1.0 TITLE PAGE

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Aclidinium Bromide in Chronic Obstructive Pulmonary Disease
NDA 202450

FDA Advisory Committee Briefing Document

Presented to:

Pulmonary-Allergy Drugs Advisory Committee

February 23, 2012

ADVISORY COMMITTEE BRIEFING MATERIALS: AVAILABLE FOR PUBLIC RELEASE

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2.0 ABBREVIATIONS

ADO	adverse event leading to dropout
AE	adverse event
ANCOVA	analysis of covariance
AUC	area under the plasma concentration versus time curve
AUC_{0-t}	area under the curve from time zero to time t
BDI	Baseline Dyspnea Index
BID	twice daily (*bis in die*)
BMI	body mass index
C_{max}	maximum plasma drug concentration
COPD	chronic obstructive pulmonary disease
CV	cardiovascular
DPI	dry-powder inhaler
ECG	electrocardiogram, electrocardiographic
FDA	US Food and Drug Administration
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
GOLD	Global Initiative for Chronic Obstructive Lung Disease
IC	inspiratory capacity
ICH	International Conference on Harmonisation
ITT	intent to treat
LOCF	last observation carried forward
MACE	major adverse cardiac events
MCID	minimum clinically important difference
MedDRA	*Medical Dictionary for Regulatory Activities*

NDA	New Drug Application
PT	preferred term
QD	once daily (*quoque die*)
QTc	QT interval corrected for heart rate
QTcB	QT interval corrected for heart rate using the Bazett formula ($QTcB = QT/(RR)^{1/2}$)
QTcF	QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$)
QTci	QT interval corrected for heart rate using an individual correction
SAE	serious adverse event
SGRQ	Saint George's Respiratory Questionnaire
SMQ	standardized MedDRA query
TDI	Transition Dyspnea Index
TEAE	treatment-emergent adverse event

3.0 EXECUTIVE SUMMARY

Chronic obstructive pulmonary disease (COPD) affects as many as 24 million people in the United States, is the fourth leading cause of death (125,000 people annually), and is a major driver of health care resource utilization. The progressive dyspnea, breathlessness, fatigue, impaired exercise capacity, and exacerbations greatly affect quality of life in patients with COPD. Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines emphasize that management of stable COPD should address symptoms and improve quality of life, and that preventing exacerbations of COPD is important because of their strong impact on patients' quality of life and prognosis (Kaplan, 2010). Ninety percent of patients with advanced COPD report dyspnea as a predominant symptom of their disease (Mahler et al, 2010). Therefore, despite available treatments, management of COPD can be improved through the development of new molecules that provide robust therapeutic benefit while minimizing unwanted side effects and risks of treatment.

3.1 PROGRAM OVERVIEW

Aclidinium bromide is a novel, long-acting dry powder inhaled muscarinic receptor antagonist that is highly selective for the M_3 receptor. The M_3 receptor mediates bronchodilation in patients with COPD, and the long residence time on the receptor allows for twice-daily (BID) dosing. In addition, aclidinium bromide has very low systemic exposure, which may explain the low incidence of anticholinergic side effects observed in the clinical program. Proper inhalation technique is facilitated by an elegant multi-dose delivery device designed for ease of use and to enhance adherence with prescribers' instructions. The potential for patient confusion that can occur with device operation with other inhalation devices is minimized with the device (Pressair®).

The clinical benefit of aclidinium bromide 400 µg BID has been conclusively demonstrated by showing meaningful bronchodilation, as measured by forced expiratory volume in 1 second (FEV_1) and relief from dyspnea in patients with moderate to severe COPD. When compared with a once-daily medication, the additional peak bronchodilator effect that is demonstrated with the evening dose may enable these patients to more comfortably perform activities with reduced dyspnea in the evening hours including exercising, walking, undressing, showering, and other of activities of daily living.

Currently marketed formulations of inhaled antimuscarinic agents have a long history of effective and safe use, with millions of patient-years of exposure in patients with COPD. Examples of these agents are ipratropium bromide (a short-acting antimuscarinic agent) and tiotropium (long-acting antimuscarinic agent). The currently marketed formulations of each drug have established the safety of this class of agents in the treatment of COPD. Likewise, aclidinium bromide has been shown to be effective, well tolerated, and safe in this clinical development program.

Aclidinium bromide provides an important new treatment option for patients with COPD and has demonstrated the following properties:

- Long lasting bronchodilatory effect due to long residence time at M_3 receptors
- Maximal bronchodilation achieved on the first day of treatment and sustained throughout the studies
- Acceptable safety and tolerability profile with a low incidence of anticholinergic side effects
- Low systemic exposure primarily resulting from rapid degradation by plasma esterases
    - Low likelihood of drug-drug interactions
    - No dose adjustments required for renal or hepatic impairment
    - No age or gender effect
    - No food effect
- Administered via an easy-to-use dry powder inhaler

Currently, tiotropium bromide (Spiriva® HandiHaler®) is the only FDA-approved long-acting muscarinic antagonist for the treatment of COPD. There is a need for new treatment options for patients with COPD given the prevalence and heterogeneity of this disease. Furthermore, given the serious nature of COPD and the requirement for polypharmacy in these patients (due to the presence of comorbid conditions [Huiart et al, 2005; Soriano et al, 2005]), the development of a new drug with a low probability of drug-drug interactions is important. Aclidinium bromide will provide an important additional long-acting muscarinic antagonist treatment option with demonstrated efficacy and safety in a patient-friendly inhalation device that is designed to minimize errors in self-administration.

The following indication is proposed:

- ***Aclidinium bromide inhalational powder 400 µg BID is indicated for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema***

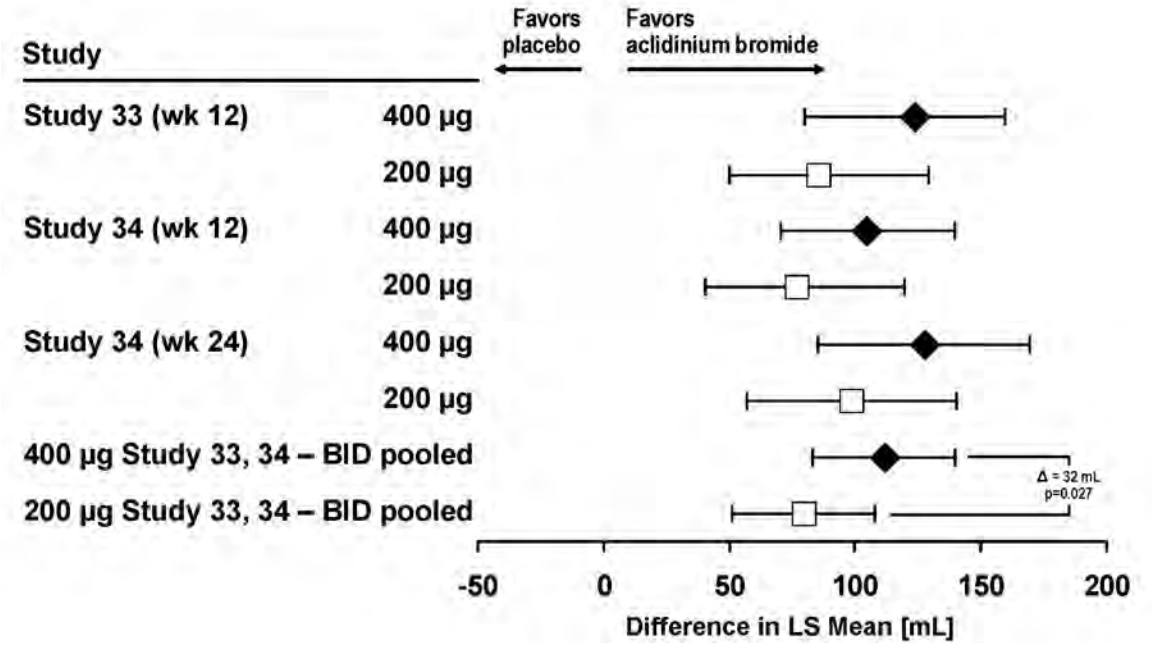
In support of this indication, the twice-daily clinical program assessed the efficacy, safety, and tolerability of aclidinium bromide administered at 100 µg, 200 µg, or 400 µg BID in 2717 COPD patients. Total exposure to aclidinium bromide BID was approximately 1400 patient-years. Additional safety support is provided by 1650 patients who received aclidinium bromide in the earlier 200 µg once-daily (QD) program for up to 1 year in placebo-controlled studies.

Dose, Regimen, and Efficacy: The 400 µg BID dose and regimen has been established as optimal based on the following study results:

- In early studies, both aclidinium bromide 200 µg and 400 µg BID provided statistically significant and persistent improvements compared to placebo in bronchodilation, as measured by trough FEV_1, peak FEV_1, and related measurements such as forced vital capacity (FVC). (The aclidinium bromide 100 µg BID dose did not produce a clinically meaningful improvement, and consequently was not assessed in further studies.)

- Results of the Phase 3 BID program (directly comparing 200 µg to 400 µg and placebo) demonstrated that aclidinium bromide 400 µg BID produced sustained clinically important improvements in lung function (ie, >100 mL) consistently outperforming the 200 µg BID dose. The 200 µg BID dose consistently showed an effect size of under 100 mL in trough FEV_1, as shown in Figure 3.1–1. A post-hoc pooled analysis of the primary efficacy endpoint, trough FEV_1, showed that the 400 µg BID dose produced statistically significant improvements compared to the 200 µg BID dose (Figure 3.1–1).

Figure 3.1–1. **Totality of Evidence, Comparison of Change From Baseline in Trough FEV_1 of Aclidinium Bromide 200 µg and 400 µg Versus Placebo at Week 12 in Study 33 and at Week 12 and Week 24 in Study 34 and Pooled Analysis (Study 33 and Study 34 at Week 12)—ITT Population**



$p \leq 0.0001$ for all comparisons versus placebo.
BID = twice daily; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; wk = week,

- Both doses (200 µg and 400 µg) of aclidinium bromide BID demonstrated statistically significant improvements compared with placebo in quality of life as assessed by the St. George's Respiratory Questionnaire (SGRQ) in pivotal Studies 33 and 34. The improvements in SGRQ total score observed with aclidinium bromide 400 µg compared to placebo in Study 34 were of a magnitude considered clinically meaningful (≥ 4 units) and are strongly supportive of the efficacy of aclidinium bromide.

- Both doses (200 µg and 400 µg) of aclidinium bromide BID demonstrated statistically significant improvements compared with placebo in breathlessness as assessed by the Transition Dyspnea Index (TDI). The change from baseline to Week 12 in TDI focal scores in Study 33 and at Week 12 and Week 24 in Study 34 showed statistically significant improvements versus placebo for aclidinium bromide 400 µg. The improvements in dyspnea observed with aclidinium bromide 400 µg compared to placebo in both studies were of a magnitude that was considered clinically meaningful (≥ 1 unit).

- Pivotal efficacy studies 33 and 34 showed statistically significant treatment differences in the reduction of overall rescue medication use at Week 12 with aclidinium bromide 400 µg compared with placebo (–0.9 puffs and –1.0 puffs, respectively).

- An exploratory analysis of the pooled population of the 2 pivotal Phase 3 efficacy studies (33 and 34) showed that aclidinium bromide 200 µg BID and aclidinium bromide 400 µg BID compared to placebo were associated with statistically significant reductions in the rate of COPD exacerbations (moderate to severe) of approximately 25% to 30% (rate ratios of 0.74 [p = 0.0259] for aclidinium bromide 200 µg and 0.71 [p = 0.0149] for aclidinium bromide 400 µg).

Safety: The safety and tolerability of aclidinium bromide have been convincingly demonstrated in the BID clinical program in 2717 patients and in the QD clinical program in 1925 patients with moderate to severe COPD. In addition, the safety profile is supported by the fact that systemic exposure to aclidinium bromide is very low (maximum plasma drug concentration [C_{max}] approximately 100 pg/mL in COPD patients) resulting primarily from rapid metabolism of the drug by plasma esterases following administration. As a result, systemic anticholinergic effects were infrequent. Based on BID individual studies, pooled BID safety data, and QD safety data, the following conclusions are supported:

- The incidence of treatment-emergent-adverse events (TEAEs) for both the 200 µg and the 400 µg BID doses was comparable to placebo.

- There was no dose-related difference between the 200 µg BID and 400 µg BID doses for TEAEs, serious adverse events (SAEs), adverse events leading to dropout (ADOs), deaths, and adverse events (AEs) of special interest.

- The incidence of SAEs with aclidinium bromide was comparable to placebo. The most common SAE observed was COPD exacerbation with incidences of 2.7% in the placebo group 1.6% in the aclidinium bromide 400 µg BID group, and 1.4% in the aclidinium bromide 200 µg BID group. In each study, and in the pooled data, the placebo group consistently had a numerically greater exacerbation rate than either aclidinium bromide treatment group.

- All-cause mortality - a total of 30 deaths (approximately 0.5%) occurred while on treatment and up to 30 days after treatment reported in the BID and QD placebo-controlled studies and in the long-term BID safety studies. The mortality rate was similar across all treatment groups. None of the deaths were judged by the investigators to be related to investigational product.

- AEs of special interest occurred infrequently and sporadically throughout the studies. In particular, cardiovascular (CV) events were carefully evaluated to confirm that treatment with aclidinium bromide was not associated with an increased incidence of major adverse cardiovascular events (MACE), including cerebrovascular events.

    - All deaths were adjudicated by a blinded independent external committee of cardiologists in academic practice to determine whether each was of CV origin or due to another etiology. The unblinded results are presented in Section 8.4.6.1; they show a similar incidence of CV death with aclidinium bromide and placebo in studies of up to 6 months' duration. Likewise, in the long-term safety studies, the frequency of CV deaths was similar to that observed in the placebo-controlled studies.

    - MACE composite (CV death, non-fatal myocardial infarction, non-fatal stroke) scores were similar for the aclidinium bromide groups as placebo. Likewise, the long-term safety studies did not reveal a CV safety signal. MACE events were rare in all treatment groups.

    - Two independent academic cardiologists evaluated the totality of the safety data in this clinical program and concluded that no CV safety signal was observed.

- A thorough QTc study and review of vital signs, electrocardiograms (ECGs) and 24-hour Holter safety showed no clinically significant findings.

- Anticholinergic effects such as dry mouth and constipation had a low incidence with no dose dependence between 200 µg BID and 400 µg BID doses. This is consistent with the low systemic exposure observed in the pharmacokinetic studies.

- No clinically significant safety signals were detected for the entire study population as well as when examined by age, sex, race, body mass index (BMI), COPD severity, or concomitant inhaled corticosteroid use.

Conclusions: Aclidinium bromide 400 µg BID will provide an important new treatment option for patients with COPD. Benefits to patients include the following:

- Aclidinium bromide 400 µg BID provided clinically meaningful efficacy (FEV_1 > 100 mL, improvements in dyspnea and health status) and outperformed the lower aclidinium bromide doses
- Tolerability was acceptable with a low incidence of anticholinergic effects
- The Pressair® device is simple to use, reducing the likelihood of errors in administration, and reliably and accurately delivers drug even in patients with severe lung disease.
- No significant safety signals were observed in the long-term safety studies.

3.2 REGULATORY HISTORY

Clinical development of aclidinium bromide commenced in 2000 with the first exploratory studies. Since aclidinium bromide entered full development in 2002, an extensive program of clinical pharmacology and clinical studies in COPD patients has investigated the efficacy and safety of aclidinium bromide, administered QD, with doses ranging from 25 µg to 800 µg. Two Phase 2 clinical investigations of safety and tolerability in patients with renal impairment and in elderly patients and a Phase 1 thorough QTcF study were conducted with QD administration.

In anticipation of submitting an NDA in 2009 for the QD regimen, Forest Laboratories, Inc., obtained feedback from the FDA on the adequacy of the clinical response observed in the pivotal studies at a pre-NDA meeting on 03 Mar 2009. Although clinical studies demonstrated the bronchodilator efficacy of aclidinium bromide administered QD in patients with COPD, the Division responded that the predose FEV_1 effect size (approximately 0.060 L) observed with aclidinium bromide 200 µg QD in 2 Phase 3 studies (M/34273/30, 2009 [ACCLAIM/COPD I]; and M/34273/31, 2008 [ACCLAIM/COPD II]), was of "*uncertain clinical significance*," and recommended "*exploration of higher doses and more frequent dosing regimens to ensure the selection of the most appropriate and efficacious dose of aclidinium bromide for marketing.*"

As no apparent safety or tolerability issues were noted in the Phase 3 aclidinium bromide 200 µg QD program, clinical studies were conducted to investigate the efficacy and safety of the BID dose regimen with higher total daily doses. This program showed that aclidinium bromide is an efficacious and safe long-acting maintenance bronchodilator treatment for patients with moderate to severe COPD. On 23 June 2011, Forest filed an NDA in support of a 400 µg BID dose of aclidinium bromide, claiming the indication for long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema.

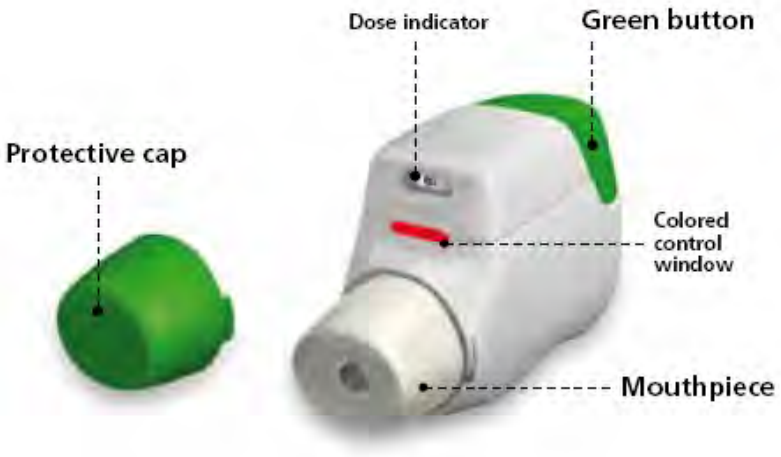
3.3 PRODUCT DESCRIPTION

Aclidinium bromide is formulated as a white or almost white inhalation powder containing aclidinium bromide, the active component, and lactose monohydrate, an excipient well accepted and widely used in pharmaceutical formulations. Aclidinium bromide is presented in a device-metered dry-powder inhaler (DPI), the Pressair® DPI Device (Figure 3.3–1).

The Pressair® DPI is designed to reliably deliver unit doses of 400 µg of micronized aclidinium bromide, a feature that is of particular importance in the intended patient population with severe respiratory compromise. Each DPI unit delivers at least 60 doses and has a dose indicator display to track the number of doses remaining. The device includes tactile, visual, and auditory safety features to limit the potential for excessive dosing. Likewise, the device will not deliver a partial dose with a poor inspiratory effort. This easy-to-use device requires just three steps (remove dust cap, depress actuator, and inhale adequately) and is appropriate for use in the elderly or severely compromised population where complicated devices could result in confusion and inadequate treatment.

The Pressair® DPI was consistently used throughout the Phase 3 aclidinium bromide clinical development program.

Figure 3.3–1. Pressair® DPI Device (Aclidinium Bromide Inhalational Powder - 60 doses)



3.4 CLINICAL DEVELOPMENT SUMMARY

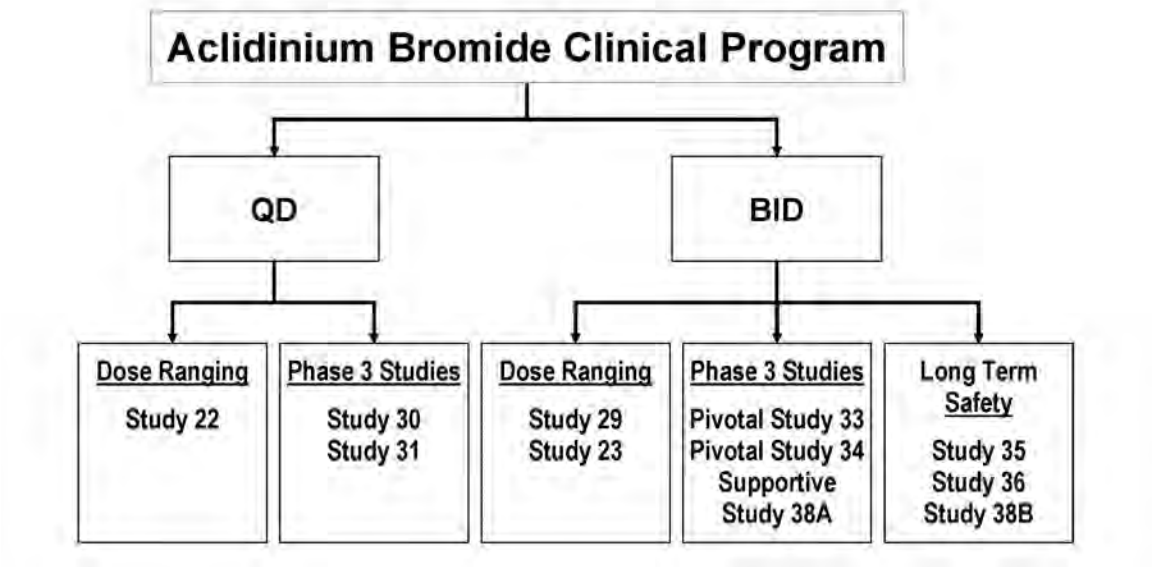
The core BID development program to assess the efficacy and safety of aclidinium bromide 400 µg BID in 1933 COPD patients consisted of 3 randomized, placebo-controlled, parallel-group Phase 3 studies (24-week Study M/34273/34 and 12-week Study LAS-MD-33 in 1389 COPD patients and an additional Phase 3 study (LAS-MD-38 [Part A]) in 544 patients); 3 Phase 3 long-term safety studies (LAS-MD-35, LAS-MD-36, and LAS-MD-38 [Part B]), and 2 supportive Phase 2 studies (M/34273/23 and M/34273/29) (Figure 3.4–1).

Please note that study identification numbers will be shortened in this briefing book from this point forward by eliminating the study prefixes (eg, Study LAS-MD-33 = Study 33; Study M/34273/34 = Study 34).

Each of the Phase 3 efficacy studies independently confirmed the efficacy of aclidinium bromide 400 µg BID compared with placebo by demonstrating statistically significant improvements in lung function and greater effect size than aclidinium bromide 200 µg BID. A clinically relevant effect was achieved for the primary efficacy parameter of trough FEV_1 in two of the phase 3 studies (change in trough FEV_1 at 12 weeks of 105 mL and 124 mL compared to placebo in Studies 34 and 33, respectively). In the third study (Study 38 [A]) a statistically significant baseline imbalance between treatment groups (in disease severity and FEV_1) was observed which makes interpretation of the results difficult. Despite the baseline imbalance, the difference in trough FEV_1 of 72 mL for aclidinium bromide 400 µg BID compared to placebo was statistically significant ($p = 0.0012$) and was supportive of the efficacy of aclidinium bromide 400 µg BID. The clinical relevance of the findings was further supported by significant improvements in quality of life and reduction in breathlessness as assessed by the SGRQ and TDI, respectively. Additionally, treatment with aclidinium bromide 400 µg BID resulted in reductions in rescue medication usage and showed a trend in reduction of exacerbations.

Although the primary focus of the long-term safety studies of aclidinium bromide 400 µg BID was to confirm long-term safety and tolerability, Study 35 provided evidence for the persistence of efficacy of aclidinium bromide over time and supported the observations from Study 34 that efficacy is maintained with prolonged administration. Aclidinium bromide 400 µg BID would provide an important additional maintenance treatment option for patients with COPD.

Figure 3.4–1. Overview of the Aclidinium Bromide COPD Clinical Program



BID = twice-daily, QD = once-daily

The following sections present brief overviews of the study designs and patient populations.

Study Design

Phase 3 Studies

The clinical efficacy program for aclidinium bromide 200 µg and 400 µg BID was conducted in North America, Europe, and South Africa. The 3 Phase 3 efficacy studies were of similar design, ie, prospective, double-blind, randomized, parallel-group, placebo-controlled, multicenter studies of 12 or 24 weeks of treatment with aclidinium bromide 200 µg, aclidinium bromide 400 µg, or placebo BID in patients with moderate to severe, stable COPD. Inclusion and exclusion criteria were very similar in the 3 studies.

Long-term Safety Studies

The long-term safety studies presented in this briefing book are organized as follows:

- Studies 35 and 36: the Double-blind, Long-Term Safety Group, comparing aclidinium bromide 200 µg BID and aclidinium bromide 400 µg BID
- Study 38 (B): the Open-label, Long-Term Safety Group, with all patients assigned to aclidinium bromide 400 µg BID

The 3 long-term safety studies were conducted in the United States and Canada. Study 35 (52 weeks) and Study 36 (a 52-week extension of Study 33) were designed to primarily evaluate the safety of aclidinium bromide 200 µg compared to 400 µg administered for up to 15 months; Study 38 (B), a 40-week aclidinium bromide 400 µg open-label extension of Study 38 (A) was conducted to augment the long-term safety exposure and to identify any new or unexpected signals with long-term exposure. These long-term safety studies were not placebo-controlled. Patients in Study 35 received either 200 µg or 400 µg of aclidinium bromide BID. Patients who received placebo in lead-in Study 33 were randomized to 200 µg and 400 µg BID after re-consent into Study 36, while all patients in Study 38 (A) who continued into 38 (B) were assigned only to open-label aclidinium bromide 400 µg BID for 40 weeks.

Patient Populations

Double-blind, Placebo-controlled Studies
Overall, the inclusion/exclusion criteria were defined to select patients broadly representative of the spectrum of the COPD population and were consistent with accepted clinical practice parameters and criteria set by the GOLD consensus panel. Patients whose primary diagnosis was asthma were excluded.

The principal characteristics of the inclusion and exclusion criteria for patient enrollment in all of the Phase 3 studies were as follows:

- Men and women aged 40 years and older
- Current or ex-smokers with a smoking history of 10 pack-years or more
- Clinical diagnosis of moderate to severe stable COPD, as per the GOLD criteria. Eligible patients must have had a postbronchodilator FEV_1 less than 80% predicted and greater than or equal to 30% of predicted and FEV_1/FVC less than 0.7
- Absence of respiratory tract infection or COPD exacerbation in the 6 weeks (3 months if hospitalization was required) prior to the screening visit
- Absence of symptomatic prostatic hypertrophy, bladder neck obstruction, or narrow-angle glaucoma
- Absence of clinically relevant respiratory conditions (except COPD) or cardiac conditions, no history or current diagnosis of asthma, allergic rhinitis, or atopy, or other clinically relevant medical conditions

Specific heart disease exclusion criteria were the same for all Phase 3 BID studies and were the following:

Clinically significant CV conditions defined as:

- Myocardial infarction in the previous 6 months
- Unstable angina, unstable arrhythmia which required changes in the pharmacological therapy or other intervention in the previous 12 months, or newly diagnosed arrhythmia in the previous 3 months
- Hospitalization within the previous 12 months for heart failure functional classes III (marked limitation of activity and only comfortable at rest) and IV (need of complete rest, confinement to bed or chair, discomfort at any physical activity and presence of symptoms at rest) as per the New York Heart Association

Patients enrolled in the Phase 3 studies were permitted to continue treatment with stable doses of inhaled corticosteroids, oral sustained-release theophylline, and/or oxygen, as required (≤ 15 hours per day). Stable doses of oral and/or parenteral corticosteroids (≤ 10 mg/day) were also permitted in the Phase 3 studies. Patients were provided with a marketed salbutamol/albuterol metered-dose inhaler, to be taken as needed. Thus, the Phase 3 clinical studies have been performed in the patient population in which therapy would be appropriate (Global Initiative for Chronic Obstructive Lung Disease, 2010).

Long-term Safety Studies

The eligibility criteria for long-term Studies 35, 36, and 38 (B) were the same as those for the BID placebo-controlled studies, with the exception of additional criteria for patient entry into extension study, Study 36. These additional criteria excluded those who had experienced clinically significant anticholinergic adverse effects in the lead-in study, Study 33, or who had prolongation of QTcB greater than 500 msec.

The principal baseline characteristics of the patient population in studies 35, 36, and 38 (B) were similar to those of the placebo-controlled studies.

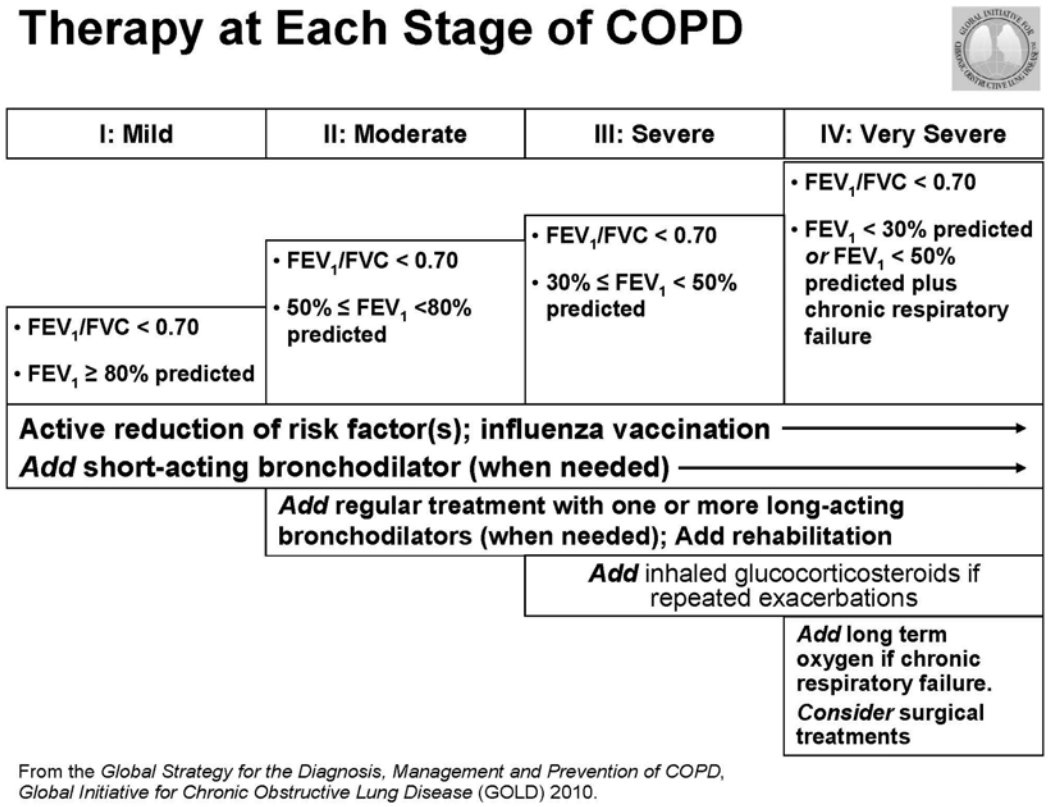
4.0 RATIONALE FOR THE USE OF ACLIDINIUM BROMIDE IN COPD

COPD is defined as *"a preventable and treatable disease with some significant extrapulmonary effects that may contribute to the severity in individual patients. Its pulmonary component is characterized by airflow limitation that is not fully reversible. The airflow limitation is usually progressive and associated with an abnormal inflammatory response of the lung to noxious particles or gases"* (Global Initiative for Chronic Obstructive Lung Disease, 2010).

COPD is a major cause of morbidity and mortality with a high and increasing prevalence, a natural history of progressive deterioration, and a loss of pulmonary function characterized by incompletely reversible expiratory airflow limitation (Mannino, 2008; Rennard, 1998). The characteristic symptoms of COPD include cough, sputum production, and chronic and progressive dyspnea. Furthermore, although COPD is primarily a lung disease, as mentioned above it has also significant systemic manifestations. Patients often have significant comorbidities such as diabetes, CV disease, muscle wasting, and bone loss (Global Initiative for Chronic Obstructive Lung Disease, 2010; Huiart et al, 2005; Soriano et al, 2005; Wouters, 2002).

Bronchodilators are central to the management of COPD and may be given on an as-needed basis for acute symptomatic relief or as a maintenance treatment for prevention or reduction of symptoms. GOLD Global Strategy recommends regular use of one or more long-acting bronchodilators in patients with COPD of at least moderate severity (Figure 4–1). Currently used bronchodilators include β_2-agonists (short and long acting), anticholinergics (short and long acting), theophylline, or a combination of these drugs. The choice of bronchodilator therapy depends on availability and individual response in terms of symptom relief and tolerability.

Figure 4–1. Therapy Recommendations for Treating COPD (GOLD Guidelines)



COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity.

Parasympathetic nerves are the dominant bronchoconstrictor neural pathway in airways, and cholinergic tone is the major reversible component in COPD (Coulson and Fryer, 2003; O'Connor et al, 1996, Postma et al, 1985). Cholinergic mechanisms are also important in the regulation of submucosal gland secretion, which is increased in COPD. Cholinergic nerves exert their bronchoconstrictor and mucus secretory effects via activation of muscarinic receptors of the M_3 subtype in airway smooth muscle and submucosal glands, respectively (Barnes 1993; O'Connor et al, 1996). Blockade of these muscarinic receptors with antagonists, such as ipratropium bromide, oxitropium bromide, and tiotropium bromide has been shown to provide clinical benefit in COPD (Beeh et al, 2002).

Short-acting inhaled anticholinergic drugs (eg, ipratropium, oxitropium) have been used in patients with symptomatic COPD since the 1970s as first-line therapy and are known to be safe and effective bronchodilators (Ferguson and Cherniack, 1993). A limitation of these agents is the need for frequent dosing (ie, up to 6 times daily). The use of long-acting bronchodilators has simplified the treatment algorithm of patients with COPD. Furthermore, long-acting bronchodilators are more beneficial with regard to quality of life (Kaplan, 2010; Vincken et al, 2002). Currently, 5 long-acting bronchodilators are available in the United States to patients with COPD: a single long-acting QD anticholinergic, tiotropium; 1 long-acting QD β_2-agonist, indacaterol, and 3 long-acting BID β_2-agonists, formoterol, arformoterol, and salmeterol.

Aclidinium bromide will provide COPD patients with an additional long-acting muscarinic antagonist (LAMA) treatment option with demonstrated efficacy, tolerability and safety in a patient-friendly inhalation device that is designed to minimize errors during self-administration.

5.0 NONCLINICAL FINDINGS

A comprehensive range of nonclinical studies have been conducted to determine the pharmacological activity, toxicology, and safety profile of aclidinium bromide.

5.1 PHARMACOLOGY

5.1.1 Primary Pharmacology

The muscarinic antagonism and selectivity for the M_3 receptor of aclidinium bromide have been assessed using a range of in vitro and in vivo pharmacology assays. Aclidinium bromide is a potent and selective muscarinic antagonist with affinity for the human muscarinic receptors in the low nanomolar range. The K_i values were 0.09, 0.1, 0.12, 0.25, and 0.16 nM for the five human M_1, M_2, M_3, M_4, and M_5 receptors, respectively, in a radioligand binding assay. Aclidinium bromide showed a long residence time on the M_3 receptor. It dissociated slowly from the M_3 receptor with a half-life of 29.2 hours versus 4.7 hours for the human M2 receptor; as a reference, tiotropium showed half-lives of 62.2 hours and 15.1 hours, and ipratropium showed half-lives of 0.47 hour and 0.08 hour for the human M_3 and M_2 receptors, respectively (Table 5.1.1–1).

Table 5.1.1–1. Radiolabeled Muscarinic Antagonists Dissociation From Muscarinic Receptors Measured as Half-life

Treatment	***M_2 dissociation half life (hours)***	***M_3 dissociation half life (hours)***	***M_3/M_2 ratio***
Aclidinium	4.7	29.2	6.2
Tiotropium	15.1	62.2	4.1
Ipratropium	0.08	0.47	5.9

Aclidinium bromide showed dose-dependent and long-lasting bronchodilatory activity in response to intravenously administered acetylcholine challenge in anesthetized guinea pigs and beagle dogs. The duration of action for aclidinium bromide (expressed as the half-life for the bronchodilatory effect) in the guinea pig model was 29 hours. Main metabolites of aclidinium bromide were inactive in preclinical assays.

5.1.2 Secondary Pharmacology

The affinity of aclidinium bromide and its two main metabolites (LAS34823 and LAS34850) to a standard panel of receptors and enzymes, excluding muscarinic receptors, was determined. Aclidinium bromide and its two major metabolites were shown to be devoid of significant affinity for any of the studied receptors or enzymes. The lack of secondary pharmacological effects suggests that aclidinium bromide has a low propensity for causing pharmacological effects unrelated to the muscarinic receptors.

5.1.3 Safety Pharmacology

Aclidinium bromide and its metabolites were shown to be devoid of any significant effects in various CV, central nervous system, respiratory, renal/urinary, and gastrointestinal safety pharmacology models.

The CV safety profile of aclidinium bromide is supported by results from the human ether-a-go-go–related gene (hERG) assay, Purkinje fiber assay, and in vivo CV safety studies in beagle dogs, guinea pigs, and Wistar rats. Aclidinium concentration levels that inhibited 50% (IC_{50}) in the hERG assay and the Purkinje fiber assay were estimated to be 145,000- and 22,000-fold, respectively, greater than the plasma C_{max} seen with the clinical dose of 400 µg. In the in vivo studies, aclidinium bromide demonstrated safety margins greater than 240-fold. The preclinical CV studies suggested that aclidinium bromide will have a broad safety margin when administered at the therapeutic doses in man.

No remarkable changes were observed in the behavioral profile or spontaneous motor activity with oral doses up to 300 mg/kg, as assessed by the Irwin test and a spontaneous locomotor activity test in mice.

Respiratory safety pharmacology studies showed that aclidinium bromide and tiotropium did not adversely affect specific pulmonary resistance, respiratory rate, or tidal volume when administered by inhalation at 1 mg/mL in conscious guinea pigs. In vitro studies of piglet trachea showed that aclidinium bromide and ipratropium at 100, 300, and 1000 µM did not significantly affect mucus transport rate. In vivo, neither aclidinium bromide nor ipratropium administered intravenously at 1000 µg/kg affected the mucus transport rate in anesthetized guinea pigs.

Aclidinium bromide administered subcutaneously in the dose range of 10 to 1000 µg/kg did not affect the urine volume excreted in rats. Tiotropium, administered subcutaneously at a dose of 100 µg/kg, produced a statistically significant decrease in the urine excreted during the first hour after treatment. No effect on peak micturition pressure, volume of urine excreted, or volume of urine retained in the bladder was observed when aclidinium bromide was administered intratracheally at doses up to 100 µg/kg in anesthetized guinea pigs. In contrast, tiotropium and ipratropium under the same experimental conditions decreased the peak micturition pressure and increased the volume of urine retained in the bladder in a statistically significant manner and showed a trend to decreasing the volume of urine excreted. The plasma levels of aclidinium bromide at 100 µg/kg in this study were 127-fold those reached in clinical practice at the human therapeutic dose of 400 µg BID. Finally, no relevant effects on renal function were found when aclidinium bromide was administered intravenously at 1 mg/kg to anesthetized beagle dogs.

The effects of aclidinium bromide, tiotropium, and ipratropium on the pilocarpine-induced sialorrhea (ie, excessive secretion of saliva) were assessed in vivo. In anesthetized mice, aclidinium bromide administered by inhalation had a half maximal effective concentration (EC_{50}) of 711 µg/mL in inducing dry mouth. In the same study, tiotropium and ipratropium showed EC_{50} values of 104 µg/mL and 369 µg/mL, respectively. In conscious rats, the median effective dose values for aclidinium bromide and tiotropium were 38 and 0.9 µg/kg, respectively, in inhibiting pilocarpine-induced sialorrhea when administered subcutaneously.

Aclidinium bromide showed low potential in inhibiting the gastrointestinal tract function in rats and guinea pigs. The median effective dose values in decreasing 24-hour fecal output in conscious rats were 501 µg/kg for aclidinium bromide and 32 µg/kg for tiotropium. In guinea pigs, aclidinium bromide did not affect colonic motility at 1000 µg/kg, whereas tiotropium bromide, at the dose of 100 µg/kg, produced a statistically significant inhibition of colonic motility.

5.1.4 Conclusions

- Aclidinium bromide is a potent and selective muscarinic receptor antagonist with a long duration of bronchodilatory action.

- The lack of secondary pharmacological effects suggests that aclidinium bromide has a low propensity for causing pharmacological effects unrelated to the muscarinic receptors.

- The results of the nonclinical safety pharmacology studies do not suggest any unique safety concern with administration of the clinical dose of 400 µg BID aclidinium bromide.

- Known anticholinergic effects, such as heart rate increase, urinary retention/urinary difficulty, dry mouth, and constipation, were less apparent in relevant preclinical models with aclidinium bromide compared to currently available muscarinic receptor antagonists (tiotropium and ipratropium).

5.2 TOXICOLOGY

The toxicology studies of aclidinium bromide address acute inhalation, intravenous, and oral toxicity in rodents; repeat-dose inhalational toxicity in mouse, rat, and dog; repeat-dose intravenous and oral toxicity in rat and dog; repeat-dose subcutaneous toxicity in rat; embryofetal development in rat and rabbit by inhalation and in rabbit by oral route; fertility and embryonic development to implantation in rat by inhalation; pre- and postnatal development in rat by inhalation; *in vitro/in vivo* genotoxicity; inhalational carcinogenicity in mouse and rat; local tolerance; and antigenicity.

In single-dose oral toxicity studies in rodents, aclidinium bromide demonstrated low toxicity, although there were clinical signs of antimuscarinic activity at doses $\geq$ 500 mg/kg. Some undetermined deaths in mice were observed at doses > 38,000 times the therapeutic dose (500 and 1000 mg/kg), which were most likely due to the pharmacologic action of aclidinium bromide.

Repeat-dose inhalation studies were conducted in rats (two 26-week studies) and dogs (one 39-week study). In rats, the clinical signs and mortality appeared to be related to swallowing problems associated with decreased salivation induced by the pharmacologic activity of the antimuscarinic drug. The no-observed-adverse-effect level of 0.04 mg/kg in rats was based on histopathologic findings, including hemosiderin deposition in the lungs. The margins of exposure in rats were 14 × and 17 × based on C_{max} and area under the plasma concentration versus time curve (AUC), respectively, relative to human exposure at an inhaled daily dose of 400 µg BID. In dogs, at the no-observed adverse-effect level of 0.22 mg/kg, the major signs were reversible pharmacologic effects (restlessness and increased heart rate). The margins of exposure in dogs were 46 × and 19 × based on C_{max} and AUC, respectively, relative to human exposure at an inhaled daily dose of 400 µg BID.

Six bacterial mutagenicity studies, described in five reports, were conducted with aclidinium bromide, each using a different batch of drug. Aclidinium bromide was negative in four of the studies and in the remaining two studies yielded an equivocal weak response only in TA98 plus S9. Six mouse lymphoma cell-culture mutagenicity studies were conducted with aclidinium bromide, each using a different batch of drug. Aclidinium bromide produced one equivocal and five positive responses in those studies in the presence of an S9 metabolic activation system. Significantly, the activity seen in these *in vitro* assays did not translate into activity in the whole animal. Aclidinium bromide tested negative in the *in vivo* mouse bone-marrow micronucleus assay and in the *in vivo* rat-hepatocyte DNA-repair assay, as measured by unscheduled DNA synthesis. Most importantly, aclidinium bromide produced no increase in tumors in either the rat or mouse long-term bioassays.

Inhalational carcinogenicity studies of 104 weeks each were conducted in both the mouse and the rat. In both species, both sexes, and at all dose levels tested, there was no evidence of any treatment-related neoplastic findings, with exposure margins (AUC) compared with human therapeutic dose exposure of greater than 124-fold in the mouse and greater than 41-fold in the rat.

Aclidinium bromide showed no teratogenic or embryotoxic effects in developmental toxicity studies conducted in rats and rabbits by inhalation at dosages up to 2.4 and 1.8 mg/kg BID, respectively. Maternal toxicity (rats and rabbits) was observed at all dose levels tested. In the rat inhalation study, slight nondose-related effects on fetal weight and ossification were observed in the treatment groups, which were associated with maternal toxicity in the form of reductions in food consumption and body weight gain.

In a rabbit developmental study by the oral route at very high dosages of up to 600 mg/kg/day, aclidinium bromide displayed reductions in fetal weights at 300 and 600 mg/kg/day, without any embryotoxic or teratogenic effects.

In the rat inhalational prenatal and postnatal development study, some reductions in food consumption in dams and body weight gain in dams and pups were observed at 0.2 and 2.4 mg/kg/day. Three developmental indices of the pups showed marginal changes at 2.4 mg/kg/day, and these corresponded to reduced pup weights.

The no-observed-adverse-effect levels for male and female fertility in the rat-fertility and early-embryonic-development inhalational study gave large margins of safety relative to clinical exposure.

In repeat-dose rat inhalational-toxicity studies, respiratory tract effects were indicative of the minor irritant potential of aclidinium bromide, but without any indication of immunologic etiology. Passive percutaneous test to determine the ability of serum samples taken from ovalbumin or aclidinium bromide-treated rats to produce an anaphylactic reaction indicated that aclidinium bromide should not have respiratory-sensitizing activity in clinical practice.

Conclusion

Based on the general toxicity studies and local tolerance studies performed, aclidinium bromide shows no evidence of any single-dose or repeat-dose tolerance concerns or any immunologically based reactions.

6.0 CLINICAL PHARMACOLOGY

6.1 PHARMACOKINETICS

6.1.1 Absorption

Aclidinium bromide is rapidly absorbed following inhalation. In healthy subjects, C_{max} of aclidinium bromide is achieved approximately 5 minutes following inhalation. In COPD patients, C_{max} is achieved approximately 10 to 15 minutes post-dose.

Aclidinium bromide plasma exposure exhibited linear and time-independent pharmacokinetic behaviour following multiple dose inhaled administration of 200, 400, or 800 µg QD or BID. The mean C_{max}, attained after inhalation of single doses of 400 µg was approximately 80 pg/mL in COPD patients and higher at 100 to 200 pg/mL in healthy subjects. C_{max} values achieved following inhalation of multiple doses were similar after the first dose and at steady state, irrespective of whether the administration regimen was QD or BID.

Approximately 55% of an administered dose is swallowed. However, due to the quaternary ammonium structure of aclidinium bromide, negligible oral absorption is seen, and the fraction of the inhaled dose that reaches the systemic circulation is low, with a mean of less than 5%.

6.1.2 Distribution

Following inhalation, whole lung deposition of aclidinium bromide averaged approximately 30% of the metered dose. Deposition within the lungs was highest in the most central lung region.

Following intravenous administration of 25 to 400 µg of aclidinium bromide, the mean values found for the apparent volumes of distribution (V_z) were between 95 L and 302 L. Following inhalation of aclidinium bromide, a high volume of distribution (V_z/f) was observed, reflecting the very low bioavailability associated with this route of administration.

6.1.3 Metabolism

Aclidinium bromide is rapidly hydrolyzed in plasma into its alcohol (LAS34823) and acid (LAS34850) metabolites by both enzymatic and non-enzymatic cleavage. The chemical (non-enzymatic) hydrolysis half-life of aclidinium bromide (in phosphate buffer [pH 7.4] at 37ºC) was very short at 1.2 hours, whereas the main human esterase involved in the enzymatic hydrolysis was butyrylcholinesterase, which is mainly located in human plasma. Minor oxidative pathways, which included hydroxylation of the parent compound and LAS34823, were also detected.

In vitro studies investigating the ability of aclidinium bromide and its major metabolites to inhibit or induce cytochrome P-450 isozymes or to inhibit esterase activities indicated that aclidinium bromide and its two main metabolites are not likely to inhibit or induce cytochrome P-450 enzymes or to inhibit esterases at the therapeutic dose.

In vitro studies investigating the ability of P-glycoprotein to alter the absorption, distribution, metabolism, and excretion (ADME) of aclidinium bromide indicated that P-glycoprotein is not expected to play a significant role in the ADME of aclidinium bromide. Further in vitro studies indicated that the ADME of co-administered P-glycoprotein substrate drugs are not expected to be affected by aclidinium bromide or its metabolites.

6.1.4 Excretion

Following single-dose administration, aclidinium bromide exhibited a very low urinary excretion, with 1% and 0.1% of the dose excreted as unchanged aclidinium bromide following intravenous and inhaled administration, respectively. The low urinary excretion of unchanged aclidinium bromide indicated that renal clearance plays a minor role in the total clearance of aclidinium bromide from plasma. Up to 65% of the dose was eliminated as metabolites in the urine, and up to 33% as metabolites in the feces.

Total clearance of aclidinium bromide from plasma is rapid with a terminal elimination half-life of approximately 2 to 3 hours after a single administration or repeat QD administration of 200 or 400 µg aclidinium bromide. Longer half-life estimates (in the range of 4 to 12 hours for most subjects) were observed with repeat BID administration of 400 µg.

6.1.5 Pharmacokinetic Assessments in Special Populations

6.1.5.1 Age and Gender

The plasma and urinary pharmacokinetic parameters of aclidinium bromide, administered via inhalation QD for 3 days, were investigated in moderate to severe COPD patients aged 40 to 59 years ("young") and aged 70 years and over ("elderly"). No differences in systemic exposure to aclidinium bromide (based on C_{max} and AUC) were observed between age groups. The higher exposure to the acid and alcohol metabolites observed in elderly patients compared to young patients is considered not clinically relevant as these metabolites appear pharmacologically inactive. No dose adjustment is considered necessary for elderly COPD patients.

6.1.5.2 Renal Impairment

The influence of renal impairment on the pharmacokinetics of single inhaled doses of aclidinium bromide (400 µg) was investigated. Renal clearance plays a minor role in the total aclidinium bromide clearance from plasma. Although renal dysfunction results in reduced renal excretion of aclidinium bromide, the impact of renal dysfunction on plasma exposure to aclidinium bromide is minor, with no statistically significant differences between the normal renal function group and each of the renal insufficiency groups (ie, mild, moderate, and severe) for plasma pharmacokinetic parameters. There was no apparent trend for subjects with lower creatinine clearance to have higher plasma exposure. Dose adjustments are not considered necessary for patients with renal impairment.

6.1.5.3 Hepatic Impairment

Hepatic metabolism plays a very minor role in the clearance of aclidinium bromide, which is metabolized mainly by chemical (non-enzymatic) and enzymatic cleavage. Dose adjustments are not considered necessary for patients with hepatic impairment.

6.1.6 Drug-Drug Interactions

Given the low aclidinium plasma concentrations achieved following therapeutic doses by inhalation and the results for the *in vitro* CYP450 and esterase metabolism studies (See Section 6.1.3), it is expected that aclidinium will not alter the disposition of drugs metabolized by CYP450 enzymes or human esterases. Hydrolysis of aclidinium to inactive metabolites accounts for the majority of the metabolism of aclidinium bromide. Specific clinical studies investigating drug-drug interaction studies have not been performed or are planned.

6.1.7 QT Prolongation

A thorough QT CV safety study was conducted as per recommendations of the ICH E14 guidance (International Conference on Harmonisation, 2005). This was a prospective, multiple-dose, randomized, parallel, placebo- and active-controlled clinical trial in male and female healthy volunteers. A total of 272 healthy subjects were randomized to one of the following four treatment arms:

- Aclidinium bromide 200 µg, dosed QD for 3 days
- Aclidinium bromide 800 µg, dosed QD for 3 days
- Placebo, dosed QD for 3 days
- Moxifloxacin 400 mg, dosed QD for 3 days

The effects of repeated QD inhaled doses of 200 µg and 800 µg aclidinium bromide on the QT interval were investigated in comparison to placebo and a positive control, moxifloxacin. Table 6.1.7–1 and Table 6.1.7–2 show the placebo- and baseline-corrected mean QT interval corrected for heart rate using an individual correction (QTci) results following dosing with aclidinium bromide and moxifloxacin on Days 1 and 3, respectively.

Table 6.1.7–1. Placebo-Corrected Least Squares Mean Change in QTci (msec) From Time-Matched Baseline on Day 1—ITT Population (Study 11)

Time post-dose	*Statistic*	*Aclidinium bromide 200 µg QD N = 68*	*Aclidinium bromide 800 µg QD N = 68*	*Moxifloxacin 400 mg QD N = 68*
5 minutes	LS Mean change[a,b]	1.1	–0.6	–2.6
	95% CI[b,c]	–2.2, 4.4	–3.9, 2.8	–5.9, 0.8
15 minutes	LS Mean change[a,b]	2.5	0.6	2.8
	95% CI[b,c]	–0.9, 5.8	–2.7, 3.9	–0.6, 6.1
30 minutes	LS Mean change[a,b]	0.7	–0.4	4.6
	95% CI[b,c]	–2.6, 4.0	–3.7, 2.9	1.3, 7.9**
1 hour	LS Mean change[a,b]	–0.3	0	7.4
	95% CI[b,c]	–3.7, 3.0	–3.4, 3.3	4.0, 10.7†
2 hours	LS Mean change[a,b]	1.5	2.1	11.8
	95% CI[b,c]	–1.8, 4.8	–1.2, 5.4	8.5, 15.1†
4 hours	LS Mean change[a,b]	–1.9	–2.0	8.1
	95% CI[b,c]	–5.2, 1.5	–5.3, 1.3	4.7, 11.4†
8 hours	LS Mean change[a,b]	0.6	–0.9	5.4
	95% CI[b,c]	–2.7, 3.9	–4.2, 2.4	2.1, 8.8**
12 hours	LS Mean change[a,b]	–0.2	–2.3	4.8
	95% CI[b,c]	–3.6, 3.1	–5.6, 1.0	1.5, 8.1**
23.5 hours	LS Mean change[a,b]	–1.6	–1.3	4.3
	95% CI[b,c]	–4.9, 17	–4.7, 2.0	1.0, 7.6*

* $p < 0.05$, ** $p < 0.01$, † $p < 0.001$.

a LS mean change (placebo-corrected) from time-matched baseline for treatment (aclidinium bromide 200 µg, aclidinium bromide 800 µg, and moxifloxacin).

b From an ANCOVA model by time point and treatment.

c p-value based on comparison of treatment vs placebo.

ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean; N = total number of subject; QD = once daily; QTci = QT interval corrected for heart rate using an individual correction.

Table 6.1.7–2. Placebo-Corrected Least Squares Mean Change in QTci (msec) From Time-Matched Baseline on Day 3—ITT Population (Study 11)

Time post-dose	*Statistic*	*Aclidinium bromide 200 µg N = 68*	*Aclidinium bromide 800 µg N = 68*	*Moxifloxacin 400 mg N = 68*
5 minutes	LS Mean change[a,b]	–0.8	0.2	2.6
	95% CI[b,c]	–4.4, 2.9	–3.5, 3.8	–1.1, 6.2
15 minutes	LS Mean change[a,b]	0.6	–1.4	6.0
	95% CI[b,c]	–3.0, 4.3	–5.0, 2.3	2.4, 9.6**
30 minutes	LS Mean change[a,b]	0.6	0.4	10.6
	95% CI[b,c]	–3.1, 4.2	–3.2, 4.1	7.0, 14.3†
1 hour	LS Mean change[a,b]	–0.6	–0.3	11.7
	95% CI[b,c]	–4.2, 3.0	–4.0, 3.3	8.1, 15.3†
2 hours	LS Mean change[a,b]	3.3	2.0	15.2
	95% CI[b,c]	–0.4, 6.9	–1.6, 5.6	11.6, 18.8†
4 hours	LS Mean change[a,b]	–0.2	–1.0	12.6
	95% CI[b,c]	–3.8, 3.5	–4.7, 2.6	9.0, 16.2†
8 hours	LS Mean change[a,b]	0.6	0.5	11.3
	95% CI[b,c]	–3.0, 4.2	–3.1, 4.2	7.7, 14.9†
12 hours	LS Mean change[a,b]	–0.5	–1.5	6.8
	95% CI[b,c]	–4.2, 3.1	–5.2, 2.1	3.2, 10.5†
23.5 hours	LS Mean change[a,b]	–3.0	–1.0	4.2
	95% CI[b,c]	–6.6, 0.7	–4.6, 2.7	0.6, 7.8*

* $p < 0.05$, ** $p < 0.01$, † $p < 0.001$.

a LS mean change (placebo-corrected) from time-matched baseline for treatment (aclidinium bromide 200 µg, aclidinium bromide 800 µg, and moxifloxacin).

b From an ANCOVA model by time point and treatment.

c p-value based on comparison of treatment vs placebo.

ANCOVA = analysis of covariance; CI = confidence interval; LS Mean = least squares mean; LAS 34273 = aclidinium bromide; N = total number of subjects; QTci = QT interval corrected for heart rate using an individual correction.

There were no statistically significant changes observed in QTci in subjects who received either aclidinium bromide 200 µg QD or 800 µg QD compared to placebo. Conversely, as expected, there were statistically significant changes observed in subjects who received moxifloxacin when compared with placebo. Pharmacokinetic analyses were limited due to low plasma concentrations relative to the sensitivity of the analytical assay. However, due to the dose-proportional and linear pharmacokinetics of aclidinium bromide, the C_{max} observed at steady state with aclidinium bromide 800 µg QD is two-fold higher than that achieved with aclidinium bromide 400 µg BID.

Conclusion

The TQT study demonstrated no clinically relevant conduction abnormalities or TQT prolongation in the aclidinium bromide groups at steady state.

7.0 CLINICAL EFFICACY

7.1 DOSE SELECTION

The clinical development program for aclidinium bromide focused originally on development of aclidinium bromide as a QD maintenance bronchodilator treatment in light of the long residence time on the M_3 receptor. Initially, a QD dose-finding 4-week study (Study 22) in moderate to severe COPD patients was conducted with doses of 25, 50, 100, 200, and 400 µg QD. Based on the results of this study, the aclidinium bromide 200 µg QD dose, which produced a mean bronchodilator effect (trough FEV_1) of approximately 148 mL, was selected for Phase 3 clinical studies. The results from the Phase 3 studies in the QD program, however, showed a mean bronchodilator effect (trough FEV_1) of approximately 60 mL which, while statistically significant, was of uncertain clinical significance. Based on the totality of the data from the Phase 3 studies of the aclidinium bromide 200 µg QD dose, Forest decided to pursue evaluation of aclidinium bromide using a BID regimen. Based on FDA feedback at a pre-NDA meeting on 03 Mar 2009, Forest evaluated higher and more frequent dosing regimens and generated new data focusing on the evaluation of aclidinium bromide at doses ranging from 100 µg to 400 µg BID. Figure 3.4–1 lists the BID studies that were conducted to collect that information.

Forest conducted two Phase 2 double-blind BID studies in COPD patients. In Study 29, the bronchodilatory dose-response of aclidinium bromide BID for doses ranging from 100 µg to 400 µg was assessed with Foradil® Aerolizer® (formoterol fumarate) and placebo as comparator treatment arms. In Study 23, the effect size of aclidinium bromide 400 µg BID was compared with the marketed product, Spiriva® HandiHaler® (tiotropium bromide inhalational powder, 18 µg).

In this briefing book, the 2 FDA-approved comparator agent formulations administered in the aclidinium bromide clinical studies are referenced as “tiotropium” and “formoterol”:

- tiotropium = Spiriva® HandiHaler® (tiotropium bromide inhalational powder, 18 µg)
- formoterol = Foradil® Aerolizer®(formoterol fumarate inhalational powder, 12 µg)

The aclidinium bromide doses tested in the 2 Phase 2 BID studies in COPD patients were as follows:

- 100 µg BID, 200 µg BID, and 400 µg BID (Study 29)
- 400 µg BID (Study 23)

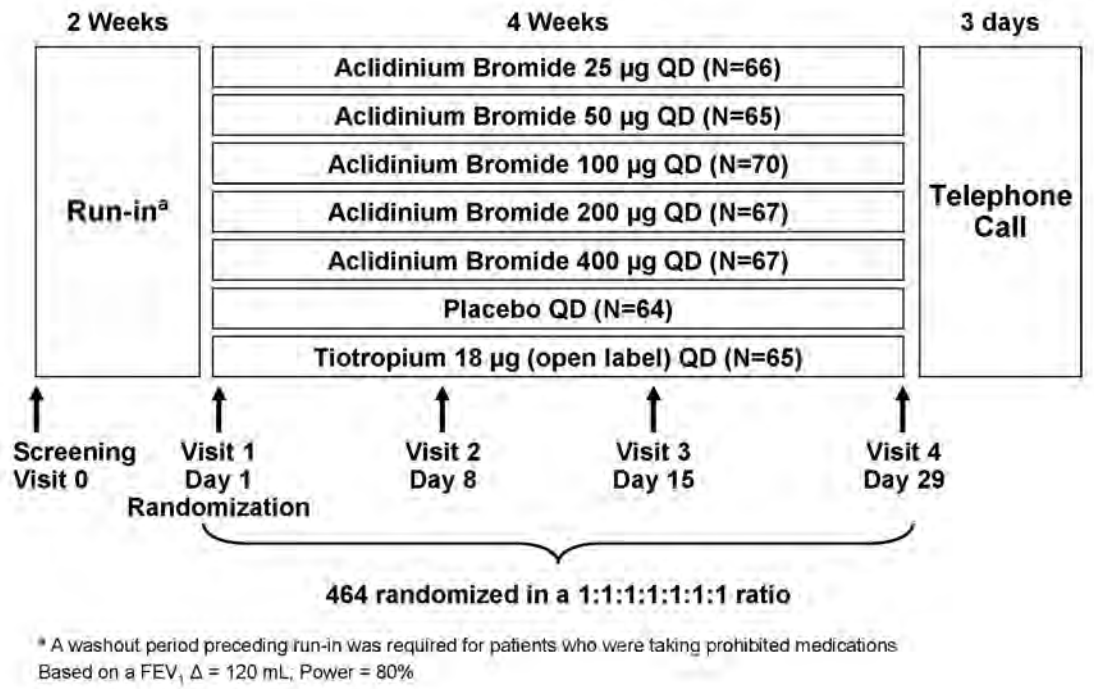
Efficacy results of the 3 dose-ranging studies in COPD patients (Study 22, Study 29, and Study 23) are presented in Sections 7.1.1, 7.1.3, and 7.1.4, respectively.

7.1.1 Study 22: Dose-Finding Study, Once-Daily Dosing

The primary objective of Phase 2 Study 22 was to assess the efficacy, safety, and tolerability of aclidinium bromide administered by inhalation for 4 weeks at 5 ascending doses (25, 50, 100, 200, and 400 µg) administered QD in patients with moderate to severe stable COPD compared to matching placebo. The study design is presented in Figure 7.1.1–1.

A sample size of 413 evaluable COPD patients (59 in each treatment group) allowed detection of a difference of 120 mL between one of the aclidinium bromide doses and the placebo group in trough FEV_1 at Visit 4 (Day 29, ie, after 28 days of investigational product administration) with 80% power, assuming an estimated common standard deviation (SD) of 230 mL and a 0.050 2-sided significance level.

Figure 7.1.1–1. Study 22 Design



BID = twice daily; FEV_1 = forced expiratory volume in 1 second; N = number of patients; QD = once daily.

As shown in Table 7.1.1–1, results at Day 29 showed that the aclidinium bromide 200 µg and 400 µg treatment arms and the tiotropium 18 µg treatment arm were statistically and clinically significantly more effective than placebo showing changes over 100 mL in improving mean trough FEV_1 ($p < 0.02$).

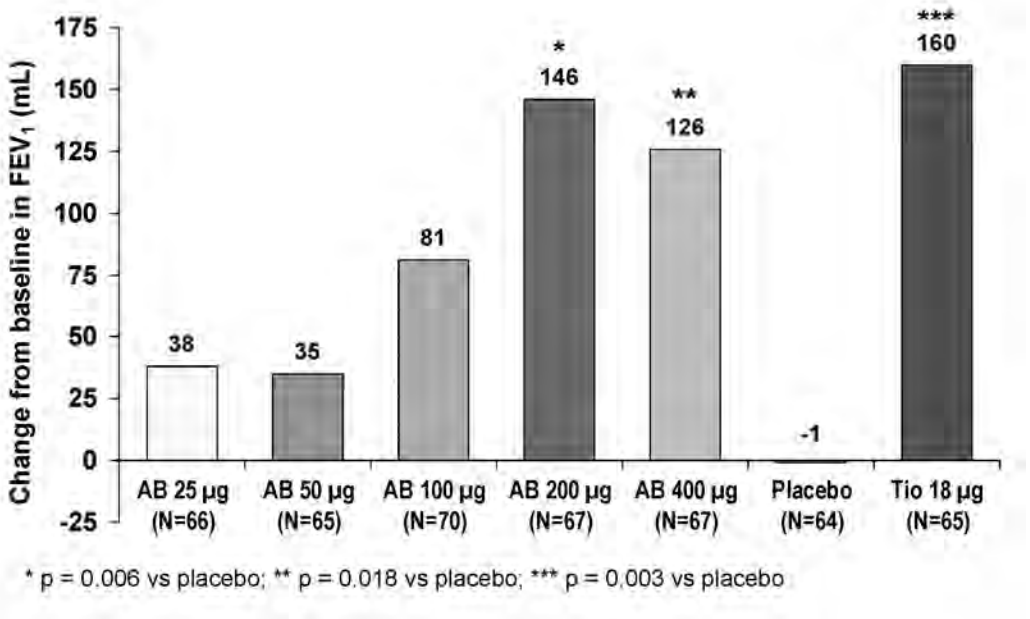
Table 7.1.1–1. Mean Trough FEV_1 (mL) and Adjusted Mean Trough FEV_1 (mL) at Day 29 (Visit 4)—ITT Population (Study 22)

Treatment	*Treatment*			*Treatment Difference vs Placebo*		
	N	*LS Mean*	*95% CI*	*LS Mean*	*95% CI*	*p-value*
AB 25 µg	65	38	–46, 122	39	–67, 145	0.469
AB 50 µg	65	35	–50, 119	36	–70, 141	0.506
AB 100 µg	69	81	1, 162	83	–22, 187	0.121
AB 200 µg	66	146	62, 231	148	42, 253	0.006
AB 400 µg	67	126	44, 209	128	22, 233	0.018
Tiotropium 18 µg	64	160	74, 246	161	55, 267	0.003
Placebo	64	–1	–88, 85	—	—	—

Note: Analysis was based on ANCOVA model with treatment and country as factors and baseline FEV_1 as a covariate.
AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; LS = least squares; N = number of patients.

As shown in Figure 7.1.1–2, based on the dose-response seen in trough FEV_1 values at Day 29, the aclidinium bromide 200 µg dose was selected for further Phase 3 QD development (ie, Study 30 and Study 31). However, despite the results of Study 22, Studies 30 and 31 did not confirm a comparable trough FEV_1 effect of aclidinium bromide 200 µg QD vs placebo.

Figure 7.1.1–2. Change From Baseline in Trough FEV_1 at Day 29—ITT Population (Study 22)



Conclusions

- Aclidinium bromide 200 µg QD and 400 µg QD and tiotropium 18 µg QD provided significant bronchodilation versus placebo

- Study results show that aclidinium bromide 200 µg QD demonstrated similar improvements in lung function as aclidinium bromide 400 µg QD

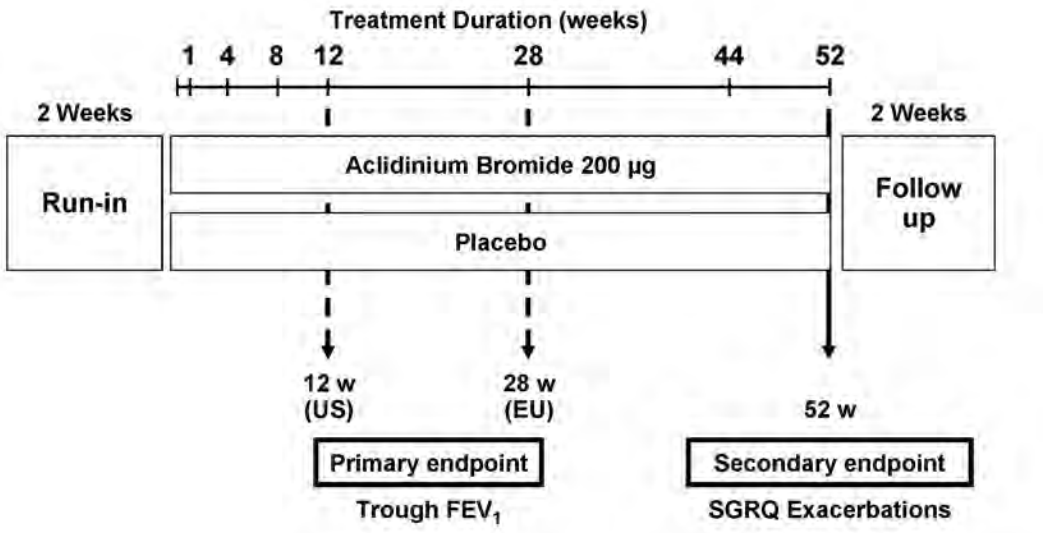
- Aclidinium bromide 200 µg was selected as the appropriate QD dose for Phase 3 QD studies (ie, Study 30 and Study 31)

7.1.2 Study 30 and Study 31: Pivotal Placebo-Controlled Studies, Once-Daily Dosing

Both pivotal QD clinical studies (30 and 31) were randomized, double-blind and placebo-controlled with a 12-month treatment duration and a 3:1 randomization to either active or placebo. Study 30 was conducted in Europe and Russia, and Study 31 was conducted in Argentina, Australia, Canada, Mexico, New Zealand, South Africa, and the United States. The design of the studies was identical and presented in Figure 7.1.2–1.

For both studies, it was estimated that a total sample size of 820 patients (615 patients in the aclidinium bromide 200 µg arm and 205 patients in the placebo arm, according to a 3:1 allocation ratio) would provide at least 90% power to detect as statistically significant a difference of 100 mL between aclidinium bromide 200 µg and placebo in trough FEV_1 after 12 weeks of treatment for the US filing and 28 weeks of treatment for the European Union filing. A 0.05 two-sided Type I error was set, and a common SD of 310 mL (based on the results from Study 22) was assumed.

Figure 7.1.2–1. Study 30 and Study 31 Design

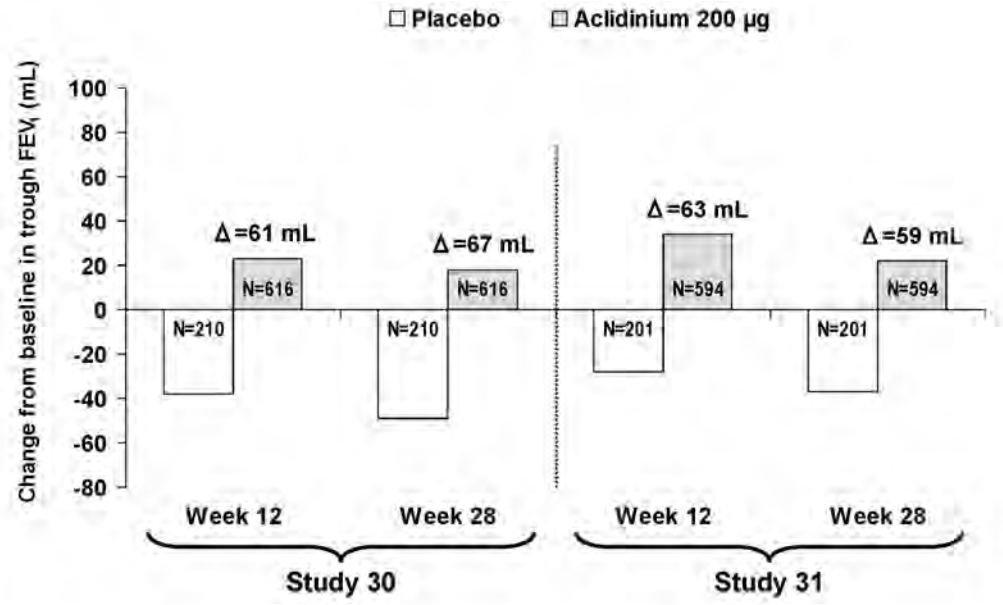


Target enrollment: aclidinium bromide = 615; placebo = 205, based on an FEV_1 difference of 100 mL; power = at least 90%.
BID = twice daily; EU = European Union; FEV_1 = forced expiratory volume in 1 second; QD = once daily; SGRQ = St. George's Respiratory Questionnaire; US = United States of America; w = weeks.

Results

As shown in Figure 7.1.2–2, Studies 30 and 31 had trough FEV_1 effect size observed with aclidinium bromide 200 µg QD compared with placebo (ie, approximately 60 mL) that was below expectations and below the aclidinium bromide 200 µg QD group results (148 mL) in the dose-range finding study, Study 22 (Table 7.1.1–1). However, the treatment differences for aclidinium bromide 200 µg vs placebo were statistically significant in both studies at Week 12 (Study 30, 61 mL [$p = 0.0005$] and Study 31, 63 mL [$p < 0.0001$]) and at Week 28 (Study 30, 67 mL [$p = 0.0002$] and Study 31, 59 mL [$p = 0.0002$]).

Figure 7.1.2–2. Change From Baseline in Trough FEV_1 Over Time—ITT Population (Study 30 and Study 31)



FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; N = number of patients

Conclusions of the QD Program

Phase 3 Studies 30 and 31 did not confirm the aclidinium bromide 200 µg QD dose as the optimal dose. The FDA suggested studying higher and more frequent dosing as well as a comparison to an active comparator for benchmarking. Based on this recommendation, a clinical development program was initiated for the aclidinium bromide BID dosing regimen, with doses ranging from 100 µg to 400 µg BID.

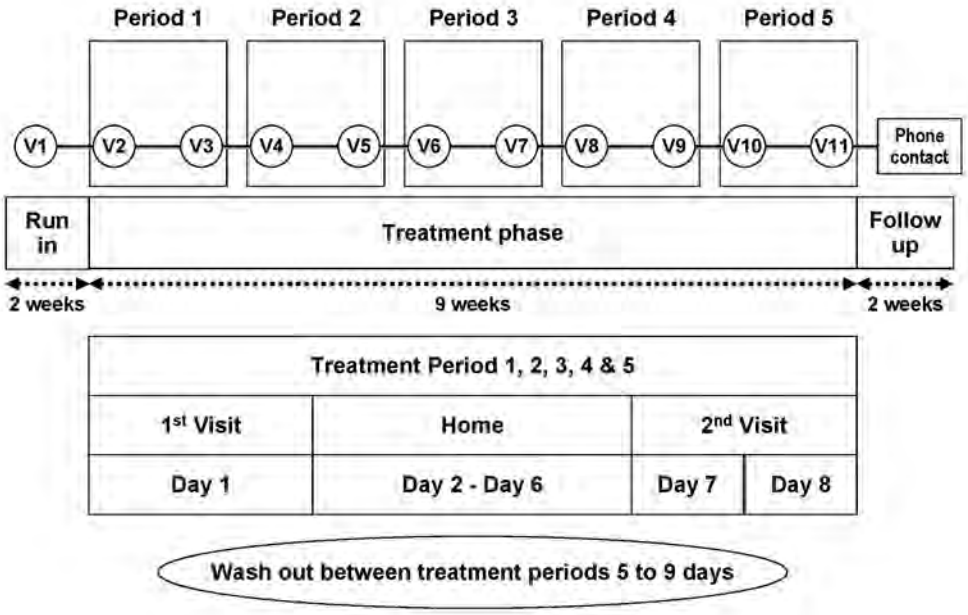
7.1.3 Study 29: Comparing Aclidinium Bromide 100 µg, 200 µg, and 400 µg BID to Placebo and to Formoterol 12 µg BID

Study 29 was a Phase 2 prospective, double-blind, double-dummy, randomized, 5 × 5 Latin square crossover, placebo- and active-comparator controlled, multinational, multicenter, clinical study in patients with moderate to severe COPD. The study was conducted in Germany (10 centers) and Belgium (1 center). The objective of the study was to assess the efficacy, safety, and tolerability of 3 doses of aclidinium bromide (100 µg, 200 µg, or 400 µg) BID compared with placebo and formoterol 12 µg BID administered via Foradil® Aerolizer in patients with moderate to severe COPD. Formoterol was selected as an active comparator because it is an approved bronchodilator with twice-daily dosing for use in COPD patients.

A sample size of 60 COPD patients (12 patients per treatment sequence) provided at least 90% power to detect a difference of 120 mL in change from baseline in normalized FEV_1 area under the curve from time 0 to 12 hours (AUC_{0-12}) after 7 days of treatment between one of the aclidinium bromide doses and placebo with a 0.05 two-sided significance level and assuming 200 mL as a SD of differences.

After a 14 ± 3 day run-in period, patients were randomized to 1 of the 5 treatment sequences using a balanced randomization ratio (1:1:1:1:1). The treatment period consisted of 5 periods of 7 treatment days each, separated by a washout period of 7 (± 2) days (Figure 7.1.3–1). Due to the effective half-life of aclidinium bromide (6-9 hours) and the effective half-life of formoterol (10 hours), a minimum 5-day washout period between treatment periods was considered adequate to avoid a relevant carryover effect.

Figure 7.1.3–1. Study 29 Design



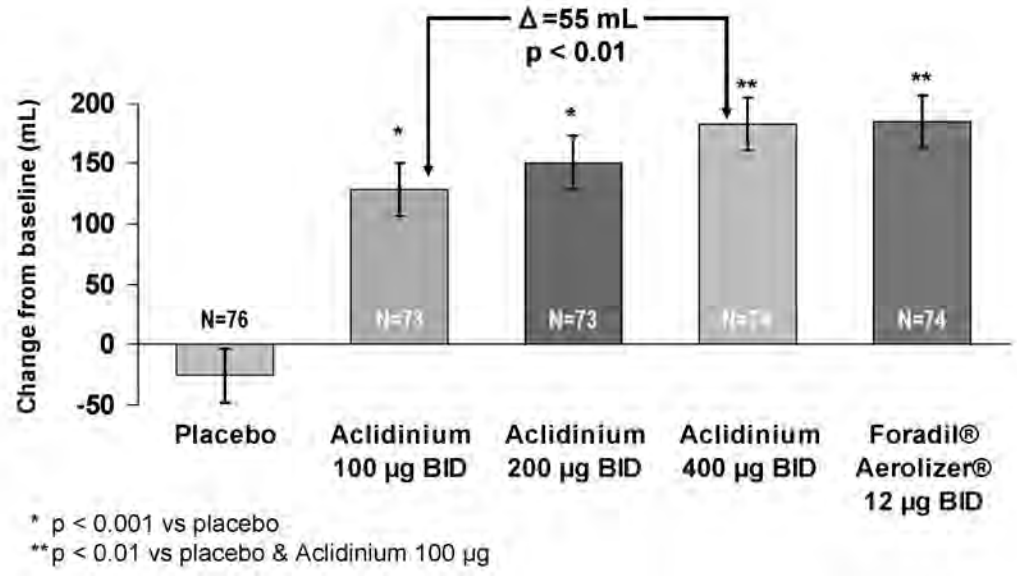
V = visit

Results

Of 79 randomized patients, 68 patients (86.1%) completed the study. Baseline demographic parameters were representative of the moderate to severe COPD population. Patients were between 41 and 81 years old (mean age was 61.1 years), 74.7% of patients were male, 100% of the patients were Caucasian, and BMI ranged from 14.7 to 38.9 kg/m^2. Overall, 45 patients (57.0%) were current smokers. The smoking consumption ranged from 10.0 to 142.5 pack-years (mean was 50.7 pack-years). A majority of patients were in GOLD COPD Stage II (59.0%) followed by COPD Stage III (41.0%). The mean baseline FEV_1 was 1.475 L (48.1% of predicted value). Overall, 42.3% of patients had a bronchodilator response (defined as an increase of 12% and 200 mL compared with baseline after 400 µg of salbutamol).

As shown in Figure 7.1.3–2, all aclidinium bromide doses showed statistically significantly greater improvements ($p < 0.001$) in the adjusted mean change from baseline in normalized FEV_1 AUC_{0-12} compared with placebo, showing a clear dose-response improvement in the primary endpoint at Day 7. The results of the aclidinium bromide 400 µg BID group (183 mL) and the formoterol group (184 mL) were comparable.

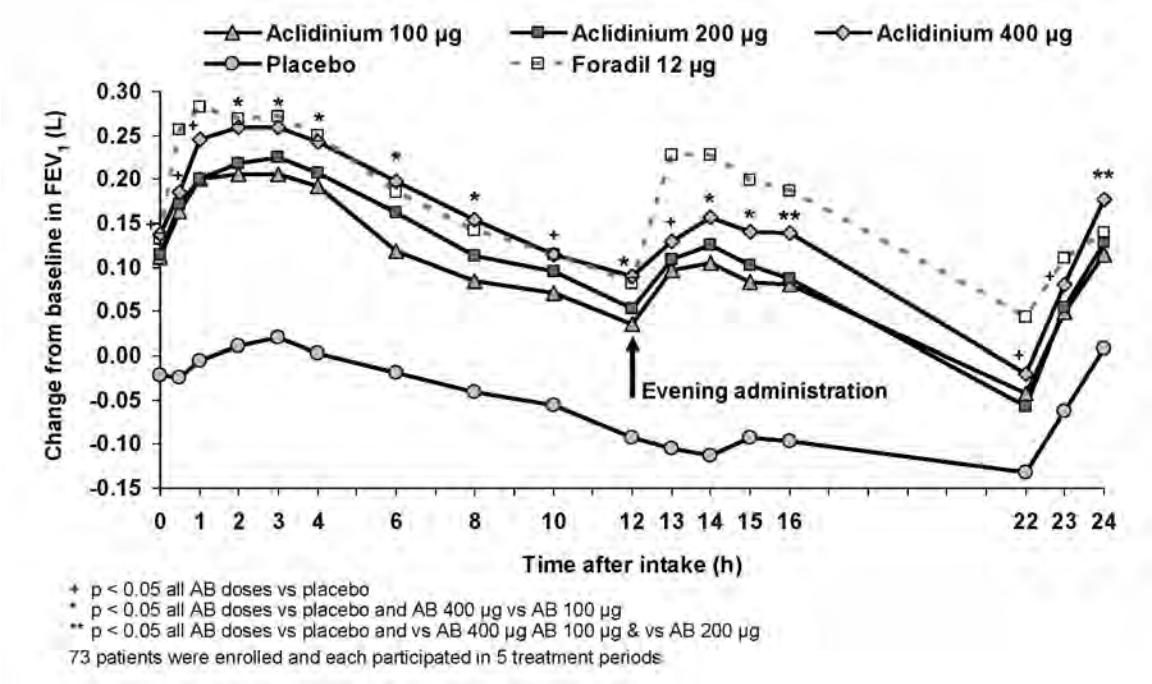
Figure 7.1.3–2. Primary Endpoint: LS Mean (± SE) Change From Baseline in Normalized FEV_1 AUC_{0-12h} (mL) at Day 7 of Treatment—ITT Population (Study 29)



AUC0-12 = area under the curve from time 0 to 12 hours; BID = twice daily; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; N = number of patients

Figure 7.1.3–3 shows the results of serial spirometry performed over 24 hours after BID dosing with aclidinium bromide (100 µg, 200 µg, and 400 µg), formoterol (12 µg), and placebo at Day 7 of treatment. The slope of the FEV_1 curve of aclidinium bromide at both 12 hours and 24 hours is comparable to the slope of the formoterol curve, thus supporting the BID dosing regimen. Aclidinium bromide 400 µg BID and formoterol 12 µg BID were statistically superior to aclidinium bromide 100 µg BID at all time points, supporting that 100 µg was a less-than-optimal dose. Over the 24 hours of serial spirometry, the change from baseline in FEV_1 measures was not statistically significantly different for the formoterol group compared to the aclidinium 400 µg BID group.

Figure 7.1.3–3. Mean Change From Baseline in FEV_1 (mL) Over 24 Hours Post Dose on Day 7—ITT Population (Study 29)

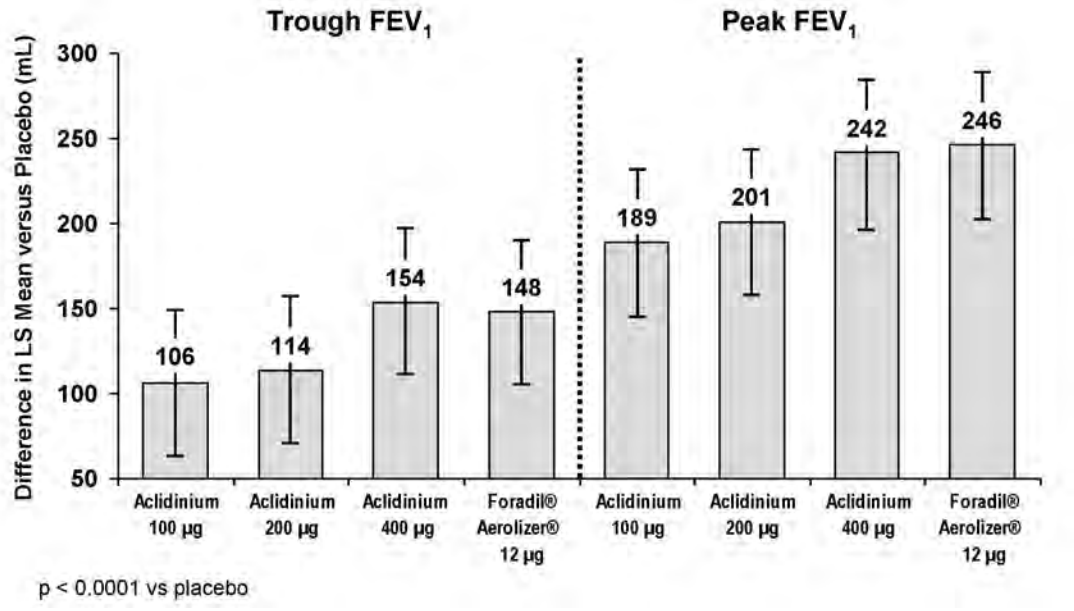


AB = aclidinium bromide; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat.

As shown in Figure 7.1.3–4, all aclidinium bromide BID doses and formoterol provided a clinically and statistically significantly greater improvement in morning predose (trough) FEV_1 after 7 days on treatment compared with placebo ($p < 0.0001$). The bronchodilation provided by aclidinium bromide 400 µg BID at the end of the dosing interval (trough) was comparable to that of formoterol 12 µg BID and statistically significantly greater than aclidinium bromide 100 µg BID (48 mL, $p = 0.0278$).

All doses of aclidinium bromide BID and formoterol provided a statistically significant higher morning peak FEV_1 when compared to placebo at Day 7 ($p < 0.0001$). The difference between the highest (400 µg BID) and the lowest (100 µg BID) doses of aclidinium bromide was statistically significant at Day 7 (53 mL, $p = 0.0160$). Peak FEV_1 values for aclidinium bromide 400 µg BID were comparable to those of formoterol 12 µg BID at Day 7 (Figure 7.1.3–4).

Figure 7.1.3–4. Treatment Differences in Change From Baseline in Trough and Peak FEV_1 (mL) Versus Placebo at Day 7—ITT Population (Study 29)



FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; LS = least squares.

Efficacy Conclusions

- A dose-response was demonstrated for bronchodilation with aclidinium bromide BID.
- All aclidinium doses provided statistically significant bronchodilation compared to placebo
- Aclidinium bromide 400 µg BID was statistically superior to aclidinium bromide 100 µg BID at most of the endpoints; therefore the 100 µg BID dose was ruled out as an optimal therapeutic dose
- The highest aclidinium dose (400 µg BID) was comparable to Foradil® Aerolizer® and demonstrated the largest clinically relevant effect compared to the lower aclidinium bromide doses (100 µg and 200 µg) tested
- The slope of the FEV_1 curve of aclidinium bromide BID was comparable to the slope of an approved BID drug (formoterol 12 µg) at both 12 and 24 hours, thus supporting the BID dose regimen of aclidinium bromide
- All treatment arms were well tolerated
- The Phase 2 data supported the choice of aclidinium bromide doses of 200 µg BID and 400 µg BID for the Phase 3 studies.

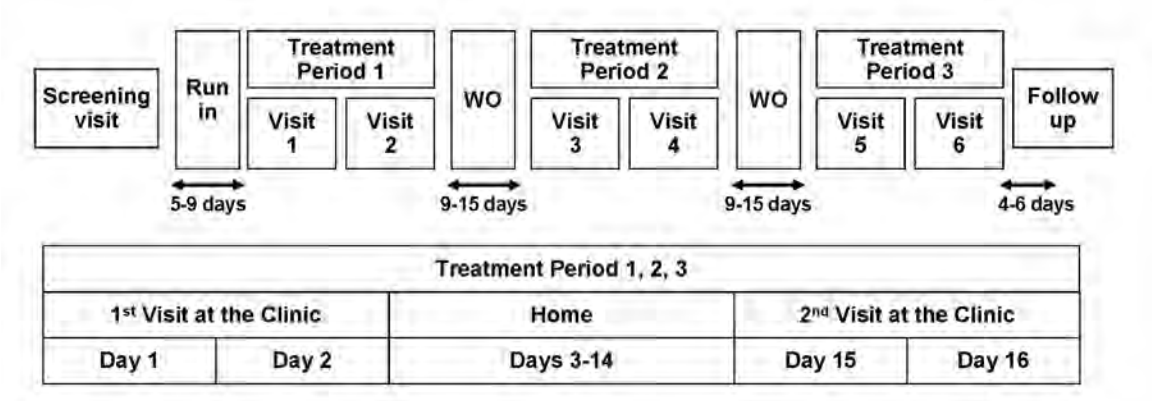
7.1.4 Study 23: Comparing Aclidinium Bromide 400 µg BID to Placebo and to Tiotropium 18 µg

Study 23 was a multiple-dose, randomized, double-blind, double-dummy, 3-period crossover, placebo- and active-comparator controlled study. The study was conducted in Germany (2 centers). The primary efficacy endpoint was the change from baseline in normalized FEV_1 AUC_{0-12} immediately after morning administration of treatment on the last day (Day 15) of the treatment period. Secondary efficacy variables included changes from baseline in normalized FEV_1 $AUC_{12-24/12h}$, and FEV_1 $AUC_{0-24/24h}$ at Day 15. The secondary variables were chosen to enable an assessment of the bronchodilation provided by aclidinium bromide over 24 hours post-morning administration.

A total sample size of 24 male and female COPD patients (4 per treatment sequence) were to be included in the study. Since this was a Phase 2a study of exploratory nature, this number of subjects was considered sufficient to meet the objectives. Taking into account a 10% drop-out rate and that the number of patients to be randomized had to be a multiple of 6 (six different sequences), a total of 30 patients, 5 patients per treatment sequence, were randomized.

At each treatment period patients received either aclidinium bromide 400 µg BID, tiotropium 18 µg, or placebo for 15 days. Each treatment period was separated by a washout period of 9 to 15 days (Figure 7.1.4–1). Due to the effective half-life of aclidinium bromide (6 to 9 hours) and the effective half-life of tiotropium (24 to 41 hours), a minimum of 9 days of washout period between treatment periods was considered adequate to avoid a relevant carryover effect.

Figure 7.1.4–1. Study 23 Design



WO = wash out period

Results

Of 30 randomized patients, 27 (90.0%) completed the study. A total of 30 patients were evaluated for efficacy (ITT Population).

Baseline demographic parameters were representative of the moderate to severe COPD population. Patients were between 43 and 73 years old (mean age was 58.4 years), 63.3% of patients were male, 100% of the patients were Caucasian, and BMI ranged from 18.5 to 38.5 kg/m^2. Overall, 19 patients (63.3%) were current smokers. The smoking consumption ranged from 18.2 to 80.0 pack-years (mean was 41.1 pack-years). A majority of patients were GOLD COPD Stage II (63.3%) followed by COPD Stage III (33.3%). The mean baseline FEV_1 was 1.467 L (47.9% of predicted value). Overall, 53.3% of patients had a bronchodilator reversibility response (defined as an increase of 12% and 200 mL compared with baseline after 400 µg of salbutamol).

The study showed aclidinium bromide 400 µg BID to have a clinically relevant bronchodilatory effect. The primary endpoint of the mean change from baseline to Day 15 in FEV_1 $AUC_{0\text{-}12/12h}$ of both aclidinium bromide and tiotropium compared with placebo were comparable and above 200 mL (Table 7.1.4–1).

Table 7.1.4–1. Treatment Comparisons for the Change From Baseline in Normalized FEV_1 $AUC_{0\text{-}12}$, $AUC_{0\text{-}24}$, and $AUC_{12\text{-}24}$ (mL) on Days 1 and 15 of Treatment-ITT Population (Study 23)

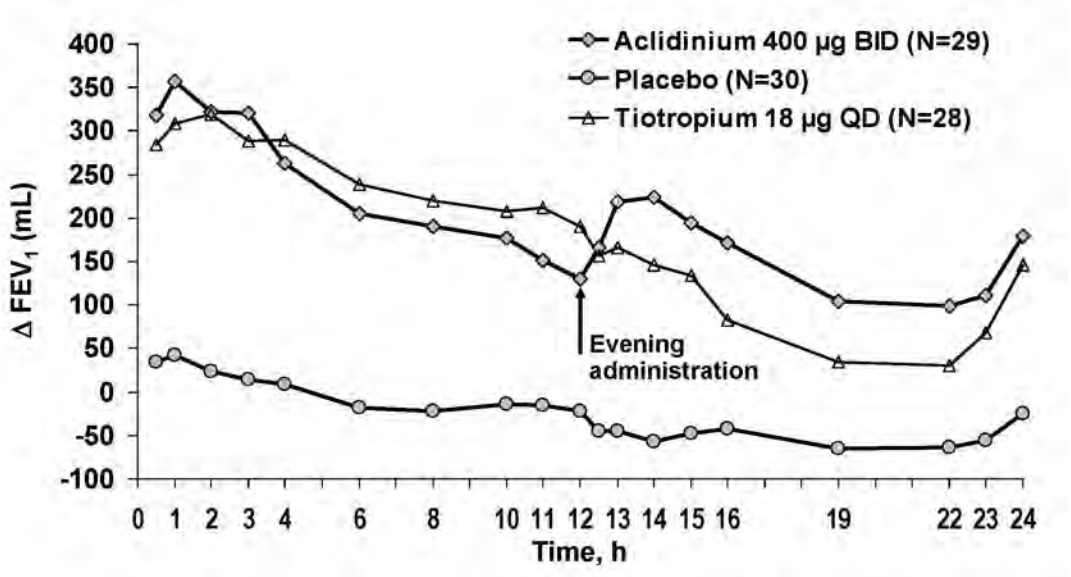
	Treatment Differences					
	Aclidinium bromide 400 µg BID vs Placebo		*Tiotropium 18 µg QD vs Placebo*		*Aclidinium bromide 400 µg BID vs Tiotropium 18 µg QD*	
	LS Mean	**p-value**	**LS Mean**	**p-value**	**LS Mean**	**p-value**
Change from baseline in FEV_1 (mL) at Day 1						
$AUC_{0\text{-}12/12h}$	214	< 0.0001	163	< 0.0001	52	0.041
$AUC_{0\text{-}24/24h}$	235	< 0.0001	162	< 0.0001	73	0.008
$AUC_{12\text{-}24/12h}$	262	< 0.0001	161	< 0.0001	101	0.002
Change from baseline in FEV_1 (mL) at Day 15						
$AUC_{0\text{-}12/12h}$	221	< 0.0001	244	< 0.0001	-23	0.572
$AUC_{0\text{-}24/24h}$	232	< 0.0001	185	< 0.0001	48	0.104
$AUC_{12\text{-}24/12h}$	207	< 0.0001	129	0.0003	78	0.020

Note: Analysis performed using ANCOVA model for crossover designs with change from baseline in normalized FEV_1 AUC at Days 1 and 15 on treatment as response.

AUC = area under the curve; BID = twice daily; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; LS = least squares; QD = once daily.

Figure 7.1.4–2 shows the results of serial spirometry performed over 24 hours after dosing with aclidinium bromide 400 µg BID, placebo BID, and tiotropium 18 µg QD on Day 15 of treatment.

Figure 7.1.4–2. LS Mean Change From Baseline in FEV_1 (mL) at Each Specific Time Point on Day 15 of Treatment—ITT Population (Study 23)



Both active treatments are statistically significant vs placebo ($p < 0.05$)
BID = twice daily; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; N = number of patients; QD = once-daily.

As shown in Table 7.1.4–2, the adjusted mean treatment differences between aclidinium bromide and placebo in morning predose (trough) FEV_1 values were 186 mL on both Days 1 and 15 ($p < 0.0001$ for both comparisons). The treatment difference between tiotropium and placebo was 122 mL on Day 1 ($p = 0.0022$) and on Day 15 was 150 mL, ($p < 0.0001$), but tiotropium is known to take 8 days to reach pharmacodynamic steady state. Adjusted mean differences between aclidinium bromide and placebo in the change from baseline in morning peak FEV_1 increased from 218 mL on Day 1 to 277 mL on Day 15 (both $p < 0.0001$). There was also an increase in the adjusted treatment differences between tiotropium and placebo from 170 mL on Day 1 to 252 mL on Day 15 (both $p < 0.0001$), respectively.

Table 7.1.4–2. Change From Baseline in Morning Pre-Dose Trough and Morning Peak FEV_1 (mL) Values on Day 1 and Day 15 of Treatment—ITT Population (Study 23)

Treatment	*N*	*LS Mean*	*Comparison*	*Treatment differences*		
				LS Mean	*95% CI (Lower, Upper)*	*p-value*
Day 1 morning predose trough FEV_1 (mL)						
AB 400 µg	29	163	AB 400 µg – Placebo	186	(112, 260)	<0.0001
Tio 18 µg	28	99	Tio 18 µg – Placebo	122	(47, 196)	0.0022
Placebo	30	–22	AB 400 µg – Tio 18 µg	64	(–11, 139)	0.0898
Day 15 morning predose trough FEV_1 (mL)						
AB 400 µg	29	143	AB 400 µg – Placebo	186	(123, 248)	<0.0001
Tio 18 µg	28	107	Tio 18 µg – Placebo	150	(86, 213)	<0.0001
Placebo	30	–43	AB 400 µg – Tio 18 µg	36	(–27, 100)	0.2560
Day 1 morning peak FEV_1 (mL)						
AB 400 µg	29	362	AB 400 µg – Placebo	218	(169, 267)	<0.0001
Tio 18 µg	28	314	Tio 18 µg – Placebo	170	(120, 220)	<0.0001
Placebo	30	144	AB 400 µg – Tio 18 µg	48	(–2, 98)	0.0586
Day 15 morning peak FEV_1 (mL)						
AB 400 µg	29	408	AB 400 µg - Placebo	277	(181, 374)	<0.0001
Tio 18 µg	28	382	Tio 18 µg – Placebo	252	(153, 350)	<0.0001
Placebo	30	131	AB 400 µg – Tio 18 µg	26	(–72, 124)	0.5862

LSMeans: Least squares mean from the ANCOVA model for cross-over designs using the change from baseline in the morning pre-dose (trough) and morning peak FEV_1 at Day 1 and Day 15 on treatment as response.

The last-observation-carried forward approach was used in this analysis.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV1 = forced expiratory volume in 1 second; Tio = tiotropium.

Conclusions

- Aclidinium bromide 400 µg BID provided clinically and statistically significant bronchodilation over 24 hours compared to placebo
- Maximum bronchodilation of aclidinium bromide 400 µg BID was achieved on the first day of treatment and was similar on Day 15 of treatment
- Aclidinium bromide 400 µg BID had a bronchodilatory profile comparable to tiotropium 18 µg QD
- All treatment arms were well tolerated

7.2 STUDY DESIGN, EFFICACY VARIABLES, AND STATISTICAL METHODS OF THE PHASE 3 EFFICACY STUDIES

The 3 Phase 3 efficacy studies (34, 33, and 38 [A]) were of similar design, ie, prospective, double-blind, randomized, parallel-group, placebo-controlled, multicenter studies of aclidinium bromide 200 µg BID, aclidinium bromide 400 µg BID, or placebo BID in patients with moderate to severe COPD.

The treatment duration was 24 weeks in Study 34 and 12 weeks in the other Phase 3 efficacy studies (33 and 38 [A]).

Following screening, all potential patients entered a 2-week run-in period to assess the stability of their COPD and to establish baseline characteristics. At the end of the double-blind treatment period, a 2-week follow-up period was included in Study 34, while patients randomized to Study 33 were given the option to continue treatment with aclidinium bromide for an additional 52 weeks in a long-term safety extension study (Study 36). Following the completion of 12 weeks of treatment in Study 38 (A), all patients still enrolled continued into the long-term safety extension Study 38 (B) where they were treated with open-label aclidinium bromide 400 µg BID only.

Study 34 was conducted at centers across Europe, Russia, and South Africa while Studies 33 and 38 (Part A) were conducted at centers in the United States and Canada. For information on patient inclusion/exclusion criteria see Section 3.4.

Efficacy Variables in the Phase 3 Placebo-Controlled Studies Were:
Primary Efficacy Parameter: The primary efficacy endpoints were the change from baseline in **trough** FEV_1 at Week 12 in Study 34 (US submission), Study 33, and Study 38 (A). Study 34 included primary efficacy at Week 24 (European submission).

Secondary Efficacy Parameters: The secondary efficacy endpoints were the change from baseline in **peak** FEV_1 at Week 12 in Study 34 (US submission), Study 33, and Study 38 (A). The proportion of patients with an improvement at Week 24 in TDI focal score of at least 1 unit and the proportion of patients with a 4-unit decrease in SGRQ total score at Week 24 compared with baseline were secondary efficacy endpoints for Study 34 only and additional efficacy parameters for Studies 33 and 38 (A).

Additional Efficacy Parameters: Besides trough and peak FEV_1, additional efficacy measures of pulmonary function included changes from baseline in trough and peak FVC, FEV_1 $AUC_{0\text{-}3/3h}$, and inspiratory capacity. Additional efficacy parameters were utilized to assess the benefit to the patient of aclidinium bromide treatment in terms of symptoms (such as dyspnea), health-related quality of life, and exacerbation control.

Statistical Methods Used In The Phase 3 Placebo-Controlled Studies (33, 34, And 38 [A])

The primary efficacy variable (change from baseline in morning predose [trough] FEV_1) was analyzed by means of an analysis-of-covariance (ANCOVA) model with treatment and sex as factors and baseline FEV_1 and age as covariates. The baseline value for FEV_1 was defined as the mean of 2 values measured before the first dose of study treatment. Trough FEV_1 was defined as the mean of 2 values within one hour prior to the morning dose of study treatment. The primary treatment comparisons were between each aclidinium bromide dose and placebo. The results of the ANCOVA model for the primary treatment comparisons were summarized using least squares means for the between-treatment group differences together with the standard error (SE), 95% CI, and p-value for each comparison.

The last-observation-carried-forward (LOCF) approach was used to impute missing postbaseline values. In addition, the linear interpolation was applied for all efficacy variables based on spirometric assessments, when one or more planned values were missing between a pair of non-missing values.

To control the Type I error for the multiple testing of the primary endpoint for the 400 µg and 200 µg doses versus placebo, Hochberg's method was used. If the comparisons of the two doses versus placebo for the primary endpoint were significant, then Hochberg's method was used for the two comparisons versus placebo for the secondary endpoint.

Sensitivity analyses of the primary efficacy variable were carried out using a direct likelihood approach on the ITT Population to assess the effect of missing data on the results. These analyses were conducted using a mixed-effects model for repeated measures on the response variable of change from baseline in morning predose (trough) FEV_1, with age and baseline FEV_1 as covariates and treatment, sex, visit, and treatment group-by-visit interaction as fixed-effect factors. The unstructured covariance matrix was used.

The change from baseline in peak FEV_1 (secondary efficacy variable in all Phase 3 efficacy studies) was analyzed using the same ANCOVA model as for the primary efficacy variable. Peak FEV_1 was defined as the highest FEV_1 value recorded in the 3 hours following the morning dose.

The proportion of patients achieving a clinically meaningful improvement in TDI focal score and the proportion of patients achieving a clinically meaningful improvement in SGRQ total score were secondary efficacy endpoints in Study 34 (no adjustments for multiple comparison were made) and additional efficacy endpoints in Study 33 and Study 38 (A). Between-treatment group comparisons of the proportion of patients who achieved at least a 1-unit increase from baseline in TDI focal score were analyzed for each Phase 3 study using a logistic regression model with treatment group, sex, age, and Baseline Dyspnea Index (BDI) score as explanatory variables. The statistical significance of the model coefficients was tested using the Wald test. The effect of aclidinium bromide 200 or 400 µg compared with placebo was measured by estimation of the odds ratio (OR) corresponding to the treatment effect and its 95% CI, based on the coefficient and SE corresponding to the treatment group in the logistic regression model. The same model was used for the 4-unit reduction in SGRQ total score using the corresponding baseline values.

Between-treatment group differences for change from baseline to the end of the study (based on the LOCF approach) in SGRQ total score and 3 dimension scores (symptoms, activity, impact) were performed using an ANCOVA model with treatment group and sex as factors and age and baseline SGRQ total score as covariates.

The improvement in dyspnea status from baseline to Weeks 4, 8, and 12 as measured by the TDI (focal score and three dimension scores) was analyzed using an ANCOVA model with treatment group and sex as factors and the BDI focal score and age as covariates.

The total number of COPD exacerbations per patient/year was analyzed by means of a Poisson regression with adjustment for dispersion (deviance scale) for rates and with treatment, sex, and baseline COPD severity as factors and age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model).

The use of as-needed rescue medication was analyzed using an ANCOVA model with treatment group as a factor and the baseline value as covariate.

For each of the two individual studies (33 and 38A), for assessment of sample size and statistical power, it was assumed that 165 subjects in each treatment group would be in the ITT Population for the analysis of the primary and the secondary efficacy parameters. To detect a treatment difference of 100 mL for the primary efficacy parameter of change from baseline in morning predose (trough) FEV_1 at Week 12 assuming a 240 mL SD, each of the 2 comparisons for the BID aclidinium dose levels versus placebo had at least 93% statistical power adjusting for the multiple comparison procedure at the overall significance level of 0.05. It was planned for each of the two studies to enroll 510 patients randomized equally to each treatment.

For study 34, a sample size of 244 evaluable patients per treatment group provided at least a 90% power to detect as significant a difference of 90 mL between any of the doses of aclidinium bromide and placebo in change from baseline in morning pre-dose (trough) FEV_1 after 12 weeks of treatment, assuming a common SD of 240 mL, using two-sided tests and adjusting for multiple treatment comparisons at the overall significance level of 0.05. It was planned to enroll 810 patients randomized equally to each treatment.

7.3 COMPARISON OF EFFICACY IN THE PHASE 3 STUDIES

This section provides a comparison and analysis of results in the Phase 3 studies that assessed the efficacy of aclidinium bromide 400 µg BID and 200 µg BID (studies 33, 34, and 38 [A]). As mentioned in Section 3.4, each of the 3 Phase 3 studies independently confirmed the efficacy of aclidinium bromide 400 µg BID compared with placebo by demonstrating statistically significant improvements in lung function and greater effect size than aclidinium bromide 200 µg BID. A clinically important effect size (ie, > 100 mL) was achieved for the primary efficacy parameter of trough FEV_1 compared to placebo in two of the phase 3 studies (studies 34 and 33). However, in the third Study (38A) the effect size was less than 100 mL. Please see Section 7.3.4.1 for an explanation of why baseline imbalances in COPD severity (found via post-hoc analysis) between patients in the aclidinium bromide treatment groups and those of patients in the placebo group made the magnitude of treatment effect on FEV_1 and other efficacy parameters difficult to interpret in Study 38 (A).

Because of the imbalance among treatment arms in COPD severity in Study 38 (A), Forest considers Study 38 (A) to be a supportive efficacy study (ie, demonstrating statistically significant efficacy differences between aclidinium bromide and placebo treatments despite baseline imbalances between the treatment groups); Studies 33 and 34 are considered to be pivotal efficacy studies. Section 7.3.3 presents efficacy results in the 2 pivotal studies (33 and 34) and Section 7.3.4 presents the efficacy results in supportive efficacy Study 38 (A).

7.3.1 Pooling Across the Phase 3 Efficacy Studies

A total of 1919 patients were included in the ITT populations of the 3 Phase 3 BID efficacy studies. A total of 1378 patients were included in the ITT populations of Study 33 and Study 34 and included in the pooled analysis of these 2 BID studies (461 treated with aclidinium bromide 200 µg BID, 459 treated with aclidinium bromide 400 µg BID, and 458 treated with placebo). Of the randomized populations in studies 33, 34, and 38 (A), 83.2%, 89.0%, and 83.5% of patients completed the respective studies. Study completion rates in the aclidinium bromide treatment groups in each study were equal to or above the completion rates for the placebo group (Table 11.2–1).

7.3.2 Demographics, Baseline Characteristics, and Patient Disposition Across the Phase 3 Efficacy Studies

Table 11.2–2, Table 11.2–3, and Table 11.2–4 in Appendix I compare demographic and baseline characteristics for the ITT population across the placebo-controlled, Phase 3 efficacy studies, which consisted of 2 pivotal studies (33 and 34) and 1 supportive study (38 [A]). The patients in these studies were representative of patients with COPD in the general population regarding demographics and baseline characteristics (Table 11.2–2) as well as medical and surgical history (Table 11.2–18). The mean age, age distribution, and severity of COPD of the patient populations in the 3 studies were generally comparable (Table 11.2–2 and Table 11.2–3).

Review of the medical histories of patients in the Safety populations showed no major differences in the categories of pre-existing medical and surgical conditions between studies 33, 34 and 38 (A) (Table 11.2–18 in Appendix I).

As shown in Table 11.2–1, the majority of patients completed the Phase 3 efficacy studies. Premature discontinuation rates in the Phase 3 BID studies were as follows: Study 33, 19.9%, 17.8% and 12.6% for placebo, aclidinium bromide 200 µg, and aclidinium bromide 400 µg BID, respectively; Study 34, 14.9%, 8.6% and 6.3% for placebo, aclidinium bromide 200 µg and aclidinium bromide 400 µg, respectively; and Study 38 (A), 17.0%, 15.8%, and 16.9% for placebo, aclidinium bromide 200 µg and aclidinium bromide 400 µg, respectively. As shown, more patients discontinued in the placebo arms than the active treatment arms across the 3 studies.

7.3.3 Efficacy Results in the 2 Pivotal Phase 3 Studies (Study 33 and Study 34)

7.3.3.1 Change From Baseline in Trough FEV_1 (Study 33 and Study 34)

As shown in Table 7.3.3.1–1, adjusted mean treatment differences (placebo subtracted) in change from baseline in trough FEV_1 for aclidinium bromide 400 and 200 µg versus placebo were 124 mL and 86 mL, respectively at Week 12 in Study 33 and 105 mL and 77 mL, respectively at Week 12, and 128 mL and 99 mL, respectively at Week 24 in Study 34. Statistically significant treatment differences considered clinically relevant (ie, greater than 100 mL [Cazzola et al, 2008]) between aclidinium bromide 400 µg and placebo were observed in both studies.

For Study 33, similar findings were observed using the mixed-effects model for repeated measures (MMRM) analysis (improvement of 132 mL [$p < 0.0001$] for the aclidinium bromide 400 µg group and 91 mL [$p = 0.0001$] in the aclidinium bromide 200 µg group, both compared with placebo). Also for Study 34, similar findings were observed using the MMRM analysis (improvement of 106 mL [p-value <0.0001] for the aclidinium bromide 400 µg group and 78 mL [p-value = 0.0002] in the aclidinium bromide 200 µg, both compared to placebo) after 12 weeks of treatment; and 133 mL [p-value <0.0001] in the aclidinium bromide 400 µg and 103 mL [p-value <0.0001] in the aclidinium bromide 200 µg and after 24 weeks of treatment.

An analysis of the pooled population from the 2 pivotal Phase 3 efficacy studies (33 and 34) at Week 12 showed that the treatment differences for aclidinium bromide 400 µg and 200 µg versus placebo were 112 mL and 80 mL, respectively ($p < 0.0001$ for both comparisons). The difference of 32 mL between the aclidinium bromide treatment arms was significant ($p = 0.0272$) (Table 7.3.3.1–1).

Table 7.3.3.1–1. Changes From Baseline in Trough FEV_1 (mL) for Studies 33, 34, and Pooled 33 and 34 at Week 12—ITT Populations

				Comparison	***Treatment Difference***		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Study: 33 (Week 12)							
AB 400 µg	190	99	14	AB 400 µg - Placebo	**124**	83, 164	< **0.0001**
AB 200 µg	184	61	15	AB 200 µg - Placebo	**86**	45, 127	< **0.0001**
Placebo	185	–24	15	AB 400 µg - AB 200 µg	**38**	–3, 78	**0.0692**
Study: 34 (Week 12)							
AB 400 µg	269	58	15	AB 400 µg - Placebo	**105**	65, 144	< **0.0001**
AB 200 µg	277	30	14	AB 200 µg - Placebo	**77**	38, 116	**0.0001**
Placebo	273	–47	15	AB 400 µg - AB 200 µg	**28**	–12, 67	**0.1671**
Study: 34 (Week 24)							
AB 400 µg	269	55	16	AB 400 µg - Placebo	**128**	85, 170	< **0.0001**
AB 200 µg	277	26	16	AB 200 µg - Placebo	**99**	57, 141	**0.0001**
Placebo	273	–73	16	AB 400 µg - AB 200 µg	**29**	–14, 71	**0.1868**
Pooled Studies: 33 and 34 (Week 12)							
AB 400 µg	459	76	10	AB 400 µg - Placebo	**112**	80, 140	< **0.0001**
AB 200 µg	461	44	10	AB 200 µg - Placebo	**80**	50, 110	< **0.0001**
Placebo	458	–35	10	AB 400 µg - AB 200 µg	**32**	0, 60	**0.0272**

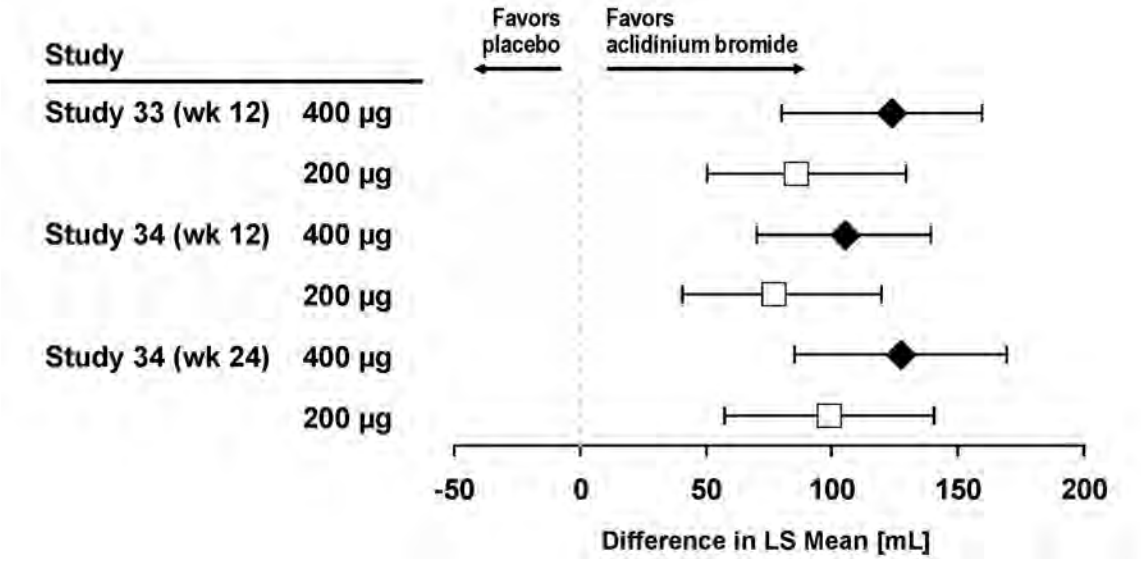
Note: Analysis is based on ANCOVA model for change from baseline in trough FEV_1, with treatment group and sex as factors, and age and baseline FEV_1 as covariates.

a LS mean for the treatment difference.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; LS = least square; n = number of patients.

Figure 7.3.3.1–1 presents a display of the information presented in Table 7.3.3.1–1.

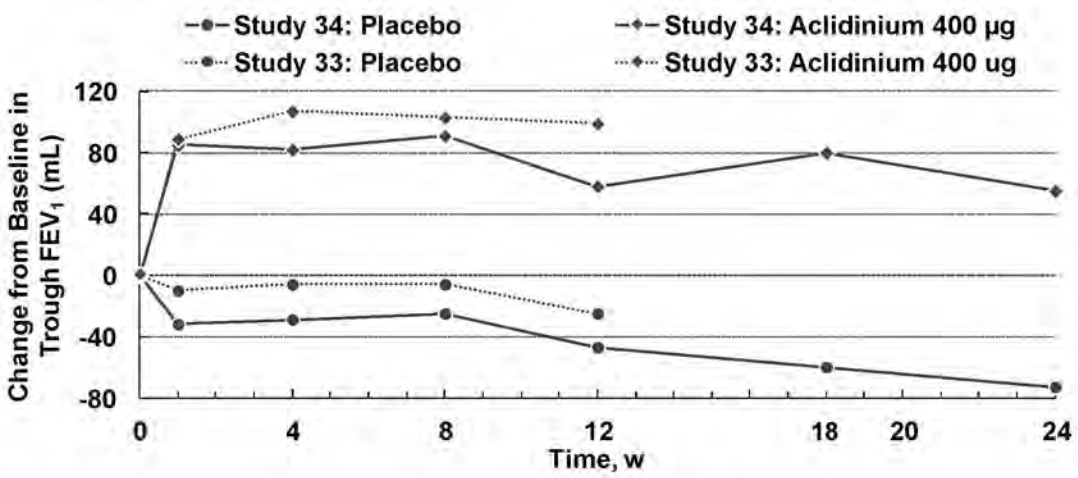
Figure 7.3.3.1–1. Comparison of Adjusted Change From Baseline in Trough FEV_1 (mL) of Aclidinium Bromide 200 µg and 400 µg Versus Placebo at Week 12 in Study 33 and at Week 12 and Week 24 in Study 34—ITT Population



$p \leq 0.0001$ for all comparisons versus placebo, wk = week.

As shown in Figure 7.3.3.1–2, the bronchodilator effect of the aclidinium bromide 400 µg dose was sustained throughout the treatment duration in Study 33 and Study 34.

Figure 7.3.3.1–2. Comparison of Change From Baseline in Trough FEV_1 (mL) Over Time for Study 33 and Study 34 for Aclidinium Bromide 400 µg—ITT Population



Difference in LS Means – AB 400 µg vs placebo (mL)

	Week 1	Week 4	Week 8	Week 12	Week 18	Week 24
Study 33	108	113	109	124	NA	NA
Study 34	117	112	116	105	140	128

AB = aclidinium bromide; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat

7.3.3.2 Change From Baseline in Peak FEV_1, Trough FVC, and Trough IC (Study 33 and Study 34)

As shown in Table 7.3.3.2–1, in each of the 2 pivotal Phase 3 efficacy studies, adjusted mean treatment differences between aclidinium bromide 400 or 200 µg and placebo in the change from baseline in peak FEV_1 at Week 12 (Study 33) and Week 12 and 24 (Study 34) were statistically significant ($p < 0.0001$ for all differences). The magnitude of the adjusted mean treatment differences between aclidinium bromide 400 or 200 µg and placebo at Week 12 in Study 33 was 192 mL and 146 mL, respectively, and in Study 34 were 191 mL and 182 mL at Week 12 and 209 mL and 185 mL at Week 24, respectively.

An analysis of the pooled population from the 2 pivotal Phase 3 efficacy studies (33 and 34) showed that the treatment differences for aclidinium bromide 400 µg and 200 µg versus placebo were 191 mL and 167 mL, respectively (both statistically significant over placebo [$p < 0.0001$]).

Table 7.3.3.2–1. Changes From Baseline in Peak FEV_1 (mL) for Studies 33, 34, and Pooled 33 and 34 at Week 12—ITT Populations

				Comparison	*Treatment Difference*		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Study: 33 (Week 12)							
AB 400 µg	190	263	16	AB 400 µg – Placebo	**192**	148, 236	< **0.0001**
AB 200 µg	184	217	16	AB 200 µg – Placebo	**146**	101, 190	< **0.0001**
Placebo	185	71	16	AB 400 µg – AB 200 µg	**46**	2, 90	**0.0409**
Study: 34 (Week 12)							
AB 400 µg	269	227	16	AB 400 µg – Placebo	**191**	149, 233	< **0.0001**
AB 200 µg	277	219	15	AB 200 µg – Placebo	**182**	141, 224	< **0.0001**
Placebo	273	37	16	AB 400 µg – AB 200 µg	**8**	–33, 50	**0.6956**
Study: 34 (Week 24)							
AB 400 µg	269	231	17	AB 400 µg – Placebo	**209**	163, 256	< **0.0001**
AB 200 µg	277	206	17	AB 200 µg – Placebo	**185**	139, 231	< **0.0001**
Placebo	273	22	17	AB 400 µg – AB 200 µg	**25**	–21, 71	0.2919
Pooled Studies: 33 and 34 (Week 12)							
AB 400 µg	459	243	11	AB 400 µg – Placebo	**191**	160, 221	< **0.0001**
AB 200 µg	461	220	11	AB 200 µg – Placebo	**167**	137, 198	< **0.0001**
Placebo	458	53	11	AB 400 µg – AB 200 µg	**24**	–7, 54	**0.1302**

Note: Analysis is based on ANCOVA model for change from baseline in peak FEV_1, with treatment group and sex as factors, and age and baseline FEV_1 as covariates.

a treatment differences in LS means.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; ITT = intent to treat; LS = least square; n = number of patients.

Changes from baseline at Week 12 for trough FVC are presented in Table 11.2–5 in Appendix I and for trough IC in Table 11.2–6 in Appendix I. The aclidinium bromide 400 µg BID dose had a higher effect compared to placebo than the aclidinium bromide 200 µg BID dose for trough FVC and trough IC across the 3 studies. These findings are consistent with the trough FEV_1 results.

7.3.3.3 Health Status and Symptom Measures (Study 33 and Study 34)

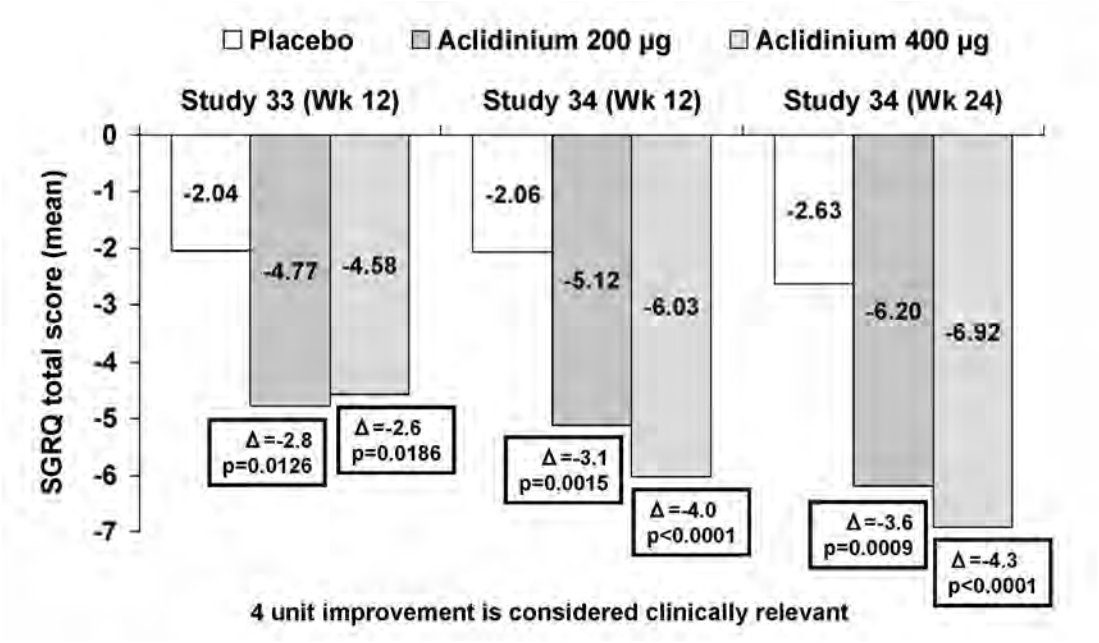
7.3.3.3.1 Saint George's Respiratory Questionnaire (Study 33 and Study 34)

Disease-specific health status was evaluated by means of a self-administered instrument, the SGRQ. This questionnaire is a standardized self-completed tool for measuring impaired health and perceived well-being ("quality of life") in respiratory diseases (Jones et al, 1991)

The SGRQ questionnaire contained 50 items divided in two parts comprising three sections: "Symptoms" concerned with respiratory symptoms, their frequency and severity; "Activity" concerned with activities that cause or are limited by breathlessness; and "Impacts" which covered a range of aspects related to social functional and psychological disturbances resulting from the disease. Part 1 (Questions 1 to 8) produced the "symptoms" score and covered the patients' recollection of their symptoms over a preceding period, which for this study was the previous month. Part 2 (Questions 9 to 17) covered the "activity" and "impacts" scores and addressed the patients' current state (for this study, the previous week). The SGRQ was scored in accordance with the recommendation from the developers outlined in the SGRQ manual and provided with the questionnaire to the centers. The calculation of the three component scores as well as the total score was performed in accordance with the SGRQ Calculator.

Statistically significant improvements in the change from baseline in SGRQ total score were observed with aclidinium bromide 400 and 200 µg versus placebo in Studies 33 and 34 (Figure 7.3.3.3.1–1 and Table 11.2–7 in Appendix I). The improvements in SGRQ total score observed with aclidinium bromide 400 µg compared to placebo in Study 34 were of a magnitude considered clinically meaningful (Cazzola et al, 2008) and are supportive of the efficacy of aclidinium bromide. At Week 24 in Study 34 (a pre-specified secondary efficacy endpoint), the difference in change from baseline versus placebo was –3.6 ($p = 0.0009$) for aclidinium bromide 200 µg and –4.3 ($p < 0.0001$) for aclidinium bromide 400 µg, thus demonstrating an improved response over time.

Figure 7.3.3.3.1–1. LS Mean for Change From Baseline in SGRQ Total Score at Week 12 in Study 33 and at Week 12 and Week 24 in Study 34—ITT Population



SGRQ = Saint George's Respiratory Questionnaire

The percentage of patients with a clinically meaningful improvement in SGRQ total score at Week 12 was statistically significantly higher with aclidinium bromide 400 µg versus placebo in Study 34 (OR = 1.9; p = 0.0004); statistical significance was also achieved at Week 24 (Figure 11.2–1 in Appendix I). The proportion of patients achieving a clinically meaningful improvement in SGRQ total score at Week 12 was statistically significantly higher with aclidinium bromide 200 µg versus placebo in Studies 33 and 34 (OR of 1.8 [p = 0.0103] and OR of 1.6 [p = 0.0119], respectively).

7.3.3.3.2 Transition Dyspnea Index (Study 33 and Study 34)

The BDI and TDI measure the severity of breathlessness in symptomatic patients (Mahler et al, 1984). The BDI measured the severity of dyspnea at the beginning of the study, and the TDI evaluated changes from this baseline measurement at Weeks 4, 8, and 12 in Study 33 and at Weeks 4, 12, and 24 in Study 34. Both indices contain an arbitrary rating for 3 categories, which are major factors affecting the development of dyspnea. These indices included the following:

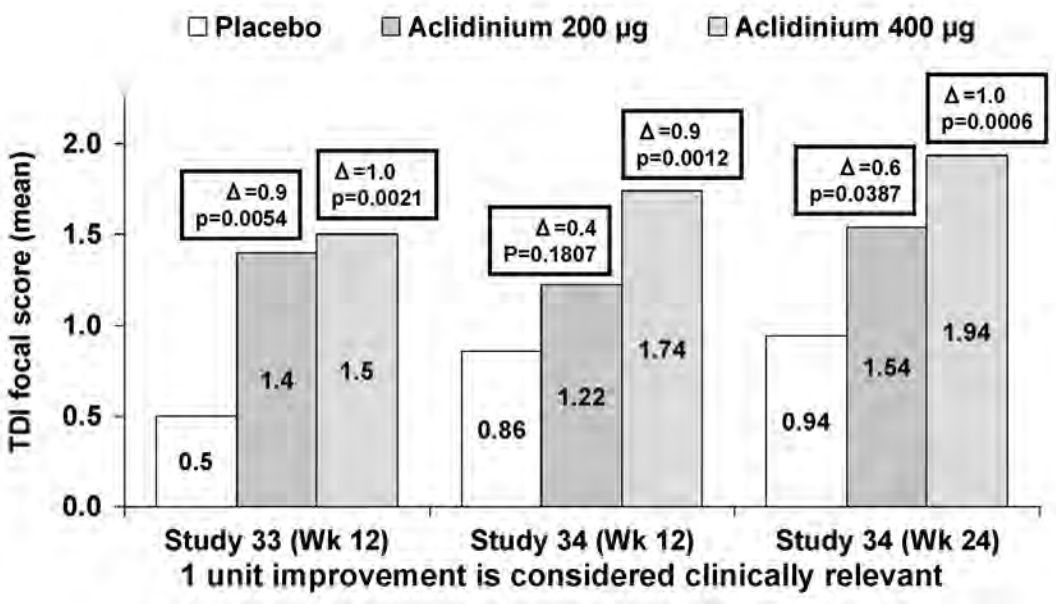
- Functional impairment, which determines the impact of breathlessness on the ability to carry out activities
- Magnitude of task, which determines the type of task that causes breathlessness
- Magnitude of effort, which establishes the level of effort needed to evoke breathlessness

The BDI includes 5 grades of severity from 0 (severe) to 4 (unimpaired), and the categories are summed to create the focal score (0-12). The lower the total score, the worse the severity of dyspnea. BDI was assessed at predose. The TDI ranges from –3 (major deterioration) to +3 (major improvement), including a 0 score to indicate “no change.” Also for the TDI, the 3 categories are added to obtain a focal score ranging from –9 (including zero) to +9. A change of 1 unit in TDI was used as the criterion for minimal meaningful improvement (Witek and Mahler, 2003). TDI responders were those with a TDI increase $\geq$ 1 unit. Patients with an increase of $<$ 1 unit were classified as nonresponders.

In the Phase 3 studies, evaluation of dyspnea (both at baseline and during treatment) was performed by an independent interviewer experienced in taking the history of respiratory disease. Based on the patient’s response, a grade reflecting the degree of impairment related to dyspnea in each category (as listed above) was selected.

As presented in Figure 7.3.3.3.2–1 and in Table 11.2–8 in Appendix I, the change from baseline to Week 12 in TDI focal scores in Study 33 and at Week 12 and Week 24 in Study 34 showed statistically significant improvements versus placebo for aclidinium bromide 400 µg. At Week 24 in Study 34 (a pre-specified secondary efficacy endpoint) the adjusted mean treatment differences from placebo were 0.6 and 1.0 units for aclidinium bromide 200 µg and aclidinium bromide 400 µg, respectively. The improvements in dyspnea observed with aclidinium bromide 400 µg compared to placebo in Studies 33 and 34 were of a magnitude that was considered clinically meaningful (Cazzola et al 2008).

Figure 7.3.3.3.2–1. Improvement From Baseline in Transition Dyspnea Index (TDI) Focal Score at Week 12 in Study 33 and at Weeks 12 and 24 in Study 34—ITT Population



The proportion of patients with clinically meaningful improvements in TDI focal score (TDI responders, 1 unit of improvement from placebo) and the treatment differences (OR) from placebo in pivotal studies 33 and 34 are presented in Figure 11.2–2 in Appendix I. Significant improvements were observed with aclidinium bromide 400 µg and 200 µg compared with placebo in the proportion of patients achieving a clinically meaningful improvement in dyspnea status (TDI focal score) at Week 12 in pivotal studies 33 and 34 and at Week 24 in Study 34. At Week 12, the ORs for aclidinium bromide 400 µg relative to placebo were 1.8-fold in Study 33 and 2.1-fold in Study 34. The OR for aclidinium bromide 200 µg relative to placebo was 2.1-fold in Study 33 and 1.5-fold in Study 34. At Week 24 ORs in Study 34 were 1.7-fold for aclidinium bromide 400 µg and 1.5-fold for aclidinium bromide 200 µg.

In summary, TDI is an important tool that demonstrates that aclidinium bromide 400 µg BID provides clinically meaningful symptom relief, in addition to the spirometric improvement demonstrated in the Phase 3 studies. These data provide supportive evidence of meaningful efficacy, as reported by patients.

7.3.3.3.3 COPD Exacerbations (Study 33 and Study 34)

The rate of COPD exacerbations per patient-year for the 2 pivotal Phase 3 efficacy studies and pooled populations are presented in Table 7.3.3.3.3–1.

The definition used for assessment of exacerbations in all 3 Phase 3 efficacy studies was similar to that used in other COPD studies which evaluated exacerbations, and was based on healthcare utilization (Wedzicha et al, 2008 and Calverley et al, 2007) as well as changes in COPD symptoms for at least 2 consecutive days. According to this definition, exacerbations were defined as moderate if they required the use of antibiotics or systemic corticosteroids, or as severe if they resulted in hospitalization (Cazzola et al, 2008). A new exacerbation was counted if the patient was off (or not required to take) systemic corticosteroids and/or antibiotics for ≥ 14 days since the prior exacerbation. If the patient was off (or not required to take) systemic corticosteroids and/or antibiotics for less than 14 days, then it was considered as a "relapse" of the previous exacerbation.

Although these studies were not powered to detect a reduction in exacerbations, reductions in the rate of moderate or severe exacerbations with aclidinium bromide 400 µg and 200 µg compared to placebo were quite apparent in the 2 pivotal studies: Study 33 (rate ratios 0.66, p = 0.0912 [aclidinium bromide 400 µg] and 0.67, p = 0.1033 [aclidinium bromide 200 µg]) and Study 34 (rate ratios 0.72, p = 0.0629 [aclidinium bromide 400 µg] and 0.74, p = 0.0845 [aclidinium bromide 200 µg]). As Study 33 was of a short duration of 12 weeks, it may not be expected to detect a full effect on exacerbations.

An exploratory pooled analysis of Studies 33 and 34 showed statistically significant reductions with aclidinium bromide 400 µg and 200 µg compared to placebo in the rate of moderate or severe exacerbations (rate ratios 0.71, p = 0.0149 [aclidinium bromide 400 µg] and 0.74, p = 0.0259 [aclidinium bromide 200 µg). These data provide further support for the efficacy of aclidinium bromide BID.

Table 7.3.3.3.3–1. Rate of Moderate or Severe Chronic Obstructive Pulmonary Disease (COPD) Exacerbations per Patient/Year for Phase 3 Efficacy Studies 33 and 34 and the Pooled Populations - ITT Populations

Study				***Comparison***	***Treatment Difference***		
Treatment	*N*	*Rate*	*95% CI*		*Rate Ratio*	*95% CI*	*p-value*
Study 33							
AB 400 µg	190	0.417	0.24, 0.71	AB 400 µg - Placebo	**0.663**	0.41, 1.07	**0.0912**
AB 200 µg	184	0.422	0.25, 0.71	AB 200 µg - Placebo	**0.670**	0.41, 1.08	**0.1033**
Placebo	185	0.629	0.38, 1.03	—	—	—	—
Study 34							
AB 400 µg	269	0.342	0.26, 0.44	AB 400 µg - Placebo	**0.723**	0.51, 1.02	**0.0629**
AB 200 µg	277	0.352	0.27, 0.45	AB 200 µg - Placebo	**0.742**	0.53, 1.04	**0.0845**
Placebo	273	0.474	0.38, 0.60	—	—	—	—
Pooled Studies: 33 and 34							
AB 400 µg	459	0.311	0.25, 0.39	AB 400 µg - Placebo	**0.712**	0.54, 0.94	**0.0149**
AB 200 µg	461	0.321	0.26, 0.40	AB 200 µg - Placebo	**0.735**	0.56, 0.96	**0.0259**
Placebo	458	0.437	0.36, 0.53	—	—	—	—

Note: Analysis is based on Poisson regression model adjusting for dispersion and with the total number of COPD exacerbations during the study as response and with study (only for pooled studies), sex, and baseline COPD severity as factors along with age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model).

AB = aclidinium bromide; CI = confidence interval; COPD = chronic obstructive pulmonary disease; ITT = intent to treat; N = number of patients in study populations.

The Exacerbations of Chronic Pulmonary Disease Tool (EXACT) is a patient-reported outcome (PRO) currently in development to measure and evaluate the effects of pharmacologic treatment on acute exacerbations of COPD. The tool is designed for use in clinical trials of COPD as an endpoint and captures the cardinal symptoms of COPD (dyspnea, cough, sputum production) and also includes additional items capturing dyspnea with activity and several systemic manifestations of COPD. It can be used to measure changes in an exacerbation over time, to show changes in the patient's health state prior to an exacerbation, during a clinician-confirmed exacerbations and recovery and return to a stable state. The tool is not designed as a differential diagnostic tool but a measure designed to provide researchers with a single, standardized, reliable, and valid method for assessing frequency, severity, and duration of exacerbations of chronic obstructive pulmonary disease. The data can be used to document severity of exacerbation episodes, time to return to a stable state and post exacerbation stable-state and post exacerbation stable-state values. The 14- item EXACT is scored from 0-100 with higher scores indicating more severe symptoms s of exacerbation. In the largest Phase 3 Study 34, daily symptoms were assessed electronically by patients each day in the evening, before bed, through the EXACT-PRO and validated in different languages (Leidy et al, 2011).

As shown in Table 7.3.3.3.3–2, the rate ratio for the aclidinium bromide 400 µg BID group compared to the placebo group (any exacerbation based on EXACT-PRO) was statistically significant (rate ratio: 0.71; p-value: 0.0118). This rate ratio corresponds to a rate reduction in COPD exacerbations of 29%. The rate ratio for the aclidinium bromide 200 µg BID group compared to the placebo group (any exacerbation based on EXACT-PRO) was statistically significant (rate ratio: 0.72; p-value: 0.0166). This rate ratio corresponds to a rate reduction in COPD exacerbations of 28%.

Table 7.3.3.3.3–2. Rate Ratio of COPD Exacerbations per Patient Year Based on EXACT-PRO-ITT Population (Study 34)

	Aclidinium bromide 200 µg BID (N=277)			Aclidinium bromide 400 µg BID (N=269)		
Type of Exacerbation	Rate ratio[a]	95% CI	p-value	Rate ratio[b]	95% CI	p-value
Any exacerbation	0.72	(0.55, 0.94)	0.0166	0.71	(0.54, 0.93)	0.0118

a Rate ratio for aclidinium bromide 200 µg BID versus placebo.

b Rate ratio for aclidinium bromide 400 µg BID versus placebo

7.3.3.3.4 Rescue Medication Use (Study 33 and Study 34)

In studies 33 and 34, the use of daily rescue medication (number of albuterol/salbutamol puffs, as recorded by the patient in an electronic diary) was collected and assessed at each study visit. The frequency of use of rescue medication for symptomatic relief may provide an indication of the degree of control of respiratory impairment, and therefore, a reduction in rescue medication usage suggests enhanced patient health status and symptomatic benefits, further confirming the efficacy of aclidinium bromide. The finding of reduced rescue medication usage in the 2 pivotal efficacy studies, 33 and 34 (as presented in Table 7.3.3.3.4–1) is complementary and supportive of the bronchodilatory and symptomatic improvements in SGRQ and TDI previously discussed.

Reductions from baseline in the use of rescue medication in the aclidinium bromide 200 µg and 400 µg treatment groups compared with placebo were 0.7 puffs/day ($p = 0.0010$) and 0.9 puffs/day ($p < 0.0001$), respectively, in Study 33 and 0.6 puffs/day ($p = 0.0614$) and 1.0 puffs/day ($p < 0.0042$), respectively, in Study 34.

The analysis of the pooled population of studies 33 and 34 showed that the treatment differences in reductions of overall rescue medication use for aclidinium bromide 400 µg and 200 µg versus placebo were 0.9 puffs/day ($p < 0.0001$) and 0.7 puffs/day ($p = 0.0024$) to the end of the studies, respectively.

Table 7.3.3.3.4–1. Changes From Baseline in Total Daily Use of Rescue Medication (Puffs/Day) in Pivotal Phase 3 Efficacy Studies 33 and 34 and the Pooled Population—ITT Populations

Study				***Comparison***	***Treatment Difference***		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Study 33							
AB 400 µg	186	–1.6	0.1	AB 400 µg – Placebo	**–0.9**	–1.3, –0.5	**< 0.0001**
AB 200 µg	182	–1.4	0.1	AB 200 µg – Placebo	**–0.7**	–1.1, –0.3	**0.0010**
Placebo	181	–0.7	0.1	—	—	—	—
Study 34							
AB 400 µg	269	–1.2	0.2	AB 400 µg – Placebo	**–1.0**	–1.6, –0.3	**0.0042**
AB 200 µg	277	–0.8	0.2	AB 200 µg – Placebo	**–0.6**	–1.3, 0.04	**0.0614**
Placebo	271	–0.2	0.2	—	—	—	—

Table 7.3.3.3.4–1. Changes From Baseline in Total Daily Use of Rescue Medication (Puffs/Day) in Pivotal Phase 3 Efficacy Studies 33 and 34 and the Pooled Population—ITT Populations

Study				*Comparison*	*Treatment Difference*		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Pooled Studies: 33 and 34							
AB 400 µg	455	–1.4	0.2	AB 400 µg – Placebo	**–0.9**	–1.4, –0.5	< **0.0001**
AB 200 µg	459	–1.1	0.2	AB 200 µg – Placebo	**–0.7**	–1.1, –0.2	**0.0024**
Placebo	452	–0.4	0.2	—	—	—	—

Note: Analysis is based on ANCOVA model for change from baseline in daily use of rescue medication, with treatment group and sex as factors, and age and baseline daily use of rescue medication as covariates. Daily rescue medication use interval was from the study start to end of study.

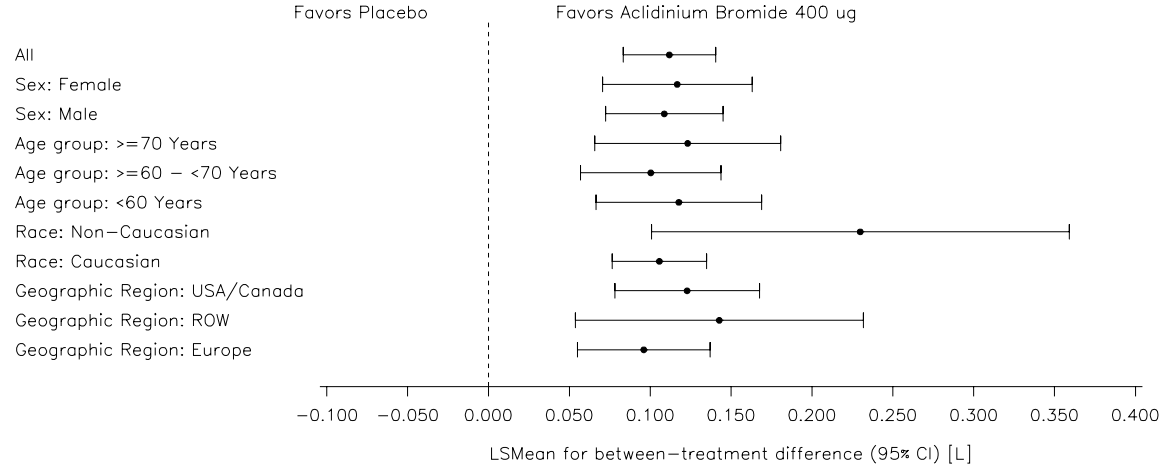
AB = aclidinium bromide; CI = confidence interval; ITT = intent to treat; n = number of patients;

a treatment differences in LS means.

7.3.3.4 Subpopulation Analyses of Primary Efficacy Endpoint in Pivotal Studies (Study 33 and Study 34 – Pooled Results)

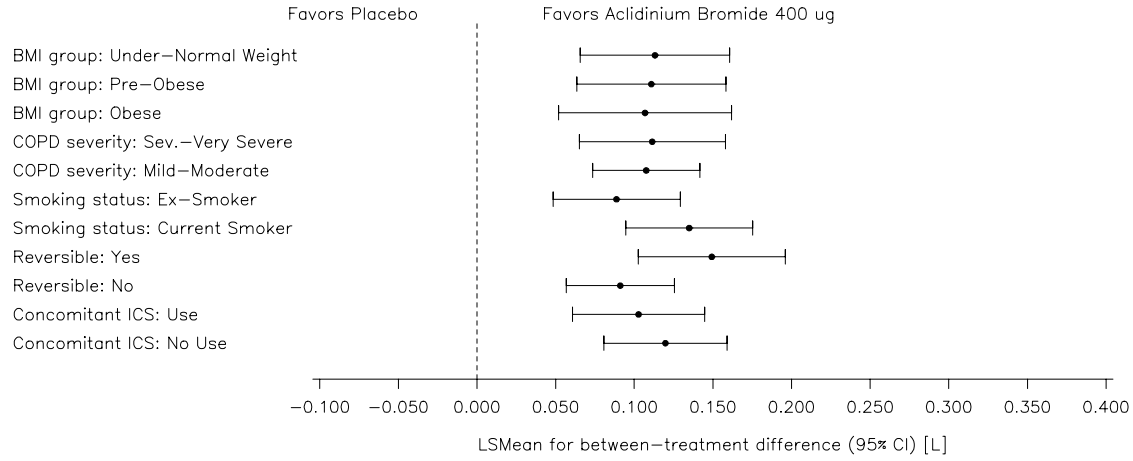
The primary efficacy measure of predose morning (trough) FEV_1 at Week 12 was analyzed in various subpopulations, ie, by sex, age group, race, geographical region, BMI group, COPD severity, smoking status, bronchodilator reversibility, and concomitant use of inhaled corticosteroids. Adjusted mean treatment differences (and 95% CIs) between aclidinium bromide 400 µg and placebo (for pooled studies 33 and 34) are presented by sex, age, race, and geographic region in Figure 7.3.3.4–1 and by BMI, COPD severity, smoking status, bronchial reversibility, and concomitant inhaled corticosteroid use in Figure 7.3.3.4–2. Figure 7.3.3.4–3 and Figure 7.3.3.4–4 present the data for these analyses for aclidinium bromide 200 µg versus placebo. Overall, there were no marked differences in efficacy in the various subgroups explored. All treatment differences in trough FEV_1 values for aclidinium bromide 400 µg (compared with placebo) were approximately 100 mL or more.

Figure 7.3.3.4–1. Treatment Differences (Aclidinium Bromide 400 µg versus Placebo) in Least Square Means (and 95% CIs) for Change From Baseline to Week 12 in Trough FEV_1 by Subgroup (Sex, Age Group, Race, and Geographic Region) in Pooled Studies 33 and 34—ITT Populations



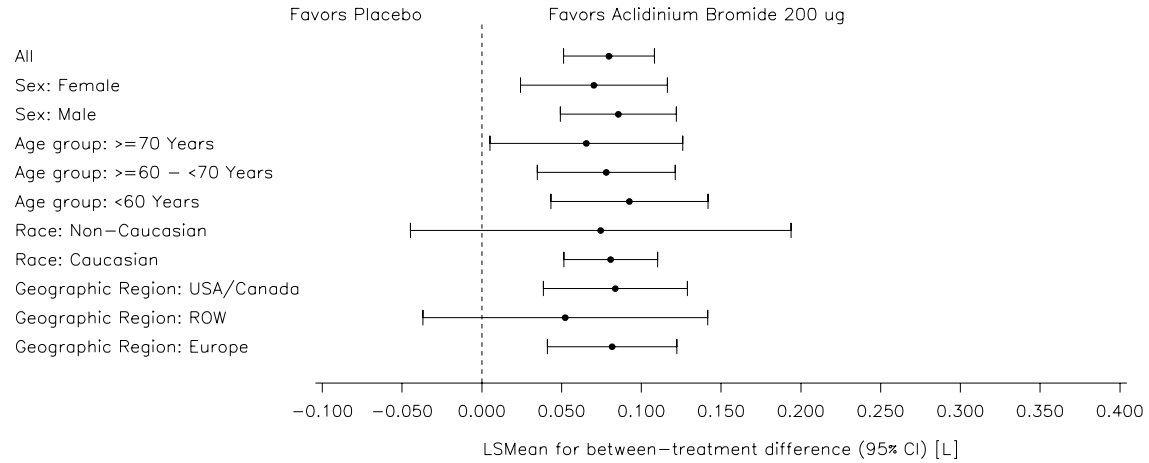
CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat.

Figure 7.3.3.4–2. Treatment Differences (Aclidinium Bromide 400 µg versus Placebo) in Least Square Means (and 95% CIs) for Change From Baseline to Week 12 in Trough FEV_1 by Subgroup (BMI, COPD Severity, Smoking Status, Bronchial Reversibility, and Concomitant ICS Use) in Pooled Studies 33 and 34—ITT Populations



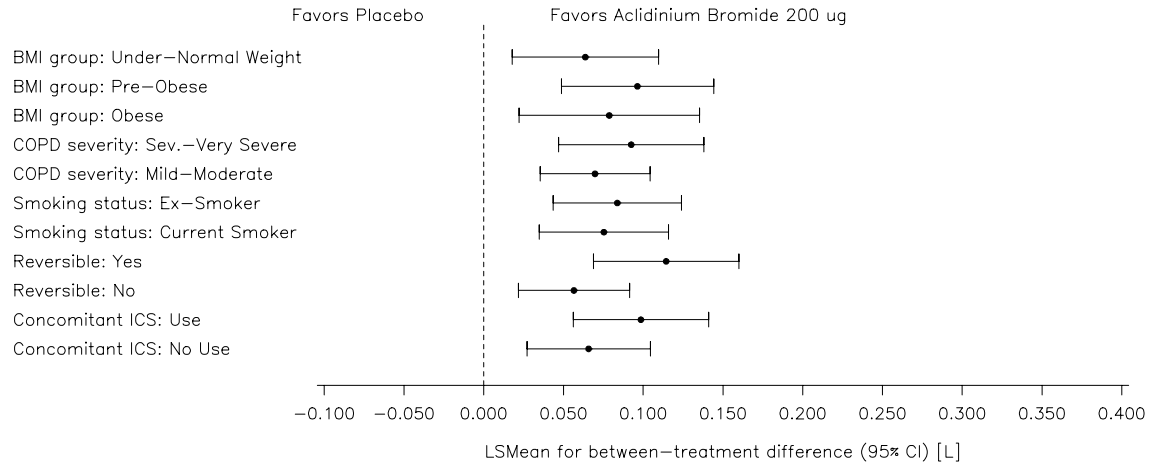
CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; ITT = intent to treat.

Figure 7.3.3.4–3. Treatment Differences (Aclidinium Bromide 200 µg versus Placebo) in Least Square Means (and 95% CIs) for Change From Baseline to Week 12 in Trough FEV_1 by Subgroup (Sex, Age Group, Race, and Geographic Region) in Pooled Studies 33 and 34—ITT Populations



CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat.

Figure 7.3.3.4–4. Treatment Differences (Aclidinium Bromide 200 µg versus Placebo) in Least Square Means (and 95% CIs) for Change From Baseline to Week 12 in Trough FEV_1 by Subgroup (BMI, COPD Severity, Smoking Status, Bronchial Reversibility, and Concomitant ICS Use) in Pooled Studies 33 and 34—ITT Populations



CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ICS = inhaled corticosteroid; ITT = intent to treat.

7.3.3.5 Conclusions of Pivotal Studies 33 and 34

Clinically significant improvements in lung function and treatment differences in change from baseline trough FEV_1 (ie, greater than 100 mL [Cazzola et al 2008]) between aclidinium bromide 400 µg BID and placebo were observed in Studies 33 and 34.

The improvements in SGRQ total score observed with aclidinium bromide 400 µg BID compared to placebo in Study 34 were of a magnitude considered clinically meaningful (Cazzola et al, 2008) and are supportive of the efficacy of aclidinium bromide. Additionally, results from the TDI demonstrated that aclidinium bromide 400 µg BID provides clinically meaningful symptom relief, in addition to the spirometric improvement demonstrated in the pivotal Phase 3 studies. These data provide confirmatory evidence of meaningful efficacy, as reported by patients.

The finding of reduced rescue medication usage in the 2 pivotal efficacy studies 33 and 34 (as presented in Table 7.3.3.3.4–1) is complementary and supportive of the bronchodilatory and symptomatic improvements in SGRQ and TDI previously discussed.

Overall, there were no marked differences in efficacy in the various subgroups explored. In general, treatment differences in trough FEV_1 values for aclidinium bromide 400 µg BID (compared with placebo) were 100 mL or more.

7.3.4 Efficacy Results in Supportive Phase 3 Study 38 (A)

7.3.4.1 Unexpected Imbalances in Baseline Characteristics of Study 38 (A)

Unexpected imbalances between treatment groups were observed in some baseline characteristics in Study 38 (A). The baseline COPD severity of patients in the aclidinium bromide 400 µg group was greater than that of patients in the placebo group, while baseline COPD severity of patients in the aclidinium bromide 200 µg group was intermediate between the placebo and aclidinium bromide 400 µg groups. For comparison purposes, Figure 7.3.4.1–1, presents baseline values for FEV_1 and COPD severity across the 3 Phase 3 studies. In Study 38 (A), imbalances between treatment groups were observed for baseline FEV_1; baseline values in the aclidinium bromide 400 µg and 200 µg treatment groups and in the placebo group were 1.25 L, 1.40 L, and 1.46 L, respectively ($p = 0.0009$, p-value is for the null hypothesis of the 3 baseline means being equal and was determined post hoc).

This imbalance in lung function severity at baseline was also reflected in the percentage of patients in Study 38 (A) with Stage II (moderate) and III (severe): the proportions of patients in the aclidinium bromide 400 µg, aclidinium bromide 200 µg, and placebo groups with Stage III (severe) COPD at baseline were 54.9%, 47.5%, and 36.8%, respectively ($p = 0.0006$, p-value is for the null hypothesis of the 3 percentages of severe COPD at baseline being equal and was determined post hoc).

Figure 7.3.4.1–1. Summary of Baseline Imbalances in Study 38 (A) and Baseline Balances in Studies 33 and 34 (p-Values Were Calculated Post Hoc)

Study 38A	Placebo (N=182)	AB 200 µg (N=181)	AB 400 µg (N=175)	p-value
Baseline FEV_1 (L)	1.46	1.40	1.25	0.0009
Severe	36.8%	47.5%	54.9%	0.0006

Study 33	Placebo (N=186)	AB 200 µg (N=184)	AB 400 µg (N=190)	p-value
Baseline FEV_1 (L)	1.38	1.35	1.35	NS
Severe	39.2%	43.5%	35.8%	NS

Study 34	Placebo (N=273)	AB 200 µg (N=277)	AB 400 µg (N=269)	p-value
Baseline FEV_1 (L)	1.48	1.49	1.48	NS
Severe	34.1%	30.4%	31.3%	NS

Given the significant imbalances among the treatment groups in baseline FEV_1 and COPD severity, the randomization of the patients in Study 38 (A) failed to generate comparable treatment groups. Such baseline imbalances made the magnitude of treatment effect on FEV_1 and other efficacy parameters difficult to interpret. Although the effect on change from baseline in trough FEV_1 was statistically superior in both aclidinium bromide treatment groups versus the placebo group (Section 7.3.4.2), the imbalance in baseline trough FEV_1 from this study makes any result difficult to interpret with confidence.

7.3.4.2 Efficacy Results for Study 38 (A)

Adjusted mean treatment differences between aclidinium bromide and placebo in the change from baseline to Week 12 in trough and peak FEV_1, SGRQ total score, TDI focal score, and use of rescue medication are presented in Table 7.3.4.2–1.

Aclidinium bromide 400 µg and 200 µg BID produced statistically significant differences versus placebo in change from baseline to Week 12 in **trough FEV_1** (primary efficacy endpoint), compared with placebo (72 mL [p = 0.0012] and 51 mL [p = 0.0192], respectively). Similar findings were observed using the MMRM analysis (improvement of 80 mL [p = 0.0011] for the aclidinium bromide 400 µg group and 54 mL [p = 0.0238] in the aclidinium bromide 200 µg group, both compared with placebo).

The adjusted mean change from baseline to Week 12 in **peak FEV_1** (secondary efficacy endpoint) was also statistically significantly greater for aclidinium bromide 400 µg and 200 µg compared with placebo (by 125 mL and 115 mL, respectively; $p < 0.0001$ for both comparisons). Aclidinium bromide 400 µg and 200 µg were associated with statistically significant improvements, compared to placebo, in the adjusted mean change from baseline to Week 12 in **TDI focal score** (by 1.0 unit [$p = 0.0054$] and 0.7 unit [$p = 0.0416$], respectively). The treatment difference in TDI between the aclidinium bromide 400 µg and placebo groups was at the level of the minimum clinically important difference (MCID) (ie, 1.0 unit) (Cazzola et al, 2008).

There were no statistically significant differences in either aclidinium bromide treatment group compared with placebo in SGRQ total score or in the use of rescue medication.

Changes from baseline at Week 12 for trough FVC are presented in Table 11.2–5 and for trough IC in Table 11.2–6.

Table 7.3.4.2–1. Changes From Baseline at Week 12 in Trough and Peak FEV_1 (mL), SGRQ, Use of Rescue Medication, and Improvement in TDI in Phase 3 Supportive Study 38 (A)—ITT Population

Study 38 (A)				*Comparison*	*Treatment Difference*		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Trough FEV_1							
AB 400 µg	177	64	16	AB 400 µg – Placebo	**72**	30, 120	**0.0012**
AB 200 µg	182	43	15	AB 200 µg – Placebo	**51**	10, 90	**0.0192**
Placebo	182	–8	15	AB 400 µg – AB 200 µg	21	–2, 60	0.3415
Peak FEV_1							
AB 400 µg	177	212	18	AB 400 µg – Placebo	**125**	70, 180	**< 0.0001**
AB 200 µg	182	201	18	AB 200 µg – Placebo	**115**	70, 160	**< 0.0001**
Placebo	182	87	18	AB 400 µg – AB 200 µg	10	–4, 60	0.6922
SGRQ total score							
AB 400 µg	172	–5.4	1.0	AB 400 µg – Placebo	**–1.1**	–3.8, 1.6	**0.4288**
AB 200 µg	178	–6.0	1.0	AB 200 µg – Placebo	**–1.7**	–4.3, 1.0	**0.2216**
Placebo	178	–4.3	1.0	AB 400 µg – AB 200 µg	—	—	—
TDI focal score							
AB 400 µg	142	1.3	0.2	AB 400 µg – Placebo	**1.0**	0.3, 1.7	**0.0054**
AB 200 µg	149	1.0	0.2	AB 200 µg – Placebo	**0.7**	0.0, 1.4	**0.0416**
Placebo	148	0.3	0.3	AB 400 µg – AB 200 µg	—	—	—
Rescue medication use (overall puffs)							
AB 400 µg	171	–1.4	0.2	AB 400 µg – Placebo	**–0.3**	–0.8, 0.2	**0.2490**
AB 200 µg	175	–1.3	0.2	AB 200 µg – Placebo	**–0.2**	–0.7, 0.4	**0.5334**
Placebo	173	–1.1	0.2	AB 400 µg – AB 200 µg	—	—	—

Note: For each endpoint in this table an ANCOVA model with the same factors and covariances as the model for the corresponding endpoint in Study 33 was used.

a treatment differences in LS means.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent to treat; LS = least squares; n = number of patients; SGRQ = St. George's respiratory Questionnaire; TDI = Transition Dyspnea Index.

There was a trend towards a reduction in the rate of moderate or severe COPD exacerbations with aclidinium bromide 400 µg BID and 200 µg BID compared to placebo (rate ratios 0.82, p = 0.3970 and 0.57, p = 0.0278, respectively) (Table 7.3.4.2–2).

Table 7.3.4.2–2. Rate of Moderate or Severe COPD Exacerbations per Patient/Year in Phase 3 Supportive Study 38 (A)—ITT Population

Study38 (A)				***Comparison***	***Treatment Difference***		
Treatment	*N*	*Rate*	*95% CI*		*Rate Ratio*	*95% CI*	*p-value*
moderate or severe exacerbations							
AB 400 µg	177	0.412	0.29, 0.58	AB 400 µg - Placebo	**0.821**	0.52, 1.29	**0.3970**
AB 200 µg	182	0.285	0.19, 0.42	AB 200 µg - Placebo	**0.569**	0.34, 0.94	**0.0278**
Placebo	182	0.501	0.37, 0.68	—	—	—	—

Note: Analysis is based on Poisson regression model adjusting for dispersion and with the total number of COPD exacerbations during the study as response and sex and baseline COPD severity as factors along with age as covariate, adjusting for the log of the corresponding total exposure time in years for a patient (as an offset variable in the model).

AB = aclidinium bromide; CI = confidence interval; COPD = Chronic Obstructive Pulmonary Disease; ITT = intent to treat; N = number of patients in study populations.

7.4 LONG-TERM SAFETY STUDIES - MAINTENANCE OF BRONCHODILATOR EFFECT

Study 35 was designed to assess long-term safety of aclidinium bromide and included assessments to evaluate long-term maintenance of bronchodilation.

Efficacy results of long-term safety Study 36 are not included in this briefing book due to the limited sample size from this study. Also efficacy results from long-term safety Study 38 (B) are not included due to only 1 treatment group (aclidinium bromide 400 µg BID) in this study.

7.4.1 Study 35

Study 35 was a long-term, randomized, double-blind, multicenter, parallel-group safety study of inhaled aclidinium bromide 200 µg or 400 µg administered BID via a multidose DPI 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. The study was conducted in the United States and Canada. From the total of 605 patients randomized, 600 patients comprised the ITT Population (310 aclidinium bromide 200 µg BID and 290 aclidinium bromide 400 µg BID).

Baseline FEV_1 was 1.443 L in the aclidinium bromide 200 µg BID group and 1.366 L in the aclidinium bromide 400 µg BID group. At the end of 52 weeks of treatment, the adjusted mean change from baseline in morning predose (trough) FEV_1 was 34 mL in the aclidinium bromide 200 µg BID group and 72 mL in the aclidinium bromide 400 µg BID group (Table 7.4.1–1). Based on post hoc analysis, there was a numerical difference between the aclidinium bromide 400 µg and 200 µg doses (p = 0.0714).

Table 7.4.1–1. Change From Baseline in Morning Predose (Trough) FEV_1 (mL) at Week 52 (LOCF): Primary Efficacy Analysis—ITT Population (Study 35)

Visit	*Value*	*Aclidinium bromide 200 µg N = 310*	*Aclidinium bromide 400 µg N = 290*
Baseline			
	Mean (in liters) (SD)	1.443 (0.569)	1.366 (0.608)
Change from baseline (mL): ANCOVA[a]			
Week 52	*LSM (SE)*	34 (15)	72 (15)
	95% CI	5, 63	42, 102
	p-value (AB 400 vs AB 200)	0.0714	

a Analyses are based on ANCOVA model for change from baseline in trough FEV_1 with treatment group and sex as factors and baseline FEV_1 and age as covariates.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the ITT Population.

At the end of 52 weeks of treatment, the adjusted mean change from baseline in peak FEV_1 was 185 mL in the aclidinium bromide 200 µg BID group and 214 mL in the aclidinium bromide 400 µg BID group (Table 7.4.1–2).

Table 7.4.1–2. Change From Baseline in Peak FEV_1 (mL) at Week 52 (LOCF): Secondary Efficacy Analysis—ITT Population (Study 35)

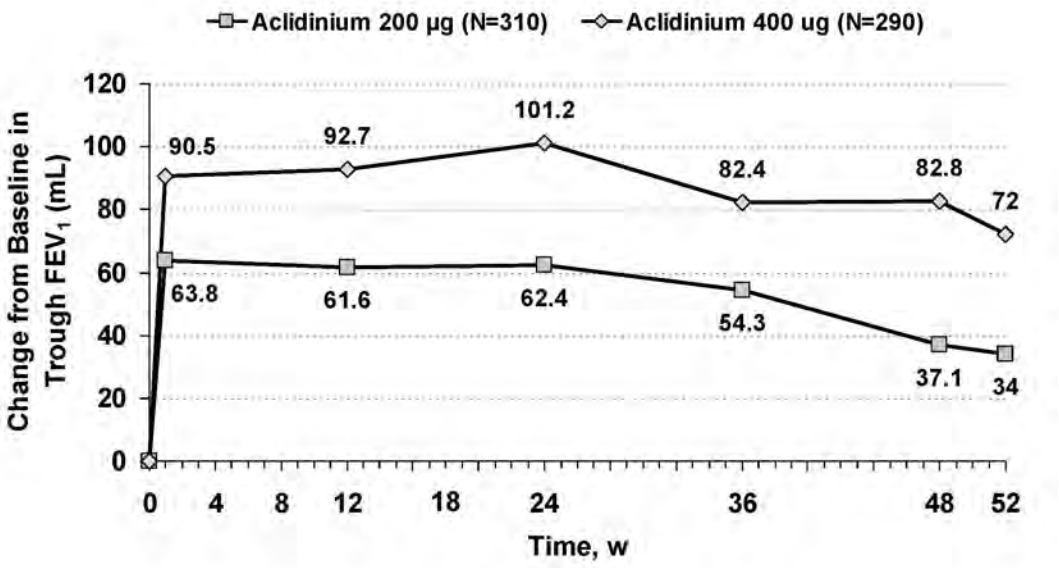
Visit	*Statistic*	*Aclidinium bromide 200 µg N = 310*	*Aclidinium bromide 400 µg N = 290*
Change from baseline (mL): ANCOVA[a]			
Week 52	*LSM (SE)*	185 (15)	214 (15)
	95% CI	156, 215	184, 244

a Analyses are based on ANCOVA model for change from baseline in peak FEV_1 with treatment group and sex as factors and baseline FEV_1 and age as covariates.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FEV_1 = forced expiratory volume in 1 second; ITT = intent-to-treat; LOCF = last observation carried forward; LSM = least squares mean; N = number of patients in the ITT Population; n = number of patients within a specified category.

Figure 7.4.1–1 displays the mean change from baseline in trough FEV_1 at Weeks 1, 12, 24, 36, 48, and 52 (LOCF). The change from baseline at each time point provided improvement in bronchodilation for both aclidinium bromide groups. After Week 24, there was a decline in trough FEV_1 in both treatment groups, most probably due to the natural decline in FEV_1 seen in COPD patients (Vestbo et al. 2011).

Figure 7.4.1–1. Persistence of Bronchodilator Effect (Trough FEV_1) Over 52 Weeks—ITT Population (Study 35)



In summary, efficacy results in Study 35 showed that both doses of aclidinium bromide showed improvement in bronchodilation from baseline and maintained that improvement from Week 1 to Week 52. As early as Week 1, aclidinium bromide 400 µg BID exhibited an apparent dose separation from aclidinium bromide 200 µg BID in providing a numerically greater bronchodilator response that was sustained throughout the study.

7.5 EFFICACY CONCLUSIONS

Several key findings across the BID program, highlighted below, provide evidence that aclidinium bromide 400 µg BID will benefit COPD patients through improvements in airflow and dyspnea, quality of life, exacerbations, and rescue medication use. Specifically, these findings include:

- **Bronchodilatory Effects**: Both aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID provide statistically significant early and persistent improvements compared to placebo in bronchodilation, as measured by trough FEV_1 and peak FEV_1. Bronchodilatory improvements are a hallmark of long-acting, maintenance treatment in patients with COPD, and aclidinium bromide meets this standard. In all of the Phase 3 studies, the 400 µg BID dose outperformed the 200 µg BID dose. In the pivotal studies, the 400 µg dose provided clinically meaningful bronchodilation, whereas the 200 µg dose fell short. Finally, based on the pooled data across the 2 pivotal Phase 3 efficacy studies (33 and 34), aclidinium bromide 400 µg BID provided a clinically important improvement in bronchodilation (trough FEV_1) that was statistically significantly greater than aclidinium bromide 200 µg BID. Also long-term Study 35 clearly supports the advantage of aclidinium bromide 400 µg over 200 µg based on trough FEV_1. Aclidinium bromide has consistently demonstrated 24-hour bronchodilator efficacy on BID dosing, with clinically relevant improvement beginning with the first dose and sustained efficacy on repeated dosing up to one year.

- **Quality of Life and Symptom Measures:** Both doses of aclidinium bromide BID demonstrated statistically significant improvements in quality of life and reduction in breathlessness as assessed by the SGRQ and TDI in the 2 pivotal Phase 3 efficacy studies (33 and 34). Further, in the case of the TDI, the improvements compared to placebo met the recognized MCID (+1 unit) at Week 12 in Study 33 and at Week 24 in Study 34. The percentage of individual patients meeting the MCID was statistically significant. In addition, the aclidinium bromide 400 µg BID dose versus placebo, produced clinically relevant improvements in lung function and symptoms. Meaningful improvements in the TDI and SGRQ allow patients to lead a more active, fulfilling life with reduced symptoms like breathlessness that significantly limit functionality.

- **Use of Rescue Medication**: Pivotal efficacy studies 33 and 34 showed statistically significant treatment differences in the reduction of overall rescue medication use at Week 12 with aclidinium bromide 400 µg BID compared with placebo (-0.9 puffs and –1.0 puffs, respectively) and are supportive of the symptomatic improvements previously demonstrated.

- **COPD Exacerbations:** Based on a preplanned analysis of exacerbation rates in Study 34 using EXACT-PRO, the aclidinium bromide 400 µg and 200 µg BID groups had statistically significant reductions relative to placebo (rate ratios 0.71 [p = 0.0118] and 0.72 [p = 0.0166], respectively. In addition, an exploratory analysis of the pooled population of the 2 pivotal Phase 3 efficacy studies (33 and 34) suggest that aclidinium bromide 400 µg BID and aclidinium bromide 200 µg BID compared to placebo were associated with statistically significant reductions in the rate of exacerbations (moderate to severe) of approximately 30% to 25% (rate ratios 0.71 [p = 0.0149] and 0.74 [p = 0.0259], respectively). These data provide promising results for future study. Additionally, it is recognized that a reduction in exacerbations may help to avoid a decrement in lung function, prevent hospitalizations, and lead to a better quality of life in COPD subjects (Niewoehner 2009 and Niewoehner et al, 2000).

In summary, based on the totality of evidence, 400 µg BID is the recommended dose for approval. Aclidinium bromide 400 µg BID consistently demonstrated a statistically significant and/or greater numeric difference compared to doses of 200 µg BID or less. Specifically, aclidinium bromide 400 µg BID demonstrated a more robust effect in bronchodilation, TDI (symptomatic improvement), SGRQ (quality of life), rescue medication usage, and exacerbation reduction.

8.0 SAFETY RESULTS

8.1 INTRODUCTION

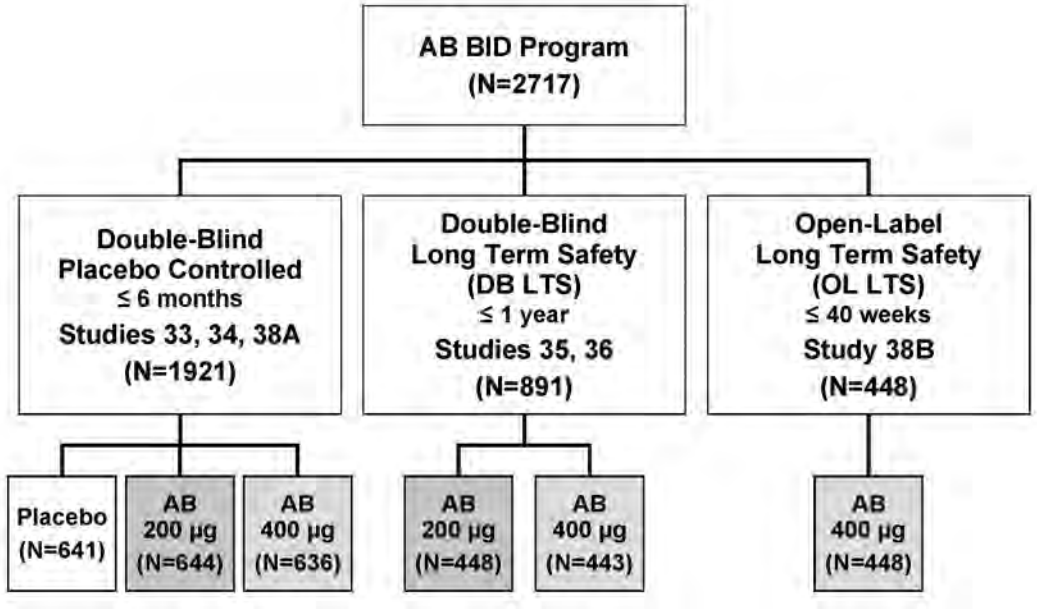
Safety variables examined in the BID studies were AEs, SAEs, ADOs, deaths, AEs of special interest (ie, CV events, cerebrovascular events, anticholinergic events, and pneumonia), vital signs, and laboratory and ECG parameters. In accordance with an FDA request, an analysis of AEs of special interest for combined occurrence rates of medically similar AEs was performed. Collapsed *Medical Dictionary for Regulatory Activities* (MedDRA) preferred terms (PTs) were provided for myocardial infarction, atrial fibrillation, angina, stroke, congestive heart failure, tachycardia, and pneumonia, as well as other events. Additionally, at the request of the Division, an analysis of Major Adverse Cardiovascular Events (MACE) was conducted (Section 8.4.6.1).

8.2 SAFETY POPULATION AND GROUPS

As shown in Figure 8.2–1, the safety population for the BID studies presented in this briefing book is divided into 3 main safety groups: the double-blind, placebo-controlled studies (33, 34, and 38 [A]), the double-blind long-term safety studies (35 and 36), and the open-label, long-term safety study (38 [B]). The safety results for the 4 BID short-term crossover studies (23, 26, 27, and 29) are not presented in this briefing book because of their relatively small size and differences in study design.

Data from the 2 double-blind long term safety studies (35 and 36) are pooled together and are presented separately from the open-label Study 38 (B) as it only had 1 treatment arm. These 3 studies were originally pooled in the ISS of the NDA. Within this briefing book, Studies 35 and 36 are now pooled primarily to determine if there was a dose related difference in AEs between the aclidinium bromide 200 µg and aclidinium bromide 400 µg treatment groups. Study 38 (B) was designed to augment our long-term safety experience with aclidinium bromide 400 µg BID.

Figure 8.2–1. Safety Groups



AB = aclidinium bromide; BID = twice-daily; DB LTS = double-blind, long-term safety; OL LTS = open-label, long-term safety

8.3 EXTENT OF EXPOSURE

A total of 2717 COPD patients were exposed to aclidinium bromide (100 µg, 200 µg, or 400 µg BID) in 9 studies. Total exposure to aclidinium bromide was 1394.9 patient-years (Table 8.3–1).

Table 8.3–1. Extent of Exposure of Aclidinium Bromide (BID) in Patients With COPD (Safety Population)

Exposure	***Placebo***	***Aclidinium Bromide***		
	N = 940	*100 µg BID N = 73*	*200 µg BID N = 1173*	*400 µg BID N = 1471*
Mean (SD), days	78.1 (61.3)	7.0 (0.2)	169.8 (138.9)	210.6 (137.0)
Median	85.0	7.0	166.0	179.0
Total patient-years of exposure	201.0	1.4	545.2	848.3
Exposure, n				
≥ 84 days (12 weeks)	516	0	847	1141
≥ 168 days (24 weeks)	196	0	564	970
≥ 336 days (48 weeks)	0	0	288	395
≥ 357 days (51 weeks)	0	0	282	387
≥ 364 days (52 weeks)	0	0	242	329

Studies 23, 26, 27, 29, 33, 34, 35, 36, 38 (A), and 38 (B). Patients in the extension studies 36 and 38 (B) or crossover studies 23, 26, 27, and 29 who had different treatment from the lead-in study or other treatment period were counted multiple times, once in each treatment period.

8.4 ADVERSE EVENTS

8.4.1 Overview of Adverse Events

Placebo-controlled Studies

An overview of AEs in the double-blind, placebo-controlled studies is presented in Table 8.4.1–1. Aclidinium bromide 400 µg BID had a similar AE profile to both placebo and 200 µg BID (approximately 50% of each group reported any TEAE). The proportion of subjects experiencing severe TEAEs or prematurely discontinuing due to an AE was similar between the aclidinium bromide 200 µg and 400 µg doses and comparable to placebo.

The incidence of non-fatal SAEs was lower in the aclidinium bromide treatment arms compared with placebo. A total of only 6 deaths were reported, and the rate was similar among treatment groups.

Table 8.4.1–1. Overview of Adverse Events: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Category	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg BID* *N = 644* *199.4 PY* *n (%)*	*400 µg BID* *N = 636* *198.4 PY* *n (%)*
At least 1 TEAE	344 **(53.7%)**	321 **(49.8%)**	319 **(50.2%)**
Any severe TEAE	43 **(6.7%)**	41 **(6.4%)**	37 **(5.8%)**
Any AE leading to study discontinuation[a]	31 (**4.8%**)	**26 (4.0%)**	27 **(4.2%)**
Any SAE[a]	20 (**3.1%**)	14 **(2.2%**)	15 (**2.4%**)
Death[b]	2 **(0.3%)**	1 **(0.2%)**	3 **(0.5%)**

a Includes non-fatal events only.

b Deaths occurring during treatment and up to 30 days after stopping investigational product.

AE = adverse event; BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SAE = serious adverse event; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

The double-blind long-term safety pool includes results from Study 35 (1-year long-term safety) and Study 36 (extension study from 12-week Study 33), and for the open-label long-term safety pool, Study 38 (B) (extension study from Study 38 [A]). As shown in Table 8.4.1–2, the percentage of patients reporting TEAEs in the double-blind, long-term safety studies (35 and 36) was similar in the aclidinium bromide 200 µg group compared with the aclidinium bromide 400 µg group (67.0% vs 68.6%, respectively) TEAE incidence in the 400 µg group in the open-label, long-term study (Study 38 [B]) was also comparable (64.5%).

Table 8.4.1–2. Overview of Adverse Events: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
At least 1 TEAE	300 (**67.0%**)	304 (**68.6%**)	289 (**64.5%**)
Any AE leading to study discontinuation[a]	46 (**10.3%**)	39 (**8.8%**)	29 (**6.5%**)
Any SAE[a]	23 (**5.1%**)	24 (**5.4%**)	25 (**5.6%**)
Death[b]	2 (**0.4%**)	2 (**0.5%**)	3 (**0.7%**)

a Includes non-fatal events only

b Deaths occurring during treatment and up to 30 days after stopping investigational product.

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.2 Common Treatment-Emergent Adverse Events by Preferred Term

Placebo-controlled Studies

TEAEs that occurred in at least 2% of patients in any treatment group in the placebo-controlled studies are summarized by PT in Table 8.4.2–1. TEAE incidence according to PT was generally similar for the 2 aclidinium bromide treatment groups and were generally comparable to placebo. The most frequent (ie, ≥ 5% incidence in either treatment group) PTs were COPD exacerbation (the only event reported at an incidence above 10%), headache, and nasopharyngitis. The percentage of patients with COPD exacerbation in the aclidinium treatment arms was lower than in the placebo arm.

TEAEs in the aclidinium bromide treatment groups that were reported at an incidence of at least 3% and greater than placebo by 1% were headache and nasopharyngitis, although the incidence of each was quite low for all groups.

Table 8.4.2–1. Treatment-Emergent Adverse Events by Preferred Term With an Incidence of ≥ 2% in Any Treatment Group: Double-blind, Placebo-controlled Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD

Preferred term	***Placebo***	***Aclidinium bromide***	
	BID N = 641 190.6 PY n (%)	*200 µg BID N = 644 199.4 PY n (%)*	*400 µg BID N = 636 198.4 PY n (%)*
Patients with at least 1 TEAE	344 **(53.7%)**	321 **(49.8%)**	319 **(50.2%)**
COPD (exacerbation)	100 **(15.6%)**	77 **(12.0%)**	75 **(11.8%)**
Headache	32 **(5.0%)**	43 **(6.7%)**	42 **(6.6%)**
Nasopharyngitis	25 **(3.9%)**	40 **(6.2%)**	35 **(5.5%)**
Cough	14 **(2.2%)**	17 **(2.6%)**	19 **(3.0%)**
Diarrhea	9 **(1.4%)**	12 **(1.9%)**	17 **(2.7%)**
Hypertension	16 **(2.5%)**	8 **(1.2%)**	10 **(1.6%)**
Back pain	12 **(1.9%)**	18 **(2.8%)**	8 **(1.3%)**
Bronchitis	13 **(2.0%)**	5 **(0.8%)**	7 **(1.1%)**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

TEAEs that occurred in at least 2% of patients in any treatment group in the long-term safety studies are summarized by PT in Table 8.4.2–2. TEAE incidence by PT in the double-blind, long-term safety studies was similar for the two aclidinium bromide treatment groups (200 µg BID and 400 µg BID). The most frequently reported event was COPD exacerbation (21.2% and 20.5%, respectively). All other individual events in the double-blind studies were reported at incidences < 6%. TEAEs reported with an incidence > 3% in either treatment group were nasopharyngitis, upper respiratory tract infection, sinusitis, headache, cough, urinary tract infection, and nausea. Incidences for these events were generally similar in the open-label, long-term Study 38 (B).

Table 8.4.2–2. Treatment-Emergent Adverse Events by Preferred Term With an Incidence of ≥ 2% in Any Treatment Group: Long-term Safety Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD

Preferred Term	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Patients with at least 1 TEAE	300 (**67.0%**)	304 (**68.8%**)	289 (**64.5%**)
COPD (exacerbation)	95 (**21.2%**)	91 (**20.5%**)	81 (**18.1%**)
Nasopharyngitis	24 (**5.4%**)	25 (**5.6%**)	21 (**4.7%**)
Sinusitis	22 (**4.9%**)	16 (**3.6%**)	19 (**4.2%**)
Upper Respiratory Tract Infection	20 (**4.5%**)	16 (**3.6%**)	26 (**5.8%**)
Cough	19 (**4.2%**)	16 (**3.6%**)	10 (**2.2%**)
Headache	15 (**3.3%**)	15 (**3.4%**)	13 (**2.9%**)
Urinary Tract Infection	13 (**2.9%**)	15 (**3.4%**)	11 (**2.5%**)
Back pain	9 (**2.0%**)	14 (**3.2%**)	10 (**2.2%**)
Arthralgia	10 (**2.2%**)	13 (**2.9%**)	—
Bronchitis	11 (**2.5%**)	11 (**2.5%**)	12 (**2.7%**)
Oedema peripheral	8 (**1.8%**)	11 (**2.5%**)	—
Contusion	6 (**1.3%**)	10 (**2.3%**)	—
Diarrhea	7 (**1.6%**)	9 (**2.0%**)	10 (**2.2%**)
Pneumonia	13 (**2.9%**)	9 (**2.0%**)	—
Dry mouth	4 (**0.9%**)	9 (**2.0%**)	—
Nausea	17 (**3.8%**)	8 (**1.8%**)	14 (**3.1%**)
Hypertension	12 (**2.7%**)	8 (**1.8%**)	12 (**2.7%**)
Insomnia	9 (**2.0%**)	8 (**1.8%**)	—
Dyspnea	13 (**2.9%**)	7 (**1.6%**)	9 (**2.0%**)
Constipation	13 (**2.9%**)	7 (**1.6%**)	—
Rash	9 (**2.0%**)	7 (**1.6%**)	—
Blood glucose increased	11 (**2.5%**)	5 (**1.1%**)	—
Fall	10 (**2.2%**)	4 (**0.9%**)	—
Gastroesophageal reflux disease	11 (**2.5%**)	4 (**0.9%**)	—
Abdominal pain	9 (**2.0%**)	3 (**0.7%**)	—
Dizziness	10 (**2.2%**)	2 (**0.5%**)	—
Fatigue	9 (**2.0%**)	—	—

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.3 All-Cause Mortality in Placebo-controlled and Long-term Safety Studies

Overall, the all-cause mortality rate for all treatment groups was approximately 0.5%. This includes the deaths from BID development program, as well as the 52-week QD program (placebo and aclidinium bromide 200 µg). The selection criteria for the QD studies were very similar to the BID studies, and therefore, this group represents a well-matched control population for comparison.

Deaths Occurring During Treatment and up to 30 Days After Stopping Investigational Product

A total of 30 deaths in the Safety Population (occurring during treatment and up to 30 days after stopping investigational product) were reported in the entire aclidinium bromide development program. Of these 30 deaths, 13 deaths were reported in the BID program: 6 deaths in the placebo-controlled studies and 7 deaths in the BID long-term safety studies. 17 deaths were reported in the QD studies. None of the 30 deaths were judged by the investigators to be related to investigational product.

Deaths Occurring More Than 30 Days After Stopping Investigational Product

A total of 8 deaths in the Safety Population (occurring more than 30 days after stopping investigational product) were reported: 4 deaths in the BID studies (1 [aclidinium bromide 200 µg], 3 [aclidinium bromide 400 µg]), and 4 deaths in the QD studies (2 [placebo], 2 [aclidinium bromide 200 µg]). None of the 8 deaths were judged by the investigators to be related to investigational product.

The all-cause mortality rates for the QD and BID studies are presented in Table 8.4.3-1. The incidence of death was low, and similar for aclidinium bromide 200 µg QD and BID and aclidinium bromide 400 µg BID compared to placebo.

In the long-term safety studies (BID), mortality was lower when compared to the placebo arm of the 1-year QD studies for both the aclidinium bromide 200 µg and aclidinium bromide 400 µg treatment arms.

Table 8.4.3–1. All Cause Mortality Rates for Deaths in QD and BID Studies—Safety Populations

Studies	***Placebo***	***Aclidinium bromide***	
		200 µg (QD)	*400 µg QD*
QD studies (30 and 31)	N = 420 n (%)	N = 1227 n (%)	Not tested
	5 **(1.2)**	11 **(0.9)**	
BID studies (33, 34, and 38 (A)	Placebo	***Aclidinium bromide***	
		200 µg (BID)	400 µg (BID)
	N = 641 n (%)	N = 644 n (%)	N = 636 n (%)
	2 **(0.3)**	1 **(0.2)**	3 **(0.5)**
BID studies (35, 36, and 38 (B)	Placebo	***Aclidinium bromide***	
		200 µg (BID)	400 µg (BID)
	Not tested	N = 448 n (%)	N = 891 n (%)
		2 **(0.4)**	5 **(0.6)**

Note: this table includes the number of deaths occurring during treatment and up to 30 days after stopping investigational product. There was 1 on-treatment death (aclidinium bromide 200 µg) in QD Phase 2 short-term 3-period (7-day) crossover Study 25. This death is not included in the table.

BID = twice daily; QD = once daily

Table 8.4.3–2 presents the frequency of death (on-treatment) by time interval in the BID and QD studies. There appears to be no cluster of mortality at any time point.

Table 8.4.3–2. Frequency of All-Cause Mortality by Time Interval (Days) to Death in BID and QD Studies—Safety Populations

Treatment Group	***Time Interval to Death (Days)***			
	0-99	*100-199*	*200-299*	*≥ 300*
Placebo QD (N = 420)	2	1	2	—
Aclidinium bromide 200 µg QD (N = 1227)	3	2	2	4
Placebo BID (N = 641)	2	—	—	—
Aclidinium bromide 200 µg BID (N = 1212)	—	2	—	1
Aclidinium bromide 400 µg BID (N = 1642)	4	—	3	1

Note: 1 death (aclidinium bromide 200 µg) which occurred in QD Phase 2 short-term 3-period (7-day) crossover Study 25 is not included in this table. There were no deaths in the BID short-term crossover studies.

QD studies were 30 and 31; BID studies were 33, 34, 38 (A), 38 (B), 35, and 36.

BID = twice daily; QD = once daily

Listings of the deaths by treatment group are presented in Table 8.4.3–3 (BID placebo-controlled studies), Table 8.4.3–4 (BID long-term safety studies), and Table 11.2–12 (Phase 1 to 3 QD studies). Mini-narratives for patients who died in the BID studies are presented in Section 11.1 of Appendix I.

In the BID program, all death cases within 30 days after the last dose of the study medication were retrieved and converted into a blinded format so that an external independent adjudication committee comprised of practicing academic cardiologists could review and evaluate the cause of death in order to identify all CV deaths. Of the 13 deaths, 5 deaths were judged by the committee to be CV deaths. The Adjudication Committee results are included in the tables below. Further information is provided in the MACE analysis in Section 8.4.6.1.

Table 8.4.3–3. Deaths Occurring in the Double-blind, Placebo-controlled Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD (Studies 33, 34, and 38 [A])

Treatment Group	*Study Number*	*Patient Number*	*Age/Sex*	*Duration of Treatment*	*Time to Death*	*Cause of Death Preferred Term*	*Adjudicated Clinical Diagnosis*
All deaths occurring during the treatment period							
Placebo (N = 641)[a]	34	1194.02	78/M	33 days	33 days	Road traffic accident	Non-CV (Trauma)
	38 (A)	108038003	49/M	43 days	48 days	Death[b]	Indeterminate[c]
Aclidinium bromide 200 µg (N = 644)[a]	34	2326.10	71/M	105 days	105 days	Myocardial infarction	CV Sudden cardiac death
Aclidinium bromide 400 µg (N = 636)[a]	33	114233015	65/M	23 days	23 days	Lung cancer metastatic	Non-CV (Lung cancer)
	34	1267.05	56/F	91 days	91 days	Cardiac failure acute	CV Sudden cardiac death
	38 (A)	135438005	56/M	28 days	55 days[d]	Cardio-respiratory arrest[c]	Non-CV (Respiratory failure)

a Number of patients in the treatment group in Studies 33, 34 and 38 (A).

b The patient was found dead (unwitnessed) at home.

c Available patient data were insufficient to judge the death as cardiovascular-related.

d The death occurred 27 days after stopping investigational product.

BID = twice daily; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; IP = investigational product.

Table 8.4.3–4. Deaths Occurring in the Long-Term Safety Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD (Studies 35, 36, and 38 [B])

Treatment Group	*Study Number*	*Patient Number*	*Age/Sex*	*Duration of Treatment*	*Time to Death*	*Cause of Death Preferred Term*	*Adjudicated Clinical Diagnosis*
All deaths occurring during the treatment period							
Aclidinium bromide 200 µg (N = 448)[a]	35	132735009	68/M	355 days	366 days	Biliary sepsis	Non-CV (Cancer/sepsis)
	36	115533001	56/M	193 days	193 days	Multiple drug overdose accidental	Non-CV (Drug overdose)
Aclidinium bromide 400 µg (N = 891)[a]	35	208235013	72/M	258 days	281 days	Subarachnoid hemorrhage	CV (Stroke)
	36	114133006	70/F	354 days	354 days	esophagitis	Non-CV (esophageal disease)
	38 (B)	136638011	48/F	262 days	263 days	Cardiac arrest	CV (Sudden death, arrhythmia)
	38 (B)	145038007	51/F	281 days	282 days	Cardiac arrest	CV Sudden death
	38 (B)	145138001	51/M	97 days	97 days	Cardio-respiratory arrest	Non-CV (Methamphetamine overdose)

a Number of patients in the treatment group Studies 35, 36 and 38 (B).

BID = twice daily; COPD = chronic obstructive pulmonary disease; CV = cardiovascular; IP = investigational product.

8.4.4 Serious Adverse Events

Placebo-controlled Studies

The overall incidence of non-fatal SAEs was similar in the aclidinium bromide 200 µg and 400 µg groups compared with placebo (2.2% and 2.4% vs 3.1%, respectively). The most frequently reported SAE was COPD (exacerbation) which was reported at a lower incidence in the aclidinium treatment groups compared to placebo (2.7% placebo, 1.4% aclidinium bromide 200 µg, and 1.6% aclidinium bromide 400 µg) (Table 8.4.4–1).

SAEs of suicidal ideation (1 [0.2%] in placebo; 2 [0.3%] in aclidinium bromide 200 µg, and 1 [0.2%] in aclidinium bromide 400 µg), bipolar disorder (2 [0.3%]) and depression (2 [0.3%]) in aclidinium bromide 200 µg were noted. The actual incidences of these CNS events were low and did not suggest a dose relationship or causal relationship with the study drug. As per Table 11.2–18 in Appendix I, approximately 24% of the patient population in both studies 33 and 38 (A) and approximately 3% of the population in Study 34 had reported a medical history of depression which could be the underlying cause of the reported events.

There were also 2 (0.3%) events of lung neoplasm reported in the aclidinium bromide 200 µg arm; none were reported in either the placebo arm or the aclidinium bromide 400 µg arm. In studies 33 and 38 (A), 1.7% to 3.7% of the patient population had reported lung neoplasm as medical history. Neoplasms in general also take an extensive period of time to develop, and so there is no likely basis for a causal relationship between the study drug and the reported events of lung neoplasms.

Table 8.4.4–1. Serious Adverse Events by Preferred Term in ≥ 2 Patients in Any Treatment Group: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Preferred terms	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg* *BID* *N = 644* *199.4 PY* *n (%)*	*400 µg* *BID* *N = 636* *198.4 PY* *n (%)*
Patients with at least 1 SAE[a]	20 (**3.1%**)	14 (**2.2%**)	15 (**2.4%**)
COPD (exacerbation)	17 **(2.7%)**	9 **(1.4%)**	10 **(1.6%)**
Acute respiratory failure	1 **(0.2%)**	—	2 **(0.3%)**
Cardiac failure congestive	—	—	2 **(0.3%)**
Angina pectoris	—	2 **(0.3%)**	1 **(0.2%)**
Pneumonia	2 **(0.3%)**	—	1 **(0.2%)**
Suicidal ideation	1 **(0.2%)**	2 **(0.3%)**	1 **(0.2%)**
Lung adenocarcinoma	—	2 **(0.3%)**	—
Bipolar disorder	—	2 **(0.3%)**	—
Depression	—	2 **(0.3%)**	—

a Includes non-fatal events only.

Note: Patients 204133001 and 208233001 both experienced the SAEs Bipolar Disorder, Depression, and Suicidal Ideation. As a result, the SAEs of Bipolar Disorder, Depression, and Suicidal Ideation are counted twice.

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SAE = serious adverse event.

Studies 33, 34, and 38 (A).

SERIOUS ADVERSE EVENTS IN QD PLACEBO-CONTROLLED STUDIES 30 AND 31

SAEs that occurred in at least 2 patients in any treatment group in QD studies 30 and 31 are summarized by preferred term in Table 11.2–13. The overall frequency of SAEs for aclidinium bromide was similar to placebo (8.8% vs 9.8%, respectively).

The most frequently occurring SAEs (i.e., ≥3 patients) with a higher incidence in the aclidinium bromide group compared to placebo were lobar pneumonia (0.3% vs 0.2%, respectively), pulmonary embolism (0.2% vs 0.0%), acute myocardial infarction (0.2% vs 0.0%), and angina unstable (0.2% vs 0.0%).

Please note that COPD (exacerbations) were not reported as SAEs in studies 30 and 31, except in case of fatal or life-threatening events, thus the number of serious COPD (exacerbations) are understated.

Long-term Safety Studies

SAEs (non-fatal events) that occurred in at least 2 patients in any treatment group in the long-term safety studies are summarized by PT in Table 8.4.4–2. Overall, the SAE rates for patients in the aclidinium bromide treatment groups were comparable: 5.1% for the 200 µg BID group and 5.4% for the 400 µg BID group in the combined safety populations of Studies 35 and 36, and 5.6% in open-label Study 38 (B) (aclidinium bromide 400 µg arm only).

The most frequently reported non-fatal SAE was COPD (exacerbation) and the incidence was similar in the aclidinium bromide 400 µg BID groups in the double-blind and open-label studies compared with the aclidinium bromide 200 µg BID group (2.9% and 3.1% vs 2.2%, respectively). The remainder of the SAEs in the double-blind controlled studies occurred infrequently (generally < 1%) and are summarized in Table 8.4.4–2. Overall, the SAE profile was similar between 200 µg BID and 400 µg BID doses. Likewise, the open-label long-term safety study revealed a low rate of SAEs, and did not reveal any unexpected events.

In the double-blind, long-term safety studies, there were two patients (0.5%) with a PT of acute renal failure in the 400 µg BID group and none in the 200 µg BID group. Also observed was a higher incidence for congestive cardiac failure and for acute myocardial infarction in the aclidinium bromide 400 µg BID group compared with the aclidinium bromide 200 µg BID group. Further information on myocardial infarction is presented in Section 8.4.6.1 (MACE) and cardiac failure in Section 8.4.6.2.1 (Cardiac Failure standardized MedDRA query [SMQ]).

Table 8.4.4–2. Serious Adverse Events in ≥ 2 Patients by Preferred Term in Any Treatment Group: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term, Safety Studies

Preferred Term	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Patients with at least 1 SAE[a]	23 (**5.1%**)	24 (**5.4%**)	25 (**5.6%**)
COPD (exacerbation)	10 (**2.2%**)	13 (**2.9%**)	14 (**3.1%**)
Pneumonia	6 (**1.3%**)	4 (**0.9%**)	2 (**0.4%**)
Respiratory failure	1 (**0.2%**)	3 (**0.7%**)	—
Acute myocardial infarction[b]	4 (**0.9%**)	3 (**0.7%**)	2 (**0.4%**)
Angina pectoris	—	2 (**0.5%**)	—
Dehydration	1 (**0.2%**)	2 (**0.5%**)	—
Colitis	—	2 (**0.5%**)	—
Renal failure	—	2 (**0.5%**)	1 (**0.2%**)
Coronary artery disease	2 (**0.4%**)	1 (**0.2%**)	4 (**0.9%**)
Anemia	—	1 (**0.2%**)	2 (**0.4%**)
Cardiac failure congestive	—	1 (**0.2%**)	2 (**0.4%**)
Pneumothorax	2 (**0.4%**)	1 (**0.2%**)	—
Cerebrovascular accident	—	—	2 (**0.4%**)
Non-cardiac chest pain	—	—	2 (**0.4%**)
Acute coronary syndrome	2 (**0.4%**)	—	—
Constipation	2 (**0.4%**)	—	—
Hematuria	2 (**0.4%**)	—	—

a Includes non-fatal events only.

b Includes 2 patients with the preferred term of "myocardial infarction" in the aclidinium bromide 200 µg group in the double-blind, long-term safety studies

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.5 Adverse Events Leading to Treatment Discontinuation (ADO)

Placebo-controlled Studies

The rate of discontinuation due to AEs was slightly higher for the placebo group than for the active treatment groups. The most common ADO was COPD exacerbation, and was likewise somewhat higher in the placebo group than in either treatment group (Table 8.4.5–1)

Table 8.4.5–1. Adverse Events Leading to Treatment Discontinuation in ≥ 2 Patients by Preferred Term in Any Treatment Group: Double-blind, Placebo-controlled Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD

System Organ Class ***Preferred Term***	***Placebo*** ***BID*** ***N = 641*** ***190.6 PY*** ***n (%)***	***Aclidinium Bromide***	
		200 µg *BID* *N = 644* *199.4 PY* *n (%)*	*400 µg* *BID* *N = 636* *198.4 PY* *n (%)*
Number (%) of Patients with at least 1 ADO[a]	31 **(4.8%)**	26 **(4.0%)**	27 **(4.2%)**
COPD (exacerbation)	16 **(2.5%)**	9 **(1.4%)**	12 **(1.9%)**
Dyspnea	3 **(0.5%)**	1 **(0.2%)**	3 **(0.5%)**
Dizziness	2 (**0.3%**)	—	—
Ventricular tachycardia	1 (**0.2%**)	—	2 (**0.3%**)

a Includes non-fatal events only.

AB = aclidinium bromide; ADO = adverse event leading to dropout; BID = twice daily; COPD = chronic obstructive pulmonary disease.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

ADO rates (non-fatal events) for patients in the aclidinium bromide treatment groups were similar for the 200 µg and 400 µg BID groups in the double-blind studies as well as for the aclidinium bromide 400 µg BID dose in the open-label study (Table 8.4.5–2).

Other than COPD exacerbation, discontinuation rates due to AEs in the aclidinium bromide 200 µg and 400 µg BID treatments groups in the long-term safety studies were ≤ 0.5% by PT. No dose-response was observed in the incidence of ADOs.

For COPD exacerbations, the rates of withdrawal in the long-term studies were comparable to the rate for placebo (ie, 2.5%) in the placebo-controlled Phase 3 studies.

Table 8.4.5–2. Adverse Events Leading to Permanent Treatment Discontinuation in ≥ 2 Patients by Preferred Term in Either Treatment Group: Long-term Safety Studies of Aclidinium Bromide Administered Twice Daily to Patients With COPD

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Number (%) of patients with at least 1 ADO[a]	46 (**10.3%**)	39 (**8.8%**)	29 (**6.5%**)
COPD (exacerbation)	13 (**2.9%**)	10 (**2.3%**)	8 (**1.8%**)
Cough	—	2 (**0.5%**)	2 (**0.4%**)
Headache	—	2 (**0.5%**)	—
Pruritus	1 (**0.2%**)	2 (**0.5%**)	—
Syncope	—	2 (**0.5%**)	—
Non-cardiac chest pain	1 (**0.2%**)	1 (**0.2%**)	2 (**0.4%**)
Fatigue	2 (**0.4%**)	—	—
Dizziness	2 (**0.4%**)	—	—
Dyspnea	1 (**0.2%**)	—	2 (**0.4%**)
Acute myocardial infarction	—	—	2 (**0.4%**)

a Includes non-fatal events only.

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.6 Treatment-Emergent Adverse Events of Special Interest

8.4.6.1 Major Adverse Cardiac Events (MACE) Analysis Results

Two analyses were performed to evaluate the overall CV risk of the drug. The 2 analyses are:

1. Analysis of MACE

2. Analysis of CV events of interest based on standard MedDRA queries (SMQs)

MACE and events of interest were analyzed and presented from the pooled Phase 3 placebo-controlled studies (BID Group 1A), the double-blind long-term safety studies (35 and 36) and the open-label, long-term safety study (38 [B]).

MACE search criteria included:

a. All death cases during treatment and within 30 days after the last dose of the study medication were retrieved and converted into a blinded format. An expert external adjudication committee evaluated all deaths to identify CV deaths. The external adjudication results are in Section 8.4.3 (All-Cause Mortality) in Table 8.4.3–3 and Table 8.4.3–4.

b. Myocardial infarction was defined as any non-fatal case that was coded to the PT in the MedDRA SMQ “myocardial infarction.”

c. Stroke was defined as any non-fatal case that was coded to the PT in the MedDRA SMQ “central nervous system hemorrhages and cerebrovascular conditions.”

Cardiovascular Death Assessment Methodology
All death cases reported while on treatment in the BID program were retrieved, blinded, and forwarded for independent review to an external adjudication committee of practicing, academic cardiologists consisting of one committee chair and two members. The two committee members were asked to identify whether the death was a CV death and also provide a clinical diagnosis.

Once the assessment results were collated, any death cases with discrepant assessments were reviewed by the committee chair who then discussed the discrepant cases with the two members and made a final unified assessment. Only the death cases assessed as CV death were included in the calculation of the MACE Composite.

The MACE Composite is the total of CV death, non-fatal myocardial infarction and non-fatal stroke within that specific dosing group.

Placebo-controlled Studies

Overall, the incidence of MACE was extremely low in this clinical program, particularly when considering the generally compromised health status of the study population, and the many risk factors that COPD patients have for MACE. In the placebo-controlled safety pool, the incidence of MACE in the aclidinium bromide 200 µg and 400 µg treatment groups was comparable to the incidence in the placebo group.

Table 8.4.6.1–1 presents the number of patients with serious major adverse cardiovascular events along with the MACE Composite. The actual incidences were very low and did not demonstrate any safety signal. The MACE Composite was similar between the placebo group (2; 0.3%), the aclidinium bromide 200 µg group (2; 0.3%) and the aclidinium bromide 400 µg group (2; 0.3%). As per Table 11.2–18 in Appendix I, approximately 25% of the study population in all 3 placebo-controlled double-blind studies had reported some type of medical history of cardiac disorders such as coronary artery disease and myocardial infarction, approximately 50% had reported hypertension, and 1.8% to 9.1% had reported obesity; any of these histories could have predisposed to the reported events.

Please note in the nonfatal stroke category in Table 8.4.6.1–1, 1 patient with the PT of "transient ischemia attack" was included in the aclidinium bromide 200 µg group. Removing this patient from the total MACE composite would result in an adjusted total MACE composite of 1 (0.2%) in the 200 µg group.

Table 8.4.6.1–1. Number (%) of Patients With Major Adverse Cardiovascular Events (Serious Events Only) and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Event	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)* *[per 1000 PY]*	*200 µg BID* *N = 644* *199.4 PY* *n (%)* *[per 1000 PY]*	*400 µg BID* *N = 636* *198.4 PY* *n (%)* *[per 1000 PY]*
MACE composite	2 (0.3) **[10.5]**	2 (0.3) **[10.0]**	2 (0.3) **[10.1]**
CV death	—	1 (0.2) **[5.0]**	1 (0.2) **[5.0]**
Nonfatal myocardial infarction	1 (0.2) **[5.2]**	—	—
Nonfatal stroke[a]	1 (0.2) **[5.2]**	1 (0.2) **[5.0]**	1 (0.2) **[5.0]**

a Transient ischemia attack was included in the non-fatal stroke category for 1 patient in the aclidinium bromide 200 µg group.

COPD = chronic obstructive pulmonary disease; CV = cardiovascular; BID = twice daily; MACE = major adverse cardiovascular events; PY = patient-years of exposure.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

Table 8.4.6.1–2 presents the number of patients with serious MACE along with the incidence of serious events per 1000 years of patient exposure in both the double-blind, long-term safety studies and the open-label, long-term safety study. The actual incidences of MACE were low in both long-term safety pools and did not suggest any safety signal.

The MACE Composite in the double-blind, long-term studies was lower in the aclidinium bromide 400 µg BID group (6; 1.4%) compared to the aclidinium bromide 200 µg groups (7: 1.6%) suggesting no dose dependency. There was only one CV death identified in the aclidinium bromide 400 µg BID group in these double-blind studies.

The MACE Composite in the open-label, long-term study was also low (7; 1.6%) and there were 2 CV deaths identified in the open-label aclidinium bromide 400 µg BID group.

Please note that in the nonfatal stroke category in Table 8.4.6.1–2, 2 patients with the PT of “carotid artery stenosis” were included: 1 patient in the aclidinium bromide 200 µg group in the double-blind, long-term safety studies and 1 patient in the aclidinium bromide 400 µg group in the open-label, long-term safety study. Additionally, in the nonfatal stroke category in Table 8.4.6.1–2, 1 patient with the PT of “transient ischemia attack” in the aclidinium bromide 400 µg group in the double-blind, long-term safety studies was included. Removing these 3 patients from the total MACE composite would result in an adjusted total MACE composite of 6 (1.3%) and 5 (1.1%) for the 200 µg and 400 µg groups in the double-blind, long-term safety studies, respectively, and 6 (1.3%) for the 400 µg group in the open-label long-term safety study.

The general COPD population is known to have various CV risk factors and it is not uncommon for this population to experience MACE. As a frame of reference, Table 11.2–9 to Table 11.2–11 in Appendix I present the incidence of CV events of interest (per 1000 patient-years of exposure) in the general COPD population based on prior population-based studies.

As shown in Table 11.2–19 in Appendix I, approximately 26% of the study population in both the double-blind and open-label long-term studies had reported a medical history of some type of cardiac disorder such as coronary artery disease (approximately 11%) and myocardial infarction (approximately 6.5%); approximately 52% had reported hypertension; 1.8% to 9.1% had reported obesity; and approximately 10% to 18% had reported a medical history of diabetes mellitus, diabetes mellitus type II or hyperglycemia. All of these conditions could be pre-existing risk factors or underlying causes for the reported events (Table 11.2–19).

Table 8.4.6.1–2. Number (%) of Patients With Major Adverse Cardiovascular Events (Serious Events Only) and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%) [per 1000 PY]	**400 µg BID N = 443 341.9 PY n (%) [per 1000 PY]**	**400 µg BID N = 448 302.3 PY n (%) [per 1000 PY])**
MACE composite	7 (1.6%) [**20.6**]	6 (1.4%) [**17.5**]	7 (1.6%) [**23.2**]
CV death	—	1 (0.2%) [**2.9**]	2 (0.4%) [**6.6**]
Non-fatal myocardial infarction	5 (1.1%) [**14.7**]	3 (0.7%) [**8.8**]	2 (0.4%) [**6.6**]
Non-fatal stroke[a]	2 (0.4%) [**5.9**]	2 (0.5%) [**5.8**]	4 (0.9%) [**13.2**]

a Carotid artery stenosis was included in the non-fatal stroke category for 2 patients: 1 patient in the aclidinium bromide 200 µg group in the double-blind long-term safety studies and 1 patient in the aclidinium bromide 400 µg group in the open-label, long-term safety study. Transient ischemia attack was included in the non-fatal stroke category for 1 patient in the aclidinium bromide 400 µg in the double-blind, long-term safety studies.

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.6.2 Analysis of Cardiac Events of Interest Based on Standardized MedDRA Queries

At the FDA's request, the combined occurrence rates of myocardial infarction, atrial fibrillation, angina, congestive heart failure, and tachycardia, the following SMQs were selected to analyze the incidence for those events. In addition, bradycardia and conduction defects were also analyzed.

Events of Interest	***Search Criteria Used***
	SMQ Ischemic Heart Disease
Myocardial infarction	SMQ Myocardial infarction
Angina	SMQ Other ischemic heart disease
Tachycardia/atrial fibrillation	SMQ Supraventricular tachyarrhythmias
Congestive heart failure	SMQ Cardiac failure
Bradycardia and conduction defects	*SMQ Bradyarrhythmia including conduction defects and disorders of sinus node function*
Conduction defects	SMQ Conduction defects

SMQ Myocardial infarction and SMQ Other ischemic heart disease fall under the parent SMQ of Ischemic heart disease.

SMQ Conduction defects falls under the parent SMQ of Bradyarrhythmia including conduction defects and disorders of sinus node function.

SMQ = standardized MedDRA query.

Placebo-controlled Studies

Table 8.4.6.2–1 presents the number of patients with serious TEAEs of cardiac disorders along with the incidence of serious events per 1000 years of patient exposure. The incidence of serious cardiac events was extremely low in this clinical program, and the small numbers do not suggest a cardiac safety signal or dose dependent cardiac AEs. However, cardiac failure and bradyarrhythmia/conduction defects/sinus node disorders will be discussed further in Section 8.4.6.2.1 and Section 8.4.6.2.2, respectively.

Table 8.4.6.2–1. Number (%) of Patients With Serious Treatment-Emergent Adverse Events of Cardiac Disorders by Specific SMQ Category and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

SMQ Category	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)* *[per 1000 PY]*	*200 µg BID* *N = 644* *199.4 PY* *n (%)* *[per 1000 PY]*	*400 µg BID* *N = 636* *198.4 PY* *n (%)* *[per 1000 PY]*
Supraventricular tachyarrhythmias	1 (0.2) **[5.2]**	—	—
Bradyarrhythmia/conduction defects/sinus node disorders	—	—	1 (0.2) **[5.0]**
Ischemic heart disease			
Myocardial infarction	1 (0.2) **[5.2]**	1 (0.2) **[5.0]**	—
Other ischemic heart disease	1 (0.2) **[5.2]**	3 (0.5) **[15.0]**	1 (0.2) **[5.0]**
Cardiac failure	1 (0.2) **[5.2]**	1 (0.2) **[5.0]**	3 (0.5) **[15.1]**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SMQ = standardized MedDRA query.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

As with the placebo-controlled studies, both long-term safety programs showed similarly small numbers of cardiac events over a period of at least one year and no CV safety signal was identified. Table 8.4.6.2–2 presents the number of patients with serious TEAEs of cardiac disorders along with the incidence of serious events per 1000 years of patient exposure. Cardiac failure and bradyarrhythmia/conduction defects/sinus node disorders will be discussed further in Section 8.4.6.2.1 and Section 8.4.6.2.2.

Table 8.4.6.2–2. Number (%) of Patients With Serious Treatment-Emergent Adverse Events of Cardiac Disorders by Specific SMQ Category and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%) [per 1000 PY]	**400 µg BID N = 443 341.9 PY n (%) [per 1000 PY]**	**400 µg BID N = 448 302.3 PY n (%) [per 1000 PY]**
Supraventricular tachyarrhythmias	—	2 (0.5%) **[5.8]**	—
Bradyarrhythmia/conduction defects/sinus node disorders	1 (0.2%) **[2.9]**	—	—
Myocardial infarction	5 (1.1%) **[14.7]**	3 (0.7%) **[8.8]**	2 (0.4%) **[6.6]**
Other ischemic heart disease	3 (0.7%) **[8.8]**	3 (0.7%) **[8.8]**	5 (1.1%) **[16.5]**
Cardiac failure	1 (0.2%) **[2.9]**	2 (0.5%) **[5.8]**	2 (0.4%) **[6.6]**

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure.
Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

As per Table 11.2–19 in Appendix I, approximately 26% of the study population in both the double-blind and open-label long-term studies had reported a medical history of some type of cardiac disorder such as coronary artery disease (approximately 11%) and myocardial infarction (approximately. 6.5%), and approximately 52% had reported hypertension and may signal preexisting disease contributing to events.

Approximately 3% of the study population in each treatment group in both the double-blind long-term studies and the open-label, long-term study had reported a medical history of atrial fibrillation. Only two incidences of SMQ supraventricular tachyarrhythmias (tachycardia/atrial fibrillation) occurred in the aclidinium bromide 400 µg group, and no incidences were reported in the aclidinium bromide 200 µg group. However, the incidence rate was low (2; 0.5%) and could have been due to chance. There were also no incidences reported in the open-label, long-term study in which patients also received aclidinium bromide 400 µg BID.

It should be noted that 8.5% of the aclidinium bromide 200 µg group had reported a medical history of myocardial infarction compared to 5.4% in the aclidinium bromide 400 µg group in the double-blind, long-term studies and 5.8% in the aclidinium bromide 400 µg group in the open-label, long-term study. The incidence rate of myocardial infarction was low and was higher in the aclidinium bromide 200 µg group (5; 1.1%) compared to the aclidinium bromide 400 µg group (3; 0.7%) suggesting no dose dependency in the double-blind, long-term studies. The incidence rate in the open-label, long-term study was also low (2; 0.4%).

The incidence rates of Other Ischemic heart diseases were also low and comparable between the aclidinium bromide 200 µg group (3; 0.7%) and the aclidinium bromide 400 µg group (3; 0.7%) suggesting no dose dependency in the double-blind, long-term safety studies. The incidence rate in the open label, long-term safety study for Other Ischemic heart disease was also low (5; 1.1%).

8.4.6.2.1 SMQ of Cardiac Failure

Placebo-controlled Studies

Table 8.4.6.2.1–1 presents the number of patients with serious TEAEs based on SMQ of cardiac failure along with the incidence of serious events per 1000 years of patient exposure. The rates were similar for all treatment groups.

It should be noted that all patients had a history of underlying CV conditions at baseline, thus increasing their risk for cardiac failure.

Table 8.4.6.2.1–1. Number (%) of Patients With Serious Treatment-Emergent Adverse Events Based on SMQ of Cardiac Failure and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

SMQ	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)* *[per 1000 PY]*	*200 µg BID* *N = 644* *199.4 PY* *n (%)* *[per 1000 PY]*	*400 µg BID* *N = 636* *198.4 PY* *n (%)* *[per 1000 PY]*
Cardiac failure	1 (0.2) **[5.2]**	1 (0.2) **[5.0]**	3 (0.5) **[15.1]**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SMQ = standardized MedDRA query.

Studies 33, 34, and 38 (A).

As per Table 11.2–18 in Appendix I, a greater percentage of patients had reported a medical history of congestive cardiac failure in the aclidinium bromide 400 µg group compared to the placebo group and the aclidinium bromide 200 µg group in all 3 placebo-controlled studies ([4.2%; 3.2%; 1.6%, respectively in Study 33], [3.3%; 1.5%; 1.8%, respectively in Study 34] and [2.8%; 1.1%; 1.1%, respectively in Study 38(A)]) which could also be the cause of the modestly higher observed rate in the aclidinium bromide 400 µg group.

Long-term Safety Studies

As with other cardiac events, the occurrence of serious cardiac failure occurred very infrequently in the long-term safety studies. The low incidence of events does not indicate a safety signal for congestive heart failure.

Table 8.4.6.2.1–1 presents the number of patients with serious TEAEs based on SMQ of cardiac failure along with the incidence of serious events per 1000 years of patient exposure for both the double-blind long-term studies and the open-label, long-term study. The incidence rates are comparable between the aclidinium bromide 200 µg group (1: 0.2%) compared to the aclidinium bromide 400 µg group (2; 0.5%) in the double-blind, long-term studies. The incidence was also low in the open-label, long-term study (2: 0.4%).

Table 8.4.6.2.1–2. Number (%) of Patients With Serious Treatment-Emergent Adverse Events Based on SMQ of Cardiac Failure and Events per 1000 Years of Exposure: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

SMQ	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%) [per 1000 PY]	**400 µg BID N = 443 341.9 PY n (%) [per 1000 PY]**	**400 µg BID N = 448 302.3 PY n (%) [per 1000 PY])**
Cardiac failure	1 (0.2%) **[2.9]**	2 (0.5%) **[5.8]**	2 (0.4%) **[6.6]**

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

All patients had a history of underlying CV conditions putting them at inherent risk for cardiac failure at baseline. As per Table 11.2–19 in Appendix I, there was a slightly higher rate of congestive cardiac failure reported as medical history by the patients in the aclidinium bromide 400 µg group (2.5%) in the double-blind, long-term studies compared to the aclidinium bromide 200 µg group (1.6%). The medical history rate of congestive cardiac failure reported in patients enrolled in the open-label, long-term study in the aclidinium bromide 400 µg group was 1.6%.

8.4.6.2.2 SMQ of Conduction Defects

Placebo-controlled Studies

The majority of the conduction defects were detected at baseline; however, the study drug was continued and there were no other associated serious cardiac events. None of the SMQs for conduction defects were considered serious by the investigators. During a comprehensive review of all subjects in the placebo-controlled studies, the mean changes from baseline in ECG parameters (PR, QRS, QT, and RR intervals) in all subjects showed no obvious between-group differences.

Table 8.4.6.2.2–1 presents nonserious conduction defects by PT that occurred in ≥ 2 patients in any treatment group in the placebo-controlled studies; there were no serious conduction defect events or serious QTc prolongation events reported. COPD patients in general are known to have underlying major cardiac conditions as cited earlier, and these conduction disorders are possibly due to those cardiac co-morbidities.

Table 8.4.6.2.2–1. Number (%) of Patients With Nonserious Treatment-Emergent Adverse Events by Preferred Term in ≥ 2 Patients in Conduction Defects SMQ: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

SMQ of Conduction Defects ***Preferred Term***	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg BID* *N = 644* *199.4 PY* *n (%)*	*400 µg BID* *N = 636* *198.4 PY* *n (%)*
Atrioventricular block first degree	1 **(0.2%)**	1 **(0.2%)**	4 **(0.6%)**
Electrocardiogram QT interval prolonged	2 **(0.3%)**	1 **(0.2%)**	2 **(0.3%)**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

The majority of the conduction defects were detected at baseline, however, the study drug was continued and there were no other associated serious cardiac events. None of the reported conduction defect events were considered to be serious in nature by the investigators.

Table 8.4.6.2.2–2 presents nonserious conduction defects by PT that occurred in ≥ 2 patients in any treatment group; there were no serious conduction defect events reported. None of the events showed dose-dependency in the double-blind, long-term safety studies.

Table 8.4.6.2.2–2. Number (%) of Patients With Nonserious Treatment-Emergent Adverse Events by Preferred Term in ≥ 2 Patients in Conduction Defects SMQ: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Bundle branch block left	6 (1.3%)	4 (0.9%)	1 (0.2%)
Atrioventricular block first degree	4 (0.9%)	2 (0.5%)	—
Electrocardiogram QT prolonged	2 (0.4%)	1 (0.2%)	1 (0.2%)
Bundle branch block right	3 (0.7%)	1 (0.2%)	—

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.6.3 Treatment-Emergent Nervous System Adverse Events

Placebo-controlled Studies

The SMQ of central nervous system hemorrhages and cerebrovascular conditions in the placebo-controlled studies revealed that there was a similar incidence of events in the placebo group compared to the 2 aclidinium bromide treatment arms. No signal for any potential dose dependency was observed (Table 8.4.6.3–1). There was no particular event that occurred more frequently to indicate a safety concern.

Table 8.4.6.3–1. Incidence of Serious and Nonserious Treatment-Emergent Adverse Events of Cerebrovascular Disorders by Specific SMQ by Preferred Term: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Specific SMQ Category ***Preferred term***	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg BID* *N = 644* *199.4 PY* *n (%)*	*400 µg BID* *N = 636* *198.4 PY* *n (%)*
SMQ—central nervous system hemorrhages and cerebrovascular conditions	3 **(0.5%)**	1 **(0.2%)**	**1 (0.2%)**
Cerebral hemorrhage	—	—	**1 (0.2%)**
Cerebral arteriosclerosis	1 **(0.2%)**	—	**—**
Cerebral ischemia	1 **(0.2%)**	—	**—**
Cerebrovascular accident	2 **(0.3%)**	—	**—**
Transient ischemia attack	—	1 **(0.2%)**	**—**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; SMQ = standardized MedDRA query; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A).

Long-term Safety Studies

In the double-blind, long-term safety studies, the incidences of cerebrovascular disorders were low and comparable between both the aclidinium bromide 200 µg (3; 0.7%) and aclidinium bromide 400 µg arm (4; 0.9%). The incidence of cerebrovascular disorders in the aclidinium bromide 400 µg arm in the open-label, long-term study was also low (5; 1.1%). There was no particular event that occurred more frequently to indicate an apparent safety concern (Table 8.4.6.3–2).

Table 8.4.6.3–2. Incidence of Serious and Nonserious Treatment-Emergent Adverse Events of Cerebrovascular Disorders by Specific SMQ: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Specific SMQ category ***Preferred Term***	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
SMQ—central nervous system hemorrhages and cerebrovascular conditions	3 (0.7%)	4 (0.9%)	5 (1.1%)
Carotid artery occlusion	—	2 (0.5%)	1 (0.2%)
Carotid artery disease	—	1 (0.2%)	—
Hemorrhagic stroke	—	1 (0.2%)	—
Transient ischemic attack	—	1 (0.2%)	—
Carotid artery stenosis	2 (0.4%)	—	2 (0.4%)
Cerebrovascular accident	1 (0.2%)	—	2 (0.4%)
Subarachnoid hemorrhage	—	1 (0.2%)	1 (0.2%)

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.6.4 Treatment-Emergent Respiratory, Thoracic and Mediastinal Adverse Events

Placebo-controlled Studies

Due to the mechanism of drug administration, oral inhalation, and the lung condition of COPD patients, the treatment-emergent respiratory, thoracic and mediastinal AEs were closely reviewed. The findings in the placebo-controlled studies are summarized in Table 8.4.6.4–1. Respiratory, thoracic, and mediastinal TEAEs, according to PT, that occurred in at least 1% of patients were dyspnea, COPD exacerbation, cough, and oropharyngeal pain. The incidences for all of these PTs in the aclidinium bromide treatment groups were comparable to placebo, with the exception of cough, which was slightly higher than placebo (2.6% aclidinium bromide 200 µg, 3.0% aclidinium bromide 400 µg, and 2.2% placebo).

Table 8.4.6.4–1. Serious and Nonserious Treatment-Emergent Respiratory, Thoracic, and Mediastinal Adverse Events by Preferred Term With an Incidence of ≥ 1% in any Treatment Group: Aclidinium Bromide Administered Twice Daily to Patient With COPD in Double-blind, Placebo-controlled Studies

Preferred Term	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg BID* *N = 644* *199.4 PY* *n (%)*	*400 µg BID* *N = 636* *198.4 PY* *n (%)*
Number (%) of Patients with at least 1 TEAE[a]	147 **(22.9%)**	117 **(18.2%)**	126 **(19.8%)**
COPD (exacerbation)	100 **(15.6%)**	77 **(12.0%)**	75 **(11.8%)**
Cough	14 **(2.2%)**	17 **(2.6%)**	19 **(3.0%)**
Dyspnea	11 **(1.7%)**	6 **(0.9%)**	9 **(1.4%)**
Oropharyngeal pain	10 **(1.6%)**	8 **(1.2%)**	7 **(1.1%)**

a In the Respiratory, Thoracic and Mediastinal System Organ Class

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A)

As the FDA had requested, combined incidences of pneumonia were analyzed. As shown in Table 8.4.6.4–2, pneumonia occurred at a similar rate in the placebo group (0.8%) compared to the aclidinium 200 µg (0.6%) and aclidinium 400 µg (0.3%) BID groups. Most of the events were mild/moderate in severity (placebo [3 moderate and 2 severe]; aclidinium bromide 200 µg BID [1 mild, 2 moderate, 1 severe] and aclidinium bromide 400 µg BID [1 moderate and 1 severe]), and none of the events were considered related to study drug. One subject who experienced bronchopneumonia while receiving aclidinium 200 µg had interrupted the study medication due to the event and 1 subject who experienced lobar pneumonia while receiving aclidinium 200 µg BID discontinued the study drug due to the event.

As COPD patients are at risk for developing pneumonia, the events were most probably due to the patient's underlying COPD.

Table 8.4.6.4–2. Incidence of Serious and Nonserious Treatment-Emergent Adverse Events of Pneumonia by Preferred Term: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Preferred Term	***Placebo***	***Aclidinium Bromide***	
	BID N = 641 190.6 PY n (%)	*200 µg BID N = 644 199.4 PY n (%)*	*400 µg BID N = 636 198.4 PY n (%)*
Number (%) of patients with at least 1 TEAE	5 **(0.8%)**	4 **(0.6%)**	2 **(0.3%)**
Pneumonia	3 **(0.5%)**	2 **(0.3%)**	2 **(0.3%)**
Bronchopneumonia	—	1 **(0.2%)**	—
Lobar pneumonia	1 **(0.2%)**	1 **(0.2%)**	—
Pneumonia viral	1 **(0.2%)**	—	—

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; TEAE = treatment-emergent adverse event.

Studies 33, 34, and 38 (A)

Long-term Safety Studies

Respiratory, thoracic, and mediastinal TEAEs, according to PT, that occurred in a least 1% of patients are listed in Table 8.4.6.4–3. Oropharyngeal pain was the only event that had a higher incidence in the aclidinium bromide 400 µg group (1.8% in both the double-blind and open-label long-term safety studies versus 1.3% in the aclidinium bromide 200 µg group in the double-blind long-term safety studies).

Table 8.4.6.4–3. Treatment-Emergent Respiratory, Thoracic, and Mediastinal Adverse Events by Preferred Term With an Incidence of ≥ 1% in any Treatment Group: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Number (%) of Patients with at least 1 TEAE	138 (30.8%)	133 (30.0%)	116 (25.9%)
COPD (exacerbation)	95 (21.2%)	91 (20.5%)	81 (18.1%)
Cough	19 (4.2%)	16 (3.6%)	10 (2.2%)
Dyspnea	13 (2.9%)	7 (1.6%)	9 (2.0%)
Oropharyngeal pain	6 (1.3%)	8 (1.8%)	8 (1.8%)
Dysphonia	6 (1.3%)	4 (0.9%)	3 (0.7%)

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

The double-blind long-term safety studies revealed a similar incidence of pneumonia-related TEAEs in the aclidinium bromide 200 µg BID group (3.1%) compared to the aclidinium bromide 400 µg group (2.9%). A numerically lower incidence of pneumonia was observed in the open-label long-term safety study (1.8%). A dose dependency was not observed (Table 8.4.6.4–4).

Table 8.4.6.4–4. Incidence of Serious and Nonserious Treatment-Emergent Adverse Events of Pneumonia by Preferred Term: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Patients with at least 1 pneumonia-related TEAE	14 (3.1%)	13 (2.9%)	8 (1.8%)
Pneumonia	13 (2.9%)	9 (2.0%)	5 (1.1%)
Lobar pneumonia	1 (0.2%)	2 (0.5%)	2 (0.4%)
Pneumonia bacterial	—	1 (0.2%)	—
Pneumonia pneumococcal	—	1 (0.2%)	—
Pneumonia primary atypical	—	1 (0.2%)	—
Eosinophilic pneumonia chronic	—	—	1 (0.2%)

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.4.6.5 Treatment-Emergent Potential Anticholinergic Adverse Events

Placebo-controlled Studies

Table 8.4.6.5–1 presents the potential anticholinergic TEAEs that occurred in 2 or more patients with an incidence greater than placebo. While there was no obvious dose-related incidence of anticholinergic events, generally, the aclidinium bromide BID groups showed slightly more anticholinergic events than placebo. The low rate observed in the program is indicative of the low systemic exposure demonstrated with aclidinium bromide BID.

Table 8.4.6.5–1. Incidence of Serious and Nonserious Treatment-Emergent Adverse Events of Anticholinergic Syndrome by Preferred Term Occurring in ≥2 Patients and With an Incidence Greater Than Placebo: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Double-blind, Placebo-controlled Studies

Category ***Preferred Term***	***Placebo***	***Aclidinium Bromide***	
	BID *N = 641* *190.6 PY* *n (%)*	*200 µg BID* *N = 644* *199.4 PY* *n (%)*	*400 µg BID* *N = 636* *198.4 PY* *n (%)*
Gastrointestinal disorders			
Dry mouth	4 **(0.6%)**	7 **(1.1%)**	5 **(0.8%)**
Dysphonia	—	2 **(0.3%)**	3 **(0.5%)**
Pharyngitis	4 **(0.6%)**	5 **(0.8%)**	2 **(0.3%)**
Renal and urinary disorders			
Urinary tract infection	6 **(0.9%)**	11 **(1.7%)**	6 **(0.9%)**
Dysuria	1 **(0.2%)**	—	2 **(0.3%)**
Urinary retention	—	—	1 **(0.2%)**
Cardiovascular disorders			
Tachycardia	—	1 **(0.2%)**	2 **(0.3%)**
Ventricular tachycardia	1 **(0.2%)**	1 **(0.2%)**	2 **(0.3%)**
Presyncope	1 **(0.2%)**	—	2 **(0.3%)**
Palpitations	1 **(0.2%)**	4 **(0.6%)**	1 **(0.2%)**
Heart rate increased	1 **(0.2%)**	2 **(0.3%)**	—
Other disorders			
Pyrexia	3 **(0.5%)**	2 **(0.3%)**	5 **(0.8%)**
Dizziness	5 **(0.8%)**	7 **(1.1%)**	4 **(0.6%)**

BID = twice daily; COPD = chronic obstructive pulmonary disease; PY = patient-years of exposure.
Studies 33, 34, and 38 (A).

Long-term Safety Studies

In the long-term studies, potential anticholinergic adverse events that occurred in > 1% of patients in either the aclidinium bromide 200 µg group or the aclidinium bromide 400 µg group had low incidences, and the incidences were generally comparable between the treatment groups in the double-blind, long-term studies (Table 8.4.6.5–2). The incidences were similarly low in the open-label, long-term study, and there is no apparent safety concern of causing potential anticholinergic adverse events.

Table 8.4.6.5–2. Incidence of Treatment-Emergent Adverse Events of Anticholinergic Syndrome by Preferred Term Occurring in ≥ 1% of Patients: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term Safety Studies

Preferred Term	***Aclidinium Bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 340.6 PY n (%)	**400 µg BID N = 443 341.9 PY n (%)**	**400 µg BID N = 448 302.3 PY n (%)**
Urinary tract infection	13 (2.9%)	15 (3.4%)	11 (2.5%)
Dry mouth	4 (0.9%)	9 (2.0%)	2 (0.4%)
Oropharyngeal pain	6 (1.3%)	8 (1.8%)	8 (1.8%)
Constipation	13 (2.9%)	7 (1.6%)	6 (1.3%)
Dysphonia	6 (1.3%)	4 (0.9%)	3 (0.7%)
Dizziness	10 (2.2%)	2 (0.5%)	7 (1.6%)

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation; PY = patient-years of exposure; SAE = serious adverse event.

Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).

8.5 OTHER SAFETY PARAMETERS

8.5.1 Clinical Laboratory

8.5.1.1 Hematology

Placebo-controlled Studies

In the Phase 3 placebo-controlled studies, the hematological data did not disclose any clinically relevant change from baseline to end of study for any parameter.

One patient receiving aclidinium bromide 200 µg was terminated prematurely from treatment due to “white blood cell increased.”

Long-term Safety Studies

The same pattern as above was seen in the long-term safety studies; no clinically relevant changes from baseline were observed in hematological data.

Two patients receiving aclidinium bromide 200 µg were terminated prematurely from treatment, 1 patient due to “eosinophilia” and 1 patient due to “platelet count decreased.”

8.5.1.2 Biochemistry

Placebo-controlled Studies
Mean change from baseline values for the chemistry determinations in the placebo-controlled studies showed no relevant changes or dose dependence in any treatment arm at end of study except for an apparent dose-associated increase in uric acid levels. However, these uric acid changes were not considered to be clinically relevant.

The frequency of patients with postbaseline potentially clinically significant values for blood chemistry parameters was generally low (approximately 5% or less) with the exception of glucose, which had a higher percentage of patients (> 5%) with values above the upper limit of the normal range: (placebo 9.5%, aclidinium bromide 200 µg 12%, and aclidinium bromide 400 µg 12%). An explanation for the numerically higher frequency of elevated blood glucose levels may rest in the fact that the study protocols did not require fasting conditions at the time of the blood sampling, and provision had not been made to record whether or not the blood sample was drawn under fasting conditions. None of the instances of elevated blood glucose levels were considered by the investigator to be related to study drug, and they occurred in patients with co-morbid pre-existing disease or active reasons to account for the glucose abnormalities. Between approximately 10% to 18% of the study population in the placebo-controlled studies had reported a medical history of diabetes mellitus, diabetes mellitus type 2 or hyperglycemia (Table 11.2–18 in Appendix I).

One placebo-treated patient was terminated prematurely from treatment due to “hypokalemia.”

Long-term Safety Studies
Non-clinically important increases in mean creatinine and mean uric acid values in both active treatment arms (with greater increases in the aclidinium bromide 400 µg arm) were observed. Additionally, greater numerical increases in alanine and aspartate aminotransferases were observed in the aclidinium bromide 400 µg group compared with the aclidinium bromide 200 µg group. Mean changes from baseline to last visit for alanine aminotransferase were 0.27 and –0.44 U/L, respectively, and for aspartate aminotransferase, 0.32 and –0.13 U/L, respectively. Other than those observations mentioned, no clinically important mean changes from baseline to end-of-study values in laboratory tests were noted.

The frequency of patients with postbaseline potentially clinically significant values for blood chemistry parameters was generally low (approximately 5% or less) with the exception of a few analytes that had a higher percentage of patients (> 5%) with values above the upper limit of the normal range in either treatment arm: glucose (20% for aclidinium bromide 200 µg and 16% for aclidinium bromide 400 µg), creatine kinase (6.9% for aclidinium bromide 200 µg and 6.7% for aclidinium bromide 400 µg), and triglycerides (4.7% for aclidinium bromide 200 µg and 8.0% for aclidinium bromide 400 µg)

Two patients receiving aclidinium bromide 200 µg were terminated prematurely from treatment, 1 patient due to “gamma-glutamyl transferase increased,” and 1 patient due to “blood creatine phosphokinase increased.” One patient receiving aclidinium bromide 400 µg was terminated prematurely due to “troponin increased.”

8.5.2 Vital Signs

Placebo-controlled Studies
Blood pressure data obtained during the placebo-controlled studies did not disclose any clinically notable mean change from baseline to end of study for either mean systolic or mean diastolic parameters (Table 11.2–14). Heart rate changes from baseline to end of study were small and were similar in the placebo and aclidinium bromide treatment groups (Table 11.2–15).

Long-term Safety Studies
The same pattern as above was seen in the long-term safety studies; no clinically relevant changes from baseline to end of study were observed in blood pressure or heart rate parameters (Table 11.2–16 and Table 11.2–17, respectively).

8.5.3 Electrocardiograms

8.5.3.1 Electrocardiographic Values Over Time

Placebo-controlled Studies
For the placebo-controlled studies, mean changes from baseline to last visit in ECG parameters (PR, QRS, QT, and RR intervals) showed no obvious between-group differences. For the QTcF, the observed increases were small (aclidinium bromide 200 µg BID 2.1%, aclidinium bromide 400 µg BID 2.3%, and placebo 1.7%).

Importantly, the percentage of patients who experienced potentially significant QTcF increases > 500 msec and QTcF increases > 60 msec in the aclidinium bromide treatment arms was low and comparable to placebo: for QTcF > 500 msec (0.0% for aclidinium bromide 200 µg, 0.3% for aclidinium bromide 400 µg, and 0.2% for placebo), for QTcF increases > 60 msec (0.6% for aclidinium bromide 200 µg, 0.3% for aclidinium bromide 400 µg, and 0.5% for placebo).

Long-term Safety Studies
Similar to placebo-controlled data, there are no evident baseline differences; changes from baseline in ECG parameters were numerically small and similar across treatment groups after longer exposure.

The percentage of patients who experienced potentially significant QTcF increases > 500 msec and QTcF increases > 60 msec in the aclidinium bromide treatment arms was low: for QTcF > 500 msec (0.2% for aclidinium bromide 200 µg, 0.5% for aclidinium bromide 400 µg), for QTcF increases > 60 msec (1.1% for aclidinium bromide 200 µg, 1.0% for aclidinium bromide 400 µg).

8.5.3.2 Holter Data

Twenty-four hour 12-lead Holter monitoring was conducted before initiation of BID investigational medication administration and again at the conclusion of the placebo-controlled treatment period for Studies 33 and 38 (A) in a subset of at least 30% of the patients at selected sites that were capable of conducting 24-hour Holter monitoring assessments.

There were no occurrences of sustained ventricular tachycardia, ventricular fibrillation, or torsades de pointes. There was a numerical increase in the number of patients exhibiting episodes of non-sustained supraventricular tachycardia (placebo 24 [14.0%]; aclidinium bromide 200 µg 44 [25.4%], and aclidinium bromide 400 µg 39 [23.9%]). Of these cases, 9 were reported as AEs (4 in placebo, 3 in aclidinium bromide 200 µg, and 2 in aclidinium bromide 400 µg). Eight were of mild severity (1 patient was discontinued in the aclidinium bromide 200 µg arm) and 1 was moderate in severity. None of these events were considered by the investigators to be serious. Based on a blinded review by external cardiologists, these events were not considered to be of clinical concern.

8.6 SAFETY CONCLUSIONS

- Both aclidinium bromide 200 µg BID and 400 µg BID doses are safe and well tolerated
- Safety profile is generally comparable to placebo, and similar between aclidinium bromide doses
- No cardiac safety signal was identified
- Low incidence of anticholinergic events (eg, dry mouth and constipation)
- No difference in all-cause mortality, CV mortality, SAEs, and discontinuation due to AEs in placebo-controlled studies
- Consistently low incidence of AEs with prolonged use.

9.0 BENEFIT—RISK ASSESSMENT

9.1 MEDICAL NEED

COPD is a major cause of morbidity and mortality, and its prevalence is increasing. Currently, COPD is estimated to be the fifth leading cause of mortality worldwide, and it is estimated that by 2020 it will be ranked as the third leading cause of death (Halbert et al, 2006).

As COPD progresses, there is worsening of airflow limitation with reductions in FEV_1 compared to predicted values, increased shortness of breath, reduced exercise capacity, and increased frequency of exacerbations. Acute exacerbations may be so severe as to require hospitalization or be life threatening. Very severe disease is associated with chronic respiratory failure. As symptom severity and the frequency of COPD exacerbations increase, the quality of life is markedly impaired.

The efficacy, safety, and clinical pharmacology of aclidinium bromide have been investigated in an extensive clinical development program with BID dosing. A total of 2717 COPD patients were exposed to aclidinium bromide (100 µg, 200 µg, or 400 µg BID) in 9 studies. Total exposure to aclidinium bromide was 1394.9 patient-years with durations up to 1 year. Given the serious nature of COPD, the necessity of polypharmacy in these patients due to the presence of co-morbid conditions (Huiart et al, 2005; Soriano et al, 2005), and the highly variable response of patients to COPD treatments, the development of additional pharmacological options, especially those with reduced potential for drug interactions and a good safety profile, is desirable.

9.2 EFFICACY

Aclidinium bromide has consistently demonstrated 24-hour bronchodilator efficacy on BID dosing, with clinically relevant improvement following the first dose and sustained efficacy on repeated dosing up to one year. Aclidinium bromide doses of 200 µg and 400 µg consistently demonstrated both statistically significant and clinically relevant differences compared to placebo for 24-hour trough FEV_1, a parameter that indicates the persistence of bronchodilator effect throughout the treatment's dosing interval. Across the range of studies, the 400 µg dose showed statistically significant and clinically relevant effect sizes compared to placebo and was more robust than the 200 µg dose, which generally showed a sub-optimal effect. For the primary efficacy variable of trough FEV_1, differences from placebo were generally well in excess 100 mL for the 400 µg dose. Also, numerically greater bronchodilation was observed from the first dose for 400 µg aclidinium bromide as compared to 200 µg dose which was consistently below a 100 mL improvement compared to placebo. With the 400 µg dose, efficacy was maintained on BID dosing for treatment periods of up to a year, with good safety and tolerability. Aclidinium bromide consistently demonstrated superior bronchodilation to placebo at all time points over the course of the study. Additionally, the 400 µg dose achieved its optimal bronchodilatory effect from the first dose onwards, and trough FEV_1 data were supported with assessments at multiple time points across the 24-hour dosing interval as shown in 24 hour serial spirometry.

The sustained 24-hour bronchodilator efficacy of aclidinium bromide BID is further supported by corresponding improvements in a range of symptomatic endpoints, particularly dyspnea (as measured using the BDI/TDI) but also in health-related quality of life (measured using the SGRQ) and rescue medication use. These endpoints showed better responses to the 400 µg dose than the 200 µg dose. These data as a whole suggest that aclidinium bromide 400 µg BID is the optimal dose that was tested, and provides clinically relevant improvement in airflow as well as symptoms.

9.3 SAFETY

The aclidinium safety database provides cumulative exposure to aclidinium bromide with doses ranging from 100 µg to 400 µg BID in COPD patients. The safety of aclidinium bromide was similar to placebo. Doses of 200 and 400 µg BID demonstrated a satisfactory overall safety profile for COPD patients studied up to 1 year of exposure. The two doses, 200 µg and 400 µg, have very similar safety and tolerability profiles.

There was no dose-related increase in anticholinergic effects at the proposed clinical doses. Specifically, events potentially related to the anticholinergic mechanism of aclidinium bromide such as dry mouth and constipation had a very low incidence. There was no safety signal for an increased risk of major cardiovascular related events or death and likewise, aclidinium bromide was not associated with other safety concerns such as COPD exacerbation or bronchospasm. No increased risk of cerebrovascular events including stroke, or respiratory events including pneumonia, were observed in either the 200 µg BID or 400 µg BID doses.

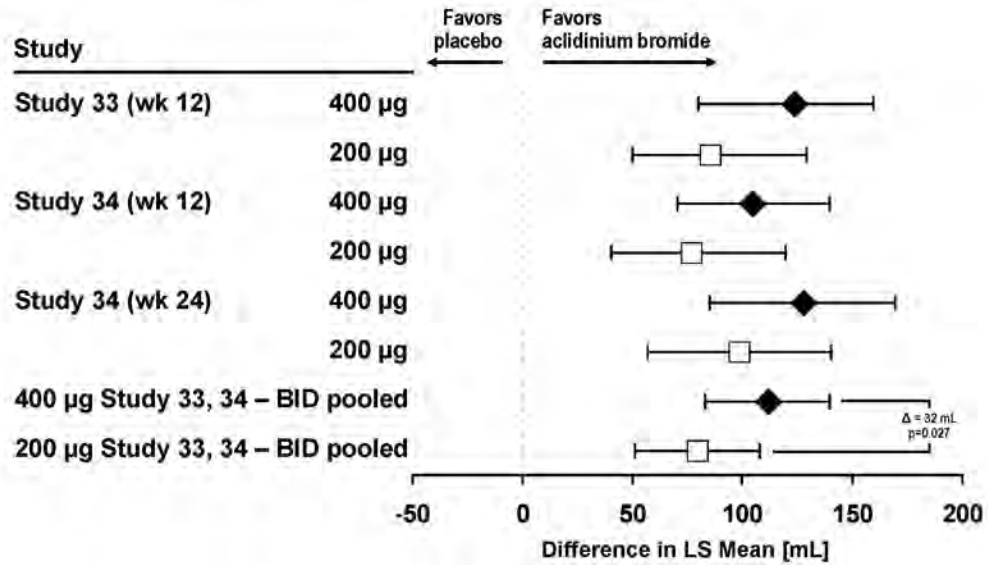
9.4 BENEFIT-RISK CONCLUSIONS

Throughout the BID development program in placebo-controlled studies of up to 6 months in duration, aclidinium bromide clearly demonstrated statistically and clinically significant improvements in trough FEV_1 along with improvements in other lung function parameters (ie, trough FVC and trough IC) in the population who will be treated with the product. Likewise, improvements were observed for health status, symptoms of dyspnea, rescue medication use, and rates of COPD exacerbations.

As shown in Figure 9.4–1, across the two pivotal studies 33 and 34 at both Week 12 and Week 24, the change from baseline in trough FEV_1 for the aclidinium bromide 400 µg BID dose was consistently above 100 mL, while the aclidinium bromide 200 µg dose consistently fell short of the generally accepted threshold of clinical relevance of 100 mL.

Pooling of the trough FEV_1 data from studies 33 and 34, demonstrates that the difference between the aclidinium bromide 400 µg and 200 µg BID doses is statistically significant and the effect size of the aclidinium bromide 400 µg represents approximately a 40% increase relative to the effect size of the aclidinium bromide 200 µg BID dose in trough FEV_1. The totality of the data supports aclidinium bromide 400 µg BID dose as the optimal dose.

Figure 9.4–1. **Totality of Evidence, Comparison of Change From Baseline in Trough FEV_1 of Aclidinium Bromide 200 µg and 400 µg Versus Placebo at Week 12 in Study 33 and at Week 12 and Week 24 in Study 34 and Pooled Analysis (Study 33 and Study 34 at Week 12)—ITT Population**



$p \leq 0.0001$ for all comparisons versus placebo, BID = twice daily; wk = week

Long-term studies demonstrate that the improvement in airflow persists for at least 1 year. The proposed 400 µg dose offers clinically relevant benefit compared to the 200 µg dose, as it is associated with a more rapid and sustained achievement of optimal bronchodilatory effect and showed greater improvements in symptom-related endpoints (particularly with respect to the key COPD symptom of dyspnea) and health-related quality of life.

A comprehensive safety review demonstrates that aclidinium bromide 400 µg BID can be administered safely. There are minimal anticholinergic side effects, a low rate of discontinuation, and no excess rate of SAEs or deaths. A specific analysis of CV-related events shows no increase in the common events that occur in this population. The device is easy to use, may facilitate better adherence to prescribers' instructions than with other more complex devices, and delivers the drug at flow rates that are easily achieved even in patients with severe COPD.

Aclidinium bromide is intended for chronic maintenance therapy. Sustained efficacy on repeated BID dosing is supported by 1-year data for the 400 µg dose. In addition, no signal has been observed to suggest any issues in terms of drug-drug interactions, which is particularly important in a patient population with a high prevalence of co-morbid diseases who are consequently likely to be using multiple medications. There is no identified subset of patients at increased adverse risk for this compound.

The benefits of aclidinium bromide 400 µg BID include improved pulmonary function as well as improvement of COPD symptoms and disease-related health status. The very low incidence of AEs, including anticipated anticholinergic events, supports the conclusion that the benefits of aclidinium bromide outweigh any observed or anticipated risks with its use, especially considering the serious nature of COPD and the need for additional therapeutic options.

9.5 CONCLUSION

Aclidinium bromide 400 µg BID has the potential to contribute significantly to the treatment of patients with COPD, given the clear evidence of sustained 24-hour efficacy with BID dosing. The safety and tolerability profile of aclidinium bromide has been well characterized suggesting no clinically relevant safety signals. Aclidinium bromide will be a safe and effective new treatment available for patients who suffer with COPD.

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11.0 APPENDIX I

11.1 MINI-NARRATIVES FOR PATIENTS WHO DIED

11.1.1 Placebo-Controlled Studies (BID Dosing)

Study 34

Patient 1194.02 (Placebo) was a 78-year-old Caucasian male, an ex-smoker with a smoking history of 61 pack years, and a medical history including COPD (with emphysema) since February 2004, as well as age-related visual impairment (since 1983). The patient experienced a severe SAE of road traffic accident while crossing the street, 33 days after starting treatment with placebo BID. This event was considered not related to treatment with placebo BID. Study medication was discontinued due to death. The patient was hospitalized and treated with medication. The patient died in the evening of the same day, due to blunt chest trauma (according to forensic report) sustained during the road traffic accident.

Patient 2326.10 (aclidinium bromide 200 µg) was a 71-year-old Asian male, and an ex-smoker with a smoking history of 47 pack years, and a medical history including COPD (with emphysema) since 2001, as well as ischaemic heart disease (since January 1992). The patient experienced a severe SAE of myocardial infarction, 105 days after starting treatment with aclidinium bromide 200 µg BID. This event was considered not related to aclidinium bromide 200 µg BID. He received no treatment for the event. Study medication was discontinued due to death. The patient died immediately due to a possible myocardial infarction following complaints of chest pain. No autopsy was performed. No more details are available.

Patient 1267.05 (aclidinium bromide 400 µg) was a 56-year-old Caucasian female, and an ex-smoker with a smoking history of 25 pack years, and a medical history including COPD (with chronic bronchitis and emphysema) since 19 November 2007, as well as hypercholesterolaemia, ischaemic heart disease and hypertension (all since 2002). The patient had been hospitalized in 2002 because of heart disease but no further details were available. The patient experienced a severe SAE of cardiac failure acute, 91 days after starting treatment with aclidinium bromide 400 µg BID. The event was considered not related to aclidinium bromide 400 µg BID. Study medication was discontinued due to death. Later on the same day the patient complained of malaise, reported elevated blood pressure (180/150 mm Hg) and orthopnoea. Patient's GP was called. Before an ECG could be performed, the patient turned grey and collapsed, circulatory and respiratory arrest occurred. Resuscitation was unsuccessful, and patient died at home in the presence of the GP. The GP performed the post-mortem examination and considered acute cardiac failure as cause probable of death. An autopsy was not performed and the death certificate was not available.

Study 33
Patient 114233015 (aclidinium bromide 400 µg) was a 65-year-old Caucasian male, an ex-smoker with a smoking history of 6 cigarettes per day for 58 years, and a medical history including COPD and headaches (since 1989), as well as atrial fibrillation, coronary artery stent placement, myocardial infarction, hyperlipidemia, sleep apnea syndrome, continuous positive airway pressure treatment, and hypertension (all since 2006). The patient experienced the severe SAEs of lung cancer with metastatic disease to the central nervous system, acute respiratory failure, and death, 12 days, 13 days, and 23 days, respectively, after starting treatment with aclidinium bromide 400 µg BID. The patient underwent surgical resection on Day 14 and the mass was confirmed to be adenocarcinoma. These events were considered not related to treatment with aclidinium bromide 400 µg BID. Study medication was discontinued due to metastatic lung cancer. At the request of the family, all treatments were discontinued on Day 23 and the patient died the same day. Death was attributed to metastatic lung cancer. An autopsy was not performed and no additional information was available.

Study 38 (A)
Patient 108038003 (placebo) was a 49-year-old white male. The patient's relevant medical history included Chronic Obstructive Pulmonary Disease (COPD) since 2008, as well as hepatitis C since 1991, depression since 1992, bipolar disorder since 2000, peptic ulcer since 2008, and anxiety since 2009. This patient also had the following relevant risk factors: former smoker from 1969 to 2008 with a total pack-year history of 58.5; and overweight, on the basis of a BMI of 29.2 kg/m^2. The death occurred during Study 38 (A), during which the patient took double-blind placebo for 43 days from 05-May-2010 to 16-Jun-2010. On [redacted] (b) (6) days after stopping investigational product, the patient was found dead at home.

Patient 135438005 (aclidinium bromide 400 µg) was a 56-year-old white male with a history of COPD since 2009 and a current smoker with a smoking history of 30 pack years. Other medical history included history of falls, chronic hypoxia (requiring continuous oxygen), hypercapnia, respiratory acidosis, bilateral atelectasis and effusions, chronic granulomatous disease, and polycythemia. The patient experienced a COPD exacerbation and was hospitalized on Day 28. The exacerbation was considered by the Investigator to be severe and not related to aclidinium bromide. Because of the exacerbation, dosing of aclidinium bromide was stopped temporarily. Twenty-seven days after stopping aclidinium bromide 400 µg, the patient experienced respiratory failure and cardio-respiratory arrest and died. The respiratory failure and cardiorespiratory arrest were considered by the Investigator to be severe and not related to aclidinium bromide.

Deaths Occurring More than 30 Days After Stopping Investigational Product in the Placebo-controlled Studies

Study 34

Patient 1278.08 (aclidinium bromide 200 µg) was a 52-year-old Caucasian male, and an ex-smoker with a smoking history of 27 pack years and a medical history of COPD (with chronic bronchitis) since 15 June 2004. The patient experienced severe SAEs of COPD and pulmonary tuberculosis, 129 days and 134 days, respectively, after starting treatment with aclidinium bromide 200 µg BID. Both events were considered not related to treatment with aclidinium bromide 200 µg BID. The study medication was permanently discontinued due to the event of COPD. The patient was hospitalized and treated with medication for these events. Thirty-three days after discontinuation of the study medication, and whilst in hospital, the patient committed suicide by jumping out of a window. The event was recorded as a severe SAE, which was considered not related to treatment with aclidinium bromide 200 µg BID.

Patient 1188.15 (aclidinium bromide 400 µg) is a 76-year-old Caucasian male, and a current smoker with a smoking history of 55 pack years and a medical history including COPD (with chronic bronchitis and emphysema) since 2006, cardiac infarction in 1995 and 2001, hypertension since 2004, leukoencephalopathy after cerebral infarction and thalamus infarction in 2005, and atrial fibrillation since 2007. The patient experienced a severe SAE of cerebral haemorrhage, 4 days after completing treatment with aclidinium bromide 400 µg BID. The event was considered not related to treatment with aclidinium bromide 400 µg BID. No action was taken with the study medication as treatment had already been completed. The patient recovered from the event of cerebral haemorrhage with important sequelae (reduced general condition, nutrition and cognition, sensomotor aphasia and high-grade right sided hemiparesis) after 26 days, following hospitalisation, treatment with medication, and functional rehabilitation. The patient experienced a severe SAE of pneumonia (and sepsis), 31 days after completing treatment with aclidinium bromide 400 µg BID. The event was considered not related to treatment with aclidinium bromide 400 µg BID. The next day the patient died due to sepsis. No autopsy was performed, however microbiological examinations revealed numerous MRSA, clostridia toxin and bacteraemia with gram-negative bacteria.

11.1.2 Long-term Safety Studies (BID Dosing)

Study 35
Patient 132735009 (**aclidinium bromide 200 µg**) was a 68-year-old Caucasian male, a current smoker with a smoking history of 55 pack-years, whose medical history included COPD (since 2002), hyperlipidemia (since 1990); gastroesophageal reflux disease, hypertension, and coronary artery disease (since 1995); myocardial infarction, angioplasty, and coronary arterial stent insertion × 3 (in 1995); type 2 diabetes mellitus (since 2000); inguinal hernia repair (in December 2007 and 2008); benign lung neoplasm (in July 2008); and body mass index consistent with overweight. On Day 342 of treatment with 200 µg aclidinium bromide, the patient experienced the SAE of bile duct stricture and was hospitalized. During hospitalization, the patient received medications and underwent diagnostic testing (including retrograde cholangiopancreatography with biliary sphincterotomy, balloon dilation and brushing of the common bile duct stricture, placement of biliary stents, and duodenal biopsies). On Day 346, the patient recovered from the bile duct stricture and was discharged the next day with a discharge diagnosis of biliary mass, hypertension, coronary artery disease, diabetes, hyperlipidemia, and gastroesophageal reflux disease. Study medication was temporarily discontinued from Days 342 through 346.

On Day 351, the biliary mass was confirmed to be pancreatic carcinoma. The patient was readmitted to the hospital on Day 355 for the nonserious adverse event of acute cholangitis and the SAE of biliary sepsis due to *Proteus mirabilis*, *Escherichia coli*, *Enterobacter spp*, and *Enterococcus*. Study medication was permanently discontinued on Day 355 due to the serious adverse event of biliary sepsis. The patient was intubated because of respiratory failure and placed on mechanical ventilation. On Day 363, an unspecified computerized tomography scan revealed several liver abscesses. The patient was treated with medications and was subsequently removed from the ventilator on Day 366. The cause of death was biliary sepsis. The death certificate reported ascending cholangitis due to, or as a consequence of, biliary sepsis and cholangiocarcinoma. The Investigator considered the serious adverse events of bile duct stenosis and biliary sepsis to be not related to the investigational product.

Patient 208235013 (**aclidinium bromide 400 µg)** was a 72-year-old Caucasian male, a current smoker with a smoking history of 58 pack-years, and a medical history that included COPD (since 2001), cardiac stents (in 1997), coronary artery bypass graft (in February 2000), hypertension (since 2003), abdominal aortic aneurysm (since August 2005), and a body mass index consistent with obesity. On Study Day 258, the patient experienced the SAE of subarachnoid hemorrhage. The patient was hospitalized, was treated with medications, and underwent diagnostic testing. The patient was diagnosed with a ruptured anterior communicating artery aneurysm, hydrocephalus, and later, during admission, with pneumonia (subsumed under the SAE term subarachnoid hemorrhage). He was intubated for the diagnostic testing and remained on ventilator support. Bilateral venous ultrasound of the lower extremities showed a small blood clot in the right femoral vein and left saphenous vein (considered secondary to the subarachnoid hemorrhage). On Day 262, an inferior vena cava filter was placed and, on Day 263, the patient underwent a percutaneous tracheostomy and placement of a percutaneous endoscopic gastrostomy tube. On Day 281, the patient died because of subarachnoid hemorrhage. A postmortem examination was not performed, and a death certificate was not available. At the time of the death, the hydrocephalus and pneumonia remained ongoing. The Investigator considered the SAE of subarachnoid hemorrhage to be not related to investigational product.

Study 38 (B)

Patient 136638011 (aclidinium bromide 400 µg) was a 48-year-old white female with a smoking history of 32 pack-years, and a medical history that included COPD (since 2008), anaemia (since 1989), spinal osteoarthritis (since 1990), female sterilization (in 1992), pneumonia (in 2008), bipolar disorder, hypertension, and post-traumatic stress disorder, (since 2008) and obesity (since 2008); (on the basis of a body mass index of 39.2 kg/m^2). The patient had initially received aclidinium bromide 400 µg BID for 84 days in Study 38 (A). The patient then received aclidinium bromide 400 µg BID in Study 38 (B) and experienced the SAE of death due to cardiac arrest 180 days later. Per CIOMS, on Study Day 180, the patient was brought from her home to an emergency room by emergency medical services (EMS) due to cardiac arrest. The family had reported that the patient appeared to have a seizure and then collapsed. A family member performed bystander cardiopulmonary resuscitation (CPR). EMS found the patient in asystole and CPR was performed. The patient was treated with epinephrine, atropine, glucose and naloxone. EMS was able to get circulation back briefly but then the patient went into ventricular fibrillation. Defibrillation was unsuccessful and CPR was continued until arrival in the emergency room. The patient was intubated with good waveform and capnography, and breath sounds were present while ventilated. The patient was noted as being unresponsive and having fixed and dilated pupils. Additional epinephrine and calcium bicarbonate were administered. The patient had infrequent pulseless electrical activity and a bedside ultrasound showed minimal cardiac activity with ectopy, considered as secondary to epinephrine. No autopsy was performed and at the time of this report, a death certificate had not been obtained by the family. The Investigator considered the event not related to the investigational product.

Patient 145038007 (aclidinium bromide 400 µg) was a 51-year-old Caucasian female, a current smoker with a smoking history of 54 pack-years, whose medical history includes COPD (since 2001); pneumonia (in 2006); hyperglycemia (since November 2009); hyperlipidemia, dizziness, and paresthesia (since December 2009); abnormal mammogram, back pain, pain in extremity, anxiety, and hypertension (since 2009); and a body mass index consistent with obesity. The patient received placebo for 83 days in Part A of the study and aclidinium bromide 400 µg for 281 days in Part B of the study. On Study Day 282, the patient died from cardiac arrest. She was found unresponsive, without respirations, and asystole. Advanced cardiac life support (ACLS) was administered and followed at the hospital, and she was treated with medications, oxygen, cardiopulmonary resuscitation, intravenous fluids, and intubation. The patient was not successfully resuscitated, and a postmortem examination was not performed. The Investigator considered the SAE of fatal cardiac arrest to be not related to investigational product.

Patient 145138001 (aclidinium bromide 400 µg) was a 51-year-old Caucasian male, a current smoker with a smoking history of 33 pack-years, and a medical history including COPD (since 2004), and hypertension, cannabinoid and alcohol abuse, hypertensive and cardiovascular disease, and atherosclerotic cardiovascular disease (dates not specified). The patient experienced the SAE of death secondary to cardiorespiratory arrest 97 days after starting treatment with aclidinium bromide 400 µg BID. This event was considered to be not related to aclidinium bromide 400 µg BID. After complaining of chest pain, the patient declined medical attention and was then found unresponsive. Resuscitative efforts were unsuccessful and the patient was pronounced dead. Two bottles of unknown prescription medications, a small bag containing a green leafy substance, illicit drugs, and a pipe were found in the patient's possession. Study medication had been discontinued on Day 91. An autopsy revealed mild to moderate atherosclerotic stenoses of the heart vessel lumens (with histologic confirmation of atheromatous plaques), concentric left ventricular hypertrophy, atherosclerosis of the aortic arch, and the thoracic and abdominal aortas. The lungs contained anthracotic pigment deposition, apical emphysematous blebs, dialed airspaces, and posterior congestion. Histopathology revealed hypertrophied cardiomyocytes, along with perivascular and interstitial fibrosis. The toxicology report was presumptive for amphetamine and cannabinoids, with 0.08 mg/L methamphetamine and 0.02 mg/L amphetamine detected in peripheral blood. Acute methamphetamine intoxication was subsumed because it was a contributing factor to the patient's hypertensive cardiomyopathy. The cause of death was cardiorespiratory arrest secondary to hypertensive and atherosclerotic cardiovascular disease. The manner of death was considered to be accidental.

Additional information regarding this patient was reported after the NDA data cut date of 2010-11-01. On Day 97, 2 adverse events of drug abuse (PT) for the use of cannabinoids and methamphetamine were reported. This was the same day the patient was found dead at home. The use of those controlled substances was considered to be not related to study treatment by the investigator.

Study 36

Patient 115533001 (aclidinium bromide 200 µg) was a 56-year-old Caucasian male, a current smoker, with a smoking history of 82 pack-years, and a medical history including COPD (since May 2008), insomnia (since 1966), neuralgia (since 2003), spinal fusion surgery (2003), and depression (since 2008). The patient experienced the fatal SAE of accidental multiple drug overdose 105 days after starting treatment with aclidinium bromide 200 µg BID. This event was considered not related to aclidinium bromide 200 µg BID. Study medication was discontinued on Day 105 due to multiple drug overdose. Postmortem examination and toxicology testing revealed the following relevant findings: toxic blood concentrations of oxycodone (0.70 mg/L) and morphine (0.33 mg/L), a toxic urine concentration of morphine (0.83 mg/ L), atherosclerotic and hypertensive cardiovascular disease, cardiac hypertrophy, interstitial fibrosis of the lungs, nephrosclerosis, and peritoneal adhesions. The reported cause of death was accidental death due to the toxic effects of oxycodone and morphine.

Patient 114133006 (aclidinium bromide 400 µg) was a 70-year-old Caucasian female, an ex-smoker with a smoking history of 50 pack-years, and a medical history including COPD (since 1999), gastroesophageal reflux disease (since 2004), nausea (2009), hip fracture (1997), and osteoporosis (since 1999) with pelvic fracture the same year. The patient experienced the fatal SAEs of spinal compression fracture, pneumonia, and esophagitis, 79 days, 190 days, and 199 days, respectively, after starting treatment with aclidinium bromide 400 µg BID. These events were considered not related to aclidinium bromide 400 µg BID. The patient had multiple hospital admissions and was treated with medications for the events. Study medication was discontinued on Day 239 following admission for esophagitis. The patient expired on Day 270. Neither a death certificate nor a cause of death was available.

Death Occurring More than 30 Days After Stopping Investigational Product in the Long-term Safety Studies

Study 35

Patient 207935013 (aclidinium bromide 400 µg) was a 63-year-old Caucasian female, a current smoker with a smoking history of 75 pack-years, whose medical history included COPD (since 1965), splenectomy (in 1970), back pain (since 2000), depression (since 2008), and sinusitis (since December 2009). On Study Day 84 after starting treatment with aclidinium bromide 200 µg, the patient experienced the SAEs of COPD exacerbation, dyspnea, and spontaneous pneumothorax. She was admitted to the hospital, underwent diagnostic testing, and was treated with antibiotics and a bronchodilator. These events resolved on Day 90, and the patient was discharged from the hospital. Due to atelectasis, a computed tomography scan of the chest was performed on Day 109 and revealed a partially necrotic mass in the right lower lobe of the lung. Bronchoscopy performed on Day 113 demonstrated a moderately differentiated invasive squamous cell carcinoma of the lung. Dosing with aclidinium bromide 200 µg was discontinued on Day 113. On Study Day 119, the patient was reported as having experienced the SAE of right lower lobe lung cancer. On Day 128, a positron emission tomography-computed tomography revealed lesions consistent with metastatic bronchogenic carcinoma. She was treated for the lung neoplasm with radiation and chemotherapy, without improvement. On Day 167, the patient was hospitalized with intractable nausea, vomiting, and chronic cough. She was treated with intravenous fluids and medications, and discharged from the hospital on Day 169. At the time of reporting, the malignant lung neoplasm was ongoing. The SAEs of COPD exacerbation, dyspnea, spontaneous pneumothorax, and lung neoplasm were considered by the Investigator to be not related to aclidinium bromide 200 µg. Additional information regarding this patient was received after the NDA database cutoff date. On Study Day 228, the patient died. The patient’s primary care physician listed the cause of death as lung cancer. A postmortem examination was not performed. The investigator considered the event not related to the investigational product.

Patient 142135024 (aclidinium bromide 400 µg) was a 73-year-old Caucasian female, an ex-smoker with a smoking history of 44 pack-years, who had a medical history that included COPD (since 2007), headaches and arthritis (since 1990), anxiety (in 1996), gout (in 1998), gastroesophageal reflux disease and hypercholesterolemia (since 2005), hyperlipidemia (since 2007), hypertension (since January 2008), diagnosis of coronary artery disease and acute myocardial infarction (in December 2008), and insomnia (since 2009). The patient was initially enrolled in Study LAS-MD-35, during which the patient took double-blind investigational product (aclidinium bromide 400 µg/puff BID) for 69 days from 2010-04-23 to 2010-06-12. On 2010-06-12, the patient experienced the nonserious adverse event of COPD exacerbation of moderate intensity. On 2010-08-23, the study site was informed by a family member that the patient had been hospitalized for pneumonia (date unknown) and subsequently died on (b) (6) (Study Day (b) (6)). Prior to her death, the study Investigator had been notified that the patient had stopped taking study medication on Study Day 69. The site was unable to obtain hospital records. The final cause of death was reported as pneumonia. No other information is available. The Investigator considered the events of COPD exacerbation and pneumonia as not related to the investigational product.

11.2 SUPPORTIVE TABLES AND FIGURES

Table 11.2–1. Patient Disposition in Studies 33, 34, and 38 (A)

Category	***Number (%) of Patients***		
	Placebo	*Aclidinium Bromide*	
		200 µg BID	**400 µg BID**
Study 33 (12 Weeks)			
Randomized patients	***(N = 186)***	***(N = 185)***	***(N = 190)***
Completed study (12 weeks)	149 (80.1)	152 (82.2)	166 (87.4)
Prematurely discontinued	37 (19.9)	33 (17.8)	24 (12.6)
Reason for discontinuation			
Withdrawal of consent	9 (4.8)	6 (3.2)	7 (3.7)
Adverse event	7 (3.8)	8 (4.3)	7 (3.7)
Insufficient therapeutic response	10 (5.4)	5 (2.7)	1 (0.5)
COPD exacerbation	7 (3.8)	4 (2.2)	1 (0.5)
Other	2 (1.1)	5 (2.7)	3 (1.6)
Protocol violation	2 (1.1)	1 (0.5)	3 (1.6)
Inclusion/exclusion criteria not met	—	2 (1.1)	2 (1.1)
Lost to follow-up	—	2 (1.1)	—

Table 11.2–1. Patient Disposition in Studies 33, 34, and 38 (A)

Category	***Number (%) of Patients***		
	Placebo	*Aclidinium Bromide*	
		200 µg BID	**400 µg BID**
Study 34 (24 Weeks)			
Randomized patients	***(N = 276)***	***(N = 280)***	***(N = 272)***
Completed study (24 weeks)	232 (84.1)	253 (90.4)	252 (92.6)
Prematurely discontinued	41 (14.9)	24 (8.6)	17 (6.3)
Reason for discontinuation			
Withdrawal of consent	17 (6.2)	9 (3.2)	7 (2.6)
Adverse event	6 (2.2)	8 (2.9)	4 (1.5)
Insufficient therapeutic response	8 (2.9)	2 (0.7)	—
COPD exacerbation	5 (1.8)	3 (1.1)	4 (1.5)
Other	3 (1.1)	—	1 (0.4)
Protocol violation	1 (0.4)	—	1 (0.4)
Lost to follow-up	1 (0.4)	2 (0.7)	—
Study 38 (A)(12 Weeks)			
Randomized patients	***(N = 182)***	***(N = 184)***	***(N = 178)***
Completed study (12 weeks)	151 (83.0)	155 (84.2)	148 (83.1)
Prematurely discontinued	31 (17.0)	29 (15.8)	30 (16.9)
Reason for discontinuation			
Withdrawal of consent	8 (4.4)	12 (6.5)	6 (3.4)
Adverse event	4 (2.2)	3 (1.6)	8 (4.5)
Insufficient therapeutic response	6 (3.3)	3 (1.6)	2 (1.1)
COPD exacerbation	4 (2.2)	1 (0.5)	6 (3.4)
Other	3 (1.6)	3 (1.6)	3 (1.7)
Protocol violation	3 (1.6)	4 (2.2)	3 (1.7)
Lost to follow-up	3 (1.6)	3 (1.6)	2 (1.1)

COPD = chronic obstructive pulmonary disease; n = number of patients in the specified category; N = number of patients in the Randomized Population.

Table 11.2–2. Demographic Characteristics of Patients Enrolled in Phase 3 Efficacy Studies, 34, 33, and 38 (A), and in the Pooled Population—ITT Population

Demographic characteristics		***Study***			***Pooled Population***	
		34	*33*	*38 (A)*	*34 and 33*	*All 3 Studies*[a]
		N = 819	**N = 559**	**N = 541**	**N = 1378**	**N = 1919**
Age (years)						
	Mean (SD)	62.4 (8.0)	64.3 (9.4)	62.8 (8.9)	63.2 (8.7)	63.1 (8.8)
	Range	41, 84	40, 89	40, 84	40, 89	40, 89
Age group (years)						
< 60	***n (%)***	297 (36.3)	154 (27.6)	186 (34.4)	451 (32.7)	637 (33.2)
≥ 60 to < 70	***n (%)***	354 (43.2)	243 (43.5)	227 (42.0)	597 (43.3)	824 (42.9)
≥ 70	***n (%)***	168 (20.5)	162 (29.0)	128 (23.7)	330 (24.0)	458 (23.9)
Gender						
Male	***n (%)***	552 (67.4)	296 (53.0)	288 (53.2)	848 (61.5)	1136 (59.2)
Female	***n (%)***	267 (32.6)	263 (47.1)	253 (46.8)	530 (38.5)	783 (40.8)
Race						
White	***n (%)***	780 (95.2)	524 (93.7)	490 (90.6)	1304 (94.6)	1794 (93.5)
Black/ African American	***n (%)***	2 (0.2)	29 (5.2)	45 (8.3)	31 (2.3)	76 (4.0)
Asian	***n (%)***	3 (0.4)	3 (0.5)	1 (0.2)	6 (0.4)	7 (0.4)
American Indian	***n (%)***	—	1 (0.2)	3 (0.6)	1 (0.1)	4 (0.2)
Other	***n (%)***	34 (4.2)	2 (0.4)	2 (0.4)	36 (2.6)	38 (2.0)
Geographical region						
US/Canada	***n (%)***	—	559 (100)	541 (100)	559 (40.6)	1100 (57.3)
Europe	***n (%)***	678 (82.8)	—	—	678 (49.2)	678 (35.3)
Rest of World	***n (%)***	141 (17.2)	—	—	141 (10.2)	141 (7.4)

a Pooled analysis of patient populations from studies 34, 33 and 38 (A).

ITT = intent to treat; N = number of patients in study population; n = number of patients; US = United States.

Table 11.2–3. Baseline COPD Status and Smoking History of Patients Enrolled in Phase 3 Efficacy Studies, 34, 33, and 38 (A), and in the Pooled Population—ITT Populations

Baseline Status		***Study***			***Pooled Population***	
		34	*33*	*38(A)*	*34 and 33*	*All 3 Studies*[a]
		N = 819	**N = 559**	**N = 541**	**N = 1378**	**N = 1919**
COPD Severity[b]						
Stage I (mild)	n (%)	—	—	2 (0.4)[c]	—	2 (0.1)
Stage II (moderate)	n (%)	554 (67.6)	327 (58.5)	287 (53.1)	881 (63.9)	1168 (60.9)
Stage III (severe)	n (%)	260 (31.8)	220 (39.4)	248 (45.8)	480 (34.8)	728 (37.9)
Stage IV (very severe)	n (%)	—	5 (0.9)	1 (0.2)[e]	5 (0.4)	6 (0.3)
Smoking History						
Current smoker	n (%)	432 (52.8)	251 (44.9)	288 (53.2)	683 (49.6)	971 (50.6)
Smoking consumption (pack years)	Mean (SD)	40.2 (19.8)	54.4 (26.8)	53.7 (29.0)	45.9 (23.9)	48.1 (25.7)
Patients With Exacerbations in the Previous 12 Months						
0	n (%)	530 (65.3)	418 (74.8)	410 (75.8)	948 (69.2)	1358 (71.0)
1	n (%)	229 (28.2)	109 (19.5)	85 (15.7)	338 (24.7)	423 (22.1)
≥ 2	n (%)	53 (6.5)	32 (5.7)	46 (8.5)	85 (6.2)	131 (6.9)
SGRQ Total Score[d]						
	n	815	550	528	1365	1893
	Mean (SD)	46.4 (16.8)	46.5 (17.1)	49.0 (17.6)	46.4 (16.9)	47.1 (17.2)
BDI Focal Score[e]						
	n	797	536	505	1333	1838
	Mean (SD)	6.8 (2.1)	6.4 (2.1)	6.2 (2.1)	6.6 (2.1)	6.5 (2.1)

a Pooled analysis of patient populations from studies 34, 33, and 38 (A).

b GOLD classification of COPD severity: Stage 1: post-bronchodilator $FEV_1 \geq 80\%$ predicted; Stage II: $50\% \leq$ post-bronchodilator $FEV_1 < 80\%$ predicted; Stage III: $30\% \leq$ post-bronchodilator $FEV_1 < 50\%$ predicted, Stage IV: post-bronchodilator $FEV_1 < 30\%$ predicted. For Stages I to IV, $FEV_1/FVC < 0.70$.

c At the time of randomization, all patients met the inclusion criterion for having moderate to severe COPD (Stage II-III). However, after blinded table review, it was determined that 2 patients had mild disease. In addition, 1 patient was listed above as having very severe disease because the height was captured incorrectly in the electronic case report form.

d SGRQ total score ranges from 0 to 100; higher scores indicate worse health status.

e BDI focal score ranges from 0 to 12; lower scores denote worse dyspnea.

BDI = Baseline Dyspnea Index; COPD = chronic obstructive pulmonary disease; GOLD = Global Initiative for Chronic Obstructive Lung Disease; ITT = intent to treat; N = number of patients in study population; n = number of patients; SGRQ = St. George's Respiratory Questionnaire.

Table 11.2–4. Baseline Lung Function of Patients Enrolled in Phase 3 Efficacy Studies, 34, 33 and 38 (A), and in the Pooled Population—ITT Populations

Baseline Lung Function Category		***Study***			***Pooled Population***	
		34	*33*	*38 (A)*	*34 and 33*	*All 3 Studies*[a]
Baseline lung function at Screening (Visit 1)[a], post-bronchodilator						
	n	814	552	538	1366	1904
FEV_1 (% predicted)	Mean (SD)	56.8 (12.8)	53.9 (13.3)	52.5 (13.4)	55.6 (13.1)	54.7 (13.2)
FEV_1/FVC (%)	Mean (SD)	49.6 (10.3)	51.8 (10.4)	51.2 (10.8)	50.5 (10.4)	50.7 (10.5)
Baseline lung function at Visit 2 (before commencement of treatment administration)						
	n	819	559	541	1378	1919
FEV_1 (L)	Mean (SD)	1.507 (0.504)	1.355 (0.541)	1.369 (0.548)	1.446 (0.524)	1.424 (0.532)
FEV_1 (% predicted)	Mean (SD)	52.5 (14.1)	47.2 (14.1)	46.6 (14.7)	50.3 (14.3)	49.3 (14.5)
Bronchial reversibility to SABA						
	n	812	549	534	1361	1895
% Reversibility[b]	Mean (SD)	11.9 (14.1)	16.4 (14.3)	15.8 (13.5)	13.7 (14.4)	14.3 (14.2)
Absolute change (L)[c]	Mean (SD)	0.150 (0.170)	0.187 (0.160)	0.182 (0.145)	0.165 (0.167)	0.170 (0.161)
Reversible[d]	n (%)	255 (31.4)	239 (43.5)	205 (38.4)	494 (36.3)	699 (36.9)

a Post-bronchodilator values.

b Calculated as: 100 x (FEV_1 [post-bronchodilator] - FEV_1 [pre-bronchodilator]) / FEV_1 (pre-bronchodilator).

c Calculated as: FEV_1 (post-bronchodilator) - FEV_1 (pre-bronchodilator).

d Defined as bronchodilator reversibility ≥ 12% and change from pre-bronchodilator FEV_1 ≥ 0.200 L.

FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity; ITT = intent to treat; n = number of patients; SABA = short-acting β_2-agonist.

Table 11.2–5. Changes From Baseline in Trough FVC (mL) for Studies 33, 34, 38 (A) at Week 12—ITT Populations

Study				***Comparison***	***Treatment Difference***		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Study: 33 (Week 12)							
AB 400 µg	190	217	22	AB 400 µg - Placebo	**219**	157, 282	**<0.0001**
AB 200 µg	184	162	23	AB 200 µg - Placebo	**165**	102, 228	**<0.0001**
Placebo	185	-3	23	AB 400 µg - AB 200 µg	**54**	—	**0.0894**
Study: 34 (Week 12)							
AB 400 µg	269	100	23	AB 400 µg - Placebo	**184**	121, 246	**<0.0001**
AB 200 µg	277	36	23	AB 200 µg - Placebo	**119**	57, 181	**0.0002**
Placebo	273	-83	23	AB 400 µg - AB 200 µg	**65**	2, 127	**0.0415**
Study: 34 (Week 24)							
AB 400 µg	269	95	26	AB 400 µg - Placebo	**224**	155, 292	**<0.0001**
AB 200 µg	277	30	25	AB 200 µg - Placebo	**159**	91, 227	**<0.0001**
Placebo	273	-128	26	AB 400 µg - AB 200 µg	**65**	-3, 133	**0.0612**
Study: 38 (A) (Week 12)							
AB 400 µg	177	152	25	AB 400 µg - Placebo	**120**	51, 189	**0.0006**
AB 200 µg	182	99	25	AB 200 µg - Placebo	**67**	-1, 136	**0.0521**
Placebo	182	31	25	AB 400 µg - AB 200 µg	**53**	—	**0.1318**

Note: Analysis is based on ANCOVA model for change from baseline in trough FVC as response with treatment group and sex as factors, and age and baseline FVC as covariates.

a LS mean for the treatment difference.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; FVC = forced vital capacity; ITT = intent to treat; LS = least square; n = number of patients.

Table 11.2–6. Changes From Baseline in Trough IC (mL) for Studies 33, 34, 38 (A) at Week 12—ITT Populations

Study				***Comparison***	***Treatment Difference***		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
Study: 33 (Week 12)							
AB 400 µg	185	67	22	AB 400 µg - Placebo	**138**	76, 199	**<0.0001**
AB 200 µg	176	48	23	AB 200 µg - Placebo	**119**	56, 181	**0.0002**
Placebo	182	-71	22	AB 400 µg - AB 200 µg	**19**	—	**0.5505**
Study: 34 (Week 12)							
AB 400 µg	262	43	20	AB 400 µg - Placebo	**133**	79, 187	**<0.0001**
AB 200 µg	265	-20	20	AB 200 µg - Placebo	**70**	16, 123	**0.0112**
Placebo	266	-90	20	AB 400 µg - AB 200 µg	**63**	10, 117	**0.0211**
Study: 34 (Week 24)							
AB 400 µg	262	17	21	AB 400 µg - Placebo	**119**	61, 177	**<0.0001**
AB 200 µg	265	-34	21	AB 200 µg - Placebo	**68**	11, 126	**0.0200**
Placebo	266	-102	21	AB 400 µg - AB 200 µg	**51**	-7, 108	**0.0856**
Study: 38 (A) (Week 12)							
AB 400 µg	172	72	23	AB 400 µg - Placebo	**113**	50, 176	**0.0004**
AB 200 µg	178	44	22	AB 200 µg - Placebo	**86**	24, 148	**0.0067**
Placebo	179	-42	22	AB 400 µg - AB 200 µg	**27**	—	**0.3947**

Note: Analysis is based on ANCOVA model for change from baseline in trough IC as response with treatment group and sex as factors, and age and baseline trough IC as covariates.

a LS mean for the treatment difference.

AB = aclidinium bromide; ANCOVA = analysis of covariance; CI = confidence interval; IC = inspiratory capacity; ITT = intent to treat; LS = least square; n = number of patients.

Table 11.2–7. Change From Baseline to Week 12 in SGRQ Total Score for Phase 3 Efficacy Studies M/34273/34, LAS-MD-33, LAS-MD-38A, and Pooled Populations—ITT Populations

Study				*Comparison*	*Treatment Difference*		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
M/34273/34 (Week 12)							
AB 400 µg	269	-6.0	0.7	AB 400 µg - Placebo	-4.0	-5.9, -2.1	< 0.0001
AB 200 µg	275	-5.1	0.7	AB 200 µg - Placebo	-3.1	-4.9, -1.2	0.0015
Placebo	271	-2.1	0.7	AB 400 µg - AB 200 µg	—	—	—
M/34273/34 (Week 24)							
AB 400 µg	269	-6.9	0.8	AB 400 µg - Placebo	-4.3	-6.4, -2.2	< 0.0001
AB 200 µg	275	-6.2	0.8	AB 200 µg - Placebo	-3.6	-5.7, -1.5	0.0009
Placebo	271	-2.6	0.8	AB 400 µg - AB 200 µg	—	—	—
LAS-MD-33(Week 12)							
AB 400 µg	189	-4.6	0.8	AB 400 µg - Placebo	-2.5	-4.7, -0.4	0.0186
AB 200 µg	180	-4.8	0.8	AB 200 µg - Placebo	-2.7	-4.9, -0.6	0.0126
Placebo	181	-2.0	0.8	AB 400 µg - AB 200 µg	—	—	—
LAS-MD-38 (Part A) (Week 12)							
AB 400 µg	172	-5.4	1.0	AB 400 µg - Placebo	-1.1	-3.8, 1.6	0.4288
AB 200 µg	178	-6.0	1.0	AB 200 µg - Placebo	-1.7	-4.3, 1.0	0.2216
Placebo	178	-4.3	1.0	AB 400 µg - AB 200 µg	—	—	—
Pooled 2 Studies: M/34273/34 and LAS-MD-33(Week 12)							
AB 400 µg	458	-5.31	0.52	AB 400 µg - Placebo	-3.4	-4.8, -1.9	< 0.0001
AB 200 µg	455	-4.90	0.52	AB 200 µg - Placebo	-3.0	-4.4, -1.5	< 0.0001
Placebo	452	-1.95	0.52	AB 400 µg - AB 200 µg	—	—	—

Note: Analysis is based on ANCOVA model for change from baseline in SGRQ total score, with treatment group and sex as factors, and age and baseline SGRQ total score as covariates.

AB = aclidinium bromide; CI = confidence interval; ITT = intent to treat; n = number of patients; PBO = placebo; St. George's Respiratory Questionnaire.

a LS mean for the treatment difference.

Figure 11.2–1. **Comparison of SGRQ Responders (4-Unit Improvement) Versus Placebo at Week 12 Across the Phase 3 Studies:(Studies 33, 34 and 38 [B]) and at Week 24 in Study 34—ITT Population**

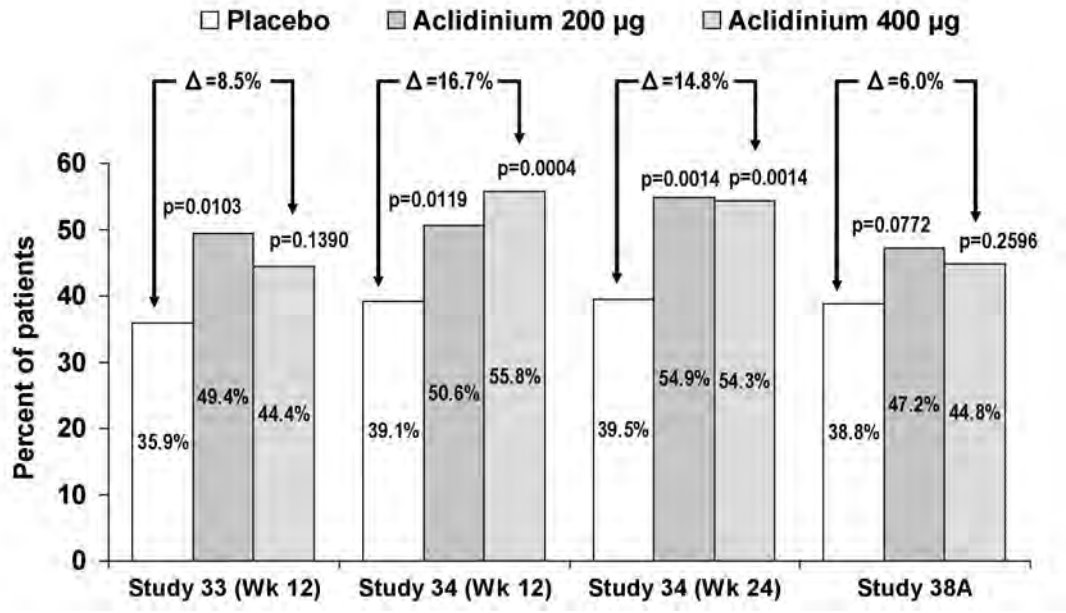

Table 11.2–8. Change From Baseline in TDI Focal Score at Week 12 for Phase 3 Efficacy Studies M/34273/34, LAS-MD-33, LAS-MD-38A, and Pooled Populations: ITT Populations

Study				*Comparison*	*Treatment Difference*		
Treatment	*n*	*LS Mean*	*SE*		*LS Mean*[a]	*95% CI*	*p-value*
M/34273/34 (Week 12)							
AB 400 µg	262	1.7	0.2	AB 400 µg - Placebo	0.9	0.3, 1.4	0.0012
AB 200 µg	270	1.2	0.2	AB 200 µg - Placebo	0.4	-0.2, 0.9	0.1807
Placebo	257	0.9	0.2	—	—	—	—
M/34273/34 (Week24)							
AB 400 µg	262	1.9	0.2	AB 400 µg - Placebo	1.0	0.4, 1.6	0.0006
AB 200 µg	270	1.5	0.2	AB 200 µg - Placebo	0.6	0.0, 1.2	0.0387
Placebo	257	0.9	0.2	—	—	—	—
LAS-MD-33 (Week 12)							
AB 400 µg	172	1.5	0.2	AB 400 µg - Placebo	1.0	0.4, 1.6	0.0021
AB 200 µg	165	1.4	0.2	AB 200 µg - Placebo	0.9	0.3, 1.6	0.0054
Placebo	161	0.5	0.2	—	—	—	—
LAS-MD-38 (Part A) (Week 12)							
AB 400 µg	142	1.3	0.2	AB 400 µg - Placebo	1.0	0.3, 1.7	0.0054
AB 200 µg	149	1.0	0.2	AB 200 µg - Placebo	0.7	0.0, 1.4	0.0416
Placebo	148	0.3	0.3	—	—	—	—
Pooled 2 Studies: M/34273/34 and LAS-MD-33 (Week 12)							
AB 400 µg	434	1.6	0.2	AB 400 µg - Placebo	0.9	0.5, 1.3	< 0.0001
AB 200 µg	435	1.3	0.2	AB 200 µg - Placebo	0.6	0.2, 1.0	0.0062
Placebo	418	0.7	0.2	—	—	—	—

Note: Analysis is based on ANCOVA model for change from baseline in TDI Focal score, with treatment group and sex as factors, and age and baseline TDI Focal score as covariates.

AB = aclidinium bromide; CI = confidence interval; ITT = intent to treat; N = number of patients; TDI = Transition Dyspnea Index.

a LS mean for the treatment difference.

Figure 11.2–2. **Comparison of TDI Responders (1-Unit Improvement) Versus Placebo at Week 12 Across the Phase 3 Studies:(33 and 34) and at Week 24 in Study 34-ITT Population**

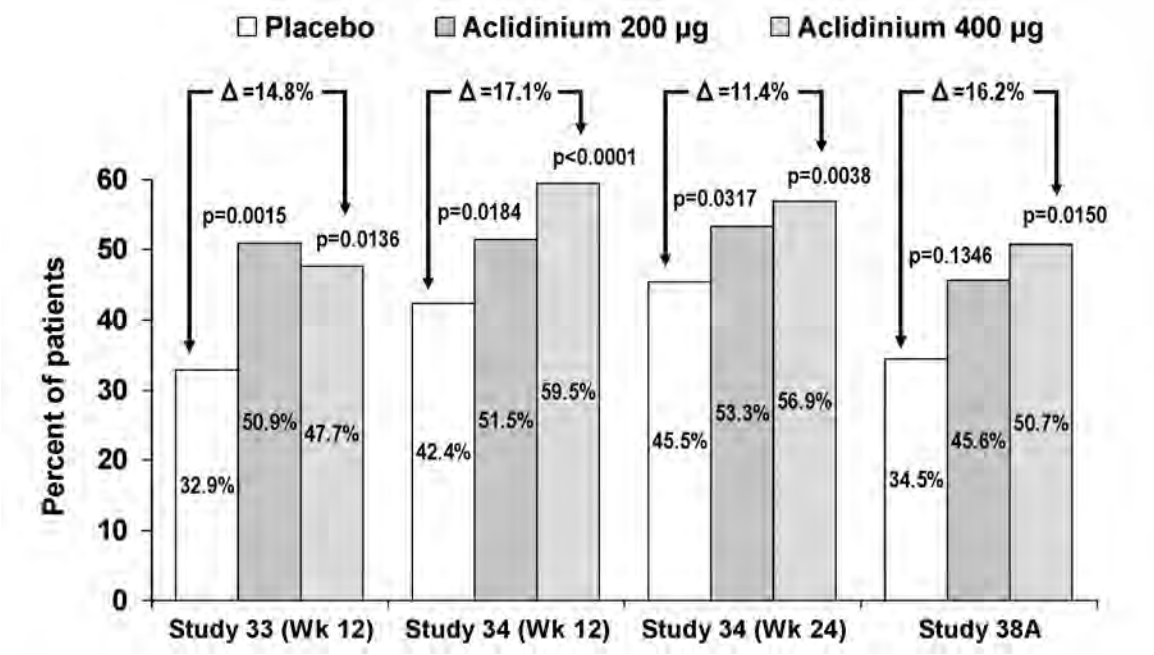

Table 11.2–9. **Incidence of Events per 1000 Patient-years of Exposure Resulting in Hospitalization in the General COPD Population (as per the Literature)**

Outcome	***Case Patient Rate[a] (N = 45,966)***	***Control Subject Rate[a] (N = 45,966)***
VT/VF/cardiac arrest	0.98	0.23
Atrial fibrillation	5.92	2.50
Other arrhythmia	2.96	1.51
Angina	5.31	2.33
MI	9.50	4.53
CHF	18.07	3.52

Table 11.2–9. Incidence of Events per 1000 Patient-years of Exposure Resulting in Hospitalization in the General COPD Population (as per the Literature)

Outcome	***Case Patient Rate[a] (N = 45,966)***	***Control Subject Rate[a] (N = 45,966)***
Stroke	8.08	5.52
Pulmonary embolism	1.29	0.43
Other CVD	23.34	10.93
Any study end point	45.57	18.37
Any CVD	64.02	27.93

a Age-adjusted rate in literature was per 100,000 person-years; data modified to reflect 1,000 person-years in this slide.
PY = patient-years of exposure; VT = ventricular tachycardia; VF = ventricular fibrillation; CVD = cardiovascular disease.
Sidney et al, *COPD and Incident Cardiovascular Disease Hospitalizations and Mortality Kaiser Permanente Medical Care Program. Chest* 2005;128;2068-2075

Table 11.2–10. Incidence of Events per 1000 Patient-years of Exposure Resulting in Death in the General COPD Population (as per the Literature)

Outcome	***Case Patient Rate[a] (N = 45,966)***	***Control Subject Rate[a] (N = 45,966)***
MI	3.86	2.14
CHF	1.09	0.31
Stroke	2.06	1.72
Pulmonary embolism	0.20	0.10
Other CVD	11.15	5.42
Any study endpoint	7.27	4.35
All CVD	18.42	9.77

a Age-adjusted rate in literature was per 100,000 person-years; data modified to reflect 1,000 person-years in this slide.

PY = patient-years of exposure; CVD = cardiovascular disease.

Sidney et al, *COPD and Incident Cardiovascular Disease Hospitalizations and Mortality: Kaiser Permanente Medical Care Program. Chest* 2005;128;2068-2075

Table 11.2–11. Incidence of Events per 1000 Patient-years of Exposure Resulting in Hospitalization/Death in the General COPD Population (as per the Literature)

	Event	***COPD Patients (N = 11,493) Event/1000 PY***	***Controls (N = 22,986) Event/1000 PY***
Cause of hospitalization:	Arrhythmia	16.44	8.18
	Angina	6.02	2.34
	Acute myocardial infarction	10.86	6.56
	Congestive heart failure	31.96	6.10
	Stroke	12.44	9.77
	Pulmonary embolism	1.72	0.31
	Any cardiovascular hospitalization	109.50	44.66
	Any hospitalization	598.36	221.23
Underlying cause of death:	Arrhythmia	1.94	0.69
	Acute myocardial infarction	5.89	3.90
	Congestive heart failure	4.10	1.00
	Stroke	4.17	3.37
	Pulmonary embolism	0.33	0.15
	Any cardiovascular mortality	31.89	15.39
	Any mortality	106.58	37.79

PY = patient-years of exposure.

Curkendall et al, *Cardiovascular Disease in COPD Patients.* AEP Vol. 16, No. 1 January 2006: 63-70

Table 11.2–12. Listing of On-Treatment Deaths in Phase 3 Clinical Studies in COPD Patients - Once-Daily Dosing of Aclidinium Bromide—Safety Population

Study ID	*Patient/Subject ID*	*Age/Sex*	*TEAE (Preferred term)*	*TEAE Relationship to IP*
Aclidinium bromide (200 µg QD) - on treatment deaths				
M/34273/30	4016.004	69/M	Sudden cardiac death	No
M/34273/30	4020.009	63/M	Sudden cardiac death	No
M/34273/30	4031.001	61/M	Gastrointestinal haemorrhage	No
M/34273/30	4076.008	64/M	Pancreatic carcinoma	No
M/34273/30	4104.007	55/M	Cardiovascular insufficiency	No
M/34273/30	4156.017	59/M	Acute abdomen	No
M/34273/30	4500.006	58/M	Pulmonary oedema	No
M/34273/31	2037.001	68/F	Respiratory failure	No
M/34273/31	2082.006	48/M	Multiple drug overdose	No
M/34273/31	2207.003	61/M	Arteriosclerosis coronary artery	No
M/34273/31	2375.034	73/F	Acute respiratory failure	No
Placebo - on treatment deaths				
M/34273/30	4091.005	54/M	Cerebrovascular accident	No
M/34273/30	4131.001	51/M	Chronic obstructive pulmonary disease	No
M/34273/30	4134.001	75/F	Peritonitis	No
M/34273/31	2253.001	72/M	Rhabdomyolysis	No
M/34273/31	2375.014	62/M	Chronic obstructive pulmonary disease	No

Note: this table includes the number of deaths occurring during treatment and up to 30 days after stopping investigational product. There was 1 on-treatment death in a patient treated with aclidinium bromide 200 µg in QD short-term 3-way crossover Study 25.

Randomization in studies 30 and 31 was a ratio of 3 aclidinium bromide to 1 placebo.

F = Female; ID = Identification; IP = Investigational product; M = Male

Table 11.2–13. Treatment-Emergent Serious Adverse Events in ≥ 2 patients by Preferred Term in Any Treatment Group: Placebo-controlled, Long-Term Safety Studies, Once Daily Dosing in COPD Patients (Study 30 and Study 31)

Preferred Term	***Placebo QD N = 420***	***Aclidinium Bromide 200 µg QD N = 1227***
Number (%) of Patients with at least 1 SAE	41 (9.8)	108 (8.8)
Pneumonia	5 (1.2)	12 (1.0)
Lobar pneumonia	1 (0.2)	4 (0.3)
Myocardial infarction	2 (0.5)	4 (0.3)
Pulmonary embolism	0 (0.0)	3 (0.2)
Acute myocardial infarction	0 (0.0)	3 (0.2)
Angina unstable	0 (0.0)	3 (0.2)
Atrial fibrillation	1 (0.2)	2 (0.2)
Retinal detachment	0 (0.0	2 (0.2)
Abdominal pain	1 (0.2)	2 (0.2)
Constipation	0 (0.0)	2 (0.2)
Chest pain	0 (0.0)	2 (0.2)
Sudden cardiac death	0 (0.0)	2 (0.2)
Humerus fracture	0 (0.0)	2 (0.2)
Carotid artery stenosis	0 (0.0)	2 (0.2)
Cerebrovascular accident	1 (0.2)	2 (0.2)
Transient ischemic attack	0 (0.0)	2 (0.2)
Acute respiratory failure	0 (0.0)	2 (0.2)
COPD[a]	4 (1.0)	2 (0.2)
Epistaxis	0 (0.0)	2 (0.2)
Respiratory failure	4 (1.0)	2 (0.2)
Angina pectoris	2 (0.5)	1 (0.1)
Renal cell carcinoma	2 (0.5)	0 (0.0)
Syncope	2 (0.5)	0 (0.0)
Rib fracture	2 (0.5)	0 (0.0)

a COPD (exacerbations) were not reported as SAEs in studies 30 and 31, except in case of fatal or life-threatening events.

COPD = chronic obstructive pulmonary disease exacerbation

Studies 30 and 31

Table 11.2–14. Vital Signs: Mean Change From Baseline to End of Study for Double-blind, Placebo-Controlled Studies With Twice Daily Administration of Aclidinium Bromide in Patients With COPD (BID Group 1A)

Test	***Placebo***		***Aclidinium bromide***			
	BID N = 641		*200 µg BID N = 644*		*400 µg BID N = 636*	
	Baseline Mean (SD)	**Mean (SD) Change From Baseline**	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**
Systolic blood pressure, mm Hg	129.1 (14.7)	-1.4 (14.7)	129.5 (14.9)	-0.3 (14.1)	130.0 (15.2)	-1.2 (14.5)
Diastolic blood pressure, mm Hg	77.6 (9.5)	-1.0 (9.1)	78.1 (9.6)	-0.5 (9.3)	77.9 (9.3)	-0.6 (9.2)

BID = twice daily; COPD = chronic obstructive pulmonary disease; N = number of patients.
Studies: 33, 34, and 38(A).

Table 11.2–15. Mean Changes From Baseline to Last Visit for Heart Rate Values: Double-Blind, Placebo-Controlled Studies (BID Group 1A)

	Placebo		***Aclidinium Bromide***			
	BID N = 641		*200 µg BID N = 644*		*400 µg BID N = 636*	
Test	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**
Heart Rate	73.3 (12.5)	-3.0 (11.0)	73.5 (12.9)	-3.7 (11.1)	73.9 (13.0)	-3.0 (11.6)

BID = twice daily; µg = microgram; msec = milliseconds; N = number of patients; SD = standard deviation
Studies: 33, 34, 38 (A)

Table 11.2–16. Vital Signs: Mean Change From Baseline to Last Visit for Long-term Safety Studies With Twice Daily Administration of Aclidinium Bromide to Patients With COPD (BID Group 1B)

	Aclidinium bromide			
	200 µg BID N = 568		*400 µg BID N = 1005*	
Test	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**	**Baseline Mean (SD)**	**Mean (SD) Change From Baseline**
Systolic Blood Pressure (mm Hg)	127.3 (15.0)	0.7 (15.2)	129.1 (15.1)	-1.6 (15.3)
Diastolic Blood Pressure (mm Hg)	76.3 (9.1)	0.1 (9.3)	76.3 (9.4)	-0.4 (9.6)

BID = twice daily; mm Hg = millimeters of mercury; N = number of patients.
Studies: 35, 33 and 36 combined, 38 (A) and 38 (B) combined.

Table 11.2–17. Mean Change From Baseline to Last Visit in Heart Rate Values: Long-Term Safety Studies (BID Group 1B)

Test	***Aclidinium bromide***	
	200 µg BID N = 568 381.8 PY	*400 µg BID N = 1005 758.0 PY*
	Mean (SD) Change From Baseline	
Heart Rate (bpm)	-2.5 (10.7)	-1.6 (11.4)

bpm = beats per minute; PY = patient-years of exposure; QTcF = QT interval corrected for heart rate using the Fridericia formula ($QTcF = QT/(RR)^{1/3}$).
Studies LAS-MD-35, LAS-MD-33 and LAS-MD-36 combined, and LAS-MD-38 (Part A) and LAS-MD-38 (Part B) combined.

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class *Preferred Term*	*Study 33*			*Study 34*			*Study 38 (A)*		
	Placebo N = 186 n (%)	*AB 200 µg N = 184 n (%)*	*AB 400 µg N = 190 n (%)*	*Placebo N = 273 n (%)*	*AB 200 µg N = 277 n (%)*	*AB 400 µg N = 269 n (%)*	*Placebo N = 182 n (%)*	*AB 200 µg N = 183 n (%)*	*AB 400 µg N = 177 n (%)*
Patients with abnormalities in any SOC	185 (99.5)	182 (98.9)	186 (97.9)	244 (89.4)	250 (90.3)	249 (92.6)	177 (97.3)	182 (99.5)	177 (100.0)
Blood and lymphatic system disorders	**7 (3.8)**	**7 (3.8)**	**9 (4.7)**	**5 (1.8)**	**2 (0.7)**	**5 (1.9)**	**13 (7.1)**	**9 (4.9)**	**19 (10.7)**
Anemia	5 (2.7)	4 (2.2)	7 (3.7)	1 (0.4)	1 (0.4)	1 (0.4)	7 (3.8)	5 (2.7)	10 (5.6)
Cardiac disorders	**45 (24.2)**	**44 (23.9)**	**50 (26.3)**	**57 (20.9)**	**49 (17.1)**	**69 (25.7)**	**46 (25.3)**	**51 (27.9)**	**55 (31.1)**
Coronary artery disease	16 (8.6)	16 (8.7)	16 (8.4)	15 (5.5)	9 (3.2)	14 (5.2)	18 (9.9)	19 (10.4)	20 (11.3)
Myocardial infarction	5 (2.7)	9 (4.9)	13 (6.8)	8 (2.9)	8 (2.9)	9 (3.3)	11 (6.0)	13 (7.1)	13 (7.3)
Atrial fibrillation	7 (3.8)	7 (3.8)	4 (2.1)	3 (1.1)	2 (0.7)	10 (3.7)	5 (2.7)	6 (3.3)	6 (3.4)
Cardiac failure congestive	6 (3.2)	3 (1.6)	8 (4.2)	4 (1.5)	5 (1.8)	9 (3.3)	2 (1.1)	2 (1.1)	5 (2.8)
Myocardial ischemia	—	—	—	19 (7.0)	16 (5.8)	14 (5.2)	4 (2.2)	3 (1.6)	2 (1.1)
Surgical and medical procedures	**131 (70.4)**	**125 (67.9)**	**127 (66.8)**	**70 (25.6)**	**64 (23.1)**	**69 (25.7)**	**116 (63.7)**	**110 (60.1)**	**117 (66.1)**
Hysterectomy	27 (14.5)	33 (17.9)	33 (17.4)	15 (5.5)	15 (5.4)	12 (4.5)	22 (12.1)	29 (15.8)	28 (15.8)
Cholecystectomy	13 (7.0)	14 (7.6)	25 (13.2)	6 (2.2)	4 (1.4)	8 (3.0)	16 (8.8)	18 (9.8)	13 (7.3)
Cataract operation	16 (8.6)	11 (6.0)	12 (6.3)	4 (1.5)	3 (1.1)	5 (1.9)	11 (6.0)	12 (6.6)	10 (5.6)
Tonsillectomy	16 (8.6)	14 (7.6)	15 (7.9)	7 (2.6)	3 (1.1)	8 (3.0)	14 (7.7)	14 (7.7)	17 (9.6)
Appendicectomy	16 (8.6)	19 (10.3)	15 (7.9)	16 (5.9)	11 (4.0)	14 (5.2)	15 (8.2)	8 (4.4)	13 (7.3)
Female sterilization	16 (8.6)	12 (6.5)	16 (8.4)	—	1 (0.4)	3 (1.1)	12 (6.6)	15 (8.2)	9 (5.1)
Coronary artery bypass	10 (5.4)	6 (3.3)	7 (3.7)	2 (0.7)	—	1 (0.4)	6 (3.3)	8 (4.4)	8 (4.5)
Hip arthroplasty	8 (4.3)	6 (3.3)	4 (2.1)	1 (0.4)	3 (1.1)	3 (1.1)	2 (1.1)	2 (1.1)	3 (1.7)
Knee arthroplasty	6 (3.2)	3 (1.6)	5 (2.6)	3 (1.1)	—	1 (0.4)	6 (3.3)	5 (2.7)	4 (2.3)
Coronary artery stent insertion	3 (1.6)	3 (1.6)	3 (1.6)	—	1 (0.4)	—	7 (3.8)	7 (3.8)	8 (4.5)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class *Preferred Term*	*Study 33*			*Study 34*			*Study 38 (A)*		
	Placebo N = 186 n (%)	*AB 200 µg N = 184 n (%)*	*AB 400 µg N = 190 n (%)*	*Placebo N = 273 n (%)*	*AB 200 µg N = 277 n (%)*	*AB 400 µg N = 269 n (%)*	*Placebo N = 182 n (%)*	*AB 200 µg N = 183 n (%)*	*AB 400 µg N = 177 n (%)*
Musculoskeletal and connective tissue disorders	**125 (67.2)**	**106 (57.6)**	**123 (64.7)**	**67 (24.5)**	**80 (28.9)**	**81 (30.1)**	**107 (58.8)**	**102 (55.7)**	**108 (61.0)**
Osteoarthritis	41 (22.0)	36 (19.6)	40 (21.1)	15 (5.5)	20 (7.2)	25 (9.3)	44 (24.2)	37 (20.2)	42 (23.7)
Back pain	33 (17.7)	30 (16.3)	33 (17.4)	14 (5.1)	18 (6.5)	19 (7.1)	31 (17.0)	25 (13.7)	32 (18.1)
Osteoporosis	28 (15.1)	18 (9.8)	25 (13.2)	6 (2.2)	10 (3.6)	8 (3.0)	14 (7.7)	13 (7.1)	21 (11.9)
Arthritis	22 (11.8)	22 (12.0)	20 (10.5)	2 (0.7)	3 (1.1)	3 (1.1)	12 (6.6)	21 (11.5)	17 (9.6)
Arthralgia	9 (4.8)	13 (7.1)	13 (6.8)	1 (0.4)	—	3 (1.1)	15 (8.2)	10 (5.5)	13 (7.3)
Muscle spasms	12 (6.5)	8 (4.3)	8 (4.2)	2 (0.7)	7 (2.5)	3 (1.1)	11 (6.0)	8 (4.4)	10 (5.6)
Intervertebral disc protrusion	7 (3.8)	6 (3.3)	8 (4.3)	4 (1.5)	6 (2.2)	3 (1.1)	2 (1.1)	2 (1.1)	8 (4.5)
Spinal osteoarthritis	10 (5.4)	5 (2.7)	8 (4.2)	13 (4.8)	18 (6.5)	12 (4.5)	8 (4.4)	6 (3.3)	8 (4.5)
Pain in extremity	5 (2.7)	4 (2.2)	6 (3.2)	1 (0.4)	1 (0.4)	—	8 (4.4)	5 (2.7)	6 (3.4)
Musculoskeletal pain	9 (4.8)	5 (2.7)	7 (3.7)	3 (1.1)	1 (0.4)	5 (1.9)	3 (1.6)	2 (1.1)	1 (0.6)
Neck pain	3 (1.6)	7 (3.8)	2 (1.1)	1 (0.4)	1 (0.4)	1 (0.4)	7 (3.8)	4 (2.2)	2 (1.1)
Osteopenia	6 (3.2)	5 (2.7)	3 (1.6)	1 (0.4)	1 (0.4)	—	8 (4.4)	8 (4.4)	7 (4.0)
Intervertebral disc degeneration	15 (8.1)	8 (4.3)	4 (2.1)	3 (1.1)	3 (1.1)	2 (0.7)	2 (1.1)	—	6 (3.4)
Vascular disorders	**111 (59.7)**	**110 (59.8)**	**109 (57.4)**	**144 (52.7)**	**140 (50.5)**	**149 (55.4)**	**106 (58.2)**	**117 (63.9)**	**105 (59.3)**
Hypertension	108 (58.1)	103 (56.0)	98 (51.6)	128 (46.9)	119 (43.0)	132 (49.1)	100 (54.9)	109 (59.6)	97 (54.8)
Aortic aneurysm	2 (1.1)	7 (3.8)	2 (1.1)	—	1 (0.4)	3 (1.1)	4 (2.2)	6 (3.3)	5 (2.8)
Peripheral vascular disorder	6 (3.2)	2 (1.1)	6 (3.2)	—	—	1 (0.4)	6 (3.3)	5 (2.7)	3 (1.7)
Arteriosclerosis	3 (1.6)	—	5 (2.6)	7 (2.6)	6 (2.2)	8 (3.0)	1 (0.5)	1 (0.5)	—
Varicose vein	4 (2.2)	2 (1.1)	4 (2.1)	8 (2.9)	7 (2.5)	8 (3.0)	3 (1.6)	2 (1.1)	—
Peripheral arterial occlusive disease	—	—	1 (0.5)	1 (0.4)	1 (0.4)	3 (1.1)	3 (1.6)	4 (2.2)	6 (3.4)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class *Preferred Term*	*Study 33*			*Study 34*			*Study 38 (A)*		
	Placebo *N = 186* *n (%)*	*AB 200 µg* *N = 184* *n (%)*	*AB 400 µg* *N = 190* *n (%)*	*Placebo* *N = 273* *n (%)*	*AB 200 µg* *N = 277* *n (%)*	*AB 400 µg* *N = 269* *n (%)*	*Placebo* *N = 182* *n (%)*	*AB 200 µg* *N = 183* *n (%)*	*AB 400 µg* *N = 177* *n (%)*
Metabolism and nutrition disorders	**102 (54.8)**	**96 (52.2)**	**108 (56.8)**	**78 (28.6)**	**70 (25.3)**	**70 (26.0)**	**89 (48.9)**	**100 (54.6)**	**87 (49.2)**
Hypercholesterolemia	45 (24.2)	25 (13.6)	53 (27.9)	32 (11.7)	29 (10.5)	24 (8.9)	45 (24.7)	37 (20.2)	36 (20.3)
Hyperlipidemia	42 (22.6)	48 (26.1)	39 (20.5)	11 (4.0)	4 (1.4)	4 (1.5)	30 (16.5)	40 (21.9)	33 (18.6)
Type 2 diabetes mellitus	22 (11.8)	18 (9.8)	17 (8.9)	12 (4.4)	11 (4.0)	10 (3.7)	12 (6.6)	25 (13.7)	17 (9.6)
Diabetes mellitus	9 (4.8)	6 (3.3)	7 (3.7)	17 (6.2)	19 (6.9)	18 (6.7)	5 (2.7)	6 (3.3)	5 (2.8)
Obesity	17 (9.1)	11 (6.0)	8 (4.2)	7 (2.6)	5 (1.8)	7 (2.6)	6 (3.3)	4 (2.2)	10 (5.6)
Gout	5 (2.7)	6 (3.3)	6 (3.2)	3 (1.1)	5 (1.8)	7 (2.6)	9 (4.9)	4 (2.2)	8 (4.5)
Hypertriglyceridemia	2 (1.1)	—	1 (0.5)	1 (0.4)	3 (1.1)	1 (0.4)	—	1 (0.5)	3 (1.7)
Hypokalemia	4 (2.2)	—	3 (1.6)	2 (0.7)	1 (0.4)	3 (1.1)	1 (0.5)	—	1 (0.6)
Glucose tolerance impaired	1 (0.5)	4 (2.2)	5 (2.6)	2 (0.7)	1 (0.4)	1 (0.4)	2 (1.1)	—	2 (1.1)
Hyperglycemia	3 (1.6)	1 (0.5)	3 (1.6)	—	—	1 (0.4)	2 (1.1)	2 (1.1)	—
Dyslipidemia	3 (1.6)	2 (1.1)	6 (3.2)	9 (3.3)	2 (0.7)	3 (1.1)	3 (1.6)	10 (5.5)	6 (3.4)
Hyperuricemia	—	—	—	7 (2.6)	8 (2.9)	8 (3.0)	1 (0.5)	—	—
Gastrointestinal disorders	**106 (57.0)**	**84 (45.7)**	**100 (52.6)**	**59 (21.6)**	**72 (26.0)**	**67 (24.9)**	**89 (48.9)**	**77 (42.1)**	**79 (44.6)**
Gastroesophageal reflux disease	64 (34.4)	53 (28.8)	59 (31.1)	10 (3.7)	10 (3.6)	17 (6.3)	55 (30.2)	48 (26.2)	47 (26.6)
Dyspepsia	10 (5.4)	12 (6.5)	11 (5.8)	16 (5.9)	15 (5.4)	13 (4.8)	11 (6.0)	4 (2.2)	4 (2.3)
Constipation	13 (7.0)	5 (2.7)	11 (5.8)	3 (1.1)	7 (2.5)	6 (2.2)	11 (6.0)	4 (2.2)	6 (3.4)
Hemorrhoids	14 (7.5)	9 (4.9)	7 (3.7)	2 (0.7)	2 (0.7)	3 (1.1)	2 (1.1)	—	10 (5.6)
Colonic polyp	10 (5.4)	7 (3.8)	7 (3.7)	—	3 (1.1)	—	4 (2.2)	6 (3.3)	7 (4.0)
Duodenal ulcer	1 (0.5)	—	3 (1.6)	6 (2.2)	4 (1.4)	10 (3.7)	—	—	—
Hiatus hernia	15 (8.1)	4 (2.2)	6 (3.2)	9 (3.3)	4 (1.4)	4 (1.5)	4 (2.2)	8 (4.4)	5 (2.8)
Gastritis	2 (1.1)	3 (1.6)	1 (0.5)	5 (1.8)	9 (3.2)	7 (2.6)	—	2 (1.1)	2 (1.1)
Diarrhea	5 (2.7)	4 (2.2)	4 (2.1)	1 (0.4)	2 (0.7)	—	3 (1.6)	4 (2.2)	3 (1.7)
Diverticulum	7 (3.8)	6 (3.3)	9 (4.7)	1 (0.4)	2 (0.7)	1 (0.4)	1 (0.5)	1 (0.5)	8 (4.5)
Inguinal hernia	4 (2.2)	3 (1.6)	8 (4.2)	2 (0.7)	4 (1.4)	2 (0.7)	1 (0.5)	4 (2.2)	7 (4.0)
Irritable bowel syndrome	2 (1.1)	4 (2.2)	9 (4.7)	2 (0.7)	2 (0.7)	3 (1.1)	6 (3.3)	4 (2.2)	3 (1.7)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class ***Preferred Term***	***Study 33***			***Study 34***			***Study 38 (A)***		
	Placebo *N = 186* *n (%)*	*AB 200 µg* *N = 184* *n (%)*	*AB 400 µg* *N = 190* *n (%)*	*Placebo* *N = 273* *n (%)*	*AB 200 µg* *N = 277* *n (%)*	*AB 400 µg* *N = 269* *n (%)*	*Placebo* *N = 182* *n (%)*	*AB 200 µg* *N = 183* *n (%)*	*AB 400 µg* *N = 177* *n (%)*
Psychiatric disorders	**81 (43.5)**	**77 (41.8)**	**82 (43.2)**	**29 (10.6)**	**24 (8.7)**	**25 (9.3)**	**74 (40.7)**	**76 (41.5)**	**80 (45.2)**
Depression	44 (23.7)	43 (23.4)	49 (25.8)	6 (2.2)	12 (4.3)	10 (3.7)	45 (24.7)	44 (24.0)	47 (26.6)
Anxiety	33 (17.7)	37 (20.1)	29 (15.3)	6 (2.2)	5 (1.8)	5 (1.9)	33 (18.1)	30 (16.4)	32 (18.1)
Insomnia	35 (18.8)	33 (17.9)	26 (13.7)	11 (4.0)	8 (2.9)	6 (2.2)	18 (9.9)	29 (15.8)	33 (18.6)
Nervous system disorders	**66 (35.5)**	**69 (37.5)**	**77 (40.5)**	**35 (12.8)**	**40 (14.4)**	**33 (12.3)**	**58 (31.9)**	**56 (30.6)**	**59 (33.3)**
Headache	16 (8.6)	15 (8.2)	26 (13.7)	13 (4.8)	20 (7.2)	17 (6.3)	18 (9.9)	14 (7.7)	17 (9.6)
Migraine	7 (3.8)	10 (5.4)	11 (5.8)	2 (0.7)	3 (1.1)	3 (1.1)	6 (3.3)	9 (4.9)	12 (6.8)
Sinus headache	5 (2.7)	1 (0.5)	5 (2.6)	—	—	1 (0.4)	4 (2.2)	2 (1.1)	2 (1.1)
Restless legs syndrome	5 (2.7)	5 (2.7)	7 (3.7)	2 (0.7)	1 (0.4)	—	7 (3.8)	7 (3.8)	6 (3.4)
Carpal tunnel syndrome	9 (4.8)	6 (3.3)	4 (2.1)	—	1 (0.4)	—	3 (1.6)	3 (1.6)	6 (3.4)
Hypoesthesia	1 (0.5)	7 (3.8)	6 (3.2)	—	—	—	3 (1.6)	5 (2.7)	4 (2.3)
Neuropathy peripheral	7 (3.8)	7 (3.8)	6 (3.2)	—	—	—	6 (3.3)	4 (2.2)	3 (1.7)
Sciatica	4 (2.2)	5 (2.7)	6 (3.2)	1 (0.4)	1 (0.4)	1 (0.4)	3 (1.6)	1 (0.5)	1 (0.6)
Transient ischemic attack	2 (1.1)	2 (1.1)	6 (3.2)	—	1 (0.4)	—	1 (0.5)	2 (1.1)	5 (2.8)
Infections and infestations	**71 (38.2)**	**67 (36.4)**	**61 (32.1)**	**32 (11.7)**	**38 (13.7)**	**50 (18.6)**	**48 (26.4)**	**59 (32.2)**	**55 (31.1)**
Pneumonia	19 (10.2)	11 (6.0)	12 (6.3)	4 (1.5)	8 (2.9)	5 (1.9)	8 (4.4)	12 (6.6)	15 (8.5)
Sinusitis	7 (3.8)	9 (4.9)	10 (5.3)	2 (0.7)	4 (1.4)	8 (3.0)	7 (3.8)	13 (7.1)	11 (6.2)
Chronic sinusitis	3 (1.6)	3 (1.6)	7 (3.7)	—	1 (0.4)	2 (0.7)	2 (1.1)	4 (2.2)	1 (0.6)
Herpes zoster	4 (2.2)	2 (1.1)	6 (3.2)	1 (0.4)	1 (0.4)	—	4 (2.2)	—	1 (0.6)
Cellulitis	6 (3.2)	1 (0.5)	4 (2.1)	—	—	—	1 (0.5)	2 (1.1)	1 (0.6)
Hepatitis C	3 (1.6)	7 (3.8)	4 (2.1)	2 (0.7)	1 (0.4)	—	2 (1.1)	7 (3.8)	3 (1.7)
Rhinitis	2 (1.1)	7 (3.8)	4 (2.1)	6 (2.2)	3 (1.1)	4 (1.5)	1 (0.5)	6 (3.3)	1 (0.6)
Diverticulitis	8 (4.3)	3 (1.6)	3 (1.6)	1 (0.4)	0	1 (0.4)	1 (0.5)	5 (2.7)	4 (2.3)
Urinary tract infection	2 (1.1)	5 (2.7)	3 (1.6)	2 (0.7)	0	1 (0.4)	1 (0.5)	4 (2.2)	1 (0.6)
Appendicitis	1 (0.5)	6 (3.3)	2 (1.1)	—	—	—	2 (1.1)	5 (2.7)	4 (2.3)
Bronchitis	6 (3.2)	2 (1.1)	2 (1.1)	—	—	1 (0.4)	3 (1.6)	3 (1.6)	4 (2.3)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class *Preferred Term*	*Study 33*			*Study 34*			*Study 38 (A)*		
	Placebo *N = 186* *n (%)*	*AB 200 µg* *N = 184* *n (%)*	*AB 400 µg* *N = 190* *n (%)*	*Placebo* *N = 273* *n (%)*	*AB 200 µg* *N = 277* *n (%)*	*AB 400 µg* *N = 269* *n (%)*	*Placebo* *N = 182* *n (%)*	*AB 200 µg* *N = 183* *n (%)*	*AB 400 µg* *N = 177* *n (%)*
Immune system disorders	**69 (37.1)**	**55 (29.9)**	**66 (34.7)**	**11 (4.0)**	**12 (4.3)**	**9 (3.3)**	**49 (26.9)**	**63 (34.4)**	**58 (32.8)**
Drug hypersensitivity	38 (20.4)	40 (21.7)	48 (25.3)	4 (1.5)	7 (2.5)	5 (1.9)	33 (18.1)	39 (21.3)	37 (20.9)
Seasonal allergy	24 (12.9)	16 (8.7)	13 (6.8)	1 (0.4)	2 (0.7)	2 (0.7)	20 (11.0)	25 (13.7)	17 (9.6)
Respiratory, thoracic and mediastinal disorders	**67 (36.0)**	**70 (38.0)**	**65 (34.2)**	**24 (8.8)**	**24 (8.7)**	**18 (6.7)**	**52 (28.6)**	**48 (26.2)**	**56 (31.6)**
Rhinitis allergic	17 (9.1)	12 (6.5)	23 (12.1)	7 (2.6)	8 (2.9)	6 (2.2)	8 (4.4)	11 (6.0)	20 (11.3)
Sleep apnea syndrome	18 (9.7)	18 (9.8)	17 (8.9)	8 (2.9)	1 (0.4)	2 (0.7)	17 (9.3)	14 (7.7)	12 (6.8)
Rhinitis seasonal	6 (3.2)	4 (2.2)	4 (2.1)	—	1 (0.4)	1 (0.4)	6 (3.3)	4 (2.2)	1 (0.6)
Eye disorders	**37 (19.9)**	**49 (26.6)**	**37 (19.5)**	**22 (8.1)**	**19 (6.9)**	**16 (5.9)**	**42 (23.1)**	**41 (22.4)**	**42 (23.7)**
Cataract	15 (8.1)	15 (8.2)	15 (7.9)	7 (2.6)	7 (2.5)	6 (2.2)	20 (11.0)	24 (13.1)	18 (10.2)
Myopia	9 (4.8)	9 (4.9)	7 (3.7)	3 (1.1)	3 (1.1)	2 (0.7)	10 (5.5)	6 (3.3)	6 (3.4)
Presbyopia	4 (2.2)	4 (2.2)	6 (3.2)	2 (0.7)	—	—	7 (3.8)	7 (3.8)	7 (4.0)
Glaucoma	1 (0.5)	4 (2.2)	2 (1.1)	—	—	—	1 (0.5)	1 (0.5)	1 (0.6)
Open angle glaucoma	1 (0.5)	3 (1.6)	—	—	—	1 (0.4)	1 (0.5)	2 (1.1)	3 (1.7)
Hypermetropia	3 (1.6)	6 (3.3)	3 (1.6)	1 (0.4)	2 (0.7)	—	5 (2.7)	4 (2.2)	6 (3.4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**50 (26.9)**	**32 (17.4)**	**39 (20.5)**	**9 (3.3)**	**11 (4.0)**	**11 (4.1)**	**29 (15.9)**	**33 (18.0)**	**33 (18.6)**
Lung neoplasm	4 (2.2)	6 (3.3)	7 (3.7)	—	—	1 (0.4)	6 (3.3)	4 (2.2)	3 (1.7)
Basal cell carcinoma	15 (8.1)	3 (1.6)	5 (2.6)	1 (0.4)	2 (0.7)	—	4 (2.2)	6 (3.3)	6 (3.4)
Lung neoplasm malignant	—	1 (0.5)	3 (1.6)	—	—	1 (0.4)	1 (0.5)	4 (2.2)	1 (0.6)
Benign lung neoplasm	—	1 (0.5)	1 (0.5)	—	—	—	—	1 (0.5)	4 (2.3)
Reproductive system and breast disorders	**36 (19.4)**	**51 (27.7)**	**40 (21.1)**	**16 (5.9)**	**14 (5.1)**	**15 (5.6)**	**31 (17.0)**	**37 (20.2)**	**30 (16.9)**
Benign prostatic hyperplasia	15 (8.1)	19 (10.3)	18 (9.5)	9 (3.3)	10 (3.6)	13 (4.8)	15 (8.2)	18 (9.8)	11 (6.2)
Erectile dysfunction	8 (4.3)	14 (7.6)	7 (3.7)	3 (1.1)	—	2 (0.7)	12 (6.6)	9 (4.9)	14 (7.9)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class *Preferred Term*	*Study 33*			*Study 34*			*Study 38 (A)*		
	Placebo *N = 186* *n (%)*	*AB 200 µg* *N = 184* *n (%)*	*AB 400 µg* *N = 190* *n (%)*	*Placebo* *N = 273* *n (%)*	*AB 200 µg* *N = 277* *n (%)*	*AB 400 µg* *N = 269* *n (%)*	*Placebo* *N = 182* *n (%)*	*AB 200 µg* *N = 183* *n (%)*	*AB 400 µg* *N = 177* *n (%)*
Investigations	**38 (20.4)**	**38 (20.7)**	**34 (17.9)**	**5 (1.8)**	**8 (2.9)**	**6 (2.2)**	**31 (17.0)**	**37 (20.2)**	**28 (15.8)**
Blood cholesterol increased	12 (6.5)	8 (4.3)	5 (2.6)	—	—	—	10 (5.5)	9 (4.9)	4 (2.3)
Cardiac murmur	3 (1.6)	3 (1.6)	6 (3.2)	1 (0.4)	—	—	7 (3.8)	4 (2.2)	4 (2.3)
Colonoscopy	7 (3.8)	—	4 (2.1)	—	—	—	3 (1.6)	6 (3.3)	3 (1.7)
Skin and subcutaneous tissue disorders	**29 (15.6)**	**36 (19.6)**	**40 (21.1)**	**13 (4.8)**	**14 (5.1)**	**22 (8.2)**	**25 (13.7)**	**26 (14.2)**	**30 (16.9)**
Psoriasis	2 (1.1)	8 (4.3)	8 (4.2)	6 (2.2)	2 (0.7)	3 (1.1)	2 (1.1)	5 (2.7)	3 (1.7)
Eczema	2 (1.1)	7 (3.8)	3 (1.6)	2 (0.7)	5 (1.8)	6 (2.2)	2 (1.2)	4 (2.2)	2 (1.1)
Injury, poisoning and procedural complications	**23 (12.4)**	**31 (16.8)**	**31 (16.3)**	**22 (8.1)**	**14 (5.1)**	**27 (10.0)**	**32 (17.6)**	**28 (15.3)**	**29 (16.4)**
General disorders and administration site conditions	**25 (13.4)**	**30 (16.3)**	**29 (15.3)**	**11 (4.0)**	**4 (1.4)**	**8 (3.0)**	**16 (8.8)**	**21 (11.5)**	**22 (12.4)**
Edema peripheral	8 (4.3)	13 (7.1)	11 (5.8)	8 (2.9)	4 (1.4)	5 (1.9)	6 (3.3)	10 (5.5)	8 (4.5)
Fatigue	5 (2.7)	5 (2.7)	3 (1.6)	—	—	—	6 (3.3)	4 (2.2)	5 (2.8)
Renal and urinary disorders	**28 (15.1)**	**22 (12.0)**	**33 (17.4)**	**15 (5.5)**	**14 (5.1)**	**23 (8.6)**	**30 (16.5)**	**27 (14.8)**	**22 (12.4)**
Nephrolithiasis	7 (3.8)	4 (2.2)	9 (4.7)	5 (1.8)	5 (1.8)	8 (3.0)	6 (3.3)	5 (2.7)	7 (4.0)
Renal failure	1 (0.5)	1 (0.5)	3 (1.6)	1 (0.4)	—	1 (0.4)	1 (0.5)	2 (1.1)	—
Hematuria	6 (3.2)	3 (1.6)	2 (1.1)	—	2 (0.7)	4 (1.5)	1 (0.5)	2 (1.1)	2 (1.1)
Renal failure chronic	1 (0.5)	1 (0.5)	1 (0.5)	—	—	1 (0.4)	5 (2.7)	4 (2.2)	1 (0.6)
Renal failure acute	—	—	—	—	—	—	3 (1.6)	—	—
Hypertonic bladder	1 (0.5)	4 (2.2)	1 (0.5)	—	—	—	4 (2.2)	6 (3.3)	5 (2.8)
Hepatobiliary disorders	**6 (3.2)**	**12 (6.5)**	**10 (5.3)**	**17 (6.2)**	**18 (6.5)**	**17 (6.3)**	**8 (4.4)**	**11 (6.0)**	**7 (4.0)**
Cholelithiasis	1 (0.5)	5 (2.7)	7 (3.7)	6 (2.2)	3 (1.1)	7 (2.6)	6 (3.3)	6 (3.3)	3 (1.7)
Ear and labyrinth disorders	**23 (12.4)**	**19 (10.3)**	**25 (13.2)**	**7 (2.6)**	**7 (2.5)**	**13 (4.8)**	**16 (8.8)**	**19 (10.4)**	**14 (7.9)**
Tinnitus	1 (0.5)	3 (1.6)	1 (0.5)	2 (0.7)	1 (0.4)	1 (0.4)	7 (3.8)	4 (2.2)	4 (2.3)

Table 11.2–18. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%—Aclidinium Bromide Administered Twice Daily to Patients With COPD in Placebo-controlled Studies 33, 34 and 38 (A)

System Organ Class ***Preferred Term***	***Study 33***			***Study 34***			***Study 38 (A)***		
	Placebo *N = 186* *n (%)*	*AB 200 µg* *N = 184* *n (%)*	*AB 400 µg* *N = 190* *n (%)*	*Placebo* *N = 273* *n (%)*	*AB 200 µg* *N = 277* *n (%)*	*AB 400 µg* *N = 269* *n (%)*	*Placebo* *N = 182* *n (%)*	*AB 200 µg* *N = 183* *n (%)*	*AB 400 µg* *N = 177* *n (%)*
Social circumstances	**37 (19.9)**	**41 (22.3)**	**34 (17.9)**	**49 (17.9)**	**48 (17.3)**	**44 (16.4)**	**40 (22.0)**	**31 (16.9)**	**43 (24.3)**
Postmenopause	22 (11.8)	24 (13.0)	21 (11.1)	31 (11.4)	31 (11.2)	28 (10.4)	31 (17.0)	25 (13.7)	37 (20.9)
Menopause	10 (5.4)	8 (4.3)	8 (4.2)	18 (6.6)	15 (5.4)	16 (5.9)	2 (1.1)	2 (1.1)	3 (1.7)
Endocrine disorders	**19 (10.2)**	**26 (14.1)**	**31 (16.3)**	**18 (6.6)**	**12 (4.3)**	**15 (5.6)**	**18 (9.9)**	**19 (10.4)**	**29 (16.4)**
Hypothyroidism	18 (9.7)	22 (12.0)	18 (9.5)	9 (3.3)	7 (2.5)	11 (4.1)	15 (8.2)	14 (7.7)	26 (14.7)

Studies 33, 34, and 38(A)

AB = aclidinium bromide; COPD = chronic obstructive pulmonary disease; SOC = system organ class.

Table 11.2–19. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term, Safety Studies

System Organ Class *Preferred Term*	*Aclidinium bromide*		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 n (%)	**400 µg BID N = 443 n (%)**	**400 µg BID N = 448 n (%)**
Patients with abnormalities in any SOC	438 (97.8)	435 (98.2)	442 (98.7)
Surgical and medical procedures	**280 (62.5)**	**277 (62.5)**	**276 (61.6)**
Hysterectomy	72 (16.1)	62 (14.0)	64 (14.3)
Cholecystectomy	31 (6.9)	39 (8.8)	32 (7.1)
Cataract operation	35 (7.8)	37 (8.4)	25 (5.6)
Tonsillectomy	33 (7.4)	37 (8.4)	37 (8.3)
Appendicectomy	37 (8.3)	32 (7.2)	29 (6.5)
Female sterilization	30 (6.7)	27 (6.1)	29 (6.5)
Coronary artery bypass	20 (4.5)	20 (4.5)	18 (4.0)
Hip arthroplasty	6 (1.3)	14 (3.2)	5 (1.1)
Knee arthroplasty	8 (1.8)	10 (2.3)	14 (3.1)
Coronary artery stent insertion	15 (3.3)	9 (2.0)	17 (3.8)
Musculoskeletal and connective tissue disorders	**256 (57.1)**	**276 (62.3)**	**261 (58.3)**
Osteoarthritis	71 (15.8)	77 (17.4)	104 (23.2)
Back pain	60 (13.4)	69 (15.6)	64 (14.3)
Osteoporosis	41 (9.2)	49 (11.1)	37 (8.3)
Arthritis	61 (13.6)	48 (10.8)	35 (7.8)
Arthralgia	30 (6.7)	26 (5.9)	31 (6.9)
Muscle spasms	22 (4.9)	20 (4.5)	22 (4.9)
Spinal osteoarthritis	15 (3.3)	16 (3.6)	22 (4.9)
Pain in extremity	9 (2.0)	15 (3.4)	17 (3.8)
Musculoskeletal pain	13 (2.9)	14 (3.2)	6 (1.3)
Neck pain	12 (2.7)	14 (3.2)	7 (1.6)
Osteopenia	16 (3.6)	14 (3.2)	19 (4.2)
Intervertebral disc degeneration	14 (3.1)	13 (2.9)	6 (1.3)
Vascular disorders	**265 (59.2)**	**244 (55.1)**	**272 (60.7)**
Hypertension	245 (54.7)	230 (51.9)	254 (56.7)
Aortic aneurysm	11 (2.5)	4 (0.9)	14 (3.1)
Peripheral vascular disorder	14 (3.1)	9 (2.0)	11 (2.5)

Table 11.2–19. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term, Safety Studies

System Organ Class *Preferred Term*	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 n (%)	**400 µg BID N = 443 n (%)**	**400 µg BID N = 448 n (%)**
Metabolism and nutritional disorders	**228 (50.9)**	**227 (51.2)**	**231 (51.6)**
Hypercholesterolemia	78 (17.4)	93 (21.0)	93 (20.8)
Hyperlipidemia	96 (21.4)	86 (19.4)	92 (20.5)
Type 2 diabetes mellitus	37 (8.3)	37 (8.4)	46 (10.3)
Diabetes mellitus	27 (6.0)	21 (4.7)	14 (3.1)
Obesity	30 (6.7)	17 (3.8)	18 (4.0)
Gout	14 (3.1)	15 (3.4)	17 (3.8)
Hypertriglyceridemia	6 (1.3)	4 (0.9)	4 (0.9)
Hypokalemia	3 (0.7)	4 (0.9)	2 (0.4)
Glucose tolerance impaired	3 (0.7)	3 (0.7)	3 (0.7)
Hyperglycemia	1 (0.2)	1 (0.2)	3 (0.7)
Dyslipidemia	6 (1.3)	7 (1.6)	16 (3.6)
Gastrointestinal disorders	**224 (50.0)**	**213 (48.1)**	**198 (44.2)**
Gastroesophageal reflux disease	145 (32.4)	120 (27.1)	120 (26.8)
Dyspepsia	29 (6.5)	21 (4.7)	15 (3.3)
Constipation	13 (2.9)	16 (3.6)	15 (3.3)
Hemorrhoids	15 (3.3)	16 (3.6)	8 (1.8)
Colonic polyp	14 (3.1)	13 (2.9)	12 (2.7)
Hiatus hernia	16 (3.6)	12 (2.7)	14 (3.1)
Gastritis	9 (2.0)	5 (1.1)	3 (0.7)
Diarrhea	5 (1.1)	4 (0.9)	8 (1.8)
Psychiatric disorders	**178 (39.7)**	**184 (41.5)**	**184 (41.1)**
Depression	108 (24.1)	101 (22.8)	107 (23.9)
Anxiety	65 (14.5)	73 (16.5)	75 (16.7)
Insomnia	75 (16.7)	67 (15.1)	67 (15.0)
Nervous system disorders	**166 (37.1)**	**161 (36.3)**	**141 (31.5)**
Headache	47 (10.5)	44 (9.9)	43 (9.6)
Migraine	18 (4.0)	20 (4.5)	20 (4.5)
Sinus headache	7 (1.6)	14 (3.2)	7 (1.6)
Restless leg syndrome	17 (3.8)	9 (2.0)	14 (3.1)
Carpal tunnel syndrome	11 (2.5)	9 (2.0)	11 (2.5)

Table 11.2–19. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term, Safety Studies

System Organ Class *Preferred Term*	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 n (%)	**400 µg BID N = 443 n (%)**	**400 µg BID N = 448 n (%)**
Infections and infestations	**155 (34.6)**	**158 (35.7)**	**128 (28.6)**
Pneumonia	40 (8.9)	37 (8.4)	30 (6.7)
Sinusitis	21 (4.7)	16 (3.6)	23 (5.1)
Immune system disorders	**127 (28.3)**	**151 (34.1)**	**142 (31.7)**
Drug hypersensitivity	75 (16.7)	108 (24.4)	94 (21.0)
Seasonal allergy	40 (8.9)	38 (8.6)	53 (11.8)
Respiratory, thoracic and mediastinal disorders	**138 (30.8)**	**140 (31.6)**	**125 (27.9)**
Rhinitis allergic	33 (7.4)	39 (8.8)	29 (6.5)
Sleep apnea syndrome	33 (7.4)	34 (7.7)	34 (7.6)
Rhinitis seasonal	14 (3.1)	9 (2.0)	11 (2.5)
Cardiac disorders	**124 (27.7)**	**115 (26.0)**	**128 (28.6)**
Coronary artery disease	57 (12.7)	45 (10.2)	48 (10.7)
Myocardial infarction	38 (8.5)	24 (5.4)	26 (5.8)
Cardiac failure congestive	7 (1.6)	11 (2.5)	7 (1.6)
Atrial fibrillation	15 (3.3)	12 (2.7)	16 (3.6)
Eye disorders	**107 (23.9)**	**104 (23.5)**	**107 (23.9)**
Cataract	38 (8.5)	41 (9.3)	52 (11.6)
Myopia	18 (4.0)	21 (4.7)	20 (4.5)
Presbyopia	7 (1.6)	8 (1.8)	18 (4.0)
Glaucoma	5 (1.1)	1 (0.2)	2 (0.4)
Open angle glaucoma	10 (2.2)	4 (0.9)	6 (1.3)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**90 (20.1)**	**94 (21.2)**	**75 (16.7)**
Lung neoplasm	4 (0.9)	13 (2.9)	12 (2.7)
Basal cell carcinoma	14 (3.1)	9 (2.0)	12 (2.7)
Lung neoplasm malignant	2 (0.4)	8 (1.8)	5 (1.1)
Benign lung neoplasm	6 (1.3)	3 (0.7)	3 (0.7)
Reproductive system and breast disorders	**100 (22.3)**	**92 (20.8)**	**82 (18.3)**
Benign prostatic hyperplasia	38 (8.5)	42 (9.5)	41 (9.2)
Erectile dysfunction	29 (6.5)	25 (5.6)	28 (6.3)

Table 11.2–19. Medical and Surgical History by System Organ Class and Preferred Term With an Incidence ≥ 3% in Any Treatment Group and Preferred Terms of Interest With Incidences < 3%: Aclidinium Bromide Administered Twice Daily to Patients With COPD in Long-term, Safety Studies

System Organ Class *Preferred Term*	***Aclidinium bromide***		
	Double-blind long-term safety		*Open-label long-term safety*
	200 µg BID N = 448 n (%)	**400 µg BID N = 443 n (%)**	**400 µg BID N = 448 n (%)**
Investigations	**104 (23.2)**	**83 (18.7)**	**83 (18.5)**
Blood cholesterol increased	26 (5.8)	18 (4.1)	18 (4.0)
Cardiac murmur	9 (2.0)	11 (2.5)	13 (2.9)
Skin and subcutaneous tissue disorders	**67 (15.0)**	**77 (17.4)**	**70 (15.6)**
Injury, poisoning and procedural complications	**60 (13.4)**	**69 (15.6)**	**71 (15.8)**
General disorders and administration site conditions	**69 (15.4)**	**61 (13.8)**	**41 (9.2)**
Oedema peripheral	28 (6.3)	31 (7.0)	17 (3.8)
Fatigue	16 (3.6)	9 (2.0)	12 (2.7)
Renal and Urinary disorders	**61 (13.6)**	**59 (13.3)**	**66 (14.7)**
Nephrolithiasis	15 (3.3)	15 (3.4)	17 (3.8)
Renal failure	2 (0.4)	6 (1.4)	3 (0.7)
Hematuria	6 (1.3)	4 (0.9)	4 (0.9)
Renal failure chronic	6 (1.3)	2 (0.5)	8 (1.8)
Renal failure acute	–	–	2 (0.4)
Blood and lymphatic system disorders	**21 (4.7)**	**26 (5.9)**	**31 (6.9)**
Anemia	13 (2.9)	13 (2.9)	18 (4.0)
Hepatobiliary disorders	**18 (4.0)**	**24 (5.4)**	**20 (4.5)**

BID = twice daily; COPD = chronic obstructive pulmonary disease exacerbation;
Double-blind, long-term safety = Study 35 and Study 36; Open-label, long-term safety = Study 38 (B).