaningful improvement in quality-of-life (≥ 4 point improvement from baseline in SGRQ total score) compared with the aclidinium bromide 200-µg group. Specifically, at Week 52 the percentage of responders was 42.6% in the aclidinium bromide 200-µg group and 45.2% in the aclidinium bromide 400-µg group. For both EQ-5D parameters, there were numerical increases from Baseline at Week 12 up to Week 52 observed for both aclidinium bromide dose groups.
Rescue Medication: Treatment with aclidinium bromide reduced the use of rescue medication by 1.4 puffs per day, which is approximately half of the rescue medication used at baseline.

Safety Results: Aclidinium bromide at doses of 200 µg and 400 µg was safe and well tolerated. The most commonly reported treatment-emergent adverse events (TEAEs) (ie, incidence ≥ 5% in either treatment group) included: COPD exacerbation (19.3% for aclidinium bromide 200 µg, and 19.9% for aclidinium bromide 400 µg). All other TEAEs occurred in less than 5% of the patients in either group. The incidence of TEAEs was generally similar between treatment groups.

Diarrhea, dry mouth, back pain, and arthralgia occurred more frequently (> 1% difference) in the aclidinium bromide 400-µg group than in the aclidinium bromide 200-µg group. The incidence of these TEAEs was less than 4% in the aclidinium bromide 400-µg group. The incidence of these events considered treatment related was lower in the aclidinium bromide 400-µg group than in the aclidinium bromide 200-µg group, with the exception of dry mouth.

A total of 59 patients prematurely discontinued the study due to an AE; the percentage of patients who discontinued was 10.0% in the aclidinium bromide 200-µg group and 9.6% in the aclidinium bromide 400-µg group. The most commonly reported AE resulting in discontinuation was COPD exacerbation (9 patients [2.9%] for aclidinium bromide 200 µg, and 8 patients [2.7%] for aclidinium bromide 400 µg). All other TEAEs resulting in premature discontinuation were single occurrences in either treatment group.

The percentage of patients who had an on-therapy serious adverse event (SAE) was similar between treatment groups (9.3% for aclidinium bromide 200 µg, and 10.0% for aclidinium bromide 400 µg). The types of on-therapy SAEs were experienced by a similar proportion of patients in each treatment group. The most commonly reported SAE was COPD exacerbation (5 patients [1.6%] for aclidinium bromide 200 µg, and 6 patients [2.1%] for aclidinium bromide 400 µg).

Two patients died during the double-blind treatment period or within 30 days after the last dose of study treatment (1 due to biliary sepsis [aclidinium bromide 200 µg] and 1 due to subarachnoid hemorrhage [aclidinium bromide 400 µg]). Neither death was considered to be related to the study treatment.

Typically expected inhaled anticholinergic effects such as dry mouth and constipation occurred in small numbers of patients at comparable incidences between treatment groups (dry mouth and constipation were < 3% between treatment groups).

TEAEs of special interest to the aclidinium bromide clinical program (cardiac and cerebrovascular) did not reveal any findings of clinical concern. The incidence of cardiac AEs was 7.7% in the aclidinium bromide 200-µg group, and 4.1% in the aclidinium bromide 400-µg group.

One patient in the aclidinium bromide 400-µg group had a severe transient ischemic attack on Day 18 that was considered to be serious but not related to the study treatment. The patient had a history of coronary artery disease, coronary bypass surgery, and hypertension.

The percentage of patients experiencing COPD exacerbations of any severity (mild, moderate, or severe) was 19.3% for aclidinium bromide 200 µg and 18.6% for aclidinium bromide 400 µg. Moderate or severe exacerbations were noted for 16.4% of the patients for aclidinium bromide 200 µg, and 17.2% of the patients for aclidinium bromide 400 µg. Severe exacerbations were noted in 5 patients for aclidinium bromide 200 µg and 4 patients for aclidinium bromide 400 µg. (Note: Numbers based on patients being counted for each COPD exacerbation severity which differs from the COPD severity as the TEAE).

The changes from baseline in clinical laboratory tests, vital signs, and ECG parameters were similar between treatment groups.

CONCLUSIONS

- [redacted]

Date of the Report 27 December 2011