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/formoterol fumarate fixed-dose combination (FDC)	**Volume:**	
Name of Active Ingredient: (3R)-3-[(hydroxy)di(thi ophen-2-yl)acetyloxyl]-1-(3-phenoxypropyl)-1λ5-azabicyclo[2.2.2]octan-1-ylium bromide and (±)-N-[2-hydroxy-5-[(1RS)-1-hydroxy-2-[[(1RS)-2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]phenyl] formamide, (E)-2-butenedioate (2:1 salt) dihydrate	**Page:**	

Study Number: LAC-MD-36

Title of Study: A Phase III, Long-Term, Randomized, Double-blind, Extension Study of the Efficacy, Safety and Tolerability of Two Fixed-Dose Combinations of Aclidinium Bromide/Formoterol Fumarate, Aclidinium Bromide, Formoterol Fumarate, and Placebo for 28-Weeks Treatment in Patients with Moderate to Severe, Stable Chronic Obstructive Pulmonary Disease (COPD)

Investigators: [redacted]

Study Center(s): [redacted]

Publication (reference): None at the time of this report

Study Period (years): First Patient First Visit: 06 Apr 2012 Last Patient Last Visit: 04 Jun 2013	**Development Phase:** 3

Objectives:

The objectives of this study were to evaluate the following in patients with moderate to severe COPD:

1. Long-term safety and tolerability of 2 fixed-dose combinations (FDCs) of inhaled aclidinium bromide/formoterol fumarate, aclidinium bromide, formoterol fumarate and placebo
2. Long-term efficacy, pharmacoeconomic, and health-related quality of life

Study Design:

This was a multicenter, double-blind, placebo- and active-controlled, parallel group, 28-week treatment, extension study of the lead-in study, Study LAC-MD-31. Patients were randomized in a 1:1:1:1:1 ratio to an FDC of aclidinium bromide 400/12 µg, an FDC of aclidinium bromide 400/6 µg, monotherapy with one of the components of the FDCs (aclidinium 400 µg or formoterol 12 µg), or placebo, all administered twice daily, in the lead-in study. Those patients who chose to continue the treatment in the extension study and met the eligibility for the extension study remained on the same treatment as they were randomized to in the lead-in study.

Diagnosis and Main Criteria for Inclusion:

Patients with a diagnosis of stable moderate to severe COPD who completed the treatment phase of the lead-in study, LAC-MD-31

Number of Patients:

	Placebo	*FDC 400/12 µg*	*FDC 400/6 µg*	*Aclidinium 400 µg*	*Formoterol 12 µg*	*Total*
Randomized Population, N	337	338	338	340	339	1692
Combined Safety and ITT-Exacerbations populations, N	332	335	333	337	332	1669
Combined Intent-to-Treat (ITT) Population, N	331	335	333	337	332	1668
Enrolled Population, N	146	184	205	194	192	921
Extension Safety Population, N	146	182	204	194	192	918

The Randomized Population consisted of all patients in the Screened Population who were randomized to a treatment group in the lead-in study, LAC-MD-31.

The Combined Safety Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product in the lead-in study, LAC-MD-31.

The Combined ITT Population consisted of all patients in the Combined Safety Population who had a baseline assessment in the lead-in study (Visit 2 of LAC-MD-31) and at least 1 postbaseline assessment of forced expiratory volume in 1 second (FEV_1) in the lead-in study, LAC-MD-31.

The Combined ITT-Exacerbation Population consisted of all patients in the Randomized Population who took at least 1 dose of double-blind investigational product in the lead-in study, LAC-MD-31.

The Enrolled Population consisted of all patients from the lead-in study, LAC-MD-31, who signed informed consent at Visit 1 of this extension study (last visit [Visit 7] of Study LAC-MD-31).

The Extension Safety Population consisted of all patients in the Enrolled Population who took at least 1 dose of double-blind investigational product in this extension study.

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

- Aclidinium/formoterol FDC 400/12 µg, lot ABFF015
- Aclidinium/formoterol FDC 400/6 µg, lot ABFF009
- Aclidinium bromide monotherapy 400 µg, lot DPI061
- Formoterol fumarate monotherapy 12 µg, lots K16-185

All products were administered twice daily (once in the morning and once in the evening) via investigational product inhaler.

Reference Therapy, Dose and Mode of Administration, Batch Number:
Placebo via investigational product inhaler, lot DPI055

Duration of Treatment: 28-week double-blind treatment in the extension period following the 24 week double-blind treatment in the lead-in period

Criteria for Evaluation:

Efficacy

Because the objective of this study was to assess the long-term safety and tolerability of 2 FDCs versus monotherapies and placebo, efficacy parameters were not classified as primary, secondary, and additional, and were analyzed for descriptive purposes.

- Morning predose and morning postdose pulmonary function as assessed by pulmonary function tests, which included FEV_1, forced vital capacity (FVC), and inspiratory capacity (IC) at every visit including all visits in the lead-in study, LAC-MD-31
- Dyspnea status as measured by Baseline Dyspnea Index/Transition Dyspnea Index (TDI)
- Health-related quality of life as measured by St. George's Respiratory Questionnaire (SGRQ) in total and 3-dimension scores
- COPD exacerbations based on the electronic case report form (eCRF)
- COPD exacerbations derived from the Exacerbations of Chronic Pulmonary Disease Tool (EXACT) questionnaire
- Daily COPD symptoms derived from the EXACT questionnaire
- Rescue medication use

Safety: Adverse event (AE) recording, clinical laboratory evaluations (hematology, chemistry, urinalysis, theophylline), electrocardiograms, vital signs (including pulse rate, sitting systolic and diastolic blood pressure, respiratory rate, and body weight), major adverse cardiovascular events (MACE), and serum pregnancy tests.

Health economics and outcomes research (HEOR): Nighttime Symptoms of COPD Instrument (NiSCI), Early Morning Symptoms of COPD Instrument (EMSCI), exploratory nighttime and early morning symptom questions, Patient's Global Impression of Change (PGIC), and Health Resource Utilization Questionnaire

Statistical Methods:

Disposition: The number of randomized patients in the 6 study populations (ie, Randomized, Combined Safety, Combined ITT, Combined ITT-Exacerbation, Enrolled, and Extension Safety populations) was summarized by treatment group and study center for the extension study and the combined lead-in and extension studies.

The number and percentage of patients who completed the double-blind treatment period and the number and percentage of patients who prematurely discontinued during the same period were presented for each treatment group and pooled across treatment groups for the Randomized and Enrolled populations. The reasons for premature discontinuation from the double-blind treatment period were summarized (number and percentage) by treatment group for the Randomized and Enrolled populations.

For the extension study, prematurely discontinued patients were analyzed descriptively by Kaplan-Meier survival curves for the Randomized and Enrolled populations. For the combined lead-in and extensions studies, prematurely discontinued patients were analyzed descriptively by Kaplan Meier survival curves for the Randomized Population only.

Demographics and Other Baseline Characteristics: Demographic parameters were summarized by treatment group for the Combined Safety, Combined ITT, and Extension Safety populations. For continuous variables, the numbers of nonmissing observations, mean, SD, median, minimum, and maximum were presented. No statistical tests were performed.

Efficacy: All efficacy analyses were based on the Combined ITT Population, except for the COPD exacerbations, which were based on the Combined ITT-Exacerbation Population. All statistical calculations were 2-sided, performed at the 5% level of significance for main effects, unless otherwise specified. All 95% confidence intervals were 2-sided.

Safety: Unless otherwise specified, all safety analyses were performed using the Extension Safety Population for the extension study, and using the Combined Safety Population for the combined lead-in and extension studies.

HEOR: The analyses of all HEOR parameters were based on the Combined ITT Population using observed data.

SUMMARY OF RESULTS:

Disposition:

Overall Summary of Patient Disposition: Randomized Population

This extension study was planned after the enrollment of the lead-in study LAC-MD-31 had begun. All patients were required to sign a separate consent form to participate in the extension study LAC-MD-36. The percentage of patients who completed the lead-in study and did not enroll in the extension study was higher in the placebo treatment group (26.7% of the Randomized Population) than in any of the active treatment groups (ranging from 21.0% in the FDC 400/6 µg treatment group to 26.0% in the FDC 400/12 µg treatment group). A total of 1322 patients completed the lead-in study and were thus eligible for enrollment into the extension study (78.1% of the Randomized Population from LAC-MD-31). A total of 921 out of the 1322 randomized patients (54.4%) signed the informed consent and enrolled into the extension study. Of the 921 patients who enrolled into the extension study, 780 patients (46.1% of the Randomized Population) completed the extension study and 141 patients (8.3% of the Randomized Population) prematurely discontinued from the extension study.

Lead-in Study Disposition: Randomized Population

A total of 78.1% of patients who were randomized into the lead-in study completed the lead-in study and 21.9% of randomized patients prematurely discontinued from the lead-in study. A higher percentage of patients in the active treatment groups completed the lead-in study (78.8% to 81.7% across the active treatment groups) compared with the placebo group (70.0%). Overall, the placebo treatment group had the highest incidence of discontinuation (30.0%) and the FDC 400/6 µg treatment group had the lowest incidence (18.3%). The most frequently reported reasons for discontinuation from the extension study were AE (5.6%), withdrawal of consent (4.7%), and protocol violation (4.4%).

Extension-Study Disposition: Enrolled Population

A total of 84.7% of the enrolled patients completed the extension study and 15.3% of the enrolled patients prematurely discontinued the study. Similar percentages of patients across all treatment groups completed the study (82.9% [placebo treatment group] to 87.3% [FDC 400/6 µg treatment group).Overall, the placebo treatment group had the highest incidence of discontinuation (17.1%) and the FDC 400/6 µg treatment group had the lowest incidence (12.7%). The most frequently reported reasons for discontinuation were withdrawal of consent (5.0%) and AE (3.0%).

Lead-in and Extension Studies Patient Disposition: Randomized Population

A total of 78.1% of randomized patients completed the lead-in study or completed both the lead-in and extension studies and 30.2% of randomized patients discontinued in the lead-in or extension studies. Percentages of randomized patients completing the lead-in study or both the lead-in and extension studies were similar across active treatment groups (78.8% [aclidinium 400 µg] to 81.7% [FDC 400/6 µg]), and lower in the placebo treatment group (70.0%). Overall, the most frequent reasons for premature discontinuation from the lead-in study or the extension study were withdrawal of consent (7.4% of the Randomized Population) and AEs (7.2% of the Randomized Population).

Demographics and Other Baseline Characteristics: Demographic characteristics were similar in the Combined Safety Population, the Combined ITT Population, and the Extension Safety Population, and were generally well balanced across treatment groups. The average patient in the Extension Safety Population was 63.2 years of age, male (52.6%), and white (91.9%). There were no noteworthy differences among the treatment groups with respect to age, sex, race, ethnicity, weight, height, or BMI.

COPD and smoking history were similar in the Combined Safety Population, the Combined ITT Population, and the Extension Safety Population, and were generally well balanced across treatment groups. The mean duration of COPD in the Extension Safety Population was 8.6 years. The incidences of chronic bronchitis, emphysema, and the combination of chronic bronchitis and emphysema were reported in 58.0%, 59.5%, and 22.7% patients overall, respectively. A total of 174 patients (19.0%) reported having a COPD exacerbation in the 12 months prior to study entry. Most patients (54.9%) were current smokers. The mean smoking duration was 42.1 years overall (range: 1-69 years) and was similar across treatment groups.

Efficacy Results:

Efficacy of aclidinium/formoterol FDC 400/12 µg and FDC 400/6 µg BID was demonstrated across endpoints as follows:

Pulmonary Function: Over the 52 weeks of treatment, both of the FDC doses achieved statistically significant differences over placebo ($p < 0.0001$) and monotherapies in the change from baseline in FEV1 at 1-hour postdose of investigational product, and those changes were consistently higher for the FDC 400/12 µg treatment group (versus placebo: 0.280 L to 0.299 L; versus aclidinium 400 µg: 0.072 L to 0.108 L; versus formoterol 12 µg: 0.061 L to 0.0.092 L) compared to the FDC 400/6 µg treatment group (versus placebo: 0.252 L to 0.280 L; versus aclidinium 400 µg: 0.050 L to 0.087 L; versus formoterol 12 µg: 0.052 L to 0.069 L). Similar results were observed when assessing the change from baseline in FVC at 1 hour postdose and IC at 3 hours postdose.

At all visits over the 52 weeks of treatment, both of the FDC doses achieved statistically significant changes over placebo ($p < 0.0001$) in the change from baseline in morning predose (trough) FEV_1, and those changes were consistently higher for the FDC 400/12 µg treatment group (0.118 L to 0.152 L) compared to the FDC 400/6 µg treatment group (0.107 L to 0.145 L). Additionally, when compared to monotherapies, changes from baseline for the FDC 400/12 µg treatment group (versus aclidinium 400 µg: 0.008 L to 0.048 L; versus formoterol 12 µg: 0.019 L to 0.055 L) were consistently higher than changes from baseline for the FDC 400/6 µg treatment group (versus aclidinium 400 µg: -0.025 L to 0.042 L; versus formoterol 12 µg: –0.004 L to 0.049 L). Similar results were observed when assessing the change from baseline in trough FVC

Over the 52 weeks of treatment, both of the FDC doses achieved statistically significant changes over placebo ($p < 0.0001$) and monotherapies ($p \leq 0.0148$) in the change from baseline in normalized $AUC_{0\text{-}3h}$ FEV_1. Similar results were observed for the change from baseline in normalized $AUC_{0\text{-}3h}$ FVC.

Sustained effect over 52 weeks of treatment with the FDCs was further supported by statistically significant improvements in bronchodilation as demonstrated by the changes from baseline in peak FEV_1 observed for both of the FDC doses over placebo ($p < 0.0001$ for both FDC doses) and monotherapies from Day 1 to Week 52 ($p \leq 0.0009$ and $p \leq 0.0002$ for FDC 400/12 µg versus formoterol 12 µg and aclidinium 400 µg, respectively; $p \leq 0.0214$ and $p \leq 0.0124$ for FDC 400/6 µg versus formoterol 12 µg and aclidinium 400, respectively) and those changes were consistently higher in the FDC 400/12 µg treatment group (versus placebo: 0.216 L to 0.301 L; versus aclidinium 400 µg: 0.051 L to 0.112 L; versus formoterol 12 µg: 0.0621 L to 0.100 L) compared to the FDC 400/6 µg treatment group (versus placebo: 0.0208 L to 0.273 L; versus aclidinium 400 µg: 0.044 L to 0.085 L; versus formoterol 12 µg: 0.047 L to 0.069 L). Improvements in FVC were also sustained over the 52-week period.

Dyspnea and Health-Related Quality of Life: Across the 52 weeks of treatment, both of the FDCs consistently achieved statistical significance over placebo in the change from baseline in TDI focal score. Numerically greater improvements in TDI focal score were also observed in the FDCs compared to the monotherapies across the 52 weeks of treatment. Improvements in TDI focal score were numerically greater with both of the FDCs than with either constituent monotherapy at all visits up to Week 52 and were also numerically greater with the 400/12 µg dose than the 400/6 µg dose at most visits.

Both doses of the FDCs demonstrated improvements in dyspnea that were sustained over 52 weeks of treatment, as both FDC 400/12 µg and FDC 400/6 µg consistenty achieved statistical significance over placebo ($p \leq 0.0384$ and $p \leq 0.0351$ for FDC 400/12 µg and FDC 400/6 µg, respectively) in the number of patients who achieved a clinically meaningful difference in TDI focal score (≥ 1 unit).

The odds of achieving a ≥ 4-unit improvement in SGRQ total score were significantly greater in both aclidinium/formoterol FDC groups compared with placebo from Week 4 to Week 24 ($p \leq 0.0117$). The percentage of patients who improved ≥ 4 units was similar from Week 24 to Week 52 for both of the aclidinium/formoterol FDC doses.

COPD Exacerbations: A numeric reduction of 20% in the rate of moderate or severe exacerbations (eCRF) per patient per year was observed in the FDC 400/12 µg treatment group compared to the placebo treatment group (FDC 400/12 µg rate = 0.39; placebo rate = 0.49; rate ratio of 0.80 [95% CI 0.57, 1.12]), however this reduction did not reach statistical significance ($p = 0.1855$) due to the limited sample size of this study. Similarly, a numeric reduction of 6% was observed in the FDC 400/6 µg treatment group relative to placebo (rate ratio of 0.94 [95% CI 0.68, 1.30]).

Daily COPD Symptoms (E-RS): Overall, patients treated with FDC 400/12 µg or FDC 400/6 µg had greater improvements in total E-RS and each of the 3 symptoms domains as compared to placebo or either of the monotherapies.

Rescue Medication Use: Statistically significant reductions of overall daily total rescue medication use were observed in all active treatment groups compared with placebo. Treatment differences were highest in the FDC 400/12 µg treatment group (-1.08 puffs) as compared to FDC 400/6 (–1.03 puffs) and the monotherapies (-0.66 puffs and –1.00 puffs for the aclidinium 400 µg and formoterol 12 µg treatment groups, respectively).

HEOR: At Week 52, both of the FDC doses provided statistically significant improvements over placebo in nighttime and morning severity of wheezing, shortness of breath, and tightness of chest. Both FDC doses also provided statistically significant improvements over placebo in the severity of COPD symptoms limiting of morning activities.

Safety Results: The safety profiles of the Extension Safety and Combined Safety populations were similar across all safety parameters.

For the Extension Safety Population, the following safety findings were observed:

Aclidinium/formoterol administered as an FDC at doses of 400/12 µg and 400/6 µg was safe and well tolerated through 52 weeks of treatment, and the safety profile was comparable to that of placebo and the monotherapy treatments. The types and incidences of the most common treatment-emergent adverse events (TEAEs) were consistent with those observed in patients with COPD and those reported with this drug class. The percentages of patients who had an on-therapy serious adverse event (SAE) were similar between treatment groups. The number of adjudicated MACEs and cardiovascular and cerebrovascular standard MedDRA queries (SMQs) was low, and these events were reported at similar incidences between treatment groups.

The most commonly reported TEAEs (reported in ≥ 5% of patients in any treatment group) were urinary tract infection, nasopharyngitis, upper respiratory tract infection, and cough. Upper respiratory tract infection was the only preferred term (PT) reported more frequently in the placebo group (5.5%) compared with all other treatment groups (from 2.7% in the FDC 400/12 µg treatment group to 4.6% in the aclidinium 400 µg treatment group). Urinary tract infection was reported more frequently in the FDC 400/12 µg treatment group (8.8%) compared with all other treatment groups (from 4.1% in the aclidinium 400 µg treatment group to 6.4% in the FDC 400/6 µg treatment group). A similar proportion of patients reported nasopharyngitis (7.7% and 6.8%) and cough (2.7% and 2.6%) in the FDC 400/12 µg and formoterol 12 µg treatment groups, respectively.

Other commonly occurring TEAEs (those reported in >2% to < 5% of patients in any treatment group) and that occurred more frequently in the FDC 400/12 µg treatment group than in the other active groups were diarrhea, vomiting, edema peripheral, weight decreased, headache, hematuria, and oropharyngeal pain.

The majority of TEAEs were mild and moderate in intensity. The percentage of patients having 1 or more severe TEAEs was numerically higher in the placebo group (8.9%) compared with the active treatment groups (from 6.7% in the aclidinium 400 µg treatment group to 7.8% in the FDC 400/6 µg treatment group). No TEAE was reported as severe in more than 3 patients in any treatment group. The most commonly reported severe TEAEs were pneumonia (3 patients in the FDC 400/6 µg, 2 patients in the aclidinium 400 µg, and 1 patient in the formoterol 12 µg treatment groups) followed by myocardial infarction (2 patients in the aclidinium 400 µg, 1 patient in the placebo, and 1 patient in the formoterol 12 µg treatment groups).

The percentages of treatment-related TEAEs reported the FDC 400/12 µg and FDC 400/6 µg treatment groups (6.6% and 6.9%, respectively) was comparable to the percentages of treatment-related TEAEs reported in the placebo and aclidinium 400 µg treatment groups (6.8% and 7.2%, respectively), and higher than the percentage of treatment-related TEAEs reported in the formoterol 12 µg treatment group (3.6%). No treatment-related TEAE was reported in > 3 patients in any treatment group. The most commonly reported related TEAEs were headache (3 patients [1.6%] in the FDC 400/12 µg, 2 patients [1.0%] in the FDC 400/6 µg, and 1 patient [0.5%] in the aclidinium 400 µg treatment groups; and 1 patient [0.7%] in the placebo group) followed by blood creatine phosphokinase increased (2 patients [1.0%] in the FDC 400/6 µg, 2 patients [1.0%] in the aclidinium 400 µg, 1 patient [0.5%] in the FDC 400/12 µg, and 1 patient [0.5%] in the formoterol 12 µg treatment groups). The only reports of treatment-related atrial fibrillation were in the FDC 400/6 µg treatment group (2 patients [1.0%]).

The percentage of patients who had an on-therapy SAE was similar across treatment groups (from 6.8% in the placebo group to 7.7% in each of the FDC 400/12 µg and aclidinium 400 µg treatment groups). No SAE was reported in more than 3 patients in any treatment group. The most commonly reported SAE across treatment groups was pneumonia, reported in 3 patients (1.5%) in the FDC 400/6 µg and 2 patients (1.0%) in the aclidinium 400 µg treatment groups. All 5 SAEs of pneumonia were reported as severe, and none were considered by the Investigator to be related to the investigational product.

A total of 6 on-therapy deaths were reported: 2 patients [1.4%] in the placebo group (1 due to myocardial infarction and 1 etiology unknown), 2 patients [1.1%] in the FDC 400/12 µg treatment group (1 due to cardiac arrest and 1 etiology unknown), 1 patient [0.5%] in the FDC 400/6 µg treatment group (cardiopulmonary arrest), and 1 patient [0.5%] in the aclidinium 400 µg treatment group (respiratory failure). Of the 6 on-therapy deaths, the Investigator considered 1 death (0.7%; placebo group, etiology unknown) to be related to the investigational product.

The overall incidence of AEs leading to premature discontinuation was numerically higher in the placebo treatment group (4.8%), compared with all other treatment groups (from 2.1% in the formoterol 12 µg treatment group to 3.3% in the FDC 400/12 µg treatment group). Only 1 TEAE leading to discontinuation was reported in more than 1 patient (cerebrovascular accident in 2 patients in the aclidinium 400 µg treatment group).

The number of adjudicated MACEs was low and reported at similar incidences across treatment groups. A total of 8 patients had 1 or more MACEs: 1 patient (0.7%) in the placebo group (sudden cardiac death), 1 patient (0.5%) in the FDC 400/12 µg treatment group (sudden cardiac death), 2 patients (1.0%) in the FDC 400/6 µg treatment group (sudden cardiac death and angina pectoris), 3 patients (1.5%) in the aclidinium 400 µg treatment group (1 patient with myocardial infarction and 2 patients with cerebrovascular accident), and 1 patient (0.5%) in the formoterol 12 µg treatment group (myocardial infarction). All MACEs were SAEs and unrelated to the investigational product according to the Investigator

The incidence of cardiac disorders by specific SMQ category and PT for TEAEs and SAEs as well as adjudicated and non-adjudicated SAEs was comparable between treatment groups. The incidence of cardiac events by SMQ for adjudicated SAEs in the FDC 400/12 µg treatment group was numerically lower than or comparable with that observed in all other treatment groups, suggesting the addition of formoterol 12 µg to aclidinium 400 µg has no additive safety risk as compared with the monotherapy components in the study. Rates of atrial fibrillation were low across treatment groups. Cardiac events based on adjudicated SAEs were reported in the SMQs of ischemic heart disease, supraventricular tachyarrhythmia, and bradyarrhythmia. For the ischemic heart disease SMQ, 7 cardiac events were reported: 2 patients (1.0%) in the FDC 400/6 µg treatment group, 2 patients (1.0%) in the aclidinium 400 µg treatment group, 1 patient (0.5%) in the formoterol 12 µg treatment group, and 2 patients (1.4%) in the placebo group. For the supraventricular tachyarrhythmia SMQ, 1 cardiac event was reported for 1 patient (0.5%) in the FDC 400/6 µg treatment group. For the bradyarrhythmia SMQ, 2 cardiac events were reported: 1 patient (0.5%) in the formoterol 12 µg treatment group, and 1 patient (0.7%) in the placebo group. These events were not considered by the Investigator to be related to the investigational product.

The incidence of cerebrovascular disorders by specific SMQ category and PT for TEAEs and SAEs as well as adjudicated and non-adjudicated SAEs was comparable between treatment groups. The incidence of hemorrhagic cerebrovascular conditions by SMQ for adjudicated SAEs in the FDC 400/12 µg treatment group was numerically lower than or comparable with that observed in all other treatment groups, suggesting the addition of formoterol 12 µg to aclidinium 400 µg has no additive safety risk as compared with the monotherapy components in the study. Cerebrovascular events based on adjudicated SAEs were reported in the SMQs of hemorrhagic cerebrovascular conditions and ischemic cerebrovascular conditions. For the hemorrhagic cerebrovascular SMQ, 3 cerebrovascular events were reported in 2 patients (1.0%) in the aclidinium 400 µg treatment group. For the ischemic cerebrovascular SMQ, 3 cerebrovascular events were reported in 3 patients: 2 patients (1.0%) in the aclidinium 400 µg treatment group and 1 patient (0.5%) in the FDC 400/6 µg treatment group.

Urinary tract infection, constipation, dizziness, heart rate increased, palpitations, sinus tachycardia, tachycardia, throat irritation, vision blurred, and urinary retention were events that were common to both observed potential anticholinergic and β_2-agonist TEAEs .

Overall, urinary tract infection was reported most often: 8.8% and 6.4% of patients in the FDC 400/12 µg and FDC 400/6 µg treatment groups, respectively; and in 4.1%, 5.7%, and 5.5% of patients in the aclidinium 400 µg, formoterol 12 µg, and placebo treatment groups, respectively. The majority of urinary tract infections were reported in females, were mild or moderate in intensity, nonserious, and were considered by the investigator to be unrelated to treatment. No AEs of urinary tract infection led to discontinuation of treatment. Other potential anticholinergic TEAEs that were reported in more than 2 patients in any treatment group and occurred more often in the FDC 400/12 µg and/or FDC 400/6 µg treatment groups than the monotherapy or placebo treatment groups included constipation, dizziness, oropharyngeal pain, pyrexia, and cystitis. Other potential β_2-agonist TEAEs that were reported in more than 2 patients in any treatment group and occurred more often in the FDC 400/12 µg and/or FDC 400/6 µg treatment groups than the monotherapy or placebo treatment groups included headache, edema peripheral, constipation, dizziness, blood glucose increased, ECG QT prolonged, anxiety, and hyperglycemia.

The changes from baseline in clinical laboratory assessments, vital signs, and ECG parameters were small and similar between treatment groups and between populations; no results were considered to be clinically relevant according to the Investigator.

The proportions of patients with PCS postbaseline laboratory, vital signs, and ECG values were low and similar across treatment groups. The percentage of patients with PCS postbaseline laboratory values reported as TEAEs was low and comparable across treatment groups. Blood creatine phosphokinase increased (> 1.15 × ULN) was the most commonly reported TEAE associated with a PCS postbaseline laboratory value, and was reported most often in patients treated with the FDCs and formoterol 12 µg (2.1%, 1.2% and 1.8% in the FDC 400/12 µg, FDC 400/6 µg, and formoterol 12 µg treatment groups, respectively) as compared to patients treated with aclidinium 400 µg and placebo (0.6% and 0.9%, respectively). Most reports of blood creatine phosphokinase increased were mild or moderate in intensity and unrelated to treatment; none were reported as serious.

CONCLUSIONS

- [redacted]

Date of the Report 15 Oct 2013