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-38		
Title of Study: A Randomized, Double-blind, Placebo-Controlled Study Evaluating the Efficacy, Safety, and Tolerability of 2 Doses of Aclidinium Bromide Compared With Placebo for 12 Weeks in Patients With Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease Followed by a 40-Week Evaluation of the Higher Aclidinium Bromide Dose		
Investigator(s): [redacted]		
Study Center(s): [redacted]		
Publication (reference): Not applicable		
Study Period (years): Date study initiated (first patient first visit): 21 Dec 2009 (Part A) Date study finalized (last patient last visit): 13 Sep 2010 (Part A)	**Development Phase:** 3	

Objectives:

1. To assess the bronchodilator efficacy of inhaled aclidinium bromide, 200 µg and 400 µg administered twice a day (BID) for 12 weeks, compared with placebo in patients with moderate to severe stable chronic obstructive pulmonary disease (COPD)

2. To assess the long-term safety and tolerability of inhaled aclidinium bromide, 200 µg and 400 µg administered BID for 12 weeks, compared with placebo in patients with moderate to severe, stable COPD

3. To assess the long-term safety, tolerability, and efficacy of inhaled aclidinium bromide, 400 µg administered BID for an additional 40 weeks, and its benefit for health status (as measured by Baseline/Transition Dyspnea Index [BDI/TDI], St. George's Respiratory Questionnaire [SGRQ], EuroQol quality-of-life questionnaire [EQ-5D], and COPD Resource Utilization Questionnaire) and other outcomes in patients with moderate to severe, stable COPD (This objective applies to Part B of the study, the results of which will be presented in a separate report.)

Study Design:

Part A: This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, 3-arm study with a 12-week treatment period, preceded by a 2-week run-in period. In addition, 2 subset populations were used to assess 12-hour serial spirometry and 12-lead Holter evaluations.

Part B: This was a multicenter, open-label, 40-week treatment continuation of patients enrolled in Part A.

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, or electrocardiographic (ECG) abnormalities could not participate in the study.

Investigational Product, Dose and Mode of Administration, Batch Number:

Aclidinium bromide 200 µg or aclidinium bromide 400 µg administered BID, once in the morning and once in the evening, via a multidose dry-powder inhaler.

Batch numbers: DPI038 and DPI047 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.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Part A: Blinded placebo, administered via a multidose dry-powder inhaler BID Batch number: DPI031.
Part B: None.

Duration of Treatment:
Part A: 12-week treatment period; the total duration of the study was approximately 14 weeks, including a 2-week screening period.
Part B: 40-week open label treatment continuation of patients enrolled in Part A

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; St. George's Respiratory Questionnaire (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.
Safety
Adverse event (AE) recording, clinical laboratory measures, vital sign parameters, physical examinations, 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.

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.

Part A of the study was analyzed accordingly and is reported in this CSR. Part B will be analyzed and reported separately from Part A.

SUMMARY OF RESULTS:
Disposition: A total of 1236 patients were screened for eligibility and 544 were randomized to a study treatment group. The percentage of patients who completed Part A of the study was as follows: 83.0% in the placebo group, 84.2% in the aclidinium bromide 200-µg group, and 83.1% in the aclidinium bromide 400-µg group.

Number of Patients:				
	Placebo	***Aclidinium Bromide 200 µg BID***	***Aclidinium Bromide 400 µg BID***	***Total***
Screened, N	—	—	—	**1236**
Randomized, N	182	184	178	544
Safety, N (%)	182 (100)	183 (99.5)	177 (99.4)	542 (99.6)
Holter substudy, n (%)	69 (37.9)	75 (40.8)	65 (36.5)	209 (38.4)
ITT - Efficacy, N (%)	182 (100)	182 (98.9)	177 (99.4)	541 (99.4)
Spirometry substudy, n (%)	54 (29.7)	58 (31.5)	53 (29.8)	165 (30.3)
Per Protocol, N (%)	167 (91.8)	165 (89.7)	164 (92.1)	496 (91.2)

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 in Part A of the study.

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.

BID = twice daily *(bis in die);* ITT = intent to treat; N = number of patients in population; n = number of patients evaluated in subpopulation.

Demographics and Other Baseline Characteristics: At baseline, there were unexpected imbalances among the treatment groups in FEV_1 (1.249 L in the aclidinium bromide 400-µg group, 1.397 L in the aclidinium bromide 200-µg group, and 1.459 L in the placebo group) and in the percentage of patients with severe Stage III COPD (55% in the aclidinium bromide 400-µg group, 48% in the aclidinium bromide 200-µg group, and 37% in the placebo group for Stage III). Other than the imbalances in FEV_1 and in COPD severity, the treatment groups were generally comparable with respect to the other demographic and baseline characteristics.

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 0.051 L ($p = 0.0192$) and 0.072 L ($p = 0.0012$), respectively, based on the primary LOCF ITT analysis. Aclidinium bromide 400 µg showed numerical improvement over aclidinium bromide 200 µg by 0.021 L ($p = 0.3415$). Similar findings were observed using the mixed-effects model for repeated measures analysis and in the PP Population analysis.

The treatment effect observed in this trial whether based on the aclidinium bromide 400 µg bid or aclidinium bromide 200 µg bid was below expectations, and may have been affected by the significant imbalance at baseline.

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 0.115 L ($p < 0.0001$) and 0.125 L ($p < 0.0001$), respectively, based on the LOCF ITT analysis. The treatment difference between aclidinium 400 µg and aclidinium 200 µg was 0.010 L ($p = 0.6922$).

All analyses of the additional efficacy spirometric parameters based on FEV_1, 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, with the exception of Week 12 for trough FVC in the aclidinium bromide 200-µg group only ($p = 0.0521$). Summaries of these analyses are presented in the table below.

		Adjusted Mean Differences (L) of Aclidinium Bromide 200 µg BID vs Placebo		***Adjusted Mean Differences (L) of Aclidinium Bromide 400 µg BID vs Placebo***	
Endpoints		*Ranges During Weeks 1-8*	*Week 12*	*Ranges During Weeks 1-8*	*Week 12*
FEV_1	Trough	0.059-0.084	0.051	0.065-0.101	0.072
	Peak	0.151-0.165	0.115	0.175-0.186	0.125
FVC	Trough	0.099-0.153	0.067	0.157-0.196	0.120
	Peak	0.236-0.273	0.164	0.296-0.338	0.212
IC	Trough	0.062-0.088	0.086	0.090-0.126	0.113

Note: All treatment differences were statistically significant ($p < 0.0001$ for peak FEV_1 and FVC, $p < 0.05$ for trough FEV_1 and IC, and $p < 0.01$ for trough FVC with the exception of Week 12 in the aclidinium bromide 200-µg group only ($p = 0.0521$) compared with placebo.
BID = twice daily *(bis in die);* FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; IC = inspiratory capacity.

A small number of patients from the ITT population participated in the 12-hour serial spirometry substudy: 54 in the placebo group, 58 in the aclidinium bromide 200-µg group, and 53 in the aclidinium bromide 400-µg group. As observed for the total ITT population, there was an unexpected imbalance in the baseline FEV_1 values in the substudy. At Week 12, the bronchodilation provided by aclidinium bromide 400 µg compared with placebo in the change from baseline in FEV_1 was highest at Hour 3 (0.150 L, $p = 0.0040$), and this difference was generally maintained during the subsequent hours. From the comparison of the 2 doses after 12 weeks of treatment, the aclidinium bromide 400-µg dose was numerically greater than the aclidinium bromide 200-µg dose at every time point other than 1 hour post dose, but the difference was not statistically significant. The results of the substudy support BID dosing.

Dyspnea: Aclidinium bromide 200 µg and 400 µg showed a statistically significant difference ($p < 0.05$) versus placebo in favor of aclidinium bromide at Week 12 in TDI focal score. At Week 12, the adjusted mean difference in the change in dyspnea status from baseline versus placebo in TDI focal score was 0.7 and 1.0 in the aclidinium bromide 200-µg and 400-µg groups, respectively ($p = 0.0416$ and $p = 0.0054$, respectively). These differences were at the minimum clinically important difference (MCID) level of the TDI (improvement of ≥1 unit) in the aclidinium bromide 400-µg group only.

Similarly, a higher percentage of patients in the aclidinium bromide groups achieved a clinically meaningful difference in TDI at Week 12 compared with the placebo group (34.5% of the patients in the placebo group, 45.6% of the patients in the aclidinium bromide 200-µg group, and 50.7% of the patients in the aclidinium bromide 400-µg group). The difference was statistically significant versus placebo in the aclidinium bromide 400-µg group only ($p = 0.0150$).

Health Status Variables: No statistically significant differences were observed between both aclidinium doses and placebo in the change from baseline in SGRQ total score at Week 12, while it was noted that an unexpectedly high placebo response beyond the clinically meaningful threshold of 4 units was observed: -4.3 in the placebo group, -6.0 in the aclidinium bromide 200-µg group, and -5.4 in the aclidinium bromide 400-µg group. Although not statistically significant, a 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 Week 12 (38.8% in the placebo group, 47.2% in the aclidinium bromide 200-µg group, and 44.8% in the aclidinium bromide 400-µg group.

COPD Exacerbations: The number of patients experiencing COPD exacerbations of any severity (mild, moderate or severe) was 19 in the placebo group, 14 in the aclidinium bromide 200-µg group, and 19 in the aclidinium bromide 400-µg group. Moderate or severe COPD exacerbations were noted for 19 patients in the placebo group, 11 patients in the aclidinium bromide 200-µg group, and 16 patients in the aclidinium bromide 400-µg group. There was an observed numerical delay in the time to first moderate or severe exacerbation in the aclidinium groups relative to the placebo group (hazard ratio of 0.8; 95% CI = 0.4 to 1.6; p = 0.5048 for aclidinium 400 µg and hazard ratio of 0.6; 95% CI = 0.3 to 1.2; p = 0.1722 for aclidinium 200 µg) based on the ITT Population. The estimated rates of moderate to severe COPD exacerbations were numerically lower but not statistically significant between aclidinium bromide 400 µg and placebo (rate ratio: 0.82; p = 0.6345) and between aclidinium bromide 200 µg and placebo (rate ratio: 0.57; p = 0.2170). Similar results were observed with all exacerbations of any severity.

Rescue Medication: There were no statistically significant differences in the total daily use of rescue medication in both aclidinium bromide groups compared with placebo (-0.17 puffs for the aclidinium bromide 200-µg group versus placebo [p = 0.5334] and -0.31 puffs for the aclidinium bromide 400-µg group versus placebo [p = 0.2490]).

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.

Two patients died during the double-blind treatment period; one patient in the placebo group died on Day 48 of the study with no definitive cause of death, and one patient in the aclidinium bromide 400-µg group died on Day 55 of the study (27 days after the last dose of study treatment) due to cardio-respiratory arrest. Neither death was considered related to study treatment.

The incidence of on-therapy serious adverse events (SAEs) was comparable in the aclidinium bromide and placebo groups: 6.6% in the placebo group, 6.0% in the aclidinium bromide 200-µg group, and 4.5% in the aclidinium bromide 400-µg group. The most frequently reported SAE was exacerbation of COPD. Sixteen patients had serious exacerbations of COPD: 6 patients in the placebo group, 5 patients in the aclidinium bromide 200-µg group, and 5 patients in the aclidinium bromide 400-µg group. Eight of these events resulted in study termination. All COPD exacerbations were considered to be severe and only one COPD exacerbation was considered related to the study treatment. The patient with the COPD exacerbation considered related to treatment was in the aclidinium bromide 400-µg group and was discontinued from the study due to withdrawal of consent the day before the start of the SAE. No other SAE was reported by ≥ 2% of the patients.

Exacerbation of COPD was the most frequently occurring treatment-emergent adverse event (TEAE) in all treatment groups: placebo (11.5%), aclidinium bromide 200 µg (8.7%), and aclidinium bromide 400 µg (13.0%). No other TEAEs were reported by ≥ 5% of the patients. TEAEs that were reported in at least 2% of the patients (ie, 4 or more patients) in the placebo, aclidinium bromide 200-µg, or aclidinium bromide 400-µg groups, and that appear to occur at a slightly higher frequently in any aclidinium bromide group than in the placebo group included: cough (4, 6, and 8 patients, respectively); headache (6, 7, and 6 patients, respectively); diarrhea (3, 4, and 5 patients, respectively); and sinusitis (2, 5, and 5 patients, respectively).

TEAEs were reviewed for potential anticholinergic effects. The incidence of typically expected inhaled anticholinergic effects was low in both aclidinium bromide groups and similar to placebo (ie, constipation [3 patients in the placebo group and 1 patient in the aclidinium bromide 200-µg group] and dry mouth [1 patient in the placebo group, 2 patients in the aclidinium bromide 200-µg group, and 3 patients in the aclidinium bromide 400-µg group]). In the aclidinium bromide 200-µg group, 1 patient had reduced visual acuity considered mild and related to study treatment, and another patient group had transient blindness considered severe and not related to study treatment. Neither event was considered serious or led to discontinuation. One patient in the aclidinium bromide 400-µg group had optic neuritis considered severe, not serious, and related to study treatment that led to discontinuation.

The incidence of cardiovascular TEAEs was low across groups (< 2% for any event in any group). In addition, one patient in the placebo group (0.5%) had a cerebrovascular accident and one patient in the aclidinium 200-µg group had a transient ischemic attack. A total of 25 patients discontinued the study due to a TEAE (8 [4.4%], 4 [2.2%], and 13 [7.3%] 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 in 4 (2.2%), 1 (0.5%), and 6 (3.4%) patients in the placebo, aclidinium bromide 200-µg, and aclidinium bromide 400-µg groups, respectively. No other event led to discontinuation of more than one patient in any treatment 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:

- [redacted]

Date of the Report: 16-Mar-2011