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-36		
Title of Study: A Long-term, Randomized, Double-blind, Extension Study of the Safety, Tolerability and Efficacy of Aclidinium Bromide at Two Dosage Levels When Administered to Patients With Moderate to Severe Chronic Obstructive Pulmonary Disease		
Investigators: [redacted]		
Study Centers: [redacted]		
Publication (reference): Not applicable		
Study Period First Patient First Visit: 10 Aug 2009 Last Patient Last Visit/Early Termination: 28 Oct 2010		**Development Phase:** 3
Objectives 1. To evaluate the long-term safety and tolerability of inhaled aclidinium bromide, 200 µg and 400 µg administered BID, once in the morning and once in the evening, in patients with moderate to severe chronic obstructive pulmonary disease (COPD) 2. To evaluate the long-term efficacy, pharmacoeconomic and health-related quality-of-life benefits of inhaled aclidinium bromide, 200 µg and 400 µg administered BID, once in the morning and once in the evening, in patients with moderate to severe COPD		
Study Design: This was a long-term, randomized, double-blind, multicenter, multinational, parallel-group extension study. Patients completing the lead-in study, LAS-MD-33, were eligible for enrollment. The extension study consisted of a 52 week randomized, double-blind treatment period plus a follow-up telephone contact 2 weeks after the end of treatment or early termination (ET). Eligible patients received either aclidinium bromide 200 µg or 400 µg BID. Patients who received aclidinium bromide 200 µg or 400 µg BID during the lead-in study continued to receive the same dosage for the duration of the extension study. Patients who received placebo during the lead-in study were randomized in a 1:1 ratio to receive either aclidinium bromide 200 µg or 400 µg BID for the duration of this extension study.		
Diagnosis and Main Criteria for Inclusion: Patients with COPD who completed the lead-in study (LAS-MD-33) and were eligible to participate in this extension study (LAS-MD-36). (See LAS-MD-33 for inclusion/exclusion criteria.) Patients were not eligible for participation in the extension study if they had a QTcB (QTc calculated according to Bazett's formula [$QTcB = QT/RR^{1/2}$]) that was greater than 500 msec on both the predose and post dose electrocardiogram (ECG); if the QTcB was less than 500 msec at Visit 6 of LAS-MD-33 and after the cardiologist overread, the patient could be considered eligible for study participation).		
Investigational Product, Dose and Mode of Administration, Lot 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. Lot numbers: DPI025 for aclidinium bromide 200 µg and DPI028 for aclidinium bromide 400 µg. 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: Not applicable; blinded active treatment, administered via inhalation		
Duration of Treatment: 52-week treatment period.		

Criteria for Evaluation

Efficacy

Primary: Change from baseline (Visit 2 of the lead-in study [LAS-MD-33]) in morning predose (trough) FEV_1 at Week 64(of the extension study).

Secondary: Change from baseline (Visit 2 of the lead-in study [LAS-MD-33]) in peak FEV_1 at Week 64 (of the extension study).

Additional: Pulmonary function tests (FEV_1 and FVC) at peak, trough, and by time point; health-related quality of life (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; COPD exacerbations (defined as an increase in COPD symptoms during at least 2 consecutive days that resulted in a medical intervention); ECGs; and physical examinations.

Statistical Methods

Demographics and Other Baseline Characteristics: Demographic parameters and other baseline characteristics were summarized by treatment sequence (placebo – aclidinium bromide 200 µg; aclidinium bromide 200 µg – 200 µg; placebo –aclidinium bromide 400 µg; and aclidinium bromide 400 µg – 400 µg) and overall for the Safety and ITT populations. For continuous variables, the n, mean, SD, median, minimum, and maximum were presented. No statistical tests were performed.

Efficacy: Efficacy analyses were based on the ITT Population using last-observation-carried-forward (LOCF) approach. The primary efficacy parameter (change from baseline (Visit 2 of the lead-in study [LAS-MD-33]) in morning predose [trough] FEV_1 at Week 64 (of the extension study) was analyzed by means of an analysis-of-covariance (ANCOVA) model with treatment sequence and sex as factors and baseline FEV_1 and age as covariates. No statistical comparisons were made between treatment sequences.

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

SUMMARY OF RESULTS

Disposition: A total of 291 patients from the lead-in study were enrolled in the extension study. Of these patients, 139 (of whom 44 received prior treatment with placebo and 95 received prior treatment with aclidinium bromide 200 µg) were treated with aclidinium bromide 200 µg and 152 (of whom 46 received prior treatment with placebo and 106 received prior treatment with aclidinium bromide 400 µg) were treated with aclidinium bromide 400 µg. There were no differences in discontinuations between treatment sequences and treatments; both treatments were comparable with respect to the percentage of patients who discontinued prematurely: 30.9% for aclidinium bromide 200 µg and 32.2% for aclidinium bromide 400 µg (overall discontinuations were 31.6%).

Number of Patients:

Populations	***Treatments in LAS-MD-36***						***Total***
	AB 200 µg			*AB 400 µg*			
	Prior Treatment in LAS-MD-33		**Total**	**Prior Treatment in LAS-MD-33**		**Total**	
	Placebo	***AB 200 µg***		***Placebo***	***AB 400 µg***		
Enrolled Population, N	44	95	139	46	106	152	291
Safety Population, n (%)	44 (100)	93 (97.9)	137 (98.6)	46 (100)	106 (100)	152 (100)	289 (99.3)
ITT - Efficacy Population, n (%)	38 (86.4)	76 (80.0)	114 (82.0)	41 (89.1)	91 (85.8)	132 (86.8)	246 (84.5)

Demographics and Other Baseline Characteristics: There were no differences among treatment sequences and treatments with respect to the demographic and physical characteristics.

Bronchodilation Results:

Primary Endpoint: At the end of 64 weeks of treatment, the adjusted mean change from baseline in morning predose (trough) FEV_1 was -0.035 L for placebo – aclidinium bromide 200 µg, 0.069 L for aclidinium bromide 200 µg – 200 µg, 0.069 L for placebo - aclidinium bromide 400 µg, and 0.056 L for aclidinium bromide 400 µg – 400 µg. Improvement relative to baseline at Week 64 was observed for patients who remained on active treatment in the extension study and for patients who were randomized to the placebo – aclidinium bromide 400 µg treatment sequence. For those patients who were randomized to the placebo – aclidinium bromide 200 µg treatment sequence, predose trough FEV_1 was maintained over time but the effect declined substantially at Week 64.

Secondary Endpoint: At the end of 64 weeks of treatment, the adjusted mean change from baseline in peak FEV_1 was 0.111 L for placebo – aclidinium bromide 200 µg, 0.213 L for aclidinium bromide 200 µg – 200 µg, 0.222 L for placebo – aclidinium bromide 400 µg, and 0.219 L for aclidinium bromide 400 µg – 400 µg. These data were similar to findings in the primary endpoint, ie, improvement relative to baseline in peak FEV_1 at Week 64 was sustained for patients who remained on active treatment in the extension study and patients who were randomized to the placebo – aclidinium bromide 400 µg treatment sequence. Improvement relative to baseline in peak FEV_1 was partially sustained for patients who were randomized to the placebo – aclidinium bromide 200 µg treatment sequence compared with the other treatment sequences at Week 64.

Additional Efficacy Parameters: Improvement relative to baseline in multiple efficacy parameters (ie, changes in trough, peak, and normalized AUC_{0-3}, FEV_1 and FVC) through 36 weeks of study treatment was sustained for patients who remained on active treatment in the extension study and for patients who were randomized to the placebo – active treatment sequences with aclidinium bromide 200 or 400 µg. After Week 36, improvement was partially sustained for most of the additional efficacy parameters for patients who were randomized to the placebo – aclidinium bromide 200 µg treatment sequence compared with the other treatment sequences.

Health Status Variables:
SGRQ: All patients who remained on active treatment in the extension study continued to demonstrate improvement in SGRQ total scores at Weeks 24, 36, 48, and 60. At Week 64, patients who were treated on aclidinium bromide 200 µg and 400 µg throughout the study showed a clinically significant reduction from baseline in SGRQ total score of 6.9 and 8.5 points, respectively. Likewise, patients who were randomized from placebo to aclidinium bromide 200 µg and 400 µg showed a reduction from baseline in SGRQ total score of 3.6 and 5.7 points at Week 64, respectively, although only the placebo – 400 µg treatment sequence attained a clinically significant magnitude of improvement. Similar reductions were seen in the activity subscale of the SGRQ at Week 64.

Rescue Medication: At baseline, the use of rescue medication (reported in mean puffs) was 3.6 for placebo – aclidinium bromide 200 µg, 3.8 for aclidinium bromide 200 µg – 200 µg, 3.7 for placebo – aclidinium bromide 400 µg, and 4.4 for aclidinium bromide 400 µg – 400 µg. The adjusted mean of the overall use of rescue medication was similar across treatments: 2.3 puffs/day for placebo - aclidinium bromide 200 µg, 2.6 puffs/day for aclidinium bromide 200 µg – 200 µg, 2.7 puffs/day for placebo – aclidinium bromide 400 µg, and 2.2 puffs/day for aclidinium bromide 400 µg – 400 µg. Overall, the number of puffs per day of the rescue medication used by patients throughout the postbaseline period of the study was less than at the baseline in all treatment sequences.

Safety Results: Aclidinium bromide at doses of 200 µg and 400 µg was safe and well tolerated. The incidence of treatment-emergent adverse events (TEAEs) occurring between treatments was generally similar. The most commonly reported TEAEs (≥ 5% overall) included exacerbation of COPD, nasopharyngitis, and upper respiratory tract infection.

Preferred Term[a,b]	***LAS-MD-36***						***Total N = 289 n (%)***
	AB 200 µg			*AB 400 µg*			
	Prior Treatment in LAS-MD-33		**Total N = 137 n (%)**	**Prior Treatment in LAS-MD-33**		**Total N = 152 n (%)**	
	Placebo N = 44 n (%)	***AB 200 µg N = 93 n (%)***		***Placebo N = 46 n (%)***	***AB 400 µg N = 106 n (%)***		
Patients with at least 1 TEAE	*35 (79.5)*	*71 (76.3)*	*106 (77.4)*	*35 (76.1)*	*77 (72.6)*	*112 (73.7)*	*218 (75.4)*
COPD	13 (29.5)	22 (23.7)	35 (25.5)	12 (26.1)	21 (19.8)	33 (21.7)	68 (23.5)
Nasopharyngitis	4 (9.1)	5 (5.4)	9 (6.6)	2 (4.3)	10 (9.4)	12 (7.9)	21 (7.3)
Upper respiratory tract infection	3 (6.8)	6 (6.5)	9 (6.6)	2 (4.3)	6 (5.7)	8 (5.3)	17 (5.9)

Note: Percentages were relative to the Safety Population.

a *Medical Dictionary for Regulatory Activities* version 13.1 was used to code AEs.

b If a patient had more than 1 AE for a particular preferred term, the patient was counted once for that preferred term.

AB = aclidinium bromide; AE = adverse event; COPD = chronic obstructive pulmonary disease; n (%) = number (percentage) of patients who had the specified TEAE during the double-blind extension treatment phase and within 30 days of the date of last dose of double-blind extension treatment; N = the number of patients in the Safety Population; TEAE = treatment-emergent adverse event.

A total of 19 patients (13.9%) for aclidinium bromide 200 µg and 14 patients (9.2%) for aclidinium bromide 400 µg discontinued the study due to a TEAE. Exacerbation of COPD was the most commonly occurring TEAE that led to discontinuation (4 patients [2.9%] for aclidinium bromide 200 µg and 2 patients [1.3%] for aclidinium bromide 400 µg).

The percentage of patients who had an on-therapy SAE was generally similar between treatments (14.6% for aclidinium bromide 200 µg and 13.2% for aclidinium bromide 400 µg). The most commonly reported SAE was exacerbation of COPD in 3.6% of the patients in aclidinium bromide 200 µg and 4.6% in aclidinium bromide 400 µg.

One patient (0.7%) for aclidinium bromide 200 µg died from an accidental multiple drug overdose (to oxycodone and morphine) and 1 patient (0.7%) for aclidinium bromide 400 µg died from esophagitis (other SAEs at the time of death for this patient included spinal compression fracture and pneumonia). According to the Investigator, neither death was 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 treatments (dry mouth and constipation were < 3% between treatments). A review of these AEs did not reveal any increased signals for anticholinergic effects in patients receiving aclidinium bromide.

TEAEs of special interest to the aclidinium bromide clinical program did not reveal any findings of clinical concern. The incidence of cardiac AEs was low between treatments (< 5% for any event between treatments) and occurred in a numerically higher percentage of patients for aclidinium bromide 200 µg (11.7%) than for aclidinium bromide 400 µg (6.6%).

One patient who received aclidinium bromide 400 µg had a cerebrovascular AE (hemorrhagic stroke). The hemorrhagic stroke was an on-therapy SAE that the Investigator considered to be related to the study treatment. Only 3 SAEs were related to the study treatment: acute coronary syndrome (1 patient for aclidinium bromide 200 µg) and hypertension and hemorrhagic stroke (1 patient for aclidinium bromide 400 µg).

The changes from baseline in clinical laboratory tests, vital signs, and ECG parameters were similar between treatments and not clinically significant.

CONCLUSIONS

- [redacted]

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