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-33		
Title of Study: Efficacy and safety of aclidinium bromide at two dose levels (200 µg twice daily, 400 µg twice daily) vs. placebo when administered to patients with moderate to severe chronic obstructive pulmonary disease (COPD)		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication (reference): Not applicable		
Study Period First Patient First Visit: 28 Apr 2009 Last Patient Last Visit/Early Termination: 03 Nov 2009	**Development Phase:** 3	
Objectives 1. To assess the long-term bronchodilator efficacy of inhaled aclidinium bromide, 200 µg and 400 µg administered twice daily, once in the morning and once in the evening via the Genuair multidose dry-powder inhaler, as compared with placebo in patients with moderate to severe COPD 2. To assess the safety and tolerability of aclidinium bromide, 200 µg and 400 µg administered twice daily, once in the morning and once in the evening, as compared with placebo 3. To assess the benefit of aclidinium bromide, 200 µg and 400 µg administered twice daily, once in the morning and once in the evening, on COPD exacerbations, disease-related health status as measured by the St. George's Respiratory Questionnaire (SGRQ), COPD symptoms, and other outcomes in patients with moderate to severe COPD		
Study Design: This was a multicenter, multinational, randomized, double-blind, placebo-controlled, parallel-group, 3-arm study of 16 weeks' duration: a 2-week run-in period, followed by a 12-week treatment period and a 2-week follow-up phone contact/study visit. In addition, 2 subset populations were used to assess 12-hour serial spirometry and 12-lead Holter evaluations.		
Diagnosis and Main Criteria for Inclusion: Male and female outpatients, of at least 40 years of age, with a smoking history of 10 pack-years or more; stable, moderate to severe COPD as defined by criteria of the Global Initiative for Chronic Obstructive Lung Disease (GOLD); a post-salbutamol (albuterol) forced expiratory volume in 1 second (FEV_1) ≥ 30% to < 80% of predicted normal value; and a FEV_1/forced vital capacity (FVC) ratio of < 70%. Patients who had a history or presence of asthma; respiratory tract infection or COPD exacerbation in the 6 weeks (3 months if the exacerbation resulted in hospitalization) before Visit 1; or clinically relevant cardiovascular, laboratory test, or electrocardiographic (ECG) abnormalities could not participate in the study.		
Investigational Product, Dose and Mode of Administration, Batch Number: Aclidinium bromide 200 µg or 400 µg administered twice daily, once in the morning and once in the evening, via a multidose dry-powder inhaler. Batch numbers: L0002903/DPI025 and L0002902/DPI028 for 200 µg and 400 µg aclidinium bromide, respectively. Expiration date: Inhaler devices were tested in a formal stability study, in compliance with 21 CFR 211.137 (g). The stability of the inhaler devices was at least 24 months, and no devices expired for the duration of the clinical trial.		
Reference Therapy, Dose and Mode of Administration, Batch Number: Blinded placebo, administered via inhalation. Batch number: L0002901/DPI022.		
Duration of Treatment: 12-week treatment period; the total duration of the study was approximately 16 weeks, including a screening and follow-up period.		

Criteria for Evaluation

Efficacy

Primary: Change from baseline in morning predose (trough) FEV_1 at Week 12

Secondary: Change from baseline in peak FEV_1 at Week 12

Additional: Pulmonary function tests (FEV_1, FVC, inspiratory capacity [IC]) at peak, trough, and by time point; SGRQ; Transition Dyspnea Index (TDI); COPD exacerbations (defined as an increase in COPD symptoms during at least 2 consecutive days that resulted in a medical intervention); and rescue medication use. Other health outcome patient self-administered assessments included the COPD Night-Time Symptoms Questionnaire and the Daily Sleep Diary.

Safety

Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, ECGs, and Holter monitoring (substudy-patients only)

Statistical Methods

Demographics and Other Baseline Characteristics: Demographic parameters and other baseline characteristics were summarized by treatment group for the Safety and ITT populations. For continuous variables, the number of non-missing observations, mean, SD, median, minimum, and maximum were presented. No statistical tests were performed.

Efficacy: Efficacy analyses were based on the primary last-observation-carried-forward (LOCF) ITT Population. The primary efficacy parameter (change from baseline in morning predose [trough] FEV_1 at Week 12) was analyzed by means of an analysis-of-covariance (ANCOVA) model with sex and treatment group as factors and baseline FEV_1 and age as covariates. A mixed-effects model for repeated measures based on observed cases (OC) and per-protocol (PP) analyses based on LOCF were performed as sensitivity analyses of the ITT approach.

Safety: All safety parameters were analyzed descriptively. Safety analyses were based on the Safety Population, defined in the table below

SUMMARY OF RESULTS

Disposition: A total of 1062 patients were screened for eligibility and 561 were randomized to a study treatment group. The percentage of patients who completed the study was as follows: 80.1% in the placebo group, 82.2% in the aclidinium bromide 200-µg group, and 87.4% in the aclidinium bromide 400-µg group. The percentage of patients who discontinued prematurely was slightly higher in the placebo group (19.9%) compared with the aclidinium bromide treatment groups: 17.9% in the 200-µg group and 12.6% in the 400-µg group.

Number of Patients:

	Placebo	***Aclidinium Bromide 200 µg BID***	***Aclidinium Bromide 400 µg BID***	***Total***
Screened, N	—	—	—	1062[a]
Randomized, N	186	185	190	561
Safety, N (%)	186 (100)	184 (99.5)	190 (100)	560 (99.8)
Holter substudy, n (%)	103 (55.4)	98 (53.3)	99 (52.1)	300 (53.6)
ITT - Efficacy, N (%)	185 (99.5)	184 (99.5)	190 (100)	559 (99.6)
Spirometry substudy, n (%)	73 (39.5)	74 (40.2)	73 (38.4)	220 (39.4)
Per Protocol, N (%)	175 (94.1)	171 (92.4)	184 (96.8)	530 (94.5)

Screened Population included all patients who signed a written informed consent form and received a screening number.
Randomized Population included all patients in the Screened Population who were randomized to a treatment group.
Safety Population included all patients in the Randomized Population who took at least 1 dose of double-blind treatment.
ITT Population included all patients in the Safety Population who had a baseline and at least 1 postbaseline FEV_1 assessment.
Per-Protocol Population included all patients who met the main inclusion/exclusion criteria, attained a sufficient compliance to the treatment received, and did not present with relevant protocol deviations that could interfere with the efficacy assessments.
a One patient, who was enrolled and randomized at 2 study centers, was counted once in the aclidinium bromide 400-µg group, which corresponds to the first dose of double-blind treatment administered.
BID = twice daily *(bis in die);* ITT = intent to treat; N = number of patients in population; n = number of patients evaluated in subpopulation. **Final**

Demographics and Other Baseline Characteristics: The treatment groups were comparable with respect to the demographic and baseline characteristics. At baseline, the mean morning predose (trough) FEV_1 was similar across treatment groups (1.376 L in the placebo group, 1.358 L in the aclidinium bromide 200-µg group, and 1.332 L in the aclidinium bromide 400-µg group).

Efficacy Results

Primary Endpoint: At the end of 12 weeks of treatment, aclidinium bromide 200 µg and 400 µg showed a statistically significantly greater improvement in the adjusted mean change from baseline in morning predose (trough) FEV_1 over placebo by 0.086 L ($p < 0.0001$) and 0.124 L ($p < 0.0001$), respectively, based on the primary LOCF ITT analysis. Aclidinium bromide 400 µg showed greater numerical improvement over aclidinium bromide 200 µg by 0.038 L ($p = 0.069$). Similar findings were observed using the mixed-effects model for repeated measures analysis and in the PP Population analysis.

Secondary Endpoint: At the end of 12 weeks of treatment, aclidinium bromide 200 µg and 400 µg showed statistically significant greater improvement in the adjusted mean change from baseline in peak FEV_1 over placebo by 0.146 L ($p < 0.0001$) and 0.192 L ($p < 0.0001$), respectively, based on the LOCF ITT analysis. Aclidinium bromide 400 µg showed a statistically significantly greater improvement over aclidinium bromide 200 µg by 0.046 L ($p = 0.0409$).

All analyses of the additional efficacy spirometric parameters based on FEV1, FVC, and IC were statistically significant for both aclidinium bromide 200 µg and 400 µg versus placebo at all time points at Weeks 1, 4, 8, and 12. Summaries of these analyses are presented in the table below.

Endpoints		***Adjusted Mean Differences (L) of Aclidinium Bromide 200 µg BID vs Placebo***		***Adjusted Mean Differences (L) of Aclidinium Bromide 400 µg BID vs Placebo***	
		Ranges During Weeks 1-8	*Week 12*	*Ranges During Weeks 1-8*	*Week 12*
FEV_1	Trough	0.082-0.099	0.086	0.108-0.113	0.124
	Peak	0.153-0.164	0.146	0.185-0.189	0.192
FVC	Trough	0.162-0.178	0.165	0.196-0.213	0.219
	Peak	0.261-0.277	0.262	0.259-0.303	0.279
IC	Trough	0.080-0.131	0.119	0.113-0.128	0.138

Note: All treatment differences were statistically significant ($p < 0.0001$ for FEV_1 and FVC, $p < 0.01$ for IC) compared with placebo.

BID = twice daily *(bis in die);* FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity.

For the 12-hour serial spirometry substudy, at Hour 3 of Week 12, the adjusted mean difference between the aclidinium bromide 400-µg group and placebo in change from baseline in FEV_1 was 0.214 L ($p < 0.0001$); this difference was 0.151 L at 12 hours after the morning dose ($p = 0.0001$). At Hour 3 of Week 12, the aclidinium bromide 200-µg group showed a difference from placebo in change from baseline in FEV_1 of 0.113 L ($p = 0.004$). The difference was 0.052 L at 12 hours after the morning dose ($p = 0.1648$). From the comparison of the 2 doses after 12 weeks of treatment, the aclidinium bromide 400-µg dose was statistically superior to the aclidinium bromide 200-µg dose ($p \leq 0.01$ at every time point, except at Hour 10 [$p = 0.1225$]).

As noted above, based upon the Week 12 trough and peak FEV_1, and serial spirometry, the aclidinium bromide 400-µg dose provided a consistently greater bronchodilatory effect than the aclidinium bromide 200-µg dose. Moreover, at Week 12 the ITT analysis demonstrated that the adjusted mean change from baseline in normalized $AUC_{0\text{-}3h}$ FEV_1 was 0.048 L higher in the aclidinium bromide 400-µg group than in the aclidinium bromide 200-µg group ($p = 0.0267$).

Dyspnea: Aclidinium bromide 200 µg and 400 µg showed a statistically significant difference ($p < 0.05$) versus placebo in favor of aclidinium bromide at Weeks 4, 8, and 12 in TDI focal score and in 3 dimension scores (except at Week 8 for aclidinium bromide 200 µg versus placebo [$p = 0.0599$]). At Week 12, the adjusted mean difference in the change in dyspnea status from baseline versus placebo in TDI focal score and in 3 dimension scores was 0.9 and 1.0 in the aclidinium bromide 200-µg and 400-µg groups, respectively ($p < 0.01$). These estimates were close to, and at the minimum clinically important difference (MCID) level of the TDI (improvement of ≥1 unit). At Weeks 4, 8, and 12, a higher percentage of patients in the aclidinium bromide groups achieved a clinically meaningful difference in TDI compared with the placebo group ($p < 0.05$). At Week 12, 32.9% of the patients in the placebo group, 50.9% of the patients in the aclidinium bromide 200-µg group, and 47.7% of the patients in the aclidinium bromide 400-µg group achieved clinically meaningful improvement in TDI focal score. These differences were statistically significant versus placebo in the aclidinium bromide 200-µg group ($p = 0.0015$) and in the aclidinium bromide 400-µg group ($p = 0.0136$).

Health Status Variables: Aclidinium bromide 200 μg and 400 μg showed a statistically significant difference ($p < 0.05$) versus placebo in the change from baseline to Weeks 4, 8, and 12 in SGRQ total score. This improvement was most notable at Week 4 with an adjusted mean difference versus placebo of –3.2 in the aclidinium bromide 200-μg group and –3.6 in the aclidinium bromide 400-μg group ($p < 0.001$ for both aclidinium bromide arms vs placebo). At Week 12, the adjusted mean difference versus placebo in change from baseline in SGRQ total score was –2.7 ($p = 0.0126$) in the aclidinium bromide 200-μg group, and –2.5 in the aclidinium bromide 400-μg group ($p = 0.0186$). A statistically significantly higher percentage of patients in each aclidinium bromide group achieved a clinically meaningful improvement in quality of life (≥ 4 point improvement from baseline in SGRQ total score) compared with the placebo group at all time points assessed except for the aclidinium bromide 400-μg group at Week 12 (35.9% for placebo, 49.4% for aclidinium bromide 200 μg, and 44.4% for aclidinium bromide 400 μg).

COPD Exacerbations: Moderate or severe COPD exacerbations were noted for 16 patients in the placebo group, 13 patients in the aclidinium bromide 200-μg group, and 11 patients in the aclidinium bromide 400-μg group. There was a numerical trend toward reduction in the rate of moderate to severe COPD exacerbations, although the trend was not statistically significant (0.63 per patient per year for placebo and 0.42 per patient per year for both aclidinium bromide 200 μg and aclidinium bromide 400 μg). The estimated reduction in the rate of moderate to severe COPD exacerbations was 34% for aclidinium bromide 400 μg compared with placebo (rate ratio: 0.66; $p = 0.0912$) and 33% for aclidinium bromide 200 μg compared with placebo (rate ratio: 0.67; $p = 0.1033$). The estimated reduction in the rate of mild, moderate to severe exacerbations was 48% for aclidinium bromide 400 μg compared with placebo (rate ratio: 0.52; $p = 0.0094$) and 30% for aclidinium bromide 200 μg compared with placebo (rate ratio: 0.70; $p = 0.1180$).

Rescue Medication: The change from baseline in the mean daily rescue medication use (number of puffs) across the 12-week treatment period was statistically significantly lower in both aclidinium bromide groups versus placebo. The adjusted mean difference versus placebo was -0.7 ($p = 0.0010$) for the aclidinium bromide 200-μg group and -0.9 ($p < 0.0001$) for the aclidinium bromide 400-μg group.

COPD Daily Symptoms: Overall, the results showed that both aclidinium bromide doses (200 μg and 400 μg) produced improvements in the frequency, quantity, and severity/impact of nighttime and early morning symptoms. At Week 12, aclidinium bromide 200 μg and 400 μg reduced the effect of COPD symptoms on morning activity restriction due to breathlessness; the level of breathlessness in the first hour of getting up; the amount of sputum production in the last 24 hours; the effect of breathlessness and cough on patients' activities in the past 12 hours; and the frequency of occurrence in the previous night of breathlessness, wheezing, coughing, and sputum production. In general, similar effects to those detected at Week 12 were also observed at Weeks 1, 4, and 8.

Effect on Sleep: Overall, the results on sleep diary parameters were not statistically significantly different between the aclidinium bromide arms and placebo. However, significant differences were noted for the following specific variables: frequency of nighttime awakenings and ability to fall back asleep after awakening in the aclidinium bromide 400-μg group at Weeks 1, 4, 8, and 12 and quality of sleep and rating of sleep compared to normal in both active-treatment groups at Weeks 1 and 4.

Safety Results: Aclidinium bromide at doses of 200 µg and 400 µg was safe and well tolerated in patients with moderate to severe COPD. Both doses of aclidinium bromide had similar safety profiles.

One patient in the aclidinium bromide 400-µg group was diagnosed with metastatic lung and brain cancer on Day 12 and died as a result of metastatic lung cancer on Day 23. This event was not considered to be related to the study treatment.

The incidence of on-therapy serious adverse events (SAEs) was low in the aclidinium bromide and placebo groups: 2.2% in the placebo group, 4.3% in the aclidinium bromide 200-µg group, and 3.2% in the aclidinium bromide 400-µg group.

Exacerbation of COPD was the most frequently occurring treatment-emergent adverse event (TEAE) in all treatment groups, occurring at a higher incidence in the placebo group: placebo (12%), aclidinium bromide 200 µg (9%), and aclidinium bromide 400 µg (7%). TEAEs that were reported in at least 2% of the patients (ie, 3 or more patients) in any group, and that occurred more frequently in any aclidinium bromide group than in the placebo group included: arthralgia (1, 4, and 5 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); diarrhea (3, 3, and 4 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); oropharyngeal pain (3, 2, and 4 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); headache (4, 6, and 3 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); nasopharyngitis (2, 6, and 3 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); back pain (1, 5, and 3 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively); and dizziness (1, 4, and 2 patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively).

TEAEs were reviewed for potential anticholinergic effects, and no signals were apparent. The incidence of typically expected inhaled anticholinergic effects was low in both aclidinium bromide groups and similar to placebo (ie, constipation [1 patient in the placebo group and 2 patients in the aclidinium bromide 200-µg group] and dry mouth [2 patients in the placebo group, 2 patients in the aclidinium bromide 200-µg group, and 1 patient in the aclidinium bromide 400-µg group]).

The incidence of cardiovascular TEAEs was low across groups (< 2% in any group). One patient in the placebo group (0.5%) had a cerebrovascular accident.

Excluding COPD exacerbations, a total of 21 patients, 7 in each group, discontinued the study due to a TEAE (3.8%, 3.8%, and 3.7% in the placebo, aclidinium bromide 200-µg group, and aclidinium bromide 400-µg group, respectively). The most frequently reported event resulting in discontinuation was COPD exacerbation (7 patients in the placebo group, 4 patients in the aclidinium bromide 200-µg group, and 1 patient in the aclidinium bromide 400-µg group); followed by dyspnea (2 patients each in the placebo and aclidinium bromide 400-µg group).

The changes from baseline in clinical laboratory tests, vital signs, and ECG parameters were similar across treatment groups. Holter monitoring was unremarkable for patients taking aclidinium bromide.

CONCLUSIONS

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Date of the Report 21 Jan 2011