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*APPLICATION NUMBER:*

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**MEDICAL REVIEW(S)**

## CLINICAL REVIEW

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Division / Office	DPARP/OND
Reviewer Name(s)	Jennifer Rodriguez Pippins, MD, MPH
Review Completion Date	May 25, 2012
Established Name	Aclidinium bromide
(Proposed) Trade Name	Tudorza Pressair
Therapeutic Class	Long-acting anticholinergic
Applicant	Forest Laboratories, Inc.
Formulation(s)	Multi-dose DPI, 400 mcg aclidinium bromide per actuation
Dosing Regimen	400 mcg twice daily
Indication(s)	The long-term, maintenance treatment of bronchospasm associated with COPD
Intended Population(s)	COPD

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## 1 Recommendations/Risk Benefit Assessment

### 1.1 Recommendation on Regulatory Action

The clinical recommendation for this New Drug Application (NDA) is Approval. The Application contains adequate evidence of efficacy to support the proposed indication: “the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema,” and the safety profile for the proposed product is acceptable.

Forest Research Institute, Inc. (Forest) has submitted a 505(b)(1) New Drug Application (NDA) for Tudorza Pressair (established name: aclidinium bromide [aclidinium]), a new molecular entity proposed for use as a bronchodilator in patients with chronic obstructive pulmonary disease (COPD). Aclidinium is a long-acting antimuscarinic agent, which is often referred to as an anticholinergic. The proposed dose is one oral inhalation of 400 µg, twice daily (BID). There is only one other inhaled long-acting antimuscarinic agent approved in the United States: Spiriva Handihaler (tiotropium bromide), which is indicated for COPD.

The core development program conducted in support of aclidinium 400 µg BID consists of two phase 2 dose-ranging trials (M/34273/23 and M/34273/29), three phase 3 efficacy and safety trials (M/34273/33, M/34273/34, and M/34273/38 Part A), and three long-term safety trials (LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B).

This clinical review includes an integrated review of efficacy, based on the three phase 3 efficacy and safety trials. This review also includes an integrated review of safety, drawing from data both from the three phase 3 efficacy and safety trials, as well as the three long-term safety trials.

Evidence of efficacy comes from three phase 3 efficacy and safety trials conducted as part of the twice-daily clinical development program. Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A were randomized, double-blind, placebo-controlled, and parallel-group in design. These trials were similar, and each included a run-in and a double-blind treatment period. The main difference among the trials was duration; Trials LAS-MD-33 and LAS-MD-38 Part A were 12 weeks in duration as compared to Trial M/34273/34, which was 24 weeks in duration. While Trial M/34273/34 employed a longer treatment period, the primary efficacy endpoint was assessed at 12 weeks, consistent with the other two trials.

In each of the three pivotal BID efficacy and safety trials, results for the analysis of the primary endpoint, change from baseline in trough FEV1 at Week 12, were statistically

significant for the comparison between aclidinium 400 µg and placebo. While the effect size observed in Trial LAS-MD-38 Part A was smaller (72 mL), the effect sizes demonstrated for the other two trials (LAS-MD-33 and M/34273/34) were of reasonable magnitude (124 mL and 105 mL, respectively), and represent an outcome that is clinically meaningful. These results were robust to analyses conducted for various subgroups. In addition, results for secondary and other endpoints, including additional pulmonary function tests (serial FEV1 over 12 hours, FVC, and IC), COPD exacerbations, rescue medication use, and health related quality of life as measured by the St. George's Respiratory Questionnaire (SGRQ), were generally numerically supportive of the primary analysis. With regards to persistence of efficacy, the overall results for lung function parameters from Trial M/34273/34 at 24 weeks were generally consistent with the results at 12 weeks. These findings are supportive of the findings for the primary endpoint and provide evidence of continued efficacy at 6 months' time. Overall, these results provide replicate evidence of efficacy for the proposed product and indication.

The safety information for aclidinium comes primarily from the twice-daily clinical development program. Across the BID program, a total of 1471 patients with COPD were exposed to aclidinium 400 µg BID, with a mean duration of 211 days. Of these, 733 patients were exposed for 182 days or greater. The number of patients treated with aclidinium 400 µg BID for approximately 1 year or more is 329; at the time of original NDA submission only 97 patients had been exposed for a 1-year duration. While the size of the safety database is generally consistent with international guidelines,<sup>1</sup> it is relatively small compared to the size of programs for other COPD products.

There were a total of 17 deaths reported for the BID program; 13 of these deaths were considered to be on-treatment. There were 6 on-treatment deaths in the three phase 3 efficacy and safety trials (also referred to as "BID Group 1A," which is comprised of Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A), and 7 on-treatment deaths in the BID Long-Term Safety trials (comprised of Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B). For the BID Group 1A trials, slightly more on-treatment deaths are reported for the aclidinium 400 µg treatment group (n=3, 0.5%) than the placebo (n=2, 0.3%) or aclidinium 200 µg treatment groups (n=1, 0.2%). For the BID Long-Term Safety trials, the overall incidence rate for on-treatment death is higher for the 400 µg aclidinium treatment group (7.8 per 1000 PY) compared to the 200 µg aclidinium treatment group (5.9 per 1000 PY). Most events were reported only once, however, several deaths are described as being cardiovascular in origin.

A specific analysis of major adverse cardiac events (MACE), including cardiovascular deaths, was conducted. For the BID Group 1A trials, the MACE score is higher for the placebo treatment group (n=4, 0.6%), than for either of the aclidinium treatment arms

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<sup>1</sup> Guideline for Industry, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions," ICH-E1A, March 1995.

(n=2, 0.3% for both acclidinium 200 µg and acclidinium 400 µg); this is largely driven by an excess of non-fatal strokes for the placebo group as compared to the acclidinium treatment groups. Notably, however, the two cardiovascular deaths occurred in patients treated with acclidinium (n=1, 0.2% for each of the acclidinium treatment arms), while there were no cardiovascular deaths in the placebo treatment arm.

For the BID Long-Term Safety trials the overall MACE score is n=19 (2.1%), IR=29.5 per 1000 PY for the acclidinium 400 µg treatment group and n=8 (1.8%), IR=23.5 per 1000 PY for the acclidinium 200 µg treatment group. It is striking that all the cardiovascular deaths (n=4) are reported for the higher acclidinium dose of 400 µg. The incidence rate for non-fatal stroke is slightly higher for the 400 µg treatment group as compared to the 200 µg treatment group (12.4 per 1000 PY versus 8.8 per 1000 PY). There is no apparent dose-response for the event of non-fatal myocardial infarction.

Most notable from these analyses is the overall low number of events observed. It is not apparent whether this is an artifact of the relatively small sample size and short duration of these trials, or if it is an accurate depiction of acclidinium's safety profile. The cardiovascular death incidence rate observed for acclidinium 400 µg (approximately 5-6 per 1000 PY) is lower than what is generally reported for the "real world" COPD population.<sup>2</sup> While this is not unexpected given the highly controlled nature of a clinical trial, it nonetheless makes interpreting the results a challenge. It is difficult to dismiss the apparent imbalance in cardiovascular death between the treatment groups, while at the same time, impossible to conclude that the data represent a true safety signal.

The Applicant's MACE analysis is complemented by a cardiovascular assessment based on Standard MedDRA Queries (SMQs). For the BID Group 1A trials the analysis revealed a notable imbalance for the SMQ bradyarrhythmia/conduction defects/sinus node disorder, which was reported at a frequency of n=10 (1.6%) for the acclidinium 400 µg treatment arm, versus n=5 (0.8%) for the placebo treatment arm and n=6 (0.9%) for the acclidinium 200 µg treatment arm. A notable imbalance is also observed for the cardiac failure SMQ, which was reported at a frequency of n=5 (0.8%) for the acclidinium 400 µg treatment arm, versus n=2 (0.3%) for the placebo treatment arm and n=1 (0.2%) for the acclidinium 200 µg treatment arm. For the BID Long-Term Safety trials, the results for each of the SMQs are either roughly comparable between the acclidinium 200 µg and 400 µg treatment groups, or higher for the lower dose, with the exception of cardiac failure, which demonstrates an imbalance favoring the acclidinium 200 µg treatment group. The imbalance in cardiac failure observed in both the BID Group 1A and BID Long-Term Safety trials may warrant further exploration.

In addition to the analysis of cardiovascular risk, the Applicant conducted a number of analyses of particular interest and relevance, given the pharmacologic class of the

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<sup>2</sup> In a cohort study conducted in Canada a cardiovascular mortality incidence rate of 41 per 1000 PY was observed for patients with COPD. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005; 2640-6.

proposed product. These included analyses of cerebrovascular adverse events, pneumonia, and anticholinergic adverse events. In addition, the Agency requested an analysis of events related to bowel obstruction, given the increased rate of bowel obstruction observed for other anticholinergics. The results for the cerebrovascular SMQ conducted for the BID Long-Term Safety trials demonstrate an imbalance favoring the acridinium 200 µg treatment group, which had an overall frequency of n=3 (0.7%), versus n=9 (1.0%) for the acridinium 400 µg treatment group; otherwise, the results of these additional analyses generally do not support a dose-relationship between the events of concern and acridinium, but again, the ability to draw conclusions is limited by the overall low number of events and the small size of the long-term safety database.

It is this Reviewer's assessment that the size of the long-term safety database meets minimum requirements, and is therefore adequate for the assessment of safety. While the small numerical imbalances for cardiovascular and cerebrovascular events described above are noted, the data do not constitute a clear safety signal. And while the low number of deaths and serious adverse events makes the interpretation of the observed imbalances difficult, the overall paucity of events of concern is at the same time reassuring. The acridinium safety profile is therefore adequate to support approval. Nevertheless, as is often the case for new molecular entities, additional data obtained post-approval would be useful in the further characterization of proposed product's safety profile, particularly among patients at higher risk for cardiovascular events; it is noted that patients with a number of clinically significant cardiovascular conditions were excluded from the acridinium development program. A phase 4 trial is therefore recommended, as summarized in Section 1.4.

In conclusion, the demonstration of replicate evidence of efficacy as a bronchodilator, along with the acceptable safety profile, warrants a recommendation of Approval for this Application.

## 1.2 Risk Benefit Assessment

As noted in Section 1.1, the acridinium clinical development program provides replicate evidence of efficacy as a bronchodilator. The magnitude of effect is likely to be clinically meaningful.

With regards to risk, small imbalances against acridinium were noted for cardiovascular death, cardiac failure, and cerebrovascular hemorrhage. The small magnitude of these imbalances, the direction of which could be reversed by a change in the outcomes of just a few patients, hampers the interpretation of the safety data. This Reviewer struggled with the limited long-term safety data and its interpretation. Nevertheless, the size of the safety database is generally consistent with international guidelines.<sup>3</sup>

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<sup>3</sup> Guideline for Industry, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs

As described in the Code of Federal Regulations, approval of an application may be refused on the basis of a safety concern if “there is insufficient information about the drug to determine whether the product is safe for use under the conditions prescribed, recommended, or suggested in its proposed labeling.”<sup>4</sup> It is this Reviewer’s assessment that the size of the safety database meets a minimum standard that is just adequate for the assessment of safety. Given this conclusion of adequacy, the absence of a clearly delineated safety signal, and the overall paucity of events of concern, the safety profile of the acridinium is judged to be acceptable. As described in Section 1.4, a post-marketing evaluation of safety, with a particular focus on cardiovascular safety, is recommended.

Given the clear evidence of efficacy, and the acceptable safety profile, this Reviewer finds the risk/benefit profile of acridinium to be favorable. If approved, acridinium will be only the second inhaled long-acting antimuscarinic agent to become available in the United States. The existence of multiple therapeutic options, even within the same drug class, is likely to be of benefit to the public health. Together, these findings support this Reviewer’s recommendation for approval.

### **1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies**

No recommendations for postmarketing risk management activities are made.

### **1.4 Recommendations for Postmarket Requirements and Commitments**

A phase 4 postmarketing requirement (PMR) for a large trial of adequate duration in order to further evaluate long-term safety is recommended. As noted in Sections 1.1 and 1.2, the acridinium safety database meets minimum standards. To that extent, additional safety data, with a focus of cardiovascular adverse events, is desirable.

The Applicant submitted a brief summary of a proposed phase 4 study (b) (4)

The proposal is for a randomized, placebo-controlled, (b) (4) trial in 4000 patients (b) (4)

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Intended for Long-term Treatment of Non-Life-Threatening Conditions,” ICH-E1A, March 1995.

<sup>4</sup> 21 CFR 314.125(b)(4)



The final details of a PMR trial are pending at this time. The Division is currently reviewing the Applicant's proposal with a focus on trial duration, choice of treatment arms, the selection of an appropriate patient population, and the approach to statistical analysis, particularly in light of valuable feedback provided at the February 23, 2012, meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC), as summarized in Section 9.3.

## **2 Introduction and Regulatory Background**

### **2.1 Product Information**

Acclidinium inhalation powder is a breath-actuated multi-dose dry powder inhaler containing 400 µg of acclidinium per actuation, and α-lactose monohydrate, which

functions as a carrier. Each actuation delivers approximately 375 µg of aclidinium from the mouthpiece. The device, which delivers at least 60 doses, is comprised of an assembled plastic dosing mechanism with dose indicator, a drug-product storage unit containing the drug-product formulation, and a mouthpiece with a protective cap.

## 2.2 Tables of Currently Available Treatments for Proposed Indications

A summary of treatments available for the relief of airflow obstruction in patients with COPD is provided in Table 1.

**Table 1. Treatments available for the relief of airflow obstruction in COPD**

<b>Pharmacologic Class</b>	<b>Established Name</b>
Long-acting beta-adrenergic agonists	Salmeterol xinafoate
	Formoterol fumarate
	Arformoterol tartrate
	Indacaterol maleate
Short-acting anticholinergics	Ipratropium bromide
Long-acting anticholinergics	Tiotropium bromide
Combination products	
Short-acting beta-adrenergic agonist/ Anticholinergic agent	Albuterol sulfate/ Ipratropium bromide
Corticosteroid/ Long-acting beta-adrenergic agonist	Fluticasone propionate/ salmeterol xinafoate
	Budesonide/ formoterol fumarate
Methylxanthines	Theophylline

In addition to the products listed above, short-acting beta-adrenergic agents are often used in the management of COPD. While not specifically indicated for COPD, this class of drugs carries a general bronchodilator claim.

With the exception of methylxanthine, all of the products listed in Table 1 are inhalation products.

## 2.3 Availability of Proposed Active Ingredient in the United States

Aclidinium bromide is a new molecular entity and is not currently marketed in the United States.

## 2.4 Important Safety Issues With Consideration to Related Drugs

There are several other inhaled anticholinergic products approved for treatment of bronchospasm in patients with COPD. These include several formulations of the short-acting bronchodilator, ipratropium bromide, which is available as a monotherapy product (Atrovent HFA), or as a combination product with albuterol sulfate (Combivent Inhalation Aerosol, Combivent Respimat, Duoneb). In addition, Spiriva Handihaler is a once-daily inhaled long-acting anticholinergic product approved for both the maintenance treatment of bronchospasm associated with COPD, as well as for the reduction of COPD exacerbations. According to the product label for Spiriva Handihaler,<sup>5</sup> the product should be used with caution in patients with narrow-angle glaucoma, prostatic hypertrophy, or bladder neck obstruction, given the potential systemic anticholinergic effects of the drug. These effects are considered class effects and are also applicable to aclidinium. The most common adverse reactions reported for Spiriva (>5% incidence in the 1-year placebo-controlled trials) were upper respiratory tract infection, dry mouth, sinusitis, pharyngitis, non-specific chest pain, urinary tract infection, dyspepsia, and rhinitis.

The cardiovascular safety and stroke risk of inhaled anticholinergics have been discussed extensively both in the medical literature<sup>6-7</sup> and in open public forums.<sup>8</sup> Most recently, FDA provided a Follow-Up<sup>9</sup> to an Early Communication regarding the safety of tiotropium marketed as Spiriva Handihaler. In this update, FDA communicated its conclusion that the available data, including results from the UPLIFT trial, do not support an association between the use of Spiriva HandiHaler (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. A summary of the FDA's conclusions regarding the safety of tiotropium may also be found in the medical literature.<sup>10</sup>

For aclidinium, the Applicant conducted two analyses to assess cardiovascular risk: (1) an analysis of major adverse cardiac events (MACE), and (2) an analysis based on standard MedDRA queries (SMQs). To explore the potential association between

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<sup>5</sup> Spiriva Handihaler (tiotropium bromide inhalation powder) Prescribing Information, November 2011. Available at: <http://bidocs.boehringer-ingenelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/Pls/Spiriva/Spiriva.pdf>. Accessed December 20, 2011.

<sup>6</sup> Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. *JAMA* 2008; 300(12):1439-1450.

<sup>7</sup> Lee TA, Pickard S, Au DH et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-390.

<sup>8</sup> November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting.

<sup>9</sup> Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm197429.htm>; accessed October 25, 2011.

<sup>10</sup> Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

acclidinium and stroke, the Applicant conducted a SMQ for “central nervous system hemorrhages and cerebrovascular conditions.” These analyses are consistent with the Division’s recommendations during the preNDA interaction for the twice daily program and are discussed in further detail in Section 5.

## 2.5 Summary of Presubmission Regulatory Activity Related to Submission

A summary of milestone interactions that took place between the Agency and Applicant during the development of acclidinium are provided in Table 2.

**Table 2. Milestone interactions between the Agency and the Applicant**

Date	Type of Interaction	Feedback Provided by the Agency
September 30, 2003	Pre-IND Meeting	--
April 26, 2005	End-of-Phase 2 Meeting	FDA recommends the evaluation of a 400 µg QD dose, in addition to the proposed 200 µg dose
March 3, 2009	Pre-NDA Meeting, QD Program	FDA informs Forest that while Trial M/34273/30 and Trial M/34273/31 demonstrated statistically significant results for the primary endpoint of trough FEV1 at 12 weeks, the treatment difference of approximately 60 cc is of uncertain clinical significance. The Agency states that the dose and dosing interval for the proposed product have not been adequately evaluated and recommends exploration of higher doses and more frequent dosing regimens.
February 25, 2011	FDA provides preliminary comments on a Pre-NDA Meeting Briefing Package submitted by the Applicant for the BID program	FDA agrees that the data from Trials LAS-MD-33 and M/34273/34 appear to support the proposal of a 400 µg BID dose. Forest is advised that all safety information to support the product should be included at the time of initial NDA submission. Forest cancels the face-to-face meeting.

Note: BID=twice-daily; QD=once-daily

## 2.6 Other Relevant Background Information

On March 15, 2012, the Applicant provided the Division with a submission correcting the SGRQ data for Trial M/34273/34. The submission noted that a systematic error had been identified regarding the transfer of Trial M/34273/34 SGRQ data from the contract research organization to the Applicant. Given that the submission included new efficacy data, it was considered to be a major amendment. Since the submission was unsolicited and received within three months of the user fee goal date, that original goal

date was extended by three months to July 23, 2012, in order to provide time for a full review of the submission. The results described in Section 6.1.5 of this review include the updated SGRQ data for Trial M/34273/34.

## **3 Ethics and Good Clinical Practices**

### **3.1 Submission Quality and Integrity**

The submission included complete study reports for the three efficacy and safety trials, LAS-MD-33, M/34723/34, and LAS-MD-38 Part A, as well as for the one completed long-term safety trial, LAS-MD-36. Complete study reports for the two long-term safety trials that were ongoing at the time of initial submission (LAS-MD-35 and LAS-MD-38 Part B) were not submitted. The submitted study reports were appropriately indexed and organized to allow review. Appropriate case report forms, proposed labeling, and raw datasets for the major clinical trials were also submitted.

Review of the Application did not raise any data concerns. As this application is for a new molecular entity, a clinical inspection was conducted by the Office of Scientific Investigations (formerly the Division of Scientific Investigations). One foreign site was investigated for each of the following two efficacy and safety trials: LAS-MD-33 (Site #2203) and M/34723/34 (Site #4042). Sites were selected due to their enrollment of large numbers and/or large drop out rates. In addition, an inspection of the Applicant's files for LAS-MD-33, located at Forest Laboratories, Inc., in Jersey City, NJ, was also conducted. The preliminary communications from the field investigator state that there were no regulatory violations noted, and that the study data collected appear to be generally reliable.

### **3.2 Compliance with Good Clinical Practices**

A statement of Good Clinical Practice was provided for the four trials that were completed at the time of initial submission: the three efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A), and one long-term safety trial (LAS-MD-36). The submitted complete study reports indicate that informed consent was obtained.

### **3.3 Financial Disclosures**

Financial disclosure information was provided for all principal investigators (PI) and sub-investigators for Trials LAS-MD-33, M/34723/34, LAS-MD-38, LAS-MD-35, LAS-MD-36, M/34273/23, and M/34273/29. Only one investigator, (b) (6)

(b) (6) disclosed a financial interest; it is unlikely that this impacted the results of these trials.

## **4 Significant Efficacy/Safety Issues Related to Other Review Disciplines**

### **4.1 Chemistry Manufacturing and Controls**

The preliminary recommendation from the CMC review team is Approval. See Section 2.1 for a description of the product.

### **4.2 Clinical Microbiology**

The Product Quality Microbiology Review recommends Approval of the proposed product, which is a non-sterile dry powder.

### **4.3 Preclinical Pharmacology/Toxicology**

The Nonclinical Review recommends Approval.

The acridinium nonclinical development program included pharmacology, safety pharmacology, toxicology, genotoxicity, carcinogenicity, and reproductive toxicology studies. Chronic toxicology studies of up to 6 months and 9 months duration were conducted in rats and dogs, respectively, and provided adequate safety margins. Acridinium was positive in the Ames bacterial mutation assay and in the mouse lymphoma assay, but negative in the *in vivo* mouse micronucleus study and the *in vivo/in vitro* unscheduled DNA synthesis assay in male rats. Two--year carcinogenicity studies in mice and rats were negative for drug related tumors. Acridinium is designated as Pregnancy Category C.

### **4.4 Clinical Pharmacology**

The Clinical Pharmacology review team recommends Approval.

#### 4.4.1 Mechanism of Action

Aclidinium is a long-acting antimuscarinic agent (anticholinergic).

#### 4.4.2 Pharmacodynamics

##### **Phase 2 BID Dose-Ranging Trials: M/34273/23 and M/34273/29**

As described in Section 2.5 (Table 2), a pre-NDA meeting for the once-daily dosing program was held on March 3, 2009. During the preNDA interaction, the Agency informed the Applicant that while Trial M/34273/30 and Trial M/3473/31 demonstrated statistically significant results for the primary endpoint of trough FEV1 at 12 weeks, the treatment difference of approximately 60 cc was of uncertain clinical significance. The Agency stated that the dose and dosing interval for the proposed product had not been adequately evaluated and recommended exploration of higher doses and more frequent dosing regimens.

In response to the FDA's feedback received at the March 3, 2009, pre-NDA meeting, the Applicant chose to conduct two additional trials (M/34273/23 and M/34273/29) to explore the dose and dosing interval of aclidinium.

Trials M/34273/23 and M/34273/29 were each randomized, double-blind, placebo- and active-controlled, crossover trials. While the trials were similar in overall design, there were also notable differences, which are summarized in Table 3.

**Table 3. Design of the Phase 2 Twice-Daily Dose-Ranging Trials: M/34273/23 and M/34273/29**

	M/34273/23	M/34273/29
Active Comparator	Tiotropium 18 µg QD	Formoterol 12 µg BID
Doses of Aclidinium Evaluated	400 µg BID	400 µg BID 200 µg BID 100 µg BID
Duration of Run-in Period	5-9 days	14 ± 3 days
Duration of Treatment Period	15 days	7 days
Washout Interval	9 days	5 days

Source: Section 2.7.3

The primary endpoint evaluated in both trials was the change from baseline in normalized FEV1 area under the curve over the 12-hour period (FEV1 AUC<sub>0-12/12h</sub>) immediately after morning administration of treatment on the last day of the treatment period. Results for the primary endpoint are summarized in Table 4 and Figure 1.

**Table 4. Change from baseline in FEV1 AUC<sub>0-12/12h</sub>, Trial M/34273/23 and Trial M/34273/29**

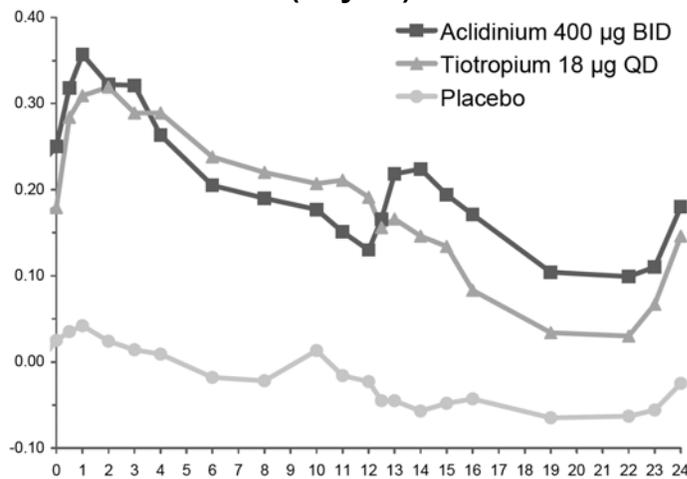
	LS Mean	p-value*
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Trial M/34273/23 (Day 15)		
A 400 µg vs P	0.221	<0.0001
Tio vs P	0.244	<0.0001
A 400 µg vs Tio	-0.023	0.572
Trial M/34273/29 (Day 7)		
A 400 µg vs P	0.208	<0.0001
A 200 µg vs P	0.176	<0.0001
A 100 µg vs P	0.154	<0.0001
F vs P	0.210	<0.0001

Key: A=aclidinium; F=formoterol 12 µg BID; P=placebo; Tio=tiotropium 18 µg QD  
 \* p-values are from the Applicant's ANCOVA analysis  
 Source: Section 2.7.3, pg. 68 (Table 2.2.1-1), and pg. 71 (Table 2.2.2-1)

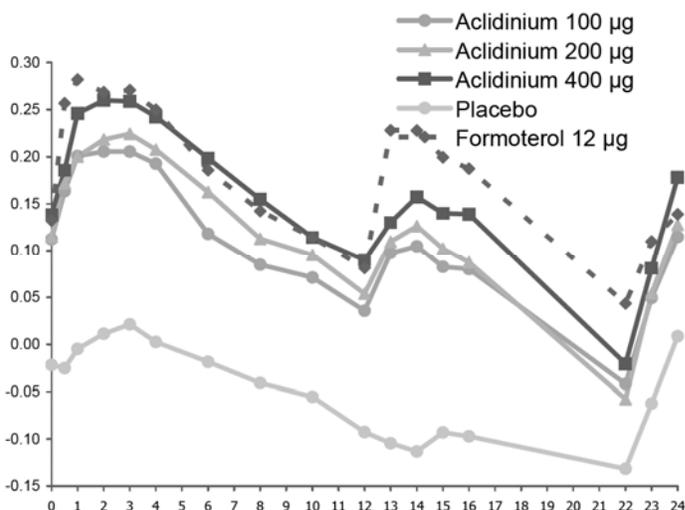
**Figure 1. Adjusted mean change from baseline in FEV1 at each time point at the End of the Treatment Period, Trial M/34273/23 and Trial M/34273/29**

**A. Trial M/34273/23 (Day 15)**



Note: Based on the Applicant's ANCOVA analysis.  
 Source: Section 2.7.3, Figure 2.2.1-1, pg. 69

**B. Trial M/34273/29 (Day 7)**



Note: Based on the Applicant's ANCOVA analysis.  
Source: Source: Section 2.7.3, Figure 2.2.2-1, pg. 73

The data from Trials M/34273/23 and M/34273/29 supported the proposed dose of acclidinium 400 mcg BID for further evaluation in Phase 3.

#### 4.4.3 Pharmacokinetics

Acclidinium has an absolute availability of approximately 6% (in healthy volunteers), and a volume of distribution of approximately 300 L (following intravenous administration). The drug is rapidly and extensively hydrolyzed to its alcohol and dienyglycolic acid derivatives, which are devoid of pharmacologic activity. Acclidinium has a total clearance of approximately 170 L/h (after an intravenous dose in young healthy volunteers). Elimination is almost entirely by hydrolysis. The estimated effective half-life is 5 to 8 hours.

Formal drug studies were not performed. *In vitro* studies indicate that it is unlikely that acclidinium would cause CYP450-related drug interactions.

No clinically significant differences in systemic exposure (AUC and  $C_{max}$ ) between elderly and younger patients, and between healthy and renally impaired patients, were observed in trials evaluating the pharmacokinetic profile of acclidinium. Dose adjustment is therefore not needed for elderly or renally impaired patients. The effects of hepatic impairment on the pharmacokinetics of acclidinium were not studied. Given that acclidinium is predominantly metabolized by chemical and enzymatic hydrolysis to inactive metabolites, it is not expected that hepatic insufficiency would have a clinically relevant impact on acclidinium pharmacokinetics.

## 5 Sources of Clinical Data

### 5.1 Tables of Studies/Clinical Trials

The core development program conducted in support of aclidinium 400 µg BID consists of two phase 2 dose-ranging trials (M/34273/23 and M/34273/29), three phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A), and three long-term safety trials (LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B). A summary of the development program is provided in Table 5.

**Table 5. Clinical Development Program (Twice-daily program)**

Trial	Design	Population	n	Treatment Arms	Duration	Key Objectives
<b>Phase 2</b>						
M/34273/23	R, DB, PC, AC, CO	Moderate-to-severe COPD	30	A 400 µg BID Tiotropium 18 µg QD P	15 days	Dose-ranging
M/34273/29	R, DB, PC, AC, CO	Moderate-to-severe COPD	79	A 400 µg BID A 200 µg BID A 100 µg BID Formoterol 12 µg BID P	7 days	Dose-ranging
<b>Phase 3</b>						
LAS-MD-33	R, DB, PC, PG	Moderate-to-severe COPD	561	A 400 µg BID A 200 µg BID P	12 weeks	Efficacy, Safety
M/34273/34	R, DB, PC, PG	Moderate-to-severe COPD	828	A 400 µg BID A 200 µg BID P	24 weeks	Efficacy, Safety
LAS-MD-38 Part A	R, DB, PC, PG	Moderate-to-severe COPD	544	A 400 µg BID A 200 µg BID P	12 weeks	Efficacy, Safety
LAS-MD-35	R, DB, PG	Moderate-to-severe COPD	605	A 400 µg BID A 200 µg BID	52 weeks	Long-term safety
LAS-MD-36 (extension of LAS-MD-33)	R, DB, PG	Successful completers of LAS-MD-33	291	A 400 µg BID A 200 µg BID	52 weeks	Long-term safety
LAS-MD-38 Part B (extension of LAS-MD-38 Part A)	R, single-arm, OL	Successful completers of LAS-MD-38 Part A	448	A 400 µg BID	40 weeks	Long-term safety

Source: Section 2.7.3; Section 2.5, pg. 23-24 (Table 4.1-1); Section 5.3.5.3.28, pg. 34 (Table 1.1.1.1-2); Section 5.3.5.2.1 (LAS-MD-35), pg. 25 (Table 1); Section 5.3.5.2.1 (LAS-MD-38 Part B), pg. 23 (Table 1)

Key: A=aclidinium; AC=active-controlled; CO=crossover; DB=double-blind; OL=open-label; P=placebo; PC=placebo-controlled; PG=parallel-group; R=randomized

## 5.2 Review Strategy

The focus of this review is on the clinical development program conducted in support of the proposed dose of aclidinium 400 µg twice daily for use as a bronchodilator in patients with COPD. The review first addresses the data presented in support of efficacy, and then the data in support of safety.

The review of efficacy focuses on the three Phase 3 efficacy and safety trials conducted as part of the twice-daily clinical development program: LAS-MD-33, M/34273/34, and LAS-MD-38 Part A. The general design of these trials is presented in Section 5.3 of this review; a discussion of the efficacy data generated by these trials is provided in Section 6.

The review of safety focuses on data generated by the aclidinium twice-daily program, namely, safety data from the three Phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A), as well as safety data from the twice-daily long-term safety trials (LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B). A summary of the safety evaluations conducted in the clinical development program is included in Section 7.1.1, and a discussion of the safety findings follows in the rest of Section 7.

It is notable that at the time of NDA submission, two of the long-term safety trials (LAS-MD-35, and LAS-MD-38 Part B) were ongoing, and the original NDA submission included limited long-term safety data. The Applicant provided a 120-day safety update on October 21, 2011, which included additional long-term safety data, however complete study reports for Trials LAS-MD-35 and LAS-MD-38 Part B were not submitted for review. Nevertheless, for most of the topics addressed in the review of safety found in Section 7, the data evaluated includes the additional information made available with the 120-day safety update.

## 5.3 Discussion of Individual Studies/Clinical Trials

A summary of the protocols for the three phase 3 trials efficacy and safety trials is provided here; the long-term safety trials and dose-ranging trials are discussed in Sections 5.1.1 and 3.4, respectively.

### **Phase 3 Efficacy and Safety Trials: LAS-MD-33, M/34273/34, LAS-MD-38 Part A**

#### ***Objectives***

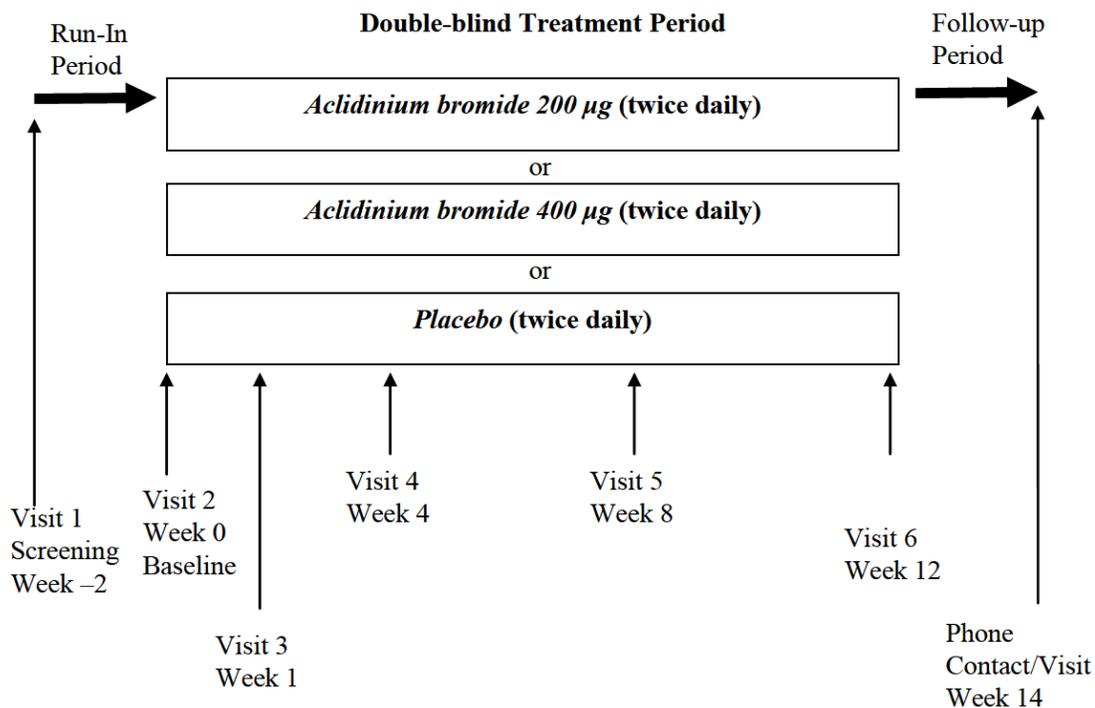
In general, the objectives of the three phase 3 efficacy and safety trials were as follows:

- To assess the efficacy of aclidinium 200 µg and 400 µg twice daily, compared to placebo, as a long-term bronchodilator in patients with moderate to severe COPD
- To assess the safety and tolerability of aclidinium 200 µg and 400 µg twice daily in patients with moderate to severe COPD
- To assess the benefit of aclidinium 200 µg and 400 µg twice daily on COPD exacerbations, disease-related health status as measured by the SGRQ, COPD symptoms, and other outcomes in patients with moderate to severe COPD

### ***General Study Design***

The three phase 3 efficacy and safety trials each employed a randomized, placebo-controlled, double-blind, parallel-group design. The trials were similar, and each included a run-in and double-blind treatment period. The main difference between trials LAS-MD-33 and LAS-MD-38 Part A as compared to M/34273/34 was the length of the treatment period, which was 12 weeks for the former two trials and 24 weeks for the latter. While Trial M/34273/34 employed a longer treatment period, the primary efficacy endpoint was assessed at 12 weeks, consistent with the other two trials. In addition, Trials LAS-MD-33 and LAS-MD-38 Part A were conducted in the United States and Canada, while the study sites for Trial M/34273/34 were located outside of North America. A summary of the trial designs for Trial LAS-MD-33 and LAS-MD-38 Part A are provided in Figure 2 and in Figure 3 for M/34273/34.

### **Figure 2. General Study Design: Trial LAS-MD-33 and LAS-MD-38 Part A**



Source: Section 5.3.5.1.1 (LAS-MD-33), pg. 36 (Figure 9.1-1)

Note: The study design of Trial LAS-MD-38 Part A does not include the follow-up period, as it precedes the Part B extension.

**Figure 3. General Study Design: Trial M/34273/34**

	Run-in	Double-blind treatment							Follow-up (FU)
		Randomisation ↓							
Visit no.	1	2	3	4	5	6	7	8	9
Week	-2	0	1	4	8	12	18	24	26
Study day	-14	1	7 +/-3	29 +/-3	57 +/-3	85 +/-3	127 +/-3	169 +/-3	+14 +/-3
Study IMP		<b>Group A: Acridinium bromide 200 µg BID for 24 weeks</b> <b>Group B: Acridinium bromide 400 µg BID for 24 weeks</b> <b>Group C: Placebo (BID for 24 weeks)</b>							

Source: Section 5.3.5.1.3 (M/34273/34), pg. 31 (Figure 1)

**Treatment arms**

The same three treatment arms were evaluated in each of the three pivotal efficacy and safety trials:

- Acridinium 200 µg BID

- Acclidinium 400 µg BID
- Placebo

In each case the treatment was delivered via the to-be-marketed device.

Patients were permitted to use either marketed albuterol HFA or salbutamol sulfate for rescue use. Use of spacers with rescue medication was permitted, but not required.<sup>11</sup> Rescue medication was to be discontinued at least 6 hours prior to a visit. A description of permissible and non-permissible concomitant medications is provided in Table 6.

**Table 6. Drugs Allowed (Y) and Drugs Not Allowed (N) as Concomitant Medications**

Drug Class	Episodic	Chronic	Washout Period (prior to Visit 1)	Comments
Long-acting inhaled anticholinergics and oral, intranasal, or parenteral anticholinergics	N	N	72 hours	
Short-acting inhaled anticholinergics	N	N	12 hours	
Short-acting β <sub>2</sub> -adrenergic agonists	Y (Only episodic use of Sponsor-permitted rescue medication)	N	6 hours	
Long-acting β <sub>2</sub> -adrenergic agonists	N	N	48 hours	
Inhaled corticosteroids	N	Y		Must be stable for 4 weeks prior to Visit 1; avoid prior to all visits
Oral or parenteral corticosteroids	N	Y		Up to 10 mg/day or 20 mg every other day of prednisone, so long as stable for 4 weeks prior to Visit 1
Combination therapies	N	N	Combivent: 12 hours Advair, Symbicort: 48 hours	
Methylxanthines	N	N (except for long-	72 hours	Long-acting theophylline allowed so long as stable for 4

<sup>11</sup> Spacer use was required during the assessment of reversibility that took place at Visit 1.

		acting theophylline)		weeks prior to Visit 1; avoid prior to all visits
H1-receptor antagonists	N	Y		Must be stable for at least 4 weeks prior to Visit 1
Cromolyn, Nedocromil	N	N	6 weeks	
Leukotriene modifiers	N	N	48 hours	
Nonselective $\beta$ -blockers	N	N	2 weeks	
Selective $\beta$ 1-blockers	N	Y		Must be stable for at least 2 weeks prior to Visit 1
Supplemental oxygen	Y	Y		Allowed if used as needed up to 15 hours/day. Must be discontinued at least 2 hours prior to each visit, and until the end of the visit

Source: Section 5.3.5.1.1 (LAS-MD-33), pg. 3061-2 (Appendix III); Section 5.3.5.1.4 (M/34273/34), pg. 115 (Post-text supplement 6); Section 5.3.5.1.1 (LAS-MD-38 Part A), pg. 2763-2764 (Appendix III)

The use of a placebo control arm in the acclidinium development program is acceptable given the following: 1) patients in the placebo arms were not untreated, since they were allowed to use short-acting beta agonists as needed; 2) other maintenance medications including inhaled and oral corticosteroids at stable doses were permitted; 3) the trials had escape criteria for patients to discontinue the study; 4) there was close clinical monitoring for COPD exacerbations; and 5) the informed consent documents clearly described the presence of a placebo arm, the possibility of no direct benefit with trial participation, and the availability of alternative therapies.

### **Population**

The population for each of the three efficacy and safety trials was comprised of adults with moderate-to-severe COPD. Inclusion and exclusion criteria are summarized in Table 7 and Table 8.

**Table 7. Inclusion Criteria**

Criterion	Trial		
	LAS-MD-33	M/34273/34	LAS-MD-38 Part A
<b>Inclusion Criteria</b>			
Male or female outpatients at least 40 years of age	X	X	X
Current or former cigarette smokers with a smoking history of at least 10 pack-years	X	X	X
Stable moderate-to-severe COPD and	X	X	X

stable airway obstruction with FEV1/FVC < 70%			
Post-bronchodilator FEV1 ≥ 30% to < 80% of predicted	X	X	X
Able to perform reproducible pulmonary function tests	X	X	X
Females: At least 1 year postmenopausal, surgically sterile, or practicing a medically acceptable method of contraception WOCP: Negative serum βhCG pregnancy test and using either double-barrier contraception or barrier method plus spermicidal agent	X	X	X
Judged to be in otherwise good stable health based on medical history, physical examination, ECG, and routine laboratory data	X		X
Able to provide written informed consent	X	X	X

Source: Section 5.3.5.1.1 (LAS-MD-33), pg. 2990-2991; Section 5.3.5.1.4 (M/34273/34), pg. 31; Section 5.3.5.1.1 (LAS-MD-38 Part A), pg. 2673

\* As defined by the 2008 Global Initiative for Chronic Obstructive Lung Disease (GOLD)

Key: βhCG=beta human chorionic gonadotropin; ECG=electrocardiogram; WOCP=women of childbearing potential

**Table 8. Exclusion Criteria**

Criterion	Trial		
	LAS-MD-33	M/34273/34	LAS-MD-38 Part A
<b>Exclusion Criteria</b>			
Hospitalized for acute COPD exacerbation within 3 months prior to Visit 1	X	X	X
Any respiratory tract infection or COPD exacerbation in the 6 weeks prior to Visit 1*	X	X	X

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Clinically significant respiratory disease other than COPD	X	X	X
History or presence of asthma	X	X	X
Chronic use of oxygen therapy $\geq$ 15 hours a day	X	X	X
BMI $\geq$ 40 kg/m <sup>2</sup>	X	X	X
Participation in an acute pulmonary rehabilitation program within the prior 6 months	X	X	X
Clinically significant cardiovascular conditions <sup>#</sup>	X	X	X
Uncontrolled HIV and/or active hepatitis infection	X	X	X
Clinically relevant abnormalities in laboratory tests, ECG (excluding QTc), physical exam or vital signs (except for those related to COPD)	X	X	X
SBP $\geq$ 200 mmHg, DBP $\geq$ 120 mmHg, HR $\geq$ 105 bpm (at rest)		X	
QTcB > 470 msec	X	X	X
History or drug or alcohol abuse within the prior 5 years	X	X	X
Physical or mental dysfunction, at the discretion of the Investigator	X	X	X
History of hypersensitivity to inhaled anticholinergics, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm) or history of acute urinary retention, symptomatic benign prostatic	X	X	X

hyperplasia, bladder neck obstruction, or narrow-angle glaucoma			
Inability to use DPI or pressurized MDI	X	X	X
Treatment with another investigational drug within 30 days or 6 half-lives (whichever is longer) prior to Visit 1	X	X	X
Prior treatment with acridinium	X	X	X
Pregnancy or lactation	X	X <sup>@</sup>	X
Current diagnosis of cancer (other than basal or squamous cell skin cancer)	X	X	X
Absence of a regular day/night, waking/sleeping cycle (eg, night-shift workers)	X	X	X
Concomitant medication use	X	X	X
Anticipated poor compliance	X	X	X
Employees or relatives of employees of study center or Applicant	X	X	X
Any other condition, at the discretion of the Investigator	X	X	X

Source: Section 5.3.5.1.1 (LAS-MD-33), pg. 2991-2993, 3120-3121; Section 5.3.5.1.4 (M/34273/34), pg. 31-33; Section 5.3.5.1.1 (LAS-MD-38 Part A), pg. 2674-2676

<sup>\*</sup> Patients who developed a respiratory tract infection or exacerbation during the run-in period were to be discontinued prior to randomization

<sup>#</sup> Clinically significant cardiovascular conditions included myocardial infarction during the prior 6 months, newly diagnosed arrhythmia during the prior 3 months, unstable angina, unstable arrhythmia, and/or NYHA class III or IV heart failure requiring hospitalization in the prior 12 months

<sup>@</sup> For trial M/34273/34 this was worded as an inclusion criteria, i.e., “non-pregnant, non-lactating females”

Key: BMI=body mass index; DPI=dry-powder inhaler; MDI=metered-dose inhaler

### **Procedures**

A schedule of the main trial procedures and assessments for Trials LAS-MD-33 and M/34273/34 are provided in this section in Table 9 and Table 10, respectively; these tables are followed by a description of procedures common to all three trials. Table 32 in Section 5.1.1 provides a schedule of procedures for both Part A and Part B of Trial LAS-MD-38.

**Table 9. Schedule of Selected Procedures and Assessments, Trial LAS-MD-33**

Visit	Run-in Period	Treatment Period					Follow-up Phone Call
	1 Screening	2 Baseline	3	4	5	6/ET	
Week	-2	0	1	4	8	12	14
Physical Examination	X					X	
Vital Signs	X	X	X	X	X	X	
Pregnancy Test	X					X	
Clinical Laboratory Testing	X					X	
12-lead ECG	X	X	X			X	
Predose Spirometry	X	X	X	X	X	X	
BDI/TDI		X		X	X	X	
SGRQ		X		X	X	X	
Daily Sleep Diary and Night-Time Symptoms (Welte) Questionnaire	Daily beginning at Visit 1						
Postdose Spirometry (0-3 hours)		X	X	X	X	X	
Postdose Spirometry (0-12 hours), substudy		X		X		X	
Bronchodilator Test	X						
Rescue Medication Use		X	X	X	X	X	
COPD exacerbations	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X
24-hour Holter, substudy		X				X	

Source: Section 5.3.5.1.1 (Trial LAS-MD-33 Volume 1), pg. 50-52 (Table 9.5.1.1-1)  
 Key: ET=early termination

**Table 10. Schedule of Selected Procedures and Assessments, Trial M/34273/34**

Visit	Run-in Period	Treatment Period							Follow-up
	1 (S)	2	3	4	5	6	7	8	9

Week	-2	0	1	4	8	12	18	24	+2
Physical Examination and Blood Pressure	X	X		X		X		X	
Laboratory Testing including Pregnancy Test	X					X		X	
12-lead ECG	X	X	X	X		X		X	
Predose Spirometry	X	X	X	X	X	X	X	X	
BDI/TDI		X		X		X		X	
SGRQ		X		X		X		X	
EQ-5D		X		X		X		X	
Postdose Spirometry (0-3 hours)		X	X	X		X		X	
Postdose Spirometry (0-12 hours), substudy		X				X		X	
Bronchodilator Test	X								
COPD exacerbations		X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

Source: Section 5.3.5.1.3 (Trial M/34273/34), pg. 44-45 (Table 2)  
 Key: S=screening

### Visit 1 (Screening, Week -2)

During Visit 1 the following procedures and assessments took place: signing of informed consent, medical history, concomitant medication review, physical examination (including vital signs), clinical laboratory tests, ECG, spirometry, dispensing of rescue medication, training on pMDI use (if necessary), reversibility assessment, inclusion/exclusion criteria evaluation, and electronic diary training. Patients meeting all inclusion/exclusion criteria were allowed to proceed to Visit 2.

Patients participating in the Holter sub-study (approximately 20-30% of patients in Trials LAS-MD-33 and LAS-MD-38 Part A) had a device placed between 5 days to 1 day prior to Visit 2, during the morning hours. Patients were instructed to return 24 hours later for Holter monitor removal.

### Visit 2 (Baseline, Week 0)

During Visit 2 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation (if yes, patient was not randomized), review of electronic diary, ECG, physical examination and/or vital signs, and review of inclusion/exclusion criteria. Eligible patients were randomized, and completed the following procedures and

assessments: training on the use of the multidose DPI and pMDI (if necessary), Baseline Dyspnea Index (BDI), St. George's Respiratory Questionnaire (SGRQ), and spirometry. Trial medication and rescue medication (if necessary) were dispensed. The first dose of double-blind treatment was administered. Following the administration of trial medication an ECG was obtained and spirometry performed; additional spirometric assessments were conducted for patients in the serial spirometry sub-study. For patients in the serial spirometry sub-study, the evening dose of treatment was administered in the clinic following the final spirometric assessment.

#### Visit 3 (Week 1)

During Visit 3 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of electronic diary, assessment of compliance, ECG, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry, ECG.

#### Visit 4 (Week 4)

During Visit 4 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of electronic diary, assessment of compliance, physical examination and/or vital signs, ECG (Trial M/34273/34 only), TDI (not for LAS-MD-38 Part A), SGRQ, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: ECG (Trial M/34273/34 only), spirometry. Additional spirometric assessments were conducted for patients in the serial spirometry sub-study (Trial LAS-MD-33 only).

#### Visit 5 (Week 8)

During Visit 5 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of electronic diary, assessment of compliance, vital signs, TDI, SGRQ, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry (not performed for Trial M/34273/34).

Patients participating in the Holter sub-study (Trials LAS-MD-33 and LAS-MD-38 Part A) had a device placed between 5 days to 1 day prior to Visit 6, during the morning hours. Patients were instructed to return 24 hours later for Holter monitor removal.

#### Visit 6 (Week 12)

During Visit 6 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, clinical laboratory tests, assessment of compliance, physical examination (including vital signs), ECG, TDI, SGRQ, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted:

spirometry, ECG. Additional spirometric assessments were conducted for patients in the serial spirometry sub-study. For patients in the serial spirometry sub-study, the evening dose of treatment was administered in the clinic following the final spirometric assessment.

Visit 7 (Week 18, M/34273/34 only)

During Visit 7 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of electronic diary, assessment of compliance, and spirometry. After the completion of these assessments, trial medication was administered.

Visit 8 (Week 24, M/34273/34 only)

During Visit 8 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of electronic diary, clinical laboratory tests, assessment of compliance, physical examination (including vital signs), ECG, TDI, SGRQ, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry, ECG. Additional spirometric assessments were conducted for patients in the serial spirometry sub-study.

Follow-up Telephone Contact (Week 14, Trial LAS-MD-33; Visit 9, Week 26, Trial M/34273/34)

During the Follow-up Telephone Contact the following procedures and assessments took place: review of concomitant medications, review of adverse events, review of any ongoing or new COPD exacerbations.

Early Termination Visit, (Trials LAS-MD-33 and M/34273/34)

If terminated early, an attempt was made to perform the following procedures and assessments: ECG, review of AEs, confirmation of no COPD exacerbation, review of concomitant medications, spirometry, vital signs, physical examination, assessment of compliance, clinical laboratory testing, and collection of rescue medication.

## ***Endpoints***

### Primary Efficacy Endpoint

The primary efficacy endpoint for all three trials was the change from baseline in morning predose (trough) forced expiratory volume in one second (FEV1) assessed at 12 weeks. Trough FEV1 was defined as the mean of the two largest FEV1 measurements at approximately 11 and 12 hours after the evening dose.

### Secondary Efficacy Endpoint

Change from baseline in peak FEV1 assessed at 12 weeks was designated as a secondary efficacy endpoint, where peak FEV1 was defined as the maximum FEV1

measurement from among the FEV1 results obtained from time 0 through 3 hours after the morning dose.

Trial M/34273/34 also designated BDI/TDI and SGQR as secondary endpoints.

**Additional Efficacy Endpoints and Other Measures**

Additional efficacy endpoints included further pulmonary function tests (serial FEV1 over 12 hours, FVC, and IC), COPD exacerbations, rescue medication use, and patient- or evaluator-reported outcome measures (SGRQ and BDI/TDI). A variety of additional measures were evaluated in a subset of the three trials: Daily Sleep Diary, COPD Night-Time Symptoms Questionnaire, Night-time and Morning Symptoms Questionnaire, EQ-5D, EXACT-P Pro, productivity, and the COPD Resource Utilization Questionnaire.

A summary of secondary and additional efficacy endpoints and other measures is provided in Table 11, and a description of selected endpoints follows below.

**Table 11. Secondary and Additional Efficacy Endpoints and Other Measures**

Efficacy Endpoint	Trial		
	M/34273/33	M/34273/34	M/34273/38 Part A
Peak FEV1	X	X	X
FEV1 over 12 hours (substudy)	X	X	X
FVC	X	X	X
IC	X	X	X
COPD Exacerbations	X	X	X
SGRQ	X	X	X
Rescue Medication Use	X	X	X
BDI and TDI	X	X	X
Daily Sleep Diary	X		
COPD Night-Time Symptoms Questionnaire (modified Welte)	X		
Night-time and Morning Symptoms Questionnaire		X	
EQ-5D (Health-related QoL)	X*	X	X
EXACT-P PRO		X	
Productivity		X	
COPD Resource Utilization Questionnaire			X

Source: Source: Section 5.3.5.1.1 (LAS-MD-33), pg. 3020-3022; Section 5.3.5.1.4 (M/34273/34), pg. 60-67; Section 5.3.5.1.1 (LAS-MD-38 Part A), pg. 2712-2714, 2722

\* The EQ-5D assessment was added to Trial LAS-MD-33 with Protocol Amendment #2, however, Protocol Amendment #3 removed the analyses of EQ-5D since the assessment was added after all patients had been randomized and baseline values could not be obtained.

### Additional Pulmonary Function Tests

FEV1 over 12 hours was obtained following the morning dose of trial medication in a substudy of patients (approximately 20-40% of patients). Peak forced vital capacity (FVC)<sup>12</sup> was defined as the maximum FVC measurement from among the results from time 0 through 3 hours after the morning dose at each visit. Trough FVC<sup>13</sup> was defined as the mean of the two greatest FVC readings at approximately 11 and 12 hours after the evening dose at each visit. Trough inspiratory capacity (IC)<sup>14</sup> was defined as the mean of the two greatest IC readings at approximately 11 and 12 hours after the evening dose at each visit.

### COPD Exacerbations

COPD exacerbations were defined as, “an increase in COPD symptoms (eg, dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days”<sup>15</sup> and were classified as mild (self-managed with increased short-acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization), or severe (requiring overnight stay at hospital or emergency room).

It is important to note that there is no single well-accepted definition of COPD exacerbation. The Applicant’s proposed definition, which includes both a symptomatic component and a treatment requirement, is reasonable as an additional efficacy variable, with the caveat that the definition relies on the discretion of individual treating physicians and may be influenced by local practice standards. There are several inhaled products approved for COPD which carry indications related to COPD exacerbations.<sup>16,17</sup>

### Rescue Medication Use

Daily rescue medication use was defined as the number of albuterol/salbutamol puffs reported by the patient.

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<sup>12</sup> Definition specified for Trials LAS-MD-33 and LAS-MD-38 Part A.

<sup>13</sup> Definition specified for Trials LAS-MD-33 and LAS-MD-38 Part A.

<sup>14</sup> Definition specified for Trials LAS-MD-33 and LAS-MD-38 Part A.

<sup>15</sup> Section 5.3.5.1.1 (LAS-MD-33), pg. 3020

<sup>16</sup> Advair Diskus (fluticasone propionate and salmeterol inhalation powder) Prescribing Information, January 2011. Available at: [http://us.gsk.com/products/assets/us\\_advair.pdf](http://us.gsk.com/products/assets/us_advair.pdf). Accessed December 20, 2011.

<sup>17</sup> Spiriva Handihaler (tiotropium bromide inhalation powder) Prescribing Information, November 2011. Available at: <http://bidocs.boehringer-ingenheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/Pls/Spiriva/Spiriva.pdf>. Accessed December 20, 2011.

## Patient- or Evaluator-Reported Outcome Measures

### **SGRQ**

Disease-specific health related quality of life was assessed using the St. George's Respiratory Questionnaire. The SGRQ is a self-administered health related quality of life measure comprised of three components: symptoms, activity, and impacts. Scores ranging from 0 to 100 are calculated for each component, and a total score summarizes the responses to all items; a zero score indicates no impairment.<sup>18</sup> The acclidinium clinical development program used 4 units as the threshold for a minimum clinically important difference (MCID) in the SGRQ measure. There is regulatory precedent for accepting a 4-unit change as a clinically meaningful difference.<sup>19,20</sup>

### **BDI/TDI**

The Baseline and Transition Dyspnea Indexes (BDI and TDI) are interviewer-administered measures of breathlessness based on activities of daily living. The BDI is a measure for a single point in time and has a total score ranging from 0 to 12, while the TDI is a measure of change from baseline and has a total score ranging from -9 to +9, with positive score indicating improvement.<sup>21</sup> The acclidinium clinical development program proposed a 1-unit increase as the threshold for a MCID. The Agency has not previously accepted the BDI/TDI as a validated measure of dyspnea, and the limitations of these instruments, including concerns about the validity of the 1 unit threshold for MCID, have been discussed in a prior Advisory Committee meeting.<sup>22</sup>

### **Safety and Premature Discontinuation**

A description of the safety assessments conducted in the three efficacy and safety trials is provided in Section 5.1.1.

With regards to premature discontinuation, patients could be removed from the trial for any of the following reasons: nonfulfillment of inclusion/exclusion criteria (screen

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<sup>18</sup> Wilson CB, Jones PW, O'Leary CJ, Cole PJ, Wilson R. Validation of the St. George's Respiratory Questionnaire in bronchiectasis. *American Journal of Respiratory and Critical Care Medicine* 1997; 156:536-541.

<sup>19</sup> Arcapta Neohaler (indacaterol inhalation powder) Prescribing Information, July 2011. Available at: <http://www.pharma.us.novartis.com/product/pi/pdf/arcapta.pdf>. Accessed December 20, 2011.

<sup>20</sup> FDA Briefing Information for the March 8, 2011 Meeting of the Pulmonary-Allergy Drugs Advisory Committee. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM245637.pdf>. Accessed January 17, 2012.

<sup>21</sup> Mahler DA, Weinber DH, Wells CK et al. The measurement of dyspnea: contents, interobserver agreement and physiologic correlates of two new indexes. *Chest* 1984;85:751-8.

<sup>22</sup> Transcript of the September 6, 2002, Pulmonary/Allergy Drugs Advisory Committee Meeting on NDA 21-395, Spriva (tiotropium bromide), by Boehringer-Ingelheim, for chronic obstructive pulmonary disease. Available at: <http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3890t1.htm>. Accessed December 20, 2011.

failure), adverse event (depending on the nature of the event), COPD exacerbation (depending on the nature of the exacerbation), lack of efficacy, protocol noncompliance, patient request, loss to follow-up, and other and/or administrative reasons. COPD exacerbations did not automatically result in trial discontinuation, but if occurring during the treatment period could result in the delay or skipping of visits, as a study visit was generally not to be conducted until 4 weeks after the resolution of a moderate to severe episode, or 2 weeks after a mild episode.

### ***Plan for Statistical Analysis***

A high-level summary of the Applicant's prespecified statistical approach (based on the Statistical Analyses Plans and Amendments for the three trials) is provided below.

#### Analysis Populations

##### *Safety Population*

The Safety Population was defined as all randomized patients who took at least one dose of investigational product.

##### *Intent-to-Treat Population*

The intent-to-treat (ITT) population was defined as all patients in the Safety Population who had a baseline and at least one postbaseline FEV1 assessment.

##### *Per-protocol Population*

The per-protocol (PP) population was defined as all patients who met the main inclusion/exclusion criteria, were sufficiently compliant, and did not have major protocol deviations.

#### Demographic and Background Data

Demographic and other baseline data were summarized by treatment group, using descriptive statistics.

#### Statistical Testing

The chosen threshold for statistical significance was at the 0.05 level, and all statistical tests were 2-sided. The only planned adjustments for multiplicity, performed using the Hochberg method, were for the primary and secondary endpoints.

#### Missing Data

Missing postbaseline values were imputed using the last observation carried forward (LOCF) method.

#### Efficacy Analyses

All efficacy analyses were performed using data from the ITT population, except for COPD exacerbations, which was performed for both the ITT and Safety Populations.

The analyses of both the primary and secondary efficacy endpoints was pre-specified to be based on an ANCOVA model with treatment group and sex as factors and baseline FEV1 and age as covariates. Baseline FEV1 was defined as the average of two values obtained prior to the first dose of double-blind trial medication at Visit 2. The primary analysis included two comparisons: aclidinium 400 µg versus placebo, and aclidinium 200 µg versus placebo. The results of the ANCOVA model were presented using least square means and corresponding standard errors for each treatment group, the least square means difference between treatment groups and corresponding 95% confidence interval and p-value.

#### Treatment Compliance

Compliance was based on data regarding the total number of inhalations actually taken, as reported on the electronic diary, study drug record page of the eCRF, or drug accountability eCRF. Compliance was described using descriptive statistics.

#### Subgroup Analyses

Subgroup analyses (i.e. demographic and other baseline characteristics) of the efficacy data at Week 12 were conducted based on the population pooled across the three efficacy and safety trials (LAS-MD-33, LAS-MD-38A, and M/34273/34). Similar subgroup analyses were conducted using Week 24 data from Trial M/34273/34.

#### Interim Analyses

There were no interim analyses planned for these trials.

#### Safety Analysis

A descriptive presentation of the safety data for the Safety Population was planned.

#### ***Protocol Amendments***

There were a number of protocol amendments for Trials LAS-MD-33, M/34723/34, and LAS-MD-38 Part A. The most notable of these was the first amendment to Trial LAS-MD-33, which provided for the removal of a 200 µg once daily treatment arm. These amendments do not raise any questions regarding study integrity. A high-level summary of the protocol amendments for the three efficacy and safety trials follows below.

#### Trial LAS-MD-33

Original protocol: February 6, 2009

Protocol Amendment 1: March 20, 2009

- Removal of the aclidinium 200 µg once daily treatment arm

Protocol Amendment 2: July 14, 2009

- Addition of EQ-5D quality of life questionnaire
- Clarification of data used to assess reproducibility criteria

- Removal of exclusion criterion describing values for acceptable blood pressure (now based on Investigator's judgment)
- Clarification of Visit 1 spirometry timing
- Change in smoking restriction to 1 hour prior to each visit (from 8 hours); change in other restrictions to be consistent with ATS/ERS guidelines
- Addition of further efficacy analyses

Protocol Amendment 3:

- Section on statistical analysis amended to be consistent with the Statistical Analysis Plan
- Removal of EQ-5D analyses since the assessment was added after all patients had been randomized and baseline values could not be obtained
- Clarification of the process of centralized spirometry training, data handling, and best test review process
- Updating of the SGRQ to the US English version (from the UK English version)

Trial M/34273/34

Original protocol: April 23, 2009

Protocol Amendment 1: June 26, 2009

- Revision of inclusion criteria to be consistent with ATS/ERS 2005 repeatability criteria
- Wash-out period for rescue medication use during spirometric assessment increased from 4 to 5 hours
- Reduction of spirometry assessments at Screening from two to one

Protocol Amendment 2: November 24, 2010

- Non-substantive changes

Trial LAS-MD-38 Part A

Original protocol: October 28, 2009

Protocol Amendment 1: March 2, 2010

- Addition of a physical examination at Visit 6
- Clarification of the processes for spirometry training, data handling, and best test review

Protocol Amendment 2: October 14, 2010

- Clarification that Parts A and B would be analyzed and reported separately
- Allowance for patients to continue in the trial if unblinded by the Applicant (study center staff would be kept blinded) for the purpose of health authority reporting

## 6 Review of Efficacy

### **Efficacy Summary**

Evidence of efficacy comes from three Phase 3 efficacy and safety trials conducted as part of the twice-daily clinical development program. Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A, were randomized, double-blind, placebo-controlled, and parallel-group in design. These trials were similar, and each included a run-in and a double-blind treatment period. The main difference among the trials was duration; Trials LAS-MD-33 and LAS-MD-38 Part A were 12 weeks in duration as compared to Trial M/34273/34, which was 24 weeks in duration. While Trial M/34273/34 employed a longer treatment period, the primary efficacy endpoint was assessed at 12 weeks, consistent with the other two trials.

In each of the three pivotal BID efficacy and safety trials, results for the analysis of the primary endpoint, change from baseline in trough FEV1 at Week 12, were statistically significant for the comparison between aclidinium 400 µg and placebo. While the effect size observed in Trial LAS-MD-38 Part A was small (72 mL), the effect sizes demonstrated for the other two trials (LAS-MD-33 and M/34273/34) were of reasonable magnitude (124 mL and 105 mL, respectively), and represent an outcome that is clinically meaningful.

The results for the comparison between aclidinium 200 µg and placebo were also statistically significant in each of the three efficacy and safety trials, however, the effect size associated with the aclidinium 400 µg dose was larger than that for the 200 µg dose in each case, demonstrating a dose response.

These results were robust to analyses conducted for various subgroups based on demographic factors (age, sex) and on characteristics that inform baseline health status (COPD severity, bronchodilator reversibility, concomitant ICS use, and smoking status).

Results for secondary and other endpoints, including additional pulmonary function tests (serial FEV1 over 12 hours, FVC, and IC), COPD exacerbations, rescue medication use, and health related quality of life as measured by the SGRQ, were generally supportive of the primary analysis. Of note, on March 15, 2012, the Applicant provided the Division with a submission correcting the SGRQ data for Trial M/34273/34. Given that the submission included new efficacy data, it was considered to be a major amendment. Since the submission was unsolicited and received within three months of the user fee goal date, that original goal date was extended by three months to July 23, 2012, in order to provide time for a full review of the submission. The results described in Section 6.1.5 of this review include the updated SGRQ data for Trial M/34273/34, however, the data presented at the February 23, 2012, meeting of the Pulmonary Allergy Drugs Advisory Committee, and provided in the Agency's briefing package for the meeting, are based on the Applicant's original submission.

With regards to persistence of efficacy, the overall results for lung function parameters from Trial M/34273/34 at 24 weeks were generally consistent with the results at 12 weeks. These findings are supportive of the findings for the primary endpoint and provide evidence of continued efficacy at 6 months' time.

Overall, these results provide replicate evidence of efficacy for the proposed product and indication.

## 6.1 Indication

The Applicant proposes that aclidinium bromide is indicated for “the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.”

### 6.1.1 Methods

Refer to Section 3.3 for a discussion of the general design of the three phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A).

### 6.1.2 Demographics

Demographic and baseline characteristics for the pooled ITT population (Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A) are provided in Table 12.

**Table 12. Demographics and baseline characteristics for the pooled ITT population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Characteristic	Placebo N=640	Aclidinium 200 µg N=643	Aclidinium 400 µg N=636
<b>Age, year</b>			
n	640	643	636
Mean (SD)	62.8 (8.8)	62.8 (8.5)	63.5 (8.9)
Median	63.0	63.0	63.0
Min, Max	40, 89	40, 84	40, 89
<b>Sex, n (%)</b>			
Female	256 (40.0%)	262 (40.8%)	265 (41.7%)
Male	384 (60.0%)	381 (59.3%)	371 (58.3%)
<b>Race, n (%)</b>			
White	602 (94.1%)	594 (92.4%)	598 (94.0%)
Black or African American	22 (3.4%)	32 (5.0%)	22 (3.5%)
Asian	2 (0.3%)	3 (0.5%)	2 (0.3%)
American Indian or Alaskan Native	1 (0.2%)	1 (0.2%)	2 (0.3%)
Other	13 (2.0%)	13 (2.0%)	12 (1.9%)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
n	639	643	636

Mean (SD)	27.03 (5.40)	27.15 (5.19)	27.31 (5.13)
Min, Max	15.6, 39.9	15.2, 40.2	15.5, 39.9
<b>Severity of COPD, n (%)</b>			
Stage I (Mild)	2 (0.3%)	0 (0.0%)	0 (0.0%)
Stage II (Moderate)	402 (62.8%)	385 (59.9%)	381 (59.9%)
Stage III (Severe)	231 (36.1%)	249 (38.7%)	248 (39.0%)
Stage IV (Very Severe)	1 (0.2%)	4 (0.6%)	1 (0.2%)
<b>Smoking Status, n (%)</b>			
Current smoker	333 (52.0%)	321 (49.9%)	317 (49.8%)
Ex-smoker	307 (48.0%)	322 (50.1%)	319 (50.2%)

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 54 (Table 2.1A); Section 5.3.5.3.27 (ISE Volume 2), pg. 64 (Table 2.2A)

Demographic and baseline characteristics were generally well balanced across treatment arms. The vast majority of patients were of white race. While a majority of the patient population had moderate (Stage II) COPD disease, a substantial number of patients (about one-third of the total) had severe (Stage III) disease. The patient population was evenly split between current and former smokers.

### 6.1.3 Subject Disposition

The disposition of subjects participating in the three phase 3 efficacy and safety trials (Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A) is provided in Table 13.

**Table 13. Subject Disposition: Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Disposition	Placebo	Acclidinium 200 µg	Acclidinium 400 µg
All Randomized Subjects (N)	644	649	640
Number of Subjects who Completed, n (%)	533 (82.8)	561 (86.4)	567 (88.6)
Number of Subjects who Discontinued, n (%)	111 (17.2)	88 (13.6)	73 (11.4)
Primary Reason for Discontinuation, n (%)			
Adverse Event	17 (2.6)	19 (2.9)	19 (3.0)
COPD Exacerbation	16 (2.5)	8 (1.2)	11 (1.7)
Lack of Efficacy	24 (3.7)	11 (1.7)	3 (0.5)
Lost to Follow-up	4 (0.6)	7 (1.1)	2 (0.3)
Non-fulfillment of Inclusion/Exclusion Criteria	0	2 (0.3)	2 (0.3)
Other	8 (1.2)	8 (1.2)	7 (1.1)
Patient's Request	17 (2.6)	10 (1.5)	9 (1.4)
Protocol Non-compliance	7 (1.1)	5 (0.8)	7 (1.1)
Withdrawal of Informed Consent	18 (2.8)	18 (2.8)	13 (2.0)
Safety Population, n (%)	641 (99.5)	644 (99.2)	636 (99.4)
ITT Population, n (%)	640 (99.4)	643 (99.1)	636 (99.4)

PP Population, n (%)	590 (91.6)	597 (92.0)	598 (93.4)
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Note: N=number of patients randomized; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N).

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 10 (Table 1)

The percentage of patients completing the trials was highest for patients receiving aclidinium 400 µg (88.6% compared to 86.4% for aclidinium 200 µg and 82.8% for placebo). Across treatment groups, the percentage of patients discontinuing due to an adverse event ranged was approximately 3%, with a slightly higher percentage of patients in the placebo group (2.5%) discontinuing due to a COPD exacerbation as compared to the aclidinium treatment groups (1.7% and 1.2% for the 400 µg and 200 µg arms, respectively). The percentage of patients discontinuing due to a lack of efficacy was higher for patients in the placebo group (3.7%) as compared to the active treatment groups (0.5% and 1.7% for the 400 µg and 200 µg arms, respectively).

#### 6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint for all three trials was the change from baseline in morning predose (trough) forced expiratory volume in one second (FEV1) assessed at 12 weeks. Spirometry is an appropriate choice of endpoint for a purported bronchodilator. The aclidinium clinical development program specified trough FEV1 as the primary endpoint, which is in contrast to the Agency's recommendation to use post-dose FEV1 as described in the Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment,"<sup>23</sup> but is consistent with the clinical development programs of several other drug products approved for use in COPD. While not specified as the primary endpoint, the aclidinium program did include an evaluation of peak FEV1 and serial post-dose FEV1, as described below. These additional spirometric measurements are important for providing a more complete assessment of aclidinium's bronchodilatory action.

The results for the Agency's analysis of the primary endpoint (and for the analysis of trough FEV1 at week 24 for Trial M/34273/34) are provided in Table 14.

**Table 14. Change from baseline in morning predose (trough) FEV1 (L) at Week 12 or Week 24, Intent-To-Treat Population**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SE)	LS Mean (SE)	LS Mean (SE)	95% CI	P-value
<b>LAS-MD-33</b>						

<sup>23</sup> Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf>. Accessed December 19, 2011.

Acclidinium 400 mcg	190	1.328 (0.032)	0.099 (0.014)	0.124 (0.021)	0.08, 0.16	<0.001
Acclidinium 200 mcg	184	1.308 (0.033)	0.061 (0.015)	0.086 (0.021)	0.04, 0.13	<0.001
Placebo	185	1.383 (0.033)	-0.025 (0.015)	--	--	--
<b>M/34273/34</b>						
<b>Week 12</b>						
Acclidinium 400 mcg	269	1.447 (0.029)	0.058 (0.015)	0.105 (0.020)	0.07, 0.14	<0.001
Acclidinium 200 mcg	277	1.453 (0.028)	0.030 (0.014)	0.077 (0.020)	0.04, 0.12	<0.001
Placebo	273	1.419 (0.028)	-0.047 (0.015)	--	--	--
<b>Week 24</b>						
Acclidinium 400 mcg	269	1.447 (0.029)	0.055 (0.016)	0.128 (0.022)	0.08, 0.17	< 0.001
Acclidinium 200 mcg	277	1.453 (0.028)	0.026 (0.016)	0.099 (0.022)	0.06, 0.14	< 0.001
Placebo	273	1.419 (0.028)	-0.073 (0.016)	--	--	--
<b>LAS-MD-38 Part A</b>						
Acclidinium 400 mcg	177	1.255 (0.036)	0.064 (0.016)	0.072 (0.022)	0.03, 0.12	0.001
Acclidinium 200 mcg	182	1.387 (0.035)	0.043 (0.015)	0.051 (0.022)	0.01, 0.09	0.019
Placebo	182	1.418 (0.035)	-0.008 (0.015)	--	--	--

Source: Agency's Statistical Review.

Note: P-value, LS mean, and LSMD obtained from an ANCOVA model with change from baseline in trough FEV1 as response, with treatment group and sex as factors and baseline trough FEV1 and age as covariates.

While the results for the comparison between acclidinium 400 µg and placebo are statistically significant in each of the three efficacy and safety trials, the effect size observed in Trial M/34273/38 Part A is smaller (72 mL) than the effect sizes demonstrated in Trial M/34273/33 and Trial M/34273/34 (124 mL and 105 mL, respectively). The Applicant attributes this to an imbalance in patients' baseline characteristics including COPD severity, which occurred unexpectedly and despite randomization in Trial LAS-MD-38 Part A. For example, baseline FEV1 was 1.495 L, 1.397 L, and 1.249 L for the placebo, acclidinium 200 µg, and acclidinium 400 µg treatment arms, respectively. In addition, a greater proportion of patients in the acclidinium 400 µg treatment arm (54%) had Stage III (severe) COPD at baseline, than in either the acclidinium 200 µg treatment arm (47%) or placebo arm (37%). A summary of COPD severity for the ITT population, by Trial and Treatment Group, is provided in Table 15. The proportion of patients with Stage III (severe) COPD was more balanced across treatment groups for Trial M/34273/34 as compared to LAS-MD-38 Part A; in Trial LAS-MD-33 the acclidinium 200 µg treatment arm had the highest proportion of patients with Stage III (severe) disease.

**Table 15. COPD Severity, by Trial and Treatment Group, ITT Population**

	Placebo n (%)	Aclidinium 200 µg n (%)	Aclidinium 400 µg n (%)
<b>LAS-MD-33</b>			
N	185	184	190
Stage I (Mild)	0	0	0
Stage II (Moderate)	111 (60.0)	98 (53.3)	118 (62.1)
Stage III (Severe)	72 (38.9)	80 (43.5)	68 (35.8)
Stage IV (Very Severe)	1 (0.5)	3 (1.6)	1 (0.5)
<b>M/34273/34</b>			
N	273	277	269
Stage I (Mild)	0	0	0
Stage II (Moderate)	178 (65.9)	192 (69.6)	184 (68.7)
Stage III (Severe)	92 (34.1)	84 (30.4)	84 (31.3)
Stage IV (Very Severe)	0	0	0
<b>LAS-MD-38 Part A</b>			
N	182	182	177
Stage I (Mild)	2 (1.1)	0	0
Stage II (Moderate)	113 (62.1)	95 (52.2)	79 (44.6)
Stage III (Severe)	67 (36.8)	85 (46.7)	96 (54.2)
Stage IV (Very Severe)	0	1 (0.5)	0

Source: Section 5.3.5.1.1 (LAS-MD-33 Volume 1), pg. 380 (Table 14.2.6); Section 5.3.5.1.12 (M/34273/34 Statistical Report 1), pg. 206 (Table 14.2.4.2); Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), pg. 326 (Table 14.2.6)

Note: Severity based on post-bronchodilator FEV1: Stage I – FEV1 ≥80% predicted and FEV1/FVC < 0.70; Stage II – 50% ≤ FEV1 <80% predicted and FEV1/FVC < 0.70; Stage III – 30% ≤ FEV1 <50% predicted and FEV1/FVC < 0.70; Stage IV – FEV1 <30% predicted and FEV1/FVC < 0.70

While it is impossible to conclude with certainty why the effect sizes observed for acclidinium are smaller in Trial M/34273/38 Part A as compared to the other two trials, it is plausible that these differences in COPD disease severity played some role. It is also noted that the changes in trough FEV1 from baseline were actually larger in magnitude for Trial LAS-MD- 38 Part A than for Trial M/34723/34, which is somewhat reassuring. It is likely that the true effect size for difference from placebo lies somewhere between the result for trial LAS-MD-38 Part A (72 mL) and the result for LAS-MD-33 (124 mL).

As is the case for the higher acclidinium dose, the results for the comparison between acclidinium 200 µg and placebo are also statistically significant in each of the three efficacy and safety trials. Moreover, the effect size associated with the acclidinium 400 µg dose is larger than that for the 200 µg dose in each case, suggesting a dose response.

The results for Trial M/34273/34 at 24 weeks are consistent with those at 12 weeks.

Overall, the clinical program provides replicate, statistically significant results for the primary endpoint.

### 6.1.5 Analysis of Secondary Endpoints(s)

A summary of secondary and additional endpoints evaluated in the three efficacy and safety trials is provided in Table 11 found in Section 3.3. Included here is a review of the following secondary or additional endpoints: additional pulmonary function tests (peak FEV1, serial FEV1 over 12 hours, FVC, and IC), COPD exacerbations, rescue medication use, and patient- or evaluator-reported outcome measures (SGRQ and BDI/TDI).

#### **Additional Pulmonary Function Tests**

In addition to the primary endpoint, morning predose (trough) FEV1, the three efficacy and safety trials also evaluated peak FEV1, serial FEV1 over 12 hours, FVC, and IC. Additional measures of pulmonary function are often used as secondary endpoints to provide support of the primary endpoint, as described in the Agency's Draft Guidance.<sup>24</sup>

#### ***Peak FEV1***

Peak FEV1 was defined as the maximum FEV1 measurement from among the FEV1 results obtained from time 0 through 3 hours after the morning dose. The results for raw mean peak FEV1 at Week 12<sup>25</sup> ranged from 1.60 L to 1.75 L for the aclidinium 400 µg treatment group and from 1.44 L to 1.55 L for placebo in Trials LAS-MD-33 and M/34273/34. This is in contrast to the results from Trial 38 Part A, in which higher raw mean Peak FEV1 was observed for patients receiving placebo (1.55 L) than for patients treated with aclidinium 400 µg (1.47) at Week 12. Overall, these results are of unclear clinical significance.

#### ***FEV1 over 12 hours***

A 12-hour PFT substudy was conducted as part of each of the three efficacy and safety trials. The evaluation of serial post-dose FEV1 is consistent with the Agency's recommendations for the evaluation of bronchodilators in COPD.<sup>26</sup>

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<sup>24</sup> Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf>. Accessed December 19, 2011.

<sup>25</sup> Agency's analysis.

<sup>26</sup> Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf>. Accessed December 19, 2011.

The number of patients, per trial and treatment group, enrolled in the PFT substudy is provided in Table 16. Adjusted mean changes from baseline in FEV1 over 12 hours on Day 1 and at Week 12 are provided in Figure 4 and Figure 5 for Trial LAS-MD-33, Figure 6 and Figure 7 for Trial M/34273/34 (along with the results at Week 24 in Figure 8), and Figure 9 and Figure 10 for Trial LAS-MD-38 Part A.

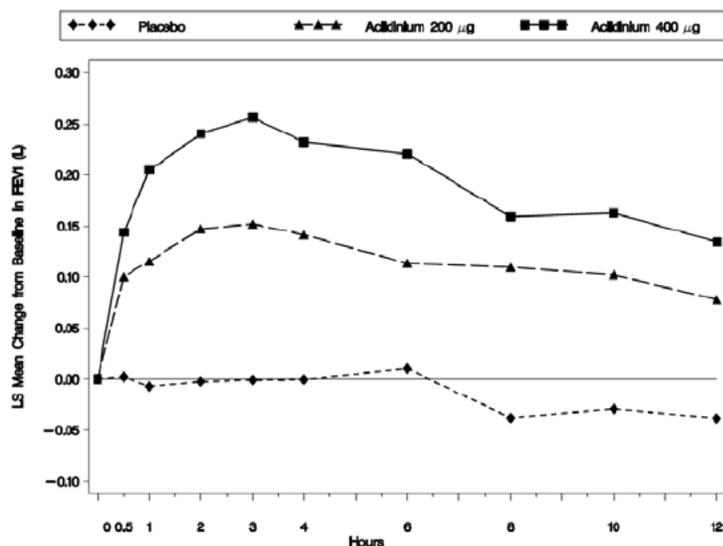
**Table 16. Number of Patients in 12-hour PFT Substudy, by Trial and Treatment Group**

	Placebo	Aclidinium 200 µg	Aclidinium 400 µg
<b>LAS-MD-33</b>			
Total Randomized, N	186	185	190
12-hour PFT Substudy, n (%)	73 (39.2)	74 (40.0)	73 (38.4)
<b>M/34273/34</b>			
Total Randomized, N	276	280	272
12-hour PFT Substudy, n (%)	62 (22.5)	64 (22.9)	65 (23.9)
<b>LAS-MD-38 Part A</b>			
Total Randomized, N	182	184	178
12-hour PFT Substudy, n (%)	54 (29.7)	58 (31.5)	53 (29.8)

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), pg 3; Section 5.3.5.1.3 (M/34273/34), pg 114 and pg 86 (Table 8); Section 5.3.5.1.1 (LAS-MD-38 Part A, Volume 1), pg 3

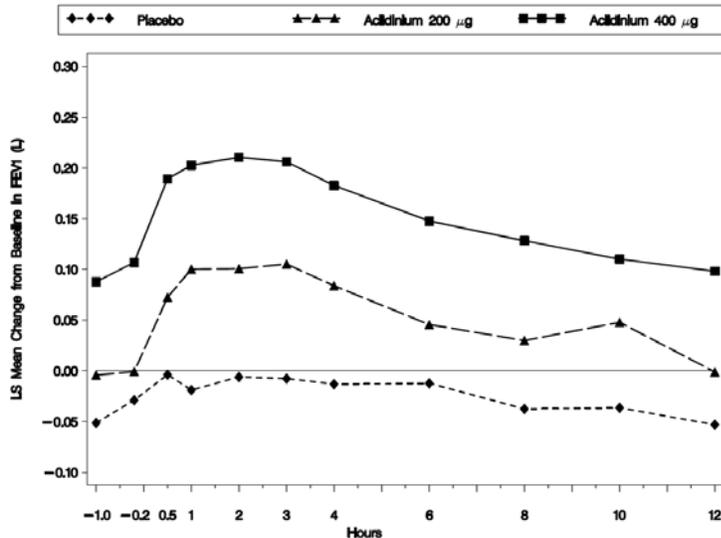
Note: Percentages are calculated as 100 x (n/N).

**Figure 4. Change from Baseline in FEV1 over 12 hours on Day 1, 12-Hour PFT Substudy: Trial LAS-MD-33**



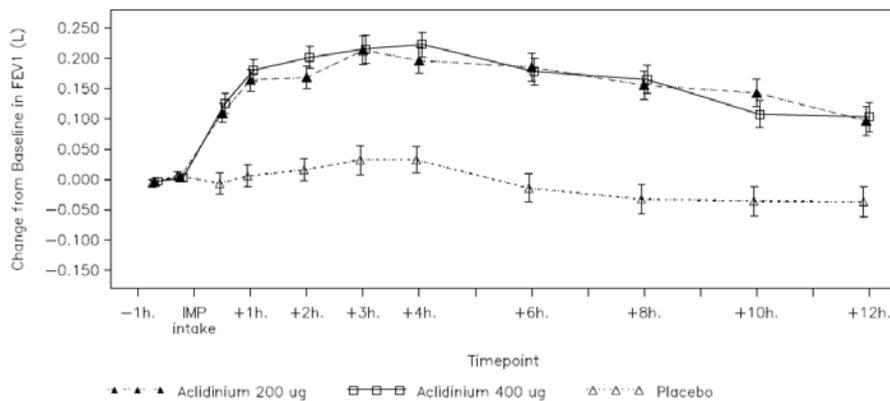
Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), pg. 151 (Figure 11.4.1.3.2-1)

**Figure 5. Change from Baseline in FEV1 over 12 hours at Week 12, 12-Hour PFT Substudy: Trial LAS-MD-33**



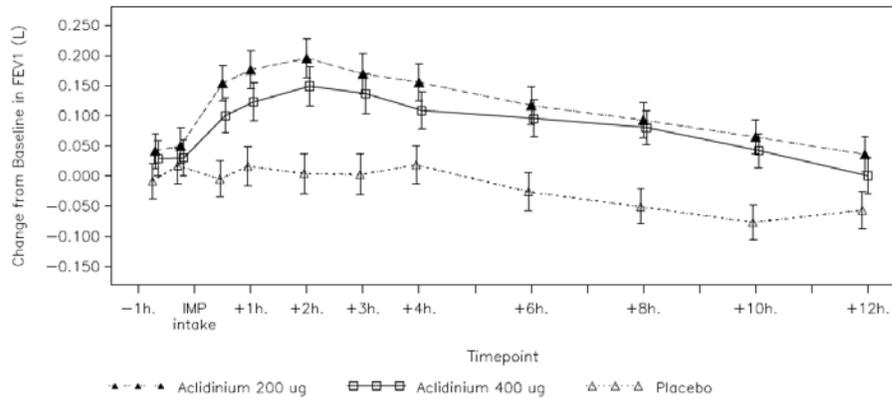
Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), pg. 152 (Figure 11.4.1.3.2-2)

**Figure 6. Change from Baseline in FEV1 over 12 hours on Day 1, 12-Hour PFT Substudy: Trial M/34273/34**



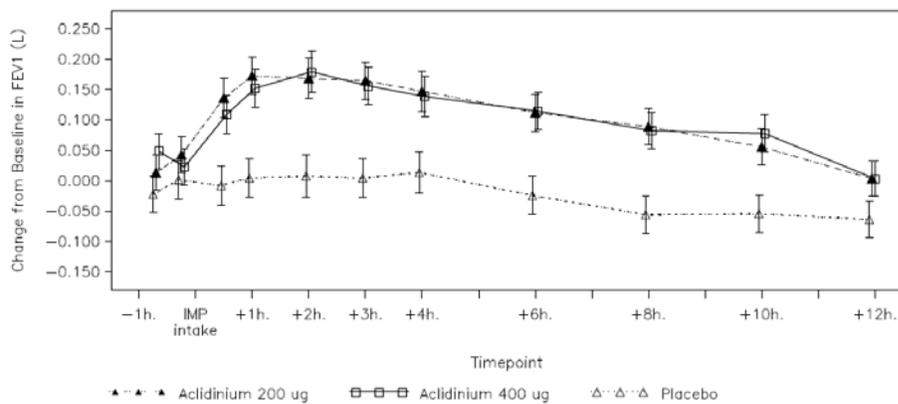
Source: Section 5.3.5.1.3 (LAS-MD-CL34), pg. 115 (Figure 9)

**Figure 7. Change from Baseline in FEV1 over 12 hours at Week 12, 12-Hour PFT Substudy: Trial M/34273/34**



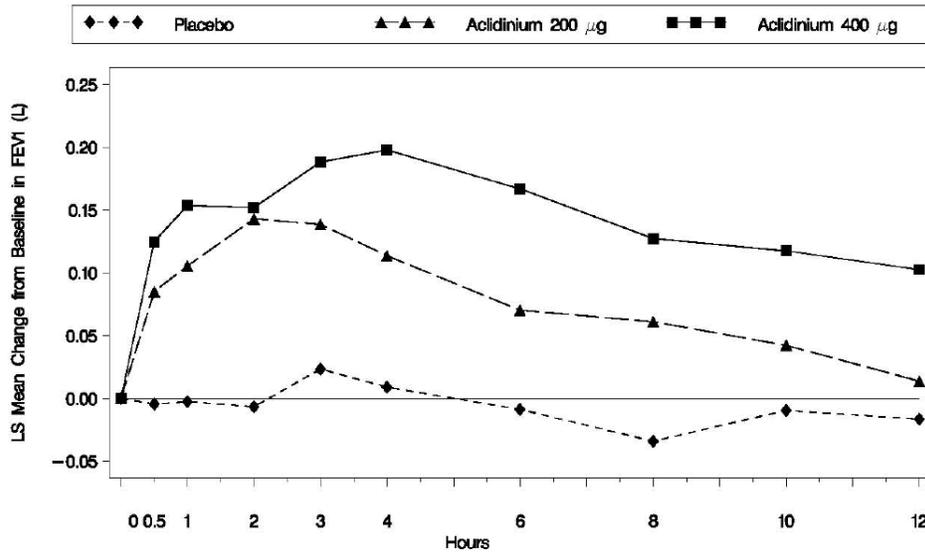
Source: Section 5.3.5.1.3 (LAS-MD-CL34), pg. 116 (Figure 10)

**Figure 8. Change from Baseline in FEV1 over 12 hours at Week 24, 12-Hour PFT Substudy: Trial M/34273/34**



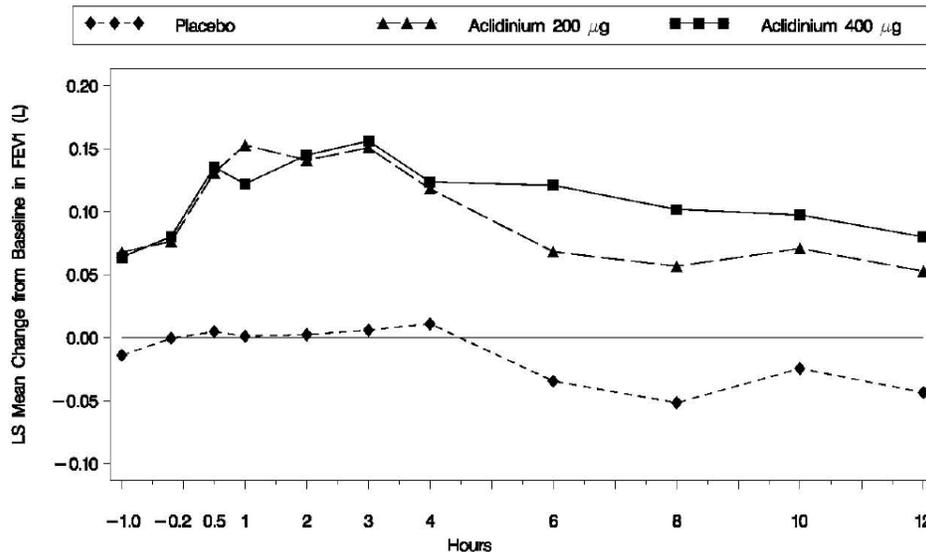
Source: Section 5.3.5.1.3 (LAS-MD-CL34), pg. 117 (Figure 11)

**Figure 9. Change from Baseline in FEV1 over 12 hours on Day 1, 12-Hour PFT Substudy: Trial LAS-MD-38 Part A**



Source: Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), pg. 145 (Figure 11.4.1.3.2-1)

**Figure 10. Change from Baseline in FEV1 over 12 hours at Week 12, 12-Hour PFT Substudy: Trial LAS-MD-38 Part A**



Source: Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), pg. 146 (Figure 11.4.1.3.2-2)

For both Trials M/34273/33 and M/34273/38 A, there is a separation between the acclidinium 400 µg and placebo curves throughout the spirometric observational period

on both Day 1 and at Week 12, supporting the persistence of effect over the 12 hour period both at the start of therapy and after 3 months of treatment. While this is also true for Trial M/34273/34, the magnitude of the separation between the curves appears to diminish somewhat between Day 1 and Week 12 or Week 24.

Results for change from baseline in FEV1 observed for the aclidinium 200 µg treatment group are variable across the trials, with a clear separation between the 400 µg and 200 µg curves (favoring the aclidinium 400 µg treatment arm) on both Day 1 and at Week 12 for Trial M/34273/33. The degree of separation between the 400 µg and 200 µg curves (and favoring 400 µg) is less for Trial M/34273/38 Part A, particularly at Week 12, and even less for Trial M/34273/34. In fact, there is a reversal observed in Trial M/34273/34 at Week 12, with the change from baseline in FEV1 observed for the aclidinium 200 µg group exceeding that of the aclidinium 400 µg treatment group, at least in the initial post-dosing period.

Overall, these PFT substudy results provide evidence of an improvement in FEV1 that persists over the dosing period, and that is present both at the initiation of treatment and after months of treatment. These results are supportive of the findings for the primary endpoint.

### FVC

Results for the Applicant's analysis of change from baseline in trough FVC assessed at Week 12 (and at week 24 for Trial M/34273/34) are provided in Table 17.

**Table 17. Change from baseline in morning trough FVC at Week 12 or Week 24, Intent-To-Treat Population**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>LAS-MD-33</b>						
Aclidinium 400 mcg	190	2.6132 (0.8670)	0.2168 (0.0224)	0.2193	0.1568, 0.2817	< 0.0001
Aclidinium 200 mcg	184	2.6468 (0.8732)	0.1624 (0.0228)	0.1649	0.1017, 0.2281	< 0.0001
Placebo	185	2.5951 (0.8714)	-0.0025 (0.0227)	--	--	--
<b>M/34273/34</b>						
<b>Week 12</b>						
Aclidinium 400 mcg	269	3.045 (0.852)	0.130 (0.026)	0.184	0.121, 0.246	< 0.0001
Aclidinium 200 mcg	277	3.066 (0.848)	0.061 (0.022)	0.119	0.057, 0.181	0.0002
Placebo	273	3.060 (0.786)	-0.048 (0.022)	--	--	--

<b>Week 24</b>						
Acclidinium 400 mcg	269	3.045 (0.852)	0.131 (0.027)	0.224	0.155, 0.292	< 0.0001
Acclidinium 200 mcg	277	3.066 (0.848)	0.062 (0.024)	0.159	0.091, 0.227	< 0.0001
Placebo	273	3.060 (0.786)	-0.086 (0.026)	--	--	--
<b>LAS-MD-38 Part A</b>						
Acclidinium 400 mcg	177	2.5755 (0.8457)	0.1515 (0.0249)	0.1201	0.0514, 0.1887	0.0349
Acclidinium 200 mcg	182	2.7287 (0.9062)	0.0988 (0.0245)	0.0674	-0.0006, 0.1355	0.0346
Placebo	182	2.7606 (0.8244)	0.0314 (0.0245)	--	--	--

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.3.2, pg. 497; Section 5.3.5.1.3 (M/34273/34), pg. 112 (Table 27); Section 5.3.5.1.12 (Study m-34273-cl34: Statistical report – 1), pg. 577, 580, and 582 (Table 14.4.7.1); Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 14.4.3.2, pg. LAS-MD-38 Part A  
 \*Applicant's ANCOVA analysis

Results for the treatment difference between acclidinium 400 µg and placebo in change from baseline in trough FVC at Week 12 are statistically significant for each of the three efficacy and safety trials. The treatment effect is approximately 220 mL for Trial LAS-MD-33 and 180 mL for Trial M/34273/34; the treatment effect is smaller (approximately 120 mL) for Trial M/34273/38 Part A. In all three trials, results for the treatment difference between acclidinium 200 µg and placebo in change from baseline in trough FVC as Week 12 are statistically significant. The effect size for the acclidinium 200 µg treatment arm is numerically smaller than that for the acclidinium 400 µg treatment arm in all three trials. The results for Trial M/34273/34 at 24 weeks are consistent with those at 12 weeks. Overall, the results for trough FVC are supportive of the findings for the primary endpoint.

### IC

Results for the Applicant's analysis of change from baseline in trough IC assessed at Week 12 (and at Week 24 for Trial M/34273/34) are provided in Table 18.

**Table 18. Change from baseline in morning trough IC at Week 12 or Week 24, Intent-To-Treat Population**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>LAS-MD-33</b>						
Acclidinium 400 mcg	190	1.9709 (0.6477)	0.0672 (0.0220)	0.1377	0.0764, 0.1991	< 0.0001
Acclidinium 200 mcg	184	1.9881 (0.6385)	0.0483 (0.0227)	0.1189	0.0564, 0.1813	0.0002
Placebo	185	1.9889	-0.0706 (0.0222)	--	--	--

		(0.6325)				
<b>M/34273/34</b>						
<b>Week 12</b>						
Acclidinium 400 mcg	269	2.182 (0.661)	0.064 (0.022)	0.133	0.079, 0.187	< 0.0001
Acclidinium 200 mcg	277	2.173 (0.638)	0.000 (0.019)	0.070	0.016, 0.123	0.0112
Placebo	273	2.168 (0.576)	-0.063 (0.019)	--	--	--
<b>Week 24</b>						
Acclidinium 400 mcg	269	2.182 (0.661)	0.041 (0.022)	0.119	0.061, 0.177	< 0.0001
Acclidinium 200 mcg	277	2.173 (0.638)	-0.010 (0.020)	0.068	0.011, 0.126	0.02
Placebo	273	2.168 (0.576)	-0.072 (0.022)	--	--	--
<b>LAS-MD-38 Part A</b>						
Acclidinium 400 mcg	177	1.8627 (0.6068)	0.0715 (0.0228)	0.1132	0.0504, 0.1760	0.0004
Acclidinium 200 mcg	182	1.9690 (0.7063)	0.0443 (0.0224)	0.0860	0.0239, 0.1481	0.0067
Placebo	182	2.0277 (0.6482)	-0.0417 (0.0224)	--	--	--

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.3.3, pg. 502; Section 5.3.5.1.3 (M/34273/34), pg. 114 (Table 29); Section 5.3.5.1.12 (Study m-34273-cl34: Statistical report – 1), pg. 795, 798, and 800 (Table 14.4.13.1); Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 14.4.3.3, pg. 441; Applicant’s ANCOVA analysis

The results for the treatment difference between acclidinium 400 µg and placebo in change from baseline in trough IC at Week 12 are statistically significant for each of the three efficacy and safety trials, with a treatment effect of approximately 110-130 mL. In all three trials, results for the treatment difference between acclidinium 200 µg and placebo in change from baseline in trough FVC at Week 12 are statistically significant, with an effect size that is generally smaller than that for the acclidinium 400 µg arm. The results for Trial M/34273/34 at 24 weeks are consistent with those at 12 weeks. Overall, the results for trough IC are supportive of the findings for the primary endpoint.

### **COPD Exacerbations**

COPD exacerbations were defined as, “an increase in COPD symptoms (eg, dyspnea, cough, sputum volume, or sputum purulence) during at least 2 consecutive days”<sup>27</sup> and were classified as mild (self-managed with increased short-acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but not requiring hospitalization), or severe (requiring overnight stay at hospital or emergency room).

<sup>27</sup> Section 5.3.5.1.1 (LAS-MD-33), pg. 3020

As discussed in Section 3.3, it is important to note that there is no single well-accepted definition of COPD exacerbation. The Applicant's proposed definition, which includes both a symptomatic component and a treatment requirement, is reasonable as an additional efficacy variable, with the caveat that the definition relies on the discretion of individual treating physicians and may be influenced by local practice standards.

Results for the Applicant's analysis of rate of COPD exacerbations (any exacerbation, as well as moderate or severe exacerbations) are provided in Table 19.

**Table 19. Rate of COPD Exacerbations per Patient/Year, Intent-To-Treat Population**

Treatment Arm	N	Rate	95% CI	Treatment difference from placebo		
				Rate Ratio	95% CI	P-value*
<b>LAS-MD-33 (Mild, Moderate, or Severe)</b>						
Acclidinium 400 mcg	190	0.411	0.23, 0.74	0.524	0.32, 0.85	0.0094
Acclidinium 200 mcg	184	0.548	0.32, 0.94	0.698	0.44, 1.10	0.1180
Placebo	185	0.785	0.46, 1.33	--	--	--
<b>LAS-MD-33 (Moderate or Severe)</b>						
Acclidinium 400 mcg	190	0.417	0.24, 0.71	0.663	0.41, 1.07	0.0912
Acclidinium 200 mcg	184	0.422	0.25, 0.71	0.670	0.41, 1.08	0.1033
Placebo	185	0.629	0.38, 1.03	--	--	--
<b>M/34273/34 (Mild, Moderate, or Severe)</b>						
Acclidinium 400 mcg	269	0.404	0.31, 0.52	0.674	0.48, 0.94	0.0195
Acclidinium 200 mcg	277	0.429	0.33, 0.55	0.715	0.52, 0.99	0.0428
Placebo	273	0.600	0.48, 0.75	--	--	--
<b>M/34273/34 (Moderate or Severe)</b>						
Acclidinium 400 mcg	269	0.342	0.25, 0.44	0.723	0.51, 1.02	0.0629
Acclidinium 200 mcg	277	0.352	0.27, 0.45	0.742	0.53, 1.04	0.0845
Placebo	273	0.474	0.38, 0.60	--	--	--
<b>LAS-MD-38 Part A (Mild, Moderate, or Severe)</b>						
Acclidinium 400 mcg	177	0.478	0.35, 0.66	0.958	0.61, 1.50	0.8528
Acclidinium 200 mcg	182	0.359	0.25, 0.52	0.718	0.44, 1.16	0.1793
Placebo	182	0.499	0.36, 0.69	--	--	--
<b>LAS-MD-38 Part A (Moderate or Severe)</b>						
Acclidinium 400 mcg	177	0.412	0.29, 0.58	0.821	0.52, 1.29	0.3970
Acclidinium 200 mcg	182	0.285	0.19, 0.42	0.569	0.34, 0.94	0.0278

Placebo	182	0.501	0.37, 0.68	--	--	--
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Source: Section 5.3.5.3.27, pg. 108-109 (Table 3.2.1.9-1)

\*Applicant's Poisson regression analysis

For two of the three efficacy and safety trials there is a statistically significant reduction in the rate of any COPD exacerbation, with rate ratio of 0.524 in Trial LAS-MD-33 (95% CI 0.32, 0.85; p=0.0094) and a rate ratio of 0.674 in Trial M/34273/34 (95% CI 0.48, 0.94; p=0.0195). There is also a trend towards a reduction in the rate of moderate or severe COPD exacerbations for these two trials, although the results are not statistically significant.

The Applicant provided an analysis of the number needed to treat (NNT); in order to prevent one COPD exacerbation (of any severity) per patient per year, the NNT was approximately 3 patients for Trial LAS-MD-33, 5 patients for trial M/34273/34, and 48 patients for trial LAS-MD-38 Part A.<sup>28</sup> The high degree of variability in these results makes it difficult to draw conclusions about their clinical relevance.

Further discussion of COPD exacerbations (e.g., discussion of exacerbation duration) is not provided in this review, given that such analyses are limited by the low overall number of exacerbations reported for the aclidinium clinical development program. Of note, the Applicant is not seeking an indication or claim related to COPD exacerbations.

### **Rescue Medication Use**

Results for the Applicant's analysis of rate of total daily use of rescue medication are provided in Table 20.

**Table 20. Change from Baseline in Total Daily Use of Rescue Medication (Puffs/day) at Week 12, Intent-To-Treat Population**

Treatment Arm	N	LS Mean (SE)	Treatment difference from placebo		
			LS Mean	95% CI	P-value*
<b>LAS-MD-33</b>					
Aclidinium 400 mcg	186	-1.6 (0.1)	-0.9	-1.3, -0.5	< 0.0001
Aclidinium 200 mcg	182	-1.4 (0.1)	-0.7	-1.1, -0.3	0.0010
Placebo	181	-0.7 (0.1)	--	--	--
<b>M/34273/34</b>					
Aclidinium 400 mcg	269	-1.2 (0.2)	-1.0	-1.6, -0.3	0.0042
Aclidinium 200 mcg	277	-0.8 (0.2)	-0.6	-1.3, 0.04	0.0614
Placebo	271	-0.2 (0.2)	--	--	--
<b>LAS-MD-38 Part A</b>					

<sup>28</sup> Applicant's correspondence dated January 19, 2012, pg. 4 (Table 2.4-1).

Acclidinium 400 mcg	171	-1.4 (0.2)	-0.3	-0.8, 0.2	0.2490
Acclidinium 200 mcg	175	-1.3 (0.2)	-0.2	-0.7, 0.4	0.5334
Placebo	173	-1.1 (0.2)	--	--	--

Source: Section 5.3.5.3.27, pg. 106-107 (Table 3.2.1.8-1)  
 \*Applicant's ANCOVA analysis

For two of the three efficacy and safety trials (LAS-MD-33 and M/34273/34), there is a statistically significant reduction in the rescue medication use at Week 12, with an effect size of approximately -1.0.

### **Patient- or Evaluator-Reported Outcome Measures**

#### **SGRQ**

Disease-specific health related quality of life was assessed in the acclidinium clinical development program using the St. George's Respiratory Questionnaire. Health-related quality-of-life instruments are described as one of the commonly used secondary efficacy endpoints in the Agency's Draft Guidance,<sup>29</sup> and there is regulatory precedent for labeling claims based on the SGRQ.<sup>30</sup>

Results for the Applicant's analysis of change in SGRQ total score are provided in Table 21 (Mean Change) and Table 22 (Proportions of Patients with Clinically Meaningful Improvement). A change in SGRQ total score of 4 units or greater was considered to represent a clinically meaningful improvement.

**Table 21. Mean Change from Baseline in SGRQ Total Score at Week 12, Intent-To-Treat Population**

Treatment Arm	N	LS Mean Change (SE)	Treatment difference from placebo		
			LS Mean	95% CI	P-value*
<b>LAS-MD-33</b>					
Acclidinium 400 mcg	189	-4.6 (0.8)	-2.5	-4.7, -0.4	0.0186
Acclidinium 200 mcg	180	-4.8 (0.8)	-2.7	-4.9, -0.6	0.0126
Placebo	181	-2.0 (0.8)	--	--	--
<b>M/34273/34</b>					

<sup>29</sup> Draft Guidance for Industry, "Chronic Obstructive Pulmonary Disease: Developing Drugs for Treatment," November 2007. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM071575.pdf>. Accessed December 19, 2011.

<sup>30</sup> Arcapta Neohaler (indacaterol inhalation powder) Prescribing Information, July 2011. Available at: <http://www.pharma.us.novartis.com/product/pi/pdf/arcapta.pdf>. Accessed December 20, 2011.

Acclidinium 400 mcg	269	-6.5 (0.7)	-4.1	-6.1, -2.1	< 0.0001
Acclidinium 200 mcg	275	-5.5 (0.7)	-3.2	-5.1, -1.2	0.0015
Placebo	271	-2.4 (0.7)	--	--	--
<b>LAS-MD-38 Part A</b>					
Acclidinium 400 mcg	172	-5.4 (1.0)	-1.1	-3.8, 1.6	0.4288
Acclidinium 200 mcg	178	-6.0 (1.0)	-1.7	-4.3, 1.0	0.2216
Placebo	178	-4.3 (1.0)	--	--	--

Source: Section 5.3.5.3.27, pg. 103 (Table 3.2.1.6-1);

For Trial M/34273/34 only: Applicant's Submission dated March 15, 2012, Section 1.11.3, pg. 14 (Table 3.2.1.6-1)

\*Applicant's ANCOVA analysis

**Table 22. Proportions of Patients with Clinically Meaningful Improvements in SGRQ Total Score at Week 12, Intent-To-Treat Population**

Treatment Arm	N	%	Treatment difference from placebo		
			Odds Ratio	95% CI	P-value*
<b>LAS-MD-33</b>					
Acclidinium 400 mcg	190	44.4	1.37	0.90, 2.09	0.1390
Acclidinium 200 mcg	184	49.4	1.75	1.14, 2.67	0.0103
Placebo	185	35.9	--	--	--
<b>M/34273/34</b>					
Acclidinium 400 mcg	269	56.9	1.96	1.38, 2.80	0.0002
Acclidinium 200 mcg	277	52.0	1.64	1.15, 2.33	0.0059
Placebo	273	39.5	--	--	--
<b>LAS-MD-38 Part A</b>					
Acclidinium 400 mcg	177	44.8	1.28	0.83, 1.97	0.2596
Acclidinium 200 mcg	182	47.2	1.47	0.96, 2.25	0.0772
Placebo	182	38.8	--	--	--

Source: Section 5.3.5.3.27, pg. 100 (Table 3.2.1.5-1);

For Trial M/34273/34 only: Applicant's Submission dated March 15, 2012, Section 1.11.3 pg. 12 (Table 3.2.1.5-1)

\*Applicant's logistic regression analysis

Results for the treatment difference for mean change in SGRQ Total Score between the acclidinium 400 µg and placebo groups are statistically significant for two of the three efficacy and safety trials (LAS-MD-33 and M/34273/34), but meet the threshold for clinically meaningful improvement in only one of the trials (M/34273/34).

In each of the three trials, a numerically greater proportion of patients in the acclidinium 400 µg treatment group experienced a clinically meaningful change in SGRQ Total

Score as compared to placebo, however, the comparison of proportions was statistically significant only for Trial M/34273/34.

**BDI/TDI**

Results for the Applicant’s analysis of mean change in Transition Dyspnea Index focal score are provided in Table 23. The acridinium clinical development program proposed a 1-unit increase as the threshold for a minimum clinically important difference. As noted in Section 3.3, the Agency has not previously accepted the BDI/TDI as a validated measure of dyspnea, and the limitations of these instruments, including concerns about the validity of the 1-unit threshold for MCID, have been discussed in a prior Advisory Committee meeting.<sup>31</sup>

**Table 23. Mean Change from Baseline in TDI Focal Score at Week 12, Intent-To-Treat Population**

Treatment Arm	N	LS Mean (SE)	Treatment difference from placebo		
			LS Mean	95% CI	P-value*
<b>LAS-MD-33</b>					
Acridinium 400 mcg	172	1.5 (0.2)	1.0	0.4, 1.6	0.0021
Acridinium 200 mcg	165	1.4 (0.2)	0.9	0.3, 1.6	0.0054
Placebo	161	0.5 (0.2)	--	--	--
<b>M/34273/34</b>					
Acridinium 400 mcg	262	1.7 (0.2)	0.9	0.3, 1.4	0.0012
Acridinium 200 mcg	270	1.2 (0.2)	0.4	-0.2, 0.9	0.1807
Placebo	257	0.9 (0.2)	--	--	--
<b>LAS-MD-38 Part A</b>					
Acridinium 400 mcg	142	1.3 (0.2)	1.0	0.3, 1.7	0.0054
Acridinium 200 mcg	149	1.0 (0.2)	0.7	0.0, 1.4	0.0416
Placebo	148	0.3 (0.3)	--	--	--

Source: Section 5.3.5.3.27, pg. 98 (Table 3.2.1.4-1)  
 \*Applicant’s ANCOVA analysis

Results for the treatment difference for mean change in TDI Focal Score between the acridinium 400 µg and placebo groups are statistically significant in all three efficacy and safety trials, but meet the Applicant’s threshold for clinically meaningful improvement in only two of the three trials (LAS-MD-33 and LAS-MD-38 Part A). In none of the three

<sup>31</sup> Transcript of the September 6, 2002, Pulmonary/Allergy Drugs Advisory Committee Meeting on NDA 21-395, Spriva (tiotropium bromide), by Boehringer-Ingelheim, for chronic obstructive pulmonary disease. Available at: <http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3890t1.htm>. Accessed December 20, 1011.

trials do the effect sizes for the aclidinium 200 µg treatment arm meet the Applicant's 1.0 threshold.

Again, it is noted that the BDI/TDI, while useful in a clinical setting, has been assessed as inadequate for use as a clinical trial endpoint from a regulatory standpoint<sup>32</sup>, and there is no regulatory precedent for labeling claims based on the BDI/TDI.

### 6.1.6 Other Endpoints

None

### 6.1.7 Subpopulations

The application includes an analysis of efficacy results for various subpopulations, including subgroups based on demographics (age, sex), as well as subgroups based on characteristics that inform baseline health status (COPD severity, bronchodilator reversibility, concomitant ICS use, and smoking status). This review considers analyses of the primary endpoint trough FEV1 at Week 12 conducted for the pooled ITT population drawn from all three efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A).

#### **Demographics**

This review presents subgroup analyses based on the demographic factors of age (Table 24) and sex (Table 25). While the Applicant also conducted a subgroup analysis based on race, the numbers of non-Caucasians are too low for these data to be informative, and so they are not presented.

#### **Age**

**Table 24. Change from baseline in morning predose (trough) FEV1 at Week 12 by Age, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>&lt; 60 years</b>						
Aclidinium 400 mcg	197	1.453 (0.544)	0.090 (0.016)	0.113	0.071, 0.155	< 0.0001
Aclidinium 200	220	1.585 (0.584)	0.056 (0.015)	0.079	0.038, 0.119	0.0002

<sup>32</sup> Transcript of the September 6, 2002, Pulmonary/Allergy Drugs Advisory Committee Meeting on NDA 21-395, Spriva (tiotropium bromide), by Boehringer-Ingelheim, for chronic obstructive pulmonary disease. Available at: <http://www.fda.gov/ohrms/dockets/ac/02/transcripts/3890t1.htm>. Accessed December 20, 1011.

mcg						
Placebo	220	1.652 (0.576)	-0.023 (0.015)	--	--	--
<b>≥ 60 years to &lt; 70 years</b>						
Aclidinium 400 mcg	272	1.442 (0.541)	0.061 (0.013)	0.088	0.052, 0.125	< 0.0001
Aclidinium 200 mcg	275	1.419 (0.526)	0.046 (0.013)	0.073	0.036, 0.109	< 0.0001
Placebo	277	1.377 (0.478)	-0.027 (0.013)	--	--	--
<b>&gt; 70 years</b>						
Aclidinium 400 mcg	167	1.206 (0.429)	0.071 (0.017)	0.103	0.054, 0.151	< 0.0001
Aclidinium 200 mcg	148	1.247 (0.451)	0.026 (0.018)	0.058	0.008, 0.108	0.0232
Placebo	143	1.290 (0.424)	-0.032 (0.018)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 800-801 (Table 6.2.1A); pg. 803 (Table 6.2.1C)  
 \*Applicant's ANCOVA analysis

## Sex

**Table 25. Change from baseline in morning predose (trough) FEV1 at Week 12 by Sex, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>Males</b>						
Aclidinium 400 mcg	371	1.588 (0.526)	0.088 (0.012)	0.096	0.065, 0.127	< 0.0001
Aclidinium 200 mcg	381	1.613 (0.556)	0.069 (0.011)	0.077	0.047, 0.108	< 0.0001
Placebo	384	1.601 (0.548)	-0.008 (0.011)	--	--	--
<b>Females</b>						
Aclidinium 400 mcg	265	1.097 (0.366)	0.060 (0.014)	0.106	0.068, 0.143	< 0.0001
Aclidinium 200 mcg	262	1.179 (0.410)	0.017 (0.014)	0.062	0.025, 0.099	0.0011
Placebo	256	1.230 (0.392)	-0.046 (0.014)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 791 (Table 6.1.1A) ; pg. 793 (Table 6.1.1C)  
 \*Applicant's ANCOVA analysis

## Baseline Health Status

This review presents the following subgroup analyses based on characteristics that inform baseline health status: COPD severity (Table 26), bronchodilator reversibility (Table 27), concomitant ICS use (Table 28), and smoking status (Table 29).

## **COPD Severity**

**Table 26. Change from baseline in morning predose (trough) FEV1 at Week 12 by COPD Severity, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>Mild/Moderate</b>						
Aclidinium 400 mcg	381	1.623 (0.492)	0.101 (0.011)	0.103	0.074, 0.133	< 0.0001
Aclidinium 200 mcg	385	1.694 (0.501)	0.065 (0.011)	0.067	0.038, 0.096	< 0.0001
Placebo	404	1.671 (0.491)	-0.002 (0.011)	--	--	--
<b>Severe/Very Severe</b>						
Aclidinium 400 mcg	249	1.018 (0.324)	0.019 (0.015)	0.095	0.057, 0.132	< 0.0001
Aclidinium 200 mcg	253	1.047 (0.341)	0.003 (0.015)	0.079	0.042, 0.117	< 0.0001
Placebo	232	1.064 (0.307)	-0.076 (0.015)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 850 (Table 6.7.1A); pg. 852 (Table 6.7.1C)

\*Applicant's ANCOVA analysis

### ***Bronchodilator Reversibility***

**Table 27. Change from baseline in morning predose (trough) FEV1 at Week 12 by Bronchodilator Reversibility, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>Reversible</b>						
Aclidinium 400 mcg	225	1.400 (0.450)	0.092 (0.014)	0.132	0.094, 0.171	< 0.0001
Aclidinium 200 mcg	238	1.381 (0.517)	0.064 (0.014)	0.104	0.066, 0.142	< 0.0001
Placebo	236	1.383 (0.049)	-0.040 (0.014)	--	--	--
<b>Not Reversible</b>						
Aclidinium 400 mcg	404	1.376 (0.563)	0.061 (0.011)	0.082	0.053, 0.111	< 0.0001
Aclidinium 200 mcg	396	1.470 (0.559)	0.029 (0.011)	0.050	0.021, 0.080	0.0008
Placebo	396	1.490 (0.539)	-0.021 (0.011)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 868 (Table 6.9.1A); pg. 870 (Table 6.9.1C)

\*Applicant's ANCOVA analysis

### ***Concomitant ICS Use***

**Table 28. Change from baseline in morning predose (trough) FEV1 at Week 12 by Concomitant ICS Use, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>Use</b>						
Aclidinium 400 mcg	258	1.333 (0.480)	0.072 (0.014)	0.095	0.057, 0.132	< 0.0001
Aclidinium 200 mcg	257	1.319 (0.447)	0.064 (0.014)	0.087	0.050, 0.124	< 0.0001
Placebo	268	1.391 (0.505)	-0.022 (0.013)	--	--	--
<b>No Use</b>						
Aclidinium 400 mcg	378	1.417 (0.552)	0.074 (0.011)	0.104	0.073, 0.135	< 0.0001
Aclidinium 200 mcg	386	1.515 (0.589)	0.031 (0.011)	0.061	0.030, 0.092	0.0001
Placebo	372	1.497 (0.533)	-0.030 (0.011)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 877 (Table 6.10.1A); pg. 879 (Table 6.10.1C)

\*Applicant's ANCOVA analysis

### Smoking Status

**Table 29. Change from baseline in morning predose (trough) FEV1 at Week 12 by Smoking Status, Pooled Intent-To-Treat Population, Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A**

Treatment Arm	N	Baseline	Change from baseline	Treatment difference from placebo		
		Mean (SD)	LS Mean (SE)	LS Mean	95% CI	P-value*
<b>Current Smoker</b>						
Aclidinium 400 mcg	317	1.438 (0.532)	0.090 (0.012)	0.117	0.084, 0.151	< 0.0001
Aclidinium 200 mcg	321	1.493 (0.559)	0.031 (0.012)	0.058	0.025, 0.091	0.0006
Placebo	333	1.507 (0.529)	-0.027 (0.012)	--	--	--
<b>Former Smoker</b>						
Aclidinium 400 mcg	319	1.329 (0.513)	0.056 (0.012)	0.083	0.049, 0.117	< 0.0001
Aclidinium 200 mcg	322	1.379 (0.526)	0.057 (0.012)	0.084	0.050, 0.118	< 0.0001
Placebo	307	1.393 (0.512)	-0.027 (0.013)	--	--	--

Source: Section 5.3.5.3.27 (ISE Volume 2), pg. 859 (Table 6.8.1A); pg. 761 (Table 6.8.1C)

\*Applicant's ANCOVA analysis

For each of the subgroup analyses conducted, the results across categories are consistent with the analysis for the overall ITT population: both the aclidinium 400 µg and 200 µg treatment arms demonstrate a statistically significant treatment effect

compared to placebo for the primary endpoint of trough FEV1 at Week 12, with the effect size for the 400 µg dose generally exceeding that observed for the 200 µg dose. These results are supportive of the findings for the primary endpoint.

#### 6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

See Section 3.4 for a discussion of Trials M/34273/23 and M/34273/29, which support the choice of proposed dose and dosing interval (400 µg twice-daily) of aclidinium. Also relevant are the three efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A) which evaluated both the proposed aclidinium dose of 400 µg, as well as a lower 200 µg dose. The results for the primary endpoint, as well as for most of the secondary and additional endpoints, demonstrate larger effect sizes for the 400 µg dose as compared to the 200 µg dose, as described in Sections 4.1.4 and 4.1.5. These data support the selection of the proposed aclidinium dose of 400 µg BID.

#### 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The primary evidence for persistence of efficacy up to 6 months comes from the 24-week results of Trial M/34273/34, which are discussed in Sections 4.1.4 and 4.1.5.

#### 6.1.10 Additional Efficacy Issues/Analyses

In addition to the primary efficacy and safety trials described above, the Applicant also conducted a 6-week trial to evaluate the effect of aclidinium 200 µg once daily on exercise endurance and lung hyperinflation. Trial LAS-MD-26 was a randomized, double-blind, placebo-controlled, parallel-group trial. The patients evaluated differed from that of the primary phase 3 efficacy and safety trials in that they were additionally required to have a functional residual capacity of at least 120% of predicted and a Mahler Baseline Dyspnea Index (BDI) focal score less than or equal to 7.

The primary endpoint evaluated in Trial LAS-MD-26 was exercise endurance time, defined as the time from the increase in work rate at 75%  $W_{max}$  to the point of symptom limitation, where  $W_{max}$  is the highest work rate the patients are able to maintain for at least 30 seconds. An electronically braked cycle ergometer was used in the trial.

One-hundred eighty-one patients were randomized to either aclidinium 200 µg once daily (n=86) or placebo (n=95). Of these 181 patients, 87.8% completed the trial (94.2% of the aclidinium group and 82.1% of the placebo group).

The result of the Applicant's analysis for the primary efficacy endpoint, change from baseline to Week 6 in endurance time, was statistically significant (LS Mean of 116.4 seconds, [95% CI: 37.3, 195.6], p=0.004), but the relevance of this finding is unclear. The Agency regards exercise endurance as an entity that is multi-factorial and

influenced by many factors, including ones unrelated to COPD. To that extent, it is difficult to confirm that any change in exercise endurance time is solely attributable to a beneficial effect of the proposed product on the lungs. Moreover, the generalizability of the results of Trial LAS-MD-26, which evaluated a dose (200 µg once daily) different from that proposed in the application, is unclear. Finally, it is noted that the results of LAS-MD-26 are not replicated elsewhere in the aclidinium program.

## 7 Review of Safety

### Safety Summary

The safety information for aclidinium comes primarily from the twice-daily clinical development program. Only limited results from the once-daily clinical development program are discussed in this review of safety (e.g. deaths and serious adverse events).

Safety assessments conducted in the clinical development program include adverse event monitoring, clinical laboratory testing, vital signs, 12-lead electrocardiograms, Holter monitoring for a subset of patients, and a thorough QT trial. This battery of assessments is considered appropriate for the evaluation of the proposed product.

Across the BID program, a total of 1471 patients with COPD were exposed to aclidinium 400 µg BID, with a mean duration of 211 days. Of these, 733 patients were exposed for 182 days or greater. The number of patients treated with aclidinium 400 µg BID for approximately one year or more is 329; at the time of original NDA submission only 97 patients had been exposed for a 1-year duration. While the size of the safety database is generally consistent with international guidelines,<sup>33</sup> it is relatively small compared to the size of programs for other COPD products.

There were a total of 17 deaths reported for the BID program; 13 of these deaths were considered to be on-treatment. There were 6 on-treatment deaths in the three placebo-controlled double-blind phase 3 efficacy and safety trials (also referred to as "BID Group 1A" which is comprised of Trials LAS-MD-33, M/34273/34, and LAS-MD-38 Part A), and 7 on-treatment deaths in the BID Long-Term Safety trials (comprised of Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B). For the BID Group 1A trials, slightly more on-treatment deaths are reported for the aclidinium 400 µg treatment group (n=3, 0.5%) than the placebo (n=2, 0.3%) or aclidinium 200 µg treatment groups (n=1, 0.2%). For the BID Long-Term Safety trials, the overall incidence rate for on-treatment death is higher for the 400 µg aclidinium treatment group (7.8 per 1000 PY) compared to the 200 µg aclidinium treatment group (5.9 per 1000 PY). Most events were reported only once, however, several deaths are described as being cardiovascular in origin.

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<sup>33</sup> Guideline for Industry, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions," ICH-E1A, March 1995.

A specific analysis of major adverse cardiac events (MACE), including cardiovascular deaths, was conducted. For the BID Group 1A trials, the MACE score is higher for the placebo treatment group (n=4, 0.6%), than for either of the acridinium treatment arms (n=2, 0.3% for both acridinium 200 µg and acridinium 400 µg); this is largely driven by an excess of non-fatal strokes for the placebo group as compared to the acridinium treatment groups. Notably, however, all of the cardiovascular deaths occurred in patients treated with acridinium (n=1, 0.2% for each of the acridinium treatment arms), while there were no cardiovascular deaths in the placebo treatment arm.

For the BID Long-Term Safety trials the overall MACE score is n=19 (2.1%), IR=29.5 per 1000 PY for the acridinium 400 µg treatment group and n=8 (1.8%), IR=23.5 per 1000 PY for the acridinium 200 µg treatment group. It is striking that all the cardiovascular deaths (n=4) are reported for the higher acridinium dose of 400 µg. The incidence rate for non-fatal stroke is slightly higher for the 400 µg treatment group as compared to the 200 µg treatment group (12.4 per 1000 PY versus 8.8 per 1000 PY). There is no apparent dose-response for the event of non-fatal myocardial infarction.

Most notable from these analyses is the overall low number of events observed. It is not apparent whether this is an artifact of the relatively small sample size and short duration of these trials, or if it is an accurate depiction of acridinium's safety profile. The cardiovascular death incidence rate observed for acridinium 400 µg (approximately 5-6 per 1000 PY) is lower than what is generally reported for the "real world" COPD population.<sup>34</sup> While this is not unexpected given the highly controlled nature of a clinical trial, it nonetheless makes interpreting the results a challenge. It is difficult to dismiss the apparent imbalance in cardiovascular death between the treatment groups, while at the same time, impossible to conclude that the data represent a true safety signal.

The Applicant's MACE analysis is complemented by a cardiovascular assessment based on Standard MedDRA Queries (SMQs). For the BID Group 1A trials the analysis revealed a notable imbalance for the SMQ bradyarrhythmia/conduction defects/sinus node disorder, which was reported at a frequency of n=10 (1.6%) for the acridinium 400 µg treatment arm, versus n=5 (0.8%) for the placebo treatment arm and n=6 (0.9%) for the acridinium 200 µg treatment arm. A notable imbalance is also observed for the cardiac failure SMQ, which was reported at a frequency of n=5 (0.8%) for the acridinium 400 µg treatment arm, versus n=2 (0.3%) for the placebo treatment arm and n=1 (0.2%) for the acridinium 200 µg treatment arm. For the BID Long-Term Safety trials, the results for each of the SMQs are either roughly comparable between the acridinium 200 µg and 400 µg treatment groups, or higher for the lower dose, with the exception of cardiac failure, which demonstrates an imbalance favoring the acridinium 200 µg

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<sup>34</sup> In a cohort study conducted in Canada a cardiovascular mortality incidence rate of 41 per 1000 PY was observed for patients with COPD. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005; 2640-6.

treatment group. The imbalance in cardiac failure observed in both the BID Group 1A and BID Long-Term Safety trials may warrant further exploration.

With regards to routine cardiovascular monitoring, in general, the frequency of individual ECG events was low and balanced across treatment groups. One exception to this is noted for the BID Long-Term Safety trials, for which there were 3 instances of potentially clinically significant ventricular tachycardia events reported as TEAEs for the acridinium 400 µg treatment group, compared to none for the 200 µg treatment group. On Holter monitoring, individual events were generally infrequent and balanced across treatment arms, with the exception of frequent PVCs and increased nonsustained supraventricular tachycardia episodes, which were both more common among patients treated with acridinium as compared to placebo. Moreover, there was no significant QT prolongation effect detected for either of the acridinium doses evaluated in the Thorough QT Study.

In addition to the analysis of cardiovascular risk, the Applicant conducted a number of analyses of particular interest and relevance, given the pharmacologic class of the proposed product. These included analyses of cerebrovascular adverse events, pneumonia, and anticholinergic adverse events. In addition, the Agency requested an analysis of events related to bowel obstruction, given the increased rate of bowel obstruction observed for other anticholinergics. The results for the cerebrovascular SMQ conducted for the BID Long-Term Safety trials demonstrate an imbalance favoring the acridinium 200 µg treatment group; otherwise, the results of these additional analyses generally do not support a dose-relationship between the events of concern and acridinium, but again, the ability to draw conclusions is limited by the overall low number of events and the small size of the long-term safety data-base.

It is this Reviewer's assessment that the size of the long-term safety database meets minimum requirements, and is therefore adequate for the assessment of safety. While the small numerical imbalances for cardiovascular and cerebrovascular events described above are noted, the data do not constitute a clear safety signal. And while the low number of deaths and serious adverse events makes the interpretation of the observed imbalances difficult, the overall paucity of events of concern is at the same time reassuring. The acridinium safety profile is therefore adequate to support approval. Nevertheless, as is often the case for new molecular entities, additional data obtained post-approval would be useful in the further characterization of proposed product's safety profile, particularly among patients at high risk for cardiovascular events. A phase 4 trial is therefore recommended, as summarized in Section 1.4.

## 7.1 Methods

### 7.1.1 Studies/Clinical Trials Used to Evaluate Safety

#### OVERVIEW

As described in Section 3.2, the focus of this review of safety is on the trials comprising the BID clinical development program for acridinium. These trials are organized in the Applicant's ISS into several groups:

- BID Dosing Group 1A, consisting of the phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A)
- BID Dosing Group 1B, consisting of the long-term safety trials (LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B)
- BID Group 1C, consisting of several short-term phase 2 crossover trials.

The majority of the data presented is drawn from the BID Group 1A and BID Group 1B trials. Given the short duration of exposure in the BID Group 1C trials, only limited safety results (e.g. deaths, serious adverse events, adverse events leading to trial discontinuation) are presented here. Similarly, limited results from the once-daily (QD) clinical development program are presented (e.g. deaths and serious adverse events). The QD data was evaluated for only for the presence of catastrophic safety findings; the once-daily safety database is most useful to the extent it allows for the identification of major safety signals, however, it can not be relied upon to support the safety of the proposed product with its twice-daily dosing regimen.

With regards to the BID Group 1B trials, several points are worth mentioning. First, it is important to note that long-term safety trials LAS-MD-36 and LAS-MD-38 Part B are both extensions of BID Group 1A trials (LAS-MD-33 and LAS-MD-38 Part A, respectively). As a result, the safety data presented in the Applicant's ISS for the BID Group 1B trials is drawn from not only the long-term extension trials, but also from the parent trials. For example, two deaths reported for the BID Group 1B trials actually took place during lead-in trials, and are also reported for BID Group 1A. This Reviewer found it more informative to consider the safety information for the long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part A) separately from that for the phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A). In addition, the original groupings of trials were constructed such that patients who were treated with acridinium in a lead-in trial (LAS-MD-33 or LAS-MD-38 Part A) but were not enrolled in an extension trial (LAS-36 or LAS-MD 38 Part B) would still be included in BID Group 1B. For example, 83 patients treated with acridinium 400 µg in Trial LAS-MD-33 were not enrolled in the LAS-MD-36 extension trial, but were still counted towards the total of 1005 patients in the acridinium 400 µg treatment group for the BID Group 1B trials. This Reviewer found it more informative to exclude patients who were in the lead-in trials but who did not roll over into the extension trials. The Applicant was asked to provide updated tables for the "BID Long-Term Safety Trials," which is defined

by this Reviewer as being comprised of patients enrolled in and events taking place during Trials LAS-MD-35, LAS-MD-36, and LAS-38 Part B. Unless otherwise noted (as indicated by use of the moniker “BID Group 1B Trials”), when discussing long-term safety data this review is referring to the BID Long-Term Safety trials.

Of critical importance, it must be noted that at the time of original NDA submission, two of the long-term safety trials (LAS-MD-35, and LAS-MD-38 Part B) were ongoing, and the original NDA submission included limited long-term safety data. The Applicant expressed an intent to submit additional safety information from these ongoing trials with the 120-day safety update during the review period. The Applicant was informed in a communication dated September 2, 2011, of the following limitations created by this approach to safety data submission:

*As stated in the pre-NDA meeting responses dated February 25, 2011, adequate safety data to support the application is expected at the time of NDA filing. We will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action. In general, we note that long-term exposure to the proposed 400 mcg BID dose of aclidinium is relatively small. The adequacy of the safety data to support the safety of your product will be a review issue and may impact approvability of the proposed product.*

The Applicant submitted the 120-day safety update on October 21, 2011. While Trials LAS-MD-35 and LAS-MD-38 Part B, are now completed, Clinical Study Reports have not been provided. Nevertheless, for most of the topics addressed in this review of safety, the data evaluated includes the additional information made available with the 120-day safety update. This is the case, for example, for the review of deaths, non-fatal SAEs, adverse events leading to dropout, submission specific concerns, and common adverse events. Due to time constraints, in some instances (e.g. the review of laboratory findings, vital signs, and ECG results) only the data included in the Applicant’s original submission was evaluated; the reader should note that this is the case whenever the term “BID Group 1B Trials” is used.

### **CLINICAL TRIALS USED TO EVALUATE SAFETY**

A brief summary of the safety evaluations conducted for the three phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, LAS-MD-38 Part A) is provided below. This is followed by a description of the protocols for the long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B).

#### **Safety Evaluations, Trials LAS-MD-33, M/34273/34, LAS-MD-38 Part A**

Safety evaluations performed in the efficacy and safety trials included physical examinations, vital signs, electrocardiograms, clinical laboratory testing, monitoring of adverse events including COPD exacerbations, and review of concomitant medications,

which were conducted according to the schedules provided in Table 9 (LAS-MD-33), Table 10 (M/34273/34), and Table 32 (LAS-MD-38 Part A). In addition, Trials LAS-MD-33 and LAS-MD-38 Part A included Holter monitoring conducted for a subset of patients (approximately 20-30% of the overall population).

### **Long-Term Safety Trials: LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B**

The Applicant conducted three long-term safety trials: a stand-alone long-term safety trial (LAS-MD-35), and two extensions of lead-in efficacy and safety trials (Trial LAS-MD-36, which was an extension of Trial LAS-MD-33; and Trial LAS-MD-38 Part B, which was an extension of Trial LAS-MD-38 Part A). The long-term safety trials were similar with regards to their objectives, patient populations, endpoints and procedures, however, Trial LAS-MD-38 Part B is distinguished from the other two trials in that it included only a single treatment arm (aclidinium 400 µg) and was open-label, whereas Trials LAS-MD-35 and LAS-MD-36 evaluated both the 400 µg and 200 µg doses of aclidinium and were double-blind.

### ***Objectives***

In general, the objectives of the three long-term safety trials were as follows:

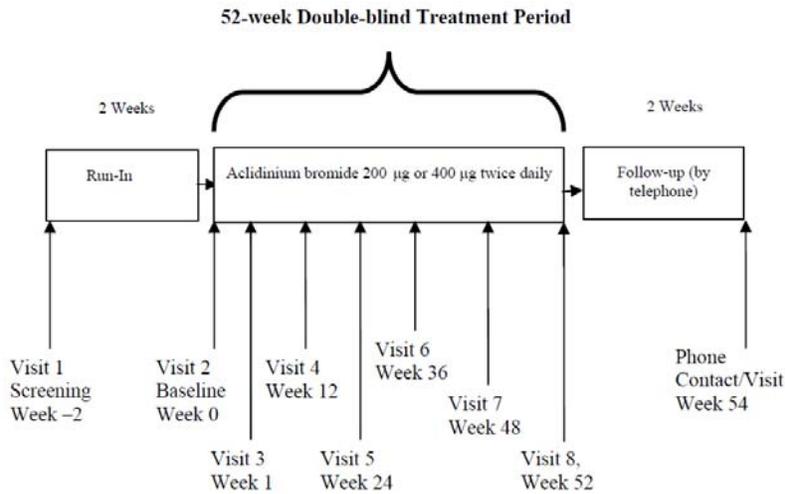
- To assess the long-term safety and tolerability of aclidinium 200 µg and/or 400 µg twice-daily in patients with moderate to severe COPD
- To assess the long-term efficacy and other benefits of aclidinium 200 µg and/or 400 µg twice daily in patients with moderate to severe COPD

### ***General Study Design***

Each of the three long-term safety trials was randomized. In addition, trials LAS-MD-35 and LAS-MD-36 each employed a double-blind and parallel group design, while Trial LAS-MD-38 Part B was open-label. The stand-alone trial (LAS-MD-35) consisted of three periods: run-in, treatment, and follow-up. The extension trials included a treatment period and a follow-up period.

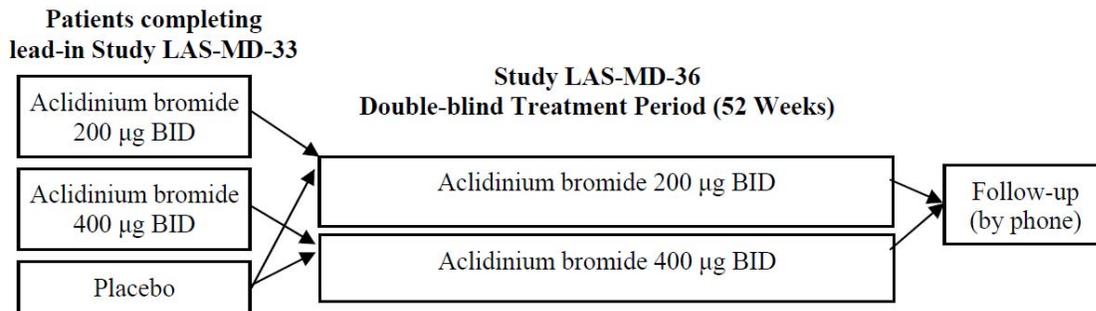
A summary of the trial designs for Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B are provided in Figure 11, Figure 12, and Figure 13, respectively.

### **Figure 11. General Study Design: Trial LAS-MD-35**



Source: Applicant's October 21, 2011, submission, Section 5.3.5.2.1 (Trial LAS-MD-35), pg. 659 (Figure 9.1-1)

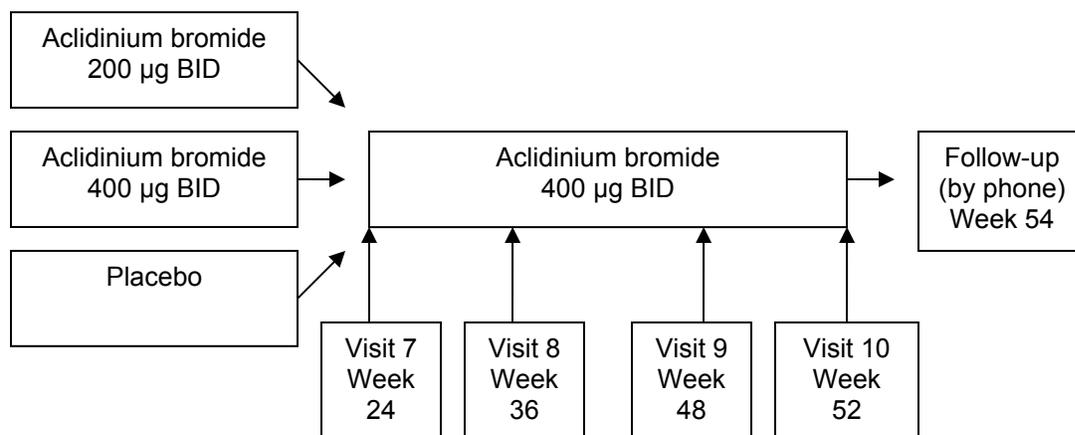
**Figure 12. General Study Design: Trial LAS-MD-36**



Source: Section 5.3.5.2.1 (Trial LAS-MD-36), pg. 32 (Figure 9.1-1)

**General Study Design: Trial LAS-MD-38 Part B**

**Figure 13. General Study Design: Trial LAS-MD-38 Part B**



Source: Applicant's October 21, 2011, submission, Section 5.3.5.2.1 (Trial LAS-MD-38 Part B), pg. 567 (Figure 9.1-1)

### **Treatment arms**

Trials LAS-MD-35 and LAS-MD-36 each evaluated two acclidinium doses, 200 µg and 400 µg, while Trial LAS-MD-38 Part B included only a 400 µg treatment arm. In each case the treatment was delivered via the to-be-marketed device.

In Trial LAS-MD-35, the stand-alone long-term safety trial, patients were randomized to either the acclidinium 200 µg or 400 µg treatment group. In Trial LAS-MD-36, patients treated with either acclidinium 200 µg or 400 µg twice daily during the lead-in trial (LAS-MD-33) continued with the same treatment. Patients in the placebo treatment arm in the lead-in trial were randomized 1:1 to receive either acclidinium 200 µg or 400 µg twice daily in Trial LAS-MD-36. In Trial LAS-MD-38 Part B, patients treated with acclidinium 400 µg twice daily during the lead-in trial (LAS-MD-38 Part A) continued with the same treatment. Patients in the placebo or acclidinium 200 µg twice daily treatment arms were switched to acclidinium 400 µg twice daily.

Patients were permitted to use either marketed albuterol HFA or salbutamol sulfate for rescue use. Use of spacers with rescue medication was permitted, but not required.<sup>35</sup> Rescue medication was to be discontinued at least 6 hours prior to a visit. Guidelines regarding permissible and non-permissible concomitant medications for the long-term safety trials were the same as those of the phase 3 efficacy and safety trials, and are provided in Table 6.

### **Population**

The population for each of the three efficacy and safety trials was comprised of adults with moderate-to-severe COPD. The inclusion and exclusion criteria for the stand-alone trial (LAS-MD-35), and for the extension trial LAS-MD-38 Part B, were the same as those described for the phase 3 efficacy and safety trials in Table 7 and Table 8. The

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<sup>35</sup> Spacer use was required during the assessment of reversibility.

inclusion criteria for Trial 36 were completion of the lead-in trial (LAS-MD-33) and the acquisition of written informed consent. Exclusion criteria for Trial LAS-MD-36 were: the use of prohibited concomitant medications; clinically relevant abnormalities in laboratory tests, vital signs, ECG, or physical exam; the presence of clinically significant anticholinergic symptoms; QTcB > 500 msec on both the pre-dose and post-dose ECG; pregnancy (or the intent to become pregnant) or lactation; life expectancy less than 1 year; noncompliance during the lead-in trial; and significant interruption of treatment during the transition from the lead-in to the extension trial.

### **Assessment of Safety**

The following safety assessments were conducted as part of the long-term safety trials: physical examination, vital signs, clinical laboratory testing, 12-lead ECG, review of concomitant medications and monitoring of adverse events, including COPD exacerbations, which were defined in the same manner as that described in Section 3.3 for the phase 3 efficacy and safety trials.

Adverse events (AE) were defined appropriately as “any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product which does not necessarily have to have a casual relationship with this treatment.”<sup>36</sup> Serious adverse events (SAE) were defined as: “any untoward medical occurrence that at any dose: results in death, is life threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, or is a congenital anomaly/birth defect,”<sup>37</sup> consistent with the *Code of Federal Regulations*<sup>38</sup>. The protocols defined treatment-emergent adverse events (TEAE) as AEs that started after the first dose of investigational product or, alternatively, as AEs that increased in severity during the treatment period; AEs occurring more than 30 days out from the last dose of trial medication were not considered to be TEAEs.

### **Assessment of Efficacy**

As with the shorter-term efficacy and safety trials, the long-term safety trials evaluated trough FEV1 as the primary efficacy endpoint and peak FEV1 as a secondary endpoint. Additional measures of efficacy evaluated included: FVC (peak and trough), rescue medication use, SGRQ, and the EQ-5D. Trial LAS-38-Part B also specified COPD exacerbations as an additional efficacy assessment.

### **Procedures**

A schedule of the main trial procedures and assessments is provided in Table 30 for Trial LAS-MD-35, Table 31 for Trial LAS-MD-36, and Table 32 for Trial LAS-MD-38 Parts A and B. Each table is followed by a description of the procedures for the respective trial.

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<sup>36</sup> Trial LAS-MD-35 protocol pg. 694

<sup>37</sup> Trial LAS-MD-35 protocol pg. 696

<sup>38</sup> 21 CFR § 312.32(a)

*Trial LAS-MD-35*

**Table 30. Schedule of Selected Procedures and Assessments, Trial LAS-MD-35**

Visit	Screening Period		Treatment Period							ET	Follow-up Phone Call
	1 Screening	2 Baseline	3	4	5	6	7	8			
Week	-2	0	1	12	24	36	48	52		54	
Physical Examination	X							X	X		
Vital Signs	X	X	X	X	X	X	X	X	X		
Pregnancy Test	X			X	X	X	X	X	X		
Clinical Laboratory Testing	X			X	X	X	X	X	X		
12-lead ECG	X	X	X	X	X	X	X	X	X		
Predose Spirometry	X	X	X	X	X	X	X	X	X		
Postbronchodilatory Spirometry	X										
SGRQ		X		X	X	X	X	X	X		
EQ-5D		X		X	X	X	X	X	X		
Postdose Spirometry (0-3 hours)		X	X	X	X	X	X	X			
Rescue Medication Use		X	X	X	X	X	X	X	X		
COPD exacerbations	X	X	X	X	X	X	X	X	X	X	
Adverse Events	X	X	X	X	X	X	X	X	X	X	
Concomitant Medications		X	X	X	X	X	X	X	X	X	

Key: ET=early termination

Source: Applicant's October 21, 2011, submission, Section 5.3.5.2.1 (LAS-MD-35), pg. 639-640

Visit 1 (Screening, Week -2)

During Visit 1 the following procedures and assessments took place: signing of informed consent, medical history, concomitant medication review, physical examination (including vital signs), clinical laboratory tests, ECG, spirometry, dispensing of rescue medication, training on pMDI use (if necessary), reversibility assessment, inclusion/exclusion criteria evaluation, and diary training. Patients meeting all inclusion/exclusion criteria were allowed to proceed to Visit 2.

Visit 2 (Baseline, Week 0)

During Visit 2 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation (if yes, patient was not randomized), review of diary, ECG, physical

examination and/or vital signs, assessment of rescue medication use, and review of inclusion/exclusion criteria. Eligible patients were randomized, and completed the following procedures and assessments: training on the use of the multidose DPI and pMDI (if necessary), St. George’s Respiratory Questionnaire (SGRQ), EQ-5D, and spirometry. Trial medication and rescue medication (if necessary) were dispensed. The first dose of double-blind treatment was administered. Following the administration of trial medication an ECG was obtained and spirometry performed.

Visit 3 (Week 1)

During Visit 3 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of diary, assessment of compliance, vital signs, ECG, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry, ECG.

Visits 4, 5, 6, 7, and 8 (Weeks 12, 24, 36, 48 and 52)

During Visits 4, 5, and 6 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, review of diary, assessment of compliance, assessment of rescue medication use, physical examination and/or vital signs, laboratory testing, ECG, SGRQ, EQ-5D, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: ECG and spirometry.

Follow-up Telephone Contact (Week 54)

During the Follow-up Telephone Contact the following procedures and assessments took place: review of concomitant medications, review of adverse events, review of any ongoing or new COPD exacerbations.

Early Termination Visit

If terminated early, an attempt was made to perform the following procedures and assessments: review of AEs, confirmation of no COPD exacerbation, review of concomitant medications, review of diary, assessment of compliance, assessment of rescue medication use, vital signs and physical examination, clinical laboratory testing, ECG, SGRQ, EQ-5D, and spirometry.

*Trial LAS-MD-36*

**Table 31. Schedule of Selected Procedures and Assessments, Trial LAS-MD-36**

Visit	1 Enrollment	Treatment Period							ET	Follow-up Phone Call
		2	3	4	5	6	7			

Week	0	1	12	24	36	48	52		54
Total Weeks (lead-in plus extension)	12	13	24	36	48	60	64		66
Physical Examination	X						X	X	
Vital Signs	X	X	X	X	X	X	X	X	
Pregnancy Test	X			X			X	X	
Clinical Laboratory Testing	X		X	X	X	X	X	X	
12-lead ECG	X	X	X	X	X	X	X	X	
Predose Spirometry	X		X	X			X	X	
SGRQ	X		X	X	X	X	X		
EQ-5D		X	X	X	X	X	X		
Baseline or Follow-up COPD Resource Utilization Questionnaire	X		X	X	X	X	X		
Postdose Spirometry (0-3 hours)	X		X	X			X		
Rescue Medication Use	X	X	X	X	X	X	X	X	
COPD exacerbations	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X

Key: ET=early termination

Source: Section 5.3.5.2.1 (LAS-MD-36 Volume 1), pg. 44-45

Visit 1 (Extension Week 0; Overall Week 12)

Enrollment in Trial LAS-MD-36 took place at Visit 1, which was also the final visit (Visit 6) of the lead-in trial (LAS-MD-33). In addition to the procedures conducted for Trial LAS-MD-33, the following also took place: signing of informed consent, review of inclusion/exclusion criteria, and COPD Resource Utilization Questionnaire. The first dose of trial medication was administered.

Visit 2 (Extension Week 1; Overall Week 13)

During Visit 2 the following procedures and assessments took place: review of concomitant medications, review of adverse events, documentation of any COPD exacerbation, ECG, vital signs, assessment of compliance, assessment of rescue medication use, and EQ-5D. Trial medication was administered.

Visits 3 (Extension Week 12; Overall Week 24), and 4 (Extension Week 24; Overall Week 36)

During Visits 3 and 4 the following procedures and assessments took place: review of concomitant medications, review of adverse events, documentation of any COPD

exacerbation, laboratory testing, ECG, vital signs, assessment of compliance, assessment of rescue medication use, SGQR, EQ-5D, COPD Resource Utilization Questionnaire, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry, ECG.

Visits 5 (Extension Week 36; Overall Week 48), and 6 (Extension Week 48; Overall Week 60)

During Visits 5 and 6 the following procedures and assessments took place: review of concomitant medications, review of adverse events, documentation of any COPD exacerbation, laboratory testing, ECG, vital signs, assessment of compliance, assessment of rescue medication use, SGQR, EQ-5D, and COPD Resource Utilization Questionnaire. Trial medication was administered.

Visit 7 (Extension Week 52; Overall Week 64), and Early Termination Visit

During Visit 7 (or Early Termination Visit) the following procedures and assessments took place: review of concomitant medications, review of adverse events, documentation of any COPD exacerbation, laboratory testing, ECG, physical exam, vital signs, assessment of compliance, assessment of rescue medication use, and spirometry. SGQR, EQ-5D, COPD Resource Utilization Questionnaire, and spirometry were conducted (Visit 7 only). Trial medication was administered (Visit 7 only), after which the following procedures and assessments were conducted: spirometry, ECG.

Follow-up Telephone Contact (Extension Week 54; Overall Week 66)

During the Follow-up Telephone Contact the following procedures and assessments took place: review of concomitant medications, review of adverse events, review of any ongoing or new COPD exacerbations.

*Trial LAS-MD-38 Part B*

**Table 32. Schedule of Selected Procedures and Assessments, Trial LAS-MD-38 Parts A and B**

Visit	RI Period	DB Treatment Period					OL Treatment Period				ET	Follow-up Phone Call
	1 (S)	2 (B)	3	4	5	6	7	8	9	10		
Week	-2	0	1	4	8	12	24	36	48	52		54
Physical Examination	X					X				X	X	
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	
Pregnancy Test	X					X	X	X	X	X	X	
Clinical Laboratory Testing	X					X	X	X	X	X	X	

Clinical Review  
 Jennifer Rodriguez Pippins, MD, MPH  
 NDA 202-450  
 Turdoza Pressair (acclidinium bromide)

12-lead ECG	X	X	X			X	X	X	X	X	X	
Pre-dose Spirometry	X	X	X	X	X	X	X	X	X	X	X	
BDI/TDI		X				X	X	X		X	X	
SGRQ		X		X	X	X	X	X	X	X	X	
EQ-5D		X		X	X	X	X	X	X	X	X	
Baseline or Follow-up COPD Resource Utilization Questionnaire		X		X	X	X	X	X	X	X	X	
Post-dose Spirometry (0-3 hours)		X	X	X	X	X	X	X	X	X		
Post-dose Spirometry (0-12 hours), substudy		X				X						
Post-bronchodilator Spirometry	X											
Rescue Medication Use		X	X	X	X	X	X	X	X	X	X	
COPD exacerbations	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X
24-hour Holter, substudy		X				X						

Source: Applicant's October 21, 2011, submission, Section 5.3.5.2.1 (LAS-MD-38 Part B), pg. 563-556  
 Key: B=baseline; DB=double-blind; ET=early termination; OL=open-label; RI=run-in; S=screening

Trials LAS-MD-38 Part A and Part B are described by the Applicant in a single protocol. Visits 1-6 comprise Part A, and are summarized in Section 3.3. Visit 7-10 and Follow-up, which comprise Part B, are summarized below.

Visits 7, 8, and 9 (Weeks 24, 36, 48)

During Visits 7, 8, and 9 the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, clinical laboratory tests, assessment of compliance, assessment of rescue medication use, physical examination and/or vital signs, ECG, TDI (not in Visit 9), SGRQ, EQ-5D, COPD Resource Utilization Questionnaire, and spirometry. Trial medication was administered, after which the following procedures and assessments were conducted: spirometry, ECG.

Visits 10 (Week 52) and Early Termination Visit

During Visit 10 (or Early Termination Visit) the following procedures and assessments took place: review of concomitant medications, review of adverse events, confirmation of no COPD exacerbation, clinical laboratory tests, assessment of compliance, assessment of rescue medication use, physical examination and/or vital signs, ECG,

TDI, SGRQ, EQ-5D, COPD Resource Utilization Questionnaire, and spirometry. Trial medication was administered (Visit 10 only), after which the following procedures and assessments were conducted: spirometry, ECG.

#### Follow-up Telephone Contact (Overall Week 54)

During the Follow-up Telephone Contact the following procedures and assessments took place: review of concomitant medications, review of adverse events, review of any ongoing or new COPD exacerbations.

#### ***Plan for Statistical Analysis***

The definitions of the analysis populations (ITT, Safety) for the long term safety trials are the same as those of the efficacy and safety trials, as described in Section 3.3. Descriptive statistics were used to summarize demographic and background data. Efficacy analyses in a manner similar to that employed in the efficacy and safety trials; all analyses were considered exploratory. The analysis of treatment compliance was based on data recorded in the patient diary. Safety analyses were conducted for the safety population. Interim analyses were conducted for the long-term safety trials (LAS-MD-35 and LAS-MD-38 Part B) that were ongoing at the time of NDA submission.

#### ***Protocol Amendments***

There were a number of protocol amendments for Trials LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B. The most notable of these was the first amendment to Trial LAS-MD-38 Part B, which provided for the removal of the acclidinium 200 µg twice daily treatment arm and an open-label design. These amendments do not raise any questions regarding study integrity. A high-level summary of the protocol amendments for the three long-term safety trials follows below.

#### Trial LAS-MD-35

Original protocol: October 8, 2009

Protocol Amendment 1: October 26, 2009

- Electronic diary replaced with paper diary

Protocol Amendment 2: October 14, 2010

- Description of interim analysis revised to provide for an interim data cut
- Definition of TEAE modified
- Blinding procedures modified to allow patients to continue in the study if unblinding by the Applicant takes place for the purpose of health authority reporting (study staff would be kept blinded)

#### Trial LAS-MD-36

Original protocol: July 21, 2009

Protocol Amendment 1: December 7, 2009

- Number of study centers changed a maximum of 160 to a maximum of 90
- First dose of trial medication changed from Visit 2 to Visit 1

- Procedures separated out for Visit 7 and Early Termination Visit
- Protocol Amendment 2: October 18, 2010
- Blinding procedures modified to allow patients to continue in the study if unblinding by the Applicant takes place for the purpose of health authority reporting (study staff would be kept blinded)
  - Definition of TEAE modified
- Protocol Amendment 3: December 16, 2010
- Modification of EQ-5D

#### Trial LAS-MD-38 Part B

Original protocol: October 28, 2009

Protocol Amendment 1: March 2, 2010

- Changing the trial design from double-blind to open-label
- Removing the 200 µg dose

Protocol Amendment 2: October 14, 2010

- Clarification that Parts A and B would be analyzed and reported separately
- Definition of TEAE modified
- Language regarding interim analysis clarified

### 7.1.2 Categorization of Adverse Events

The Applicant's Integrated Summary of Safety (ISS) focuses on treatment-emergent adverse events (TEAEs), which are defined as adverse events (AEs) with an onset date on or after the date of the first dose of investigational product (IP), or with a severity that increased on or after the date of the first dose of IP. Additionally, for Forest-conducted BID trials, in order to be considered a TEAE, an AE had to occur within 30 days of the last dose of IP. The cut-off was 15 days in the Almirall-conducted BID trials.

All TEAEs were coded, or re-coded, using the Medical Dictionary for Regulatory Activities (MedDRA), version 13.1.

### 7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

As described in Section 5.1.1, the focus of this review of safety is on the trials comprising the acridinium BID development program, and particularly on the phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A) and the long-term safety trials (LAS-MD-35, LAS-MD-36, and LAS-MD-38 Part B).

The three phase 3 efficacy and safety trials are quite similar in design, and are appropriately pooled by the Applicant as BID Group 1A. The long-term safety trials are

also generally similar, with the notable exception of the number of treatment groups: Trials LAS-MD-35 and LAS-MD-36 each evaluated aclidinium 200 µg and 400 µg whereas Trial LAS-MD-38 Part B evaluated only aclidinium 400 µg. The Applicant's approach to this difference in design was somewhat variable in the ISS; at times safety information is presented as a pooled analysis for the Applicant's BID Group 1B (e.g., overall TEAEs), while at other times information is presented separately for each of the long-term safety trials (e.g., MACE analysis results). Given the relatively small size of the overall long-term database, this review chose to pool the safety data across the long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B). As mentioned earlier, this review's "BID Long-Term Safety Trials" grouping differs from the Applicant's originally submitted long-term safety grouping ("BID Group 1B") in two aspects. First, the safety data presented in the Applicant's ISS for the BID Group 1B trials is drawn from not only the long-term extension trials, but also from the parent trials. This Reviewer found it more informative to consider the safety information for the long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part A) separately from that for the phase 3 efficacy and safety trials (LAS-MD-33, M/34273/34, and LAS-MD-38 Part A). Second, the Applicant's BID Group 1B included patients who were treated with aclidinium in a lead-in efficacy trial but who did not rollover into an extension trial. Since these patients do not represent true long-term exposure, the clinical review has concerns that the Applicant's BID Group 1B results may underestimate adverse event findings. This Reviewer found it more informative to exclude patients who were in the lead-in trials but who did not roll over into the extension trials. Unless otherwise noted (as indicated by use of the moniker "BID Group 1B Trials"), when discussing long-term safety data, this review is referring to the BID Long-Term Safety trials.

## 7.2 Adequacy of Safety Assessments

### 7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Subject disposition for the BID Long-Term Safety trials is provided in Table 33. The overall percentage of patients completing the long-term trials ranged from 61-68%, and was generally balanced across the two treatment arms. Discontinuation was most often due to an adverse event, which occurred more often for the aclidinium 200 µg treatment group (8.2%) as compared to the aclidinium 400 µg treatment group (6.6%). Similarly, discontinuation due to COPD exacerbation was also somewhat more common for patients treated with the lower dose (2.9% vs 1.9% for the 200 µg and 400 µg treatment groups, respectively).

#### **Table 33. Subject Disposition: BID Long-Term Safety Trials**

Disposition	Aclidinium 200 µg	Aclidinium 400 µg
All Randomized/Enrolled Subjects (N)	451	893
Number of Subjects who Completed, n (%)	275 (61.0)	609 (68.2)
Number of Subjects who Discontinued, n (%)	176 (39.0)	284 (31.8)
Primary Reason for Discontinuation, n (%)		
Adverse Event	37 (8.2)	59 (6.6)
COPD Exacerbation	13 (2.9)	17 (1.9)
Lack of Efficacy	26 (5.8)	31 (3.5)
Lost to Follow-up	19 (4.2)	26 (2.9)
Non-fulfillment of Inclusion/Exclusion Criteria	1 (0.2)	0
Other	32 (7.1)	43 (4.8)
Protocol Non-compliance	15 (3.3)	35 (3.9)
Withdrawal of Informed Consent	33 (7.3)	73 (8.2)
Safety Population, n (%)	448 (99.3)	891 (99.8)
ITT Population, n (%)	424 (94.0)	827 (92.6)
PP Population, n (%)	N/A	N/A

Note: N=number of patients randomized; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N).

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 12 (Table 3)

A summary of the extent of exposure for patients with COPD in the BID program is provided in Table 34. Across the BID program, a total of 1471 patients with COPD were exposed to aclidinium 400 µg BID, with a mean duration of 211 days. Of these, 733 patients were exposed for 182 days or greater. The number of patients treated with aclidinium 400 µg BID for approximately 1 year or more is 329; at the time of original NDA submission only 97 patients had been exposed for a 1 year duration.

**Table 34. Extent of Exposure of Aclidinium in Patients with COPD: Twice Daily Administration**

	Aclidinium			Placebo
	100 µg BID	200 µg BID	400 µg BID	
<b>Overall Treatment Duration (days)</b>				
N	73	1173	1471	940
Mean (SD)	7.0 (0.2)	169.8 (138.9)	210.6 (137.0)	78.1 (61.3)
Median	7.0	166.0	179.0	85.0
Min, Max	7,8	1,476	1, 463	1, 200
<b>Treatment Duration, n (%)</b>				
≥ 1 Day	73 (100)	1173 (100)	1471 (100)	940 (100)
≥ 7 Days	73 (100)	1158 (98.7)	1451 (98.6)	927 (98.6)
≥ 14 Days	0	1044 (89.0)	1351 (91.8)	819 (87.1)
≥ 28 Days	0	939 (80.1)	1214 (82.5)	597 (63.5)

≥ 84 Days	0	847 (72.2)	1141 (77.6)	516 (54.9)
≥ 168 Days	0	564 (48.1)	970 (65.9)	196 (20.9)
≥ 182 Days	0	336 (28.6)	733 (49.8)	5 (0.5)
≥ 252 Days	0	313 (26.7)	679 (46.2)	0
≥ 336 Days	0	288 (24.6)	395 (26.9)	0
≥ 357 Days		282 (24.0)	387 (26.3)	0
≥ 364 Days	0	242 (20.6)	329 (22.4)	0
<b>Total Patient Years of Exposure</b>				
	1.4	545.2	848.3	201.0

Source: Applicant's Submission dated October 21, 2011, Section 5.3.5.3.25.8, pg. 25 (Table 1.2-1)

Note: Table includes information from all BID trials conducted in COPD patients.

Note: Patients in the extension trials (LAS-MD-36 and LAS-MD-38 Part B) or crossover trials (LAC-MD-27, M/34273/23, M/34273/29, and M/40464/26) who had different treatment from the lead-in trial or other treatment period are counted multiple times, once in each treatment period.

While the size of the safety database is generally consistent with international guidelines<sup>39</sup>, it is relatively small compared to the size of programs for other COPD products. For example, the tiotropium bromide inhalation powder (Spiriva Handihaler) development program included two 1-year placebo-controlled trials, two 1-year active-controlled trials, and two 6-month placebo-controlled trials evaluating the recommended dose of tiotropium in 1308 patients.

Demographics and other baseline characteristics of the safety population for the BID Group 1A and 1B Trials are provided in Table 35 and Table 36.

**Table 35. Demographics and Other Baseline Characteristics: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

Characteristic	Placebo N=641	Acclidinium 200 µg N=644	Acclidinium 400 µg N=636
<b>Age, year</b>			
Mean (SD)	62.81 (8.8)	62.83 (8.5)	63.54 (8.9)
Median	63.0	63.0	63.0
Min, Max	40,89	40,89	40,89
<b>Sex, n(%)</b>			
Female	256 (39.9)	263 (40.8)	265 (41.7)
Male	385 (60.1)	381 (59.2)	371 (58.3)
<b>Race, n(%)</b>			
White	603 (94.1)	595 (92.4)	598 (94.0)
Black or African American	22 (3.4)	32 (5.0)	22 (3.5)
Asian	2 (0.3)	3 (0.5)	2 (0.3)
American Indian or Alaskan Native	1 (0.2)	1 (0.2)	2 (0.3)
Other	13 (2.0)	13 (2.0)	12 (1.9)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>			
Mean (SD)	27.03 (5.4)	27.15 (5.2)	27.31 (5.1)
Min, Max	15.6, 39.9	15.2, 40.2	15.5, 39.9

<sup>39</sup> Guideline for Industry, "The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life-Threatening Conditions," ICH-E1A, March 1995.

<b>Severity of COPD</b>			
Mild/Moderate	404 (63.4)	385 (60.3)	381 (60.5)
Severe/Very Severe	233 (36.6)	253 (39.7)	248 (39.5)
Missing	4	6	6
<b>Smoking Status</b>			
Current smoker	333 (52.0)	322 (50.0)	317 (49.8)
Ex-smoker	308 (48.1)	322 (50.0)	319 (50.2)

Source: Section 5.3.5.3.28, pg. 50-51 (Table 1.3.2-1)

**Table 36. Demographics and Other Baseline Characteristics: BID Long-Term Safety Trials, Safety Population**

<b>Characteristic</b>	<b>Aclidinium 200 µg N=448</b>	<b>Aclidinium 400 µg N=891</b>
<b>Age, year</b>		
n	448	891
Mean (SD)	63.08 (9.67)	63.51 (9.30)
Median	63.00	64.00
Min, Max	40.0, 89.0	40.0, 89.0
<b>Sex, n (%)</b>		
Female	190 (42.4)	406 (45.6)
Male	258 (57.6)	485 (54.4)
<b>Race, n (%)</b>		
White	407 (90.8)	823 (92.4)
Black or African American	36 (8.0)	60 (6.7)
Asian	3 (0.7)	3 (0.3)
American Indian or Alaskan Native	1 (0.2)	3 (0.3)
Other	1 (0.2)	2 (0.2)
<b>Body Mass Index (kg/m<sup>2</sup>)</b>		
n	448	890
Mean (SD)	27.48 (5.35)	27.51 (5.42)
Min, Max	13.9, 39.9	13.5, 40.2
<b>Severity of COPD</b>		
Mild/Moderate	258 (57.6)	476 (53.4)
Severe/Very Severe	186 (41.5)	408 (45.8)
Missing	4 (0.9)	7 (0.8)
<b>Smoking Status</b>		
Current smoker	225 (50.2)	448 (50.3)
Ex-smoker	223 (49.8)	443 (49.7)

Note: N=number of patients randomized; n=number of patients in the specific category

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 13 (Table 4)

Demographics and other baseline characteristics were generally well-balanced across treatment groups, for both BID Groups 1A and the BID Long-Term Safety trials.

The safety population comprising the BID clinical program has a mean age of 63-64 years. While the percentage of males was greater than females, there was still a substantial percentage (approximately 40% or greater) women evaluated in these trials. The vast majority of patients were white, with the percentage of blacks/African

Americans ranging from 3-5% for the BID Group 1A trials. Interestingly, the percentage of black/African Americans is increased for the BID Long-Term Safety trials (approximately 7.2%). The mean BMI across the program was approximately 27-28 kg/m<sup>2</sup>, with a wide range of body types represented, from underweight to obese. Regarding disease severity, a majority of patients had mild/moderate COPD (approximately 60%) in the BID Group 1A trials. Interestingly, the percentage of patients with mild/moderate disease drops somewhat (to 53-58%) in the BID Long-Term Safety trials. Across the clinical program, about half of all participants were current smokers.

The population of the BID program, as described above, does not raise any specific concerns for the evaluation of safety.

### 7.2.2 Explorations for Dose Response

The twice-daily aclidinium program (BID Group 1A and BID Long-Term Safety trials) evaluated both the proposed dose, 400 µg, as well as a lower dose, 200 µg, thereby allowing for an exploration of dose dependency for adverse events and other safety data. These analyses are embedded throughout this review of safety.

### 7.2.3 Special Animal and/or In Vitro Testing

The development program for aclidinium bromide included animal cardiac studies; see the pharmacology/toxicology review by Dr. Grace Lee for further discussion of these investigations.

The development program also included a battery of *in vitro* studies evaluating such issues as protein binding, the identification of esterases that hydrolyze aclidinium, the impact of aclidinium on hepatic cytochrome p450 activities, metabolism by liver microsomes, the capacity to induce CYP450 expression in hepatocytes, and the potential for both P-glycoprotein substrate activity and inhibitory activity. See the clinical pharmacology review by Dr. Ping Ji for further discussion of relevant findings from the *in vitro* studies.

### 7.2.4 Routine Clinical Testing

The routine clinical testing in the twice-daily development program for aclidinium included: serum chemistry, hematology, and 12-lead electrocardiograms (ECGs). In addition, Holter data was obtained for a subset of patients in Trials LAS-MD-33 and LAS-MD-38 Part A (n=172, 173, and 164 for the placebo, aclidinium 200 µg and

acridinium 400 µg treatment arms, respectively). The routine clinical testing was adequate.

### 7.2.5 Metabolic, Clearance, and Interaction Workup

The Applicant states that formal drug interaction studies were not performed, and provides the rationale that there is a low likelihood of drug-drug interactions with acridinium due to its main routine of metabolism (hydrolysis by esterases).

The ISS includes an analysis of TEAEs stratified by the use of concomitant medications. See Section 7.5.5 of this review for further discussion of this analysis.

### 7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

The Applicant's ISS includes an analysis of events of particular interest and relevance to acridinium, given its pharmacologic class and formulation (inhaled long-acting anticholinergic) including: cardiovascular adverse events, cerebrovascular adverse events, pneumonia, and anticholinergic adverse events. In addition, the Agency requested an analysis of events related to intestinal obstruction, given the increased rate of bowel obstruction previously observed for other anticholinergics. This analysis was provided by the Applicant.

## 7.3 Major Safety Results

### 7.3.1 Deaths

#### **Twice-Daily Program (BID)**

There were a total of 17 deaths reported for the BID program; 13 of these deaths were considered to be on-treatment. There were 6 on-treatment deaths in the BID Group 1A trials, and 7 on-treatment deaths in the BID Long-Term Safety trials. The overall incidence of death for the BID Group 1A trials and for the BID Long-Term Safety trials is provided in Table 37 and Table 39, respectively. A descriptive summary of the deaths for the BID Group 1A and BID Long-Term Safety trials is provided in Table 38 and Table 40, respectively. There were no deaths in the BID Group 1C trials.

**Table 37. Incidence of Death: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo	Acridinium 200 µg	Acridinium 400 µg
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	N=641 ET=190.6		N=644 ET=199.4		N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death	2 (0.3)	10.5	1 (0.2)	5.0	3 (0.5)	15.1
Any Death	2 (0.3)	10.5	2 (0.3)	10.0	4* (0.6)*	20.2*

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 11 (Table 1)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate=n/ET\*1000.

\*The Applicant reports the following values for "Any Death" in the Acclidinium 400 µg treatment group: n=3 (0.5%), Incidence Rate=15.1, stating that one death (Patient ID 1188.15, Trial M/34273/34) "was not captured in the Clinical Database from which these tables were generated" (Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 3). The above table includes this death.

**Table 38. Summary of Deaths: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment (Yes/No)	Cause of Death PT
<b>Placebo</b>						
M/34273/34	1194.02	78/M	33	33	Yes	Road Traffic Accident
LAS-MD-38A	108038003	49/M	43	48	Yes	Death
<b>Acclidinium 200 µg</b>						
M/34273/34	1278.08	52/M	133	165	No	Completed Suicide
M/34273/34	2326.10	71/M	105	105	Yes	Myocardial Infarction
<b>Acclidinium 400 µg</b>						
LAS-MD-33	114233015	65/M	12*	23	Yes	Lung Cancer Metastatic
M/34273/34	1267.05	56/F	91	91	Yes	Cardiac Failure Acute
M/34273/34	1188.15*	76/M	170 days	32 days after stopping IP	No	Sepsis
LAS-MD-38A	135438005	56/M	28	55	Yes	Cardio-respiratory Arrest

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 12 (Table 2); Section 5.3.5.3.28 (ISS Volume 1), pg. 66 (Table 2.1.3.1-1)

\* Incorrectly reported as 23 days in Section 5.3.5.3.28 (ISS Volume 1), pg. 66 (Table 2.1.3.1-1); data reported in the January 6, 2012, submission is correct.

\*The Applicant's submission does not include this death, stating that it "was not captured in the Clinical Database from which these tables were generated" (Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 3).

**Table 39. Incidence of Death: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg	Acclidinium 400 µg
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	N=448 ET=340.6		N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death	2 (0.4)	5.9	5 (0.6)	7.8
Any Death	3 (0.7)	8.8	6 (0.7)	9.3

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 15 (Table 5)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate=n/ET\*1000.

**Table 40. Summary of Deaths: BID Long-Term Safety Trials, Safety Population**

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment (Yes/No)	Cause of Death PT
<b>Acclidinium 200 µg</b>						
LAS-MD-35	132735009	68/M	355	366	Yes	Biliary Sepsis
LAS-MD-35	207935013	63/F	113	228	No	Lung Neoplasm Malignant
LAS-MD-36	115533001	56/M	105	107	Yes	Multiple Drug Overdose Accidental
<b>Acclidinium 400 µg</b>						
LAS-MD-35	142135024	73/F	51	103	No	Pneumonia*
LAS-MD-35	208235013	72/M	256	281	Yes	Subarachnoid hemorrhage
LAS-MD-36	114133006	70/F	246	270	Yes	Esophagitis
LAS-MD-38B	136638011	48/F	180	180	Yes	Cardiac Arrest
LAS-MD-38B	145038007	51/F	281	282	Yes	Cardiac Arrest
LAS-MD-38B	145138001	51/M	91	97	Yes	Cardio-respiratory Arrest

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 16 (Table 6)

\*PT originally reported as COPD in the Applicant's ISS (Section 5.3.5.3.28, pg. 70 (Table 2.1.3.2-1))

For the BID Group 1A trials, slightly more on-treatment deaths are reported for the acclidinium 400 µg treatment group (n=3, 0.5%) than the placebo (n=2, 0.3%) or acclidinium 200 µg treatment groups (n=1, 0.2%). For the BID Long-Term Safety trials, the overall incidence rate for on-treatment death is higher for the 400 µg acclidinium treatment group (7.8 per 1000 PY) compared to the 200 µg acclidinium treatment group (5.9 per 1000 PY).

While most events were reported only a single time, there are several deaths that are described as being cardiovascular in nature; a specific analysis of major adverse cardiac events (MACE), including cardiovascular deaths, follows in Section 5.3.5. Of note, the three cardiac arrests/cardio-respiratory arrests reported for the BID Long-term

Safety trials all occurred in the aclidinium 400 µg treatment group; there were no such reports for the aclidinium 200 µg treatment group.

It is noted that the interpretability of these data is hampered by the limited number of events and overall small size of the long-term safety data-base.

**Once-Daily Program (QD)**

The once-daily (QD) program evaluated aclidinium doses ranging from 25 µg to 400 µg in patients with COPD. A total of 21 patients with COPD who received at least 1 dose of investigational product died in the QD program; 17 of these deaths were considered to be on-treatment. Twelve (0.7%) on-treatment deaths occurred in patients treated with aclidinium, and 5 (0.6%) on-treatment deaths occurred in patients treated with placebo. The overall incidence of deaths in the QD program is presented in Table 41 and a summary of deaths is provided in Table 42.

**Table 41. Incidence of Death: Once-Daily Program (QD Dosing Group 1), Safety Population**

	Placebo N=819 ET=357.9		Acclidinium < 200 µg N=201 ET=15.6		Acclidinium 200 µg N=1657 ET=1101.5		Acclidinium > 200 µg N=91 ET=5.3	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
On-Treatment Death	5 (0.6)	14.0	0	--	12 (0.7)	10.9	0	--
Any Death	7 (0.9)	19.6	0	--	14 (0.8)	12.7	0	--

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 17 (Table 7)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate=n/ET\*1000.

**Table 42. Summary of All Deaths: Once-Daily Program (QD Dosing Group 1), Safety Population**

Trial ID	Patient ID	Age/Sex	Duration of Treatment	Time to Death	On-Treatment (Yes/No)	Cause of Death PT
<b>Placebo</b>						
M/34273/30	4091.005	54/M	158	158	Yes	Cerebrovascular Accident
M/34273/30	4097.004	70/M	97	148	No	Cardiopulmonary Failure
M/34273/30	4131.001	51/M	288	293	Yes	COPD
M/34273/30	4134.001	75/F	32	47	Yes	Peritonitis
M/34273/31	2029.003	79/M	176	228	No	Cardio-Respiratory

						Arrest
M/34273/31	2253.001	72/M	273	276	Yes	Rhabdomyolysis
M/34273/31	2375.014	62/M	42	43	Yes	COPD
<b>Acridinium 200 µg</b>						
M/34273/25	0964.011	44/M	5	6	Yes	Pulmonary Embolism
M/34273/30	4016.004	69/M	15	15	Yes	Sudden Cardiac Death
M/34273/30	4020.009	63/M	328	329	Yes	Sudden Cardiac Death
M/34273/30	4031.001	61/M	54	83	Yes	Gastrointestinal Hemorrhage
M/34273/30	4076.008	64/M	353	353	Yes	Pancreatic Carcinoma
M/34273/30	4104.007	55/M	98	103	Yes	Cardiovascular Insufficiency
M/34273/30	4156.017	59/M	104	106	Yes	Acute Abdomen
M/34273/30	4500.006	58/M	346	352	Yes	Pulmonary Edema
M/34273/31	2006.007	63/F	241	426	No	Lung Adenocarcinoma Metastatic
M/34273/31	2037.001	68/F	270	272	Yes	Respiratory Failure
M/34273/31	2082.006	48/M	281	280	Yes	Multiple Drug Overdose
M/34273/31	2093.002	64/M	51	328	No	Lung Cancer Metastatic
M/34273/31	2207.003	61/M	329	329	Yes	Atherosclerosis Coronary Artery
M/34273/31	2375.034	73/F	92	93	Yes	Acute Respiratory Failure

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 18-9 (Table 8)

In the QD program, the incidence rate for on-treatment death reported for patients receiving placebo (14 per 1000 PY) slightly exceeds that reported for patients receiving acridinium 200 µg (10.9 per 1000 PY).

### 7.3.2 Nonfatal Serious Adverse Events

#### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

The overall incidence and a list of non-fatal SAEs by preferred term (reported for at least 2 patients in any treatment group) for the BID Group 1A trials are provided in Table 43.

**Table 43. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in  $\geq 2$  Patients in Any Treatment Group: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 $\mu$ g N=644 ET=199.4		Acclidinium 400 $\mu$ g N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE	20 (3.1)	104.9	14 (2.2)	70.2	15 (2.4)	75.6
COPD	17 (2.7)	89.2	9 (1.4)	45.1	10 (1.6)	50.4
Acute Respiratory Failure	1 (0.2)	5.2	0	0	2 (0.3)	10.1
Cardiac Failure Congestive	0	0	0	0	2 (0.3)	10.1
Angina Pectoris	0	0	2 (0.3)	10.0	1 (0.2)	5.0
Pneumonia	2 (0.3)	10.5	0	0	1 (0.2)	5.0
Suicidal Ideation	1 (0.2)	5.2	2 (0.3)	10.0	1 (0.2)	5.0
Bipolar Disorder	0	0	2 (0.3)	10.0	0	0
Depression	0	0	2 (0.3)	10.0	0	0
Lung Adenocarcinoma	0	0	2 (0.3)	10.0	0	0

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 22 (Table 13)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate= $n/ET \times 1000$ .

The overall percentage of patients with any non-fatal serious adverse events (SAEs) ranged from 2 to 3% across treatment groups; the overall percentage was somewhat higher for the placebo group (3.1%) compared to the acclidinium treatment groups (2.2% and 2.4%, for the 200  $\mu$ g and 400  $\mu$ g treatment groups, respectively). A notable imbalance favoring acclidinium is reported for COPD exacerbation, which was more common for the placebo treatment group (2.7%) as compared to the acclidinium treatment groups (1.4% and 1.6% for the acclidinium 200  $\mu$ g and 400  $\mu$ g treatment groups, respectively).

There were more events of "cardiac failure congestive" and "angina pectoris" reported for the acclidinium treatment groups as compared to placebo, but overall the number of events reported is small. Cardiac adverse events are a submission-specific safety concern and are discussed in greater detail in Section 5.3.5 of this review.

There were slightly more cases of pneumonia reported for placebo (0.3%) than for acclidinium (none for the 200  $\mu$ g treatment group; 0.2% for the 400  $\mu$ g treatment group). Pneumonia is a submission-specific safety concern, and is discussed in greater detail in Section 5.3.5 of this review.

Suicidal ideation, bipolar disorder, and depression were reported more often for the acclidinium 200  $\mu$ g treatment arm than for placebo, however, the overall numbers are low, limiting interpretability of these data.

There were slightly more cases of lung adenocarcinoma reported as SAEs for the acclidinium 200 µg treatment group (0.3%) compared to placebo (0); the interpretability of these data is limited by the small numbers of events. The occurrence of malignancies in the acclidinium clinical development program is discussed further in Section 5.6.1 of this review.

### Long-term Safety Trials, Twice-Daily Program (BID Long-Term Safety Trials)

The overall incidence and a list of non-fatal SAEs by preferred term (reported for at least 2 patients in any treatment group) for the BID Long-Term Safety trials are provided in Table 44.

**Table 44. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 E=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE	26 (5.8)	76.3	57 (6.4)	88.5
COPD	10 (2.2)	29.4	27 (3.0)	41.9
Pneumonia	6 (1.3)	17.6	6 (0.7)	9.3
Acute Myocardial Infarction	2 (0.4)	5.9	5 (0.6)	7.8
Coronary Artery Disease	2 (0.4)	5.9	5 (0.6)	7.8
Anemia	0	0	3 (0.3)	4.7
Cardiac Failure Congestive	0	0	3 (0.3)	4.7
Renal Failure Acute	0	0	3 (0.3)	4.7
Respiratory Failure	1 (0.2)	2.9	3 (0.3)	4.7
Angina Pectoris	0	0	2 (0.2)	3.1
Bladder Cancer	0	0	2 (0.2)	3.1
Cerebrovascular Accident	1 (0.2)	2.9	2 (0.2)	3.1
Colitis	0	0	2 (0.2)	3.1
Dehydration	1 (0.2)	2.9	2 (0.2)	3.1
Influenza	0		2 (0.2)	3.1
Lobar Pneumonia	1 (0.2)	2.9	2 (0.2)	3.1
Non-cardiac Chest	1 (0.2)	2.9	2 (0.2)	3.1

Pain				
Peripheral Arterial Occlusive Disease	0	0	2 (0.2)	3.1
Pneumothorax	2 (0.4)	5.9	1 (0.1)	1.6
Pulmonary Embolism	2 (0.4)	5.9	1 (0.1)	1.6
Acute Coronary Syndrome	2 (0.4)	5.9	0	0
Constipation	2 (0.4)	5.9	0	0
Hematuria	2 (0.4)	5.9	0	0
Myocardial Infarction	2 (0.4)	5.9	0	0

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 26-27 (Table 15)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate= $n/ET \times 1000$ .

The overall incidence rate for SAEs is somewhat higher for the 400 µg acclidinium treatment group (88.5 per 1000 PY) compared to the 200 µg acclidinium treatment group (76.3 per 1000 PY); the same is true for COPD exacerbation SAEs (41.9 per 1000 PY vs. 29.4 per 1000 PY for the 400 µg and 200 µg acclidinium treatment groups, respectively). This finding for COPD exacerbations SAEs contradicts the results of the efficacy analysis for COPD exacerbations, as described in Section 5.1.5. In addition, discontinuations due to COPD exacerbation AEs were more commonly reported for placebo than for either of the acclidinium treatment groups in the BID Group 1A trials, and more common for the lower acclidinium dose in the BID Long-Term Safety trials (see Section 5.3.3). The same was also true for COPD exacerbation TEAEs in general (see Section 5.4.1).

Pneumonia-related SAEs were more commonly reported for the 200 µg treatment group (17.6 per 1000 PY) as compared to the 400 µg treatment group (9.3 per 1000 PY). Pneumonia is a submission-specific safety concern, and is discussed in greater detail in Section 5.3.4 of this review, along with cardiac adverse events.

For the other SAEs described in Table 44 the overall number of events was low, limiting the interpretability of the data. It is noted that there were three SAEs of acute renal failure are reported for the acclidinium 400 µg treatment group, compared to none for the 200 µg treatment group. Given this finding, particular attention was paid to the frequency of potentially clinically significant (PCS) laboratory assessments for creatinine, as described in Section 5.4.2. In addition, there were two SAEs of bladder cancer reported for the acclidinium 400 µg treatment group. As mentioned previously, there were two SAEs of lung adenocarcinoma reported for the acclidinium 200 µg treatment group in the BID Group 1A trials. The occurrence of malignancies in the acclidinium clinical development program is discussed further in Section 5.6.1 of this review.

### **Short-Term Trials, Twice-Daily Program (BID Group 1C)**

In the short-term trials (BID Group 1C), 6 patients experienced SAEs while on therapy. The overall frequency of SAEs was balanced across the placebo, acclidinium 200 µg,

and aclidinium 400 µg treatment groups, and is provided in Table 45. A summary of SAEs reported for the BID Group 1C trials is provided in Table 46.

**Table 45. Overall Frequency of SAEs: Short-Term Trials, Twice-Daily Program (BID Group 1C)**

	Placebo N=299	Aclidinium 100 µg N=73	Aclidinium 200 µg N=173	Aclidinium 400 µg N=197
Patients with any SAE, n (%)	3 (1.0%)	0	1 (0.6%)	2 (1.0%)

Source: Section 5.3.5.3.28, pg. 75

**Table 46. Summary of Serious Adverse Events: Short-Term Trials, Twice Daily Program (BID Group 1C)**

Trial	Patient	Age/Sex	TEAE Preferred Term
<b>Placebo</b>			
M/34273/23	4041.005	65/Male	COPD*
M/34273/29	1187.08	65/Female	COPD*
M/34273/29	4041.07	75/Female	Thermal burn
<b>Aclidinium 200 µg</b>			
M/34273/29	1499.02	65/Male	Myocardial infarction
<b>Aclidinium 400 µg</b>			
LAC-MD-27	204327014	53/M	Metastatic renal cell carcinoma
M/34273/29	1521.05	71/M	"Infective exacerbation of chronic obstructive airways disease"

Source: Section 5.3.5.3.28, pg. 4115-4119 (Table 5.6.3)

\* The preferred term "COPD" refers to COPD exacerbation.

Cardiac adverse events are a submission-specific safety concern, and will be discussed in greater detail in Section 5.3.5 of this review. The occurrence of malignancies in the aclidinium clinical development program is discussed further in Section 5.6.1 of this review.

### **Once-Daily Program (QD)**

The overall incidence and a list of non-fatal SAEs by preferred term (reported for at least 2 patients in any treatment group) for the once-daily program (QD Dosing Group 1) are provided in Table 47. There were no events reported for patients treated with aclidinium doses greater than 200 µg, and only one SAE (COPD exacerbation) reported for patients treated with aclidinium doses less than 200 µg.

**Table 47. Overall Incidence of Non-fatal SAEs and Incidence of Non-fatal SAEs by Preferred Term in ≥ 2 Patients in Any Treatment Group: Once-Daily Program (QD Dosing Group 1), Safety Population**

	Placebo N=819 ET=357.9		Acridinium 200 µg N=1657 ET=1101.5	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Any SAE	22 (2.7)	61.5	49 (3.0)	44.5
Pneumonia	5 (0.6)	14.0	12 (0.7)	10.9
Lobar Pneumonia	1 (0.1)	2.8	4 (0.2)	3.6
Myocardial Infarction	2 (0.2)	5.6	4 (0.2)	3.6
Acute Myocardial Infarction	0	0	3 (0.2)	2.7
Angina Unstable	0	0	3 (0.2)	2.7
Pulmonary Embolism	0	0	3 (0.2)	2.7
Abdominal Pain	1 (0.1)	2.8	2 (0.1)	1.8
Atrial Fibrillation	1 (0.1)	2.8	2 (0.1)	1.8
Carotid Artery Stenosis	0	0	2 (0.1)	1.8
Cerebrovascular Accident	0	0	2 (0.1)	1.8
Chest Pain	0	0	2 (0.1)	1.8
COPD	3 (0.4)	8.4	2 (0.1)	1.8
Constipation	0	0	2 (0.1)	1.8
Diverticulum	0	0	2 (0.1)	1.8
Epistaxis	0	0	2 (0.1)	1.8
Humerus Fracture	0	0	2 (0.1)	1.8
Retinal Detachment	0	0	2 (0.1)	1.8
Transient Ischemic Attack	0	0	2 (0.1)	1.8
Angina Pectoris	2 (0.2)	5.6	1 (0.1)	0.9
Respiratory	4	11.2	1	0.9

Failure	(0.5)		(0.1)	
Bronchitis	2 (0.2)	5.6	0	0
Renal Cell Carcinoma	2 (0.2)	5.6	0	0
Rib Fracture	2 (0.2)	5.6	0	0
Syncope	2 (0.2)	5.6	0	0

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 26-27 (Table 16)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate= $n/ET \times 1000$ .

The overall incidence of SAEs was generally comparable across the placebo and acclidinium 200 µg treatment arms. In most cases the overall numbers of events is low (around 2), limiting the interpretability of the data. Exceptions include pneumonia, which had an incidence rate of 14.0 per 1000 PY for the placebo group compared to an incidence rate of 10.9 per 1000 PY for the acclidinium 200 µg treatment group; lobar pneumonia exhibited a reverse pattern. Myocardial infarction was more commonly reported for placebo, with an incidence rate of 5.6 per 1000 PY, compared to the an incidence rate of 3.6 per 1000 PY for the acclidinium 200 µg treatment group; acute myocardial infarction and unstable angina exhibited a reverse pattern. Pneumonia and cardiac adverse events are both submission-specific safety concerns, and are discussed in greater detail in Section 5.3.5 of this review.

### 7.3.3 Dropouts and/or Discontinuations

#### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

The overall incidence of AEs leading to dropout, and a summary of AEs leading to dropout reported for 2 or more patients in any treatment group for the BID Group 1A trials are provided in Table 48 and Table 49, respectively.

**Table 48. Incidence of AEs Leading to Dropout: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with any non-fatal AE associated with trial discontinuation, n (%)	31 (4.8)	162.6	26 (4.0)	130.4	27 (4.2)	136.1

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 28 (Table 17)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate= $n/ET \times 1000$ .

**Table 49. Summary of AEs Leading to Dropout Reported for 2 or More Patients in Any Treatment Group: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

System Organ Class Preferred Term	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ET=198.4	
	n (%)	IR	n (%)	IR	n (%)	IR
<b>Cardiac Disorders</b>	2 (0.3)	10.5	3 (0.5)	15.0	3 (0.5)	15.1
Ventricular Tachycardia	1 (0.2)	5.2	0	0	2 (0.3)	10.1
<b>Nervous System Disorders</b>	3 (0.5)	15.7	0	0	3 (0.5)	15.1
Dizziness	2 (0.3)	10.5	0	0	0	0
<b>Respiratory, Thoracic, and Mediastinal Disorders</b>	19 (3.0)	99.7	10 (1.6)	50.2	16 (2.5)	80.6
Dyspnea	3 (0.5)	15.7	1 (0.2)	5.0	3 (0.5)	15.1
COPD	16 (2.5)	83.9	9 (1.4)	45.1	12 (1.9)	60.5

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 29-34 (Table 18)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

The overall percentage of patients with any non-fatal adverse events associated with trial discontinuation is greater for patients receiving placebo as compared to those receiving acclidinium (4.8%, 4.0%, and 4.2% for the placebo, acclidinium 200 µg, and acclidinium 400 µg treatment arms, respectively). COPD exacerbation was the most common AE leading to dropout, and was more often reported for placebo (2.5%) than for the acclidinium treatment groups (1.4% and 1.9% for the 200 µg and 400 µg treatment groups, respectively). In most cases, however, the overall numbers of events is low, limiting the interpretability of the data; this is the case for the event of ventricular tachycardia, for which there were two reports for the acclidinium 400 µg group and one report for the placebo group. Cardiac adverse events are a submission-specific safety concern, and are discussed in greater detail in Section 5.3.5 of this review.

### Long-term Safety Trials, Twice-Daily Program (BID Long-Term Safety Trials)

The overall incidence of AEs leading to dropout, and a summary of AEs leading to dropout reported for 2 or more patients in any treatment group for the BID Long-Term Safety trials are provided in Table 50 and Table 51, respectively.

**Table 50. Incidence of AEs Leading to Dropout: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448	Acclidinium 400 µg N=891

	ET=340.6		ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with any non-fatal AE associated with trial discontinuation, n (%)	46 (10.3)	135.1	68 (7.6)	105.6

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 36 (Table 21)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

**Table 51. Summary of AEs Leading to Dropout Reported for 2 or More Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population**

System Organ Class Preferred Term	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
<b>Cardiac Disorders</b>	5 (1.1)	14.7	9 (1.0)	14.0
Acute Myocardial Infarction	0	0	2 (0.2)	3.1
<b>General Disorders and Administration Site Conditions</b>	3 (0.7)	8.8	3 (0.3)	4.7
Fatigue	2 (0.4)	5.9	0	0
Non-Cardiac Chest Pain	1 (0.2)	2.9	3 (0.3)	4.7
<b>Nervous System Disorders</b>	2 (0.4)	5.9	8 (0.9)	12.4
Syncope	0	0	2 (0.2)	3.1
Headache	0	0	2 (0.2)	3.1
Dizziness	2 (0.4)	5.9	0	0
<b>Respiratory, Thoracic and Mediastinal Disorders</b>	16 (3.6)	47.0	27 (3.0)	41.9
Dyspnea	1 (0.2)	2.9	2 (0.2)	3.1
COPD	13 (2.9)	38.2	18 (2.0)	27.9
Cough	0	0	4 (0.4)	6.2
<b>Skin and Subcutaneous Tissue Disorders</b>	3 (0.7)	8.8	2 (0.2)	3.1
Pruritus	1 (0.2)	2.9	2 (0.2)	3.1

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 37-44 (Table 22)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

There was no dose response for the relationship between acclidinium and the overall incidence of events associated with trial discontinuation in the BID Long-Term Safety trials. COPD exacerbation was the most commonly reported AE leading to dropout, with an incidence rate that was higher for the acclidinium 200 µg treatment group as compared to the 400 µg treatment group (38.2 per 1000 PY and 27.9 per 1000 PY, respectively).

### **Short-Term Trials, Twice-Daily Program (BID Group 1C)**

The overall percentage of patients with any adverse event associated with trial discontinuation was higher for the placebo treatment group (2.3%) compared to the aclidinium treatment groups (0%, 1.7%, and 2.0% for the 100 µg, 200 µg, and 400 µg treatment arms, respectively), as summarized in Table 52. There were only two instances where an AE associated with trial discontinuation was reported for two or more patients in any treatment group: atrial fibrillation in the placebo group (n=2 [0.7%] for placebo, n=0 across all aclidinium treatment groups) and COPD exacerbation (n=4 [1.3%] for placebo, n=0 for the aclidinium 100 µg treatment group, n=1 [0.6%] for the aclidinium 200 µg treatment group, and n=2 [1.0%] for the 400 µg treatment group).

**Table 52. Overall Frequency of Adverse Events Associated with Trial Discontinuation: Short-Term Trials, Twice-Daily Program (BID Group 1C)**

	Placebo N=299	Aclidinium 100 µg N=73	Aclidinium 200 µg N=173	Aclidinium 400 µg N=197
Patients with any ADO, n (%)	7 (2.3)	0	3 (1.7)	4 (2.0)

Source: Section 5.3.5.3.28, pg. 4141 (Table 6.2.3)

Key: ADO=adverse event leading to dropout

Note: Only includes AEs leading to treatment discontinuation as captured on the CRF.

### 7.3.4 Significant Adverse Events

Adverse events leading to withdrawal are discussed in Section 7.3.3. There were no events leading to dose reduction, as dose reduction was not performed in the clinical trials. The overall percentage of patients with any severe adverse event was slightly higher for placebo (6.7%) as compared to the aclidinium 200 µg and 400 µg treatment groups (6.4%, 5.8%) in the BID Group 1A trials; the percentage was similar across treatment groups in the BID Group 1B trials (9.2% and 9.4% for the aclidinium 200 µg and 400 µg treatment groups, respectively).<sup>40</sup>

### 7.3.5 Submission Specific Primary Safety Concerns

The Applicant's ISS includes an analysis of events of particular interest and relevance, including cardiovascular adverse events, cerebrovascular adverse events, pneumonia, and anticholinergic adverse events; each of these categories is discussed in turn below. In addition, the Agency requested an analysis of events related to intestinal obstruction, given the increased rate of bowel obstruction observed for other anticholinergics;<sup>41</sup> this analysis was provided by the Applicant and is also presented below.

<sup>40</sup> Source: Section 5.3.5.3.28, pg. 55 (Table 2.1.1.1-1) and pg. 56 (Table 2.1.1.2-1).

<sup>41</sup> FDA Advisory Committee Meeting Materials for the November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting. Available at: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/Pulmonary-AllergyDrugsAdvisoryCommittee/UCM190463.pdf>; accessed November 21, 2011.

### **Cardiovascular Adverse Events**

The cardiovascular safety profile of inhaled anticholinergics has been discussed extensively both in the medical literature<sup>42-43</sup> and in open public forums.<sup>44</sup> Most recently, FDA provided a Follow-Up<sup>45</sup> to an Early Communication regarding the safety of tiotropium marketed as Spiriva HandiHaler. In this update, FDA communicated its conclusion that the available data, including results from the UPLIFT trial, do not support an association between the use of Spiriva HandiHaler (tiotropium) and an increased risk for stroke, heart attack, or death from a cardiovascular cause. A summary of the FDA's conclusions regarding the safety of tiotropium may also be found in the medical literature.<sup>46</sup>

The Applicant conducted two analyses to assess the cardiovascular risk of aclidinium: (1) an analysis of major adverse cardiac events (MACE), and (2) an analysis based on standard MedDRA queries (SMQs). This is consistent with the Division's recommendations during the preNDA interaction for the twice daily program.

### ***Major Adverse Cardiac Events (MACE)***

#### **MACE ANALYSIS METHODOLOGY**

The Applicant defined the MACE Score as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. The MACE analysis included the following steps:

- All death cases within 30 days after the last dose of trial medication were retrieved and reviewed (blinded) by an internal independent adjudication committee in order to identify all cardiovascular deaths
  - The adjudication committee was comprised of two licensed physicians (including one licensed cardiologist) from Forest Laboratories.
  - All death cases reported while on treatment in the BID program were retrieved, blinded, and forwarded for review.

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<sup>42</sup> Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. *JAMA* 2008; 300(12):1439-1450.

<sup>43</sup> Lee TA, Pickard S, Au DH et al. Risk of Death Associated with Medications for Recently Diagnosed Chronic Obstructive Pulmonary Disease. *Annals of Internal Medicine* 2008;149:380-390.

<sup>44</sup> November 2009 FDA Pulmonary-Allergy Drugs Advisory Committee Meeting

<sup>45</sup> Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm197429.htm>; accessed October 25, 2011.

<sup>46</sup> Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

- The adjudicating physicians were instructed to assign the cause of death into one of three categories: cardiovascular death, noncardiovascular death, or insufficient data.
- The same adjudicating physicians were asked to discuss discordant cases and make a final unanimous assessment.
- Deaths assessed as belonging to the cardiovascular death category were included in the calculation of MACE score.
- Nonfatal myocardial infarction was defined as any nonfatal case for which the event was coded to one of the “narrow” preferred terms in the MedDRA SMQ “myocardial infarction”
- Nonfatal stroke was defined as any nonfatal case for which the event was coded to one of the “narrow” preferred terms in the MedDRA SMQ “central nervous system hemorrhages and cerebrovascular conditions”

### MACE ANALYSIS RESULTS

The adjudicated results for the cardiovascular deaths assessment are provided in Table 53 for the BID Group 1A trials and in Table 54 for the BID Long-Term Safety trials. There was concurrence between the original assessments of the two adjudicators for all cases except one (US-2010-1242, BID Group 1A); this case was discussed and consensus achieved. MACE scores are presented in Table 55 and Table 56 for the BID Long-Term Safety trials.

**Table 53. Adjudicated Results for Cardiovascular Deaths Assessment: BID Placebo-Controlled Trials (BID Group 1A)**

MFR Control No.	Patients ID	Sex/ Age	Treatment	Events Reported	CV	Non-CV	Insufficient Data
<b>LAS-MD-33</b>							
US-2009-0632	114233015	M/65	Acclidinium 400	Lung cancer metastasis; metastasis to brain; acute respiratory failure		AB	
<b>M/34273/34</b>							
HU-2010-0285	1267.05	F/56	Acclidinium 400	Acute cardiac failure	AB		
ZA-2010-0358	1194.02	F/78	Placebo	Run over by motor vehicle		AB	
ZA-1020-1458	2326.10	M/71	Acclidinium 200	Possible myocardial infarction	AB		
<b>LAS-MD-38A</b>							
US-2010-1242	135438005	M/56	Acclidinium 400	Cardiopulmonary arrest and respiratory failure			AB*

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US-2010-1275	108038003	M/49	Placebo	Death			AB
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Source: Section 5.3.5.3.28, pg. 80 (Table 2.1.6.1.3-1)

\* Classified as a non-CV death in the Applicant's submission of Advisory Committee Briefing Document dated January 24, 2012, pg. 98 (Table 8.4.3-3)

Key: "A"=assessment of Physician 1; "B"=assessment of Physician 2

**Table 54. Adjudicated Results for Cardiovascular Deaths Assessment: BID Long-Term Safety Trials**

MFR Control No.	Patients ID	Sex/ Age	Treatment	Events Reported	CV	Non-CV	Insufficient Data
<b>LAS-MD-35</b>							
US-2010-1547	142135024	F/73	Aclidinium 400	Pneumonia			AB
US-2011-0331	132735009	M/68	Aclidinium 200	Biliary sepsis; Pancreatic carcinoma		AB	
US-2010-1663	207935013	F/63	Aclidinium 200	Lung neoplasm malignant		AB	
US-2011-0007	208235013	M/72	Aclidinium 400	Subarachnoid hemorrhage	AB		
<b>LAS-MD-36</b>							
US-2009-0953	115533001	M/56	Aclidinium 200	Multiple drug overdose accidental		AB	
US-2010-0527	114133006	F/70	Aclidinium 400	Esophagitis		AB*	
<b>LAS-MD-38B</b>							
US-2010-1500	145138001	M/51	Aclidinium 400	Cardiopulmonary arrest	AB <sup>#</sup>		
US-2011-0122	136638011	F/48	Aclidinium 400	Cardiac arrest	AB		
US-2011-0454	145038007	F/51	Aclidinium 400	Cardiac arrest	AB		

Source: Applicant's Submission dated October 21, 2011, Section 5.3.5.3.25.8, pg. 46 (Table 2.1.6.1.3-1)

\* Source for Patient 114133006: Section 5.3.5.3.28, pg. 80 (Table 2.1.6.1.3-1). Classified as "Insufficient Data" in the October 21, 2011, which the Applicant has identified as an error (Applicant's Submission dated February 10, 2012, pg. 4).

<sup>#</sup> Classified as a non-CV death in the Applicant's January 6, 2012 submission.

It is noted that in a submission dated January 6, 2012, the Applicant informed the Agency of the following:

*“All death cases in the Acclidinium bromide BID program were initially internally adjudicated by 2 independent physicians who had no roles or responsibilities with the Acclidinium Bromide program and results of the internal adjudication were included in the NDA. Recently, to further validate the findings, Forest requested an external adjudication of those same death cases.”<sup>47</sup>*

There was one discrepancy between the results of the initial adjudication and the subsequent adjudication reported on January 6, 2012: the death of Patient 145138001 (Trial LAS-MD-38 Part B) was originally assessed to be a cardiovascular death, however, the subsequent adjudication assessed the death to be non-cardiovascular in nature.<sup>48</sup> As there was no clear justification provided for the decision to conduct a second adjudication and the original adjudicators concurred on this case, this review reports the original results.

**Table 55. MACE Score: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
MACE Score	4 (0.6)	21.0	2 (0.3)	10.0	2 (0.3)	10.1
CV Death	0	0	1 (0.2)	5.0	1 (0.2)	5.0
Non-fatal myocardial infarction	1 (0.2)	5.2	0	0	0	0
Non-fatal stroke	3 (0.5)	15.7	1 (0.2)	5.0	1 (0.2)	5.0

Source: Applicant’s Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 52 (Table 23)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

<sup>47</sup> Applicant’s submission dated January 6, 2012, Section 5.3.5.3.28, pg. 4.

<sup>48</sup> The Applicant’s January 6, 2012, submission described the external adjudication and noted the new result for Patient 145138001. In addition, a later submission by the Applicant dated February 10, 2012 (response to the Division’s February 6, 2012, Information Request asking for clarification of discrepancies between the presentation of data in the Applicant’s Advisory Committee Briefing Document and in the NDA submission) clarified that the external adjudication also resulted in a reclassification for Patient 135438005, from “Insufficient Data” to “Non-CV.” The original adjudicators concurred in their assessments of this case, as they had for other case that was also reclassified. Given this, and the lack of a clear justification for the decision to re-adjudicate, this review reports the original results.

**Table 56. MACE Score: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
MACE Score	8 (1.8)	23.5	19 (2.1)	29.5
CV Death	0	0	4 (0.4)	6.2
Non-fatal myocardial infarction	5 (1.1)	14.7	8 (0.9)	12.4
Non-fatal stroke	3 (0.7)	8.8	8 (0.9)	12.4

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 46 (Table 25)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

For the BID Group 1A trials, the MACE score is higher for the placebo treatment group (n=4, 0.6%), than for either of the acclidinium treatment arms (n=2, 0.3% for both acclidinium 200 µg and acclidinium 400 µg); this is largely driven by an excess of non-fatal strokes for the placebo group as compared to the acclidinium treatment groups. Notably, however, all of the cardiovascular deaths occurred in patients treated with acclidinium (n=1, 0.2% for each of the acclidinium treatment arms), while there were no cardiovascular deaths in the placebo treatment arm.

For the BID Long-Term Safety trials the overall MACE score is n=19 (2.1%), IR=29.5 per 1000 PY for the acclidinium 400 µg treatment group and n=8 (1.8%), IR=23.5 per 1000 PY for the acclidinium 200 µg treatment group. It is striking that all the cardiovascular deaths (n=4) are reported for the higher acclidinium dose of 400 µg. The incidence rate for non-fatal stroke is slightly higher for the 400 µg treatment group as compared to the 200 µg treatment group (12.4 per 1000 PY versus 8.8 per 1000 PY). There is no apparent dose-response for the event of non-fatal myocardial infarction.

Most notable from these analyses is the overall low number of events observed. It is not apparent whether this is an artifact of the relatively small sample size and short duration of these trials, or if it is an accurate depiction of acclidinium's safety profile. The cardiovascular death incidence rate observed for acclidinium 400 µg (approximately 5-6 per 1000 PY) is lower than what is generally reported for the "real world" COPD population.<sup>49</sup> While this is not unexpected given the highly controlled nature of a clinical trial, it nonetheless makes interpreting the results a challenge. It is difficult to dismiss the apparent imbalance in cardiovascular death between the treatment groups, while at the same time, impossible to conclude that the data represent a true safety signal.

### **Cardiovascular Assessment based on Standard MedDRA Queries (SMQs)**

<sup>49</sup> In a cohort study conducted in Canada a cardiovascular mortality incidence rate of 41 per 1000 PY was observed for patients with COPD. Huiart L, Ernst P, Suissa S. Cardiovascular morbidity and mortality in COPD. *Chest* 2005; 2640-6.

**CARDIOVASCULAR SMQ METHODOLOGY**

The Applicant conducted a number of cardiovascular SMQs, as described in Table 57.

**Table 57. CARDIOVASCULAR SMQs Conducted**

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

Source: Section 5.3.5.3.28, pg. 82

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

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

**CARDIOVASCULAR SMQ RESULTS**

Results for the SMQs of Ischemic Heart Disease, Myocardial Infarction, Other Ischemic Heart Disease, Supraventricular Tachyarrhythmias, Bradyarrhythmia, Conduction Defects, and Cardiac Failure conducted for the placebo-controlled trials, twice-daily Program (BID Group 1A), are provided in Table 58. Results for the BID Long-Term Safety trials are provided in Table 59.

**Table 58. Cardiovascular SMQ Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

SMQ Category	Placebo N=641 ET=190.6		Acridinium 200 µg N=644 ET=199.4		Acridinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Ischemic Heart Disease	6 (0.9)	31.5	7 (1.1)	35.1	3 (0.5)	15.1
Myocardial Infarction	1 (0.2)	5.2	1 (0.2)	5.0	0	0

Other Ischemic Heart Disease	5 (0.8)	26.2	6 (0.9)	30.1	3 (0.5)	15.1
Supraventricular Tachyarrhythmias	4 (0.6)	21.0	4 (0.6)	20.1	1 (0.2)	5.0
Bradyarrhythmia	5 (0.8)	26.2	6 (0.9)	30.1	10 (1.6)	50.4
Conduction defects	3 (0.5)	15.7	6 (0.9)	30.1	8 (1.3)	40.3
Cardiac failure	2 (0.3)	10.5	1 (0.2)	5.0	5 (0.8)	25.2

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 55-56 (Table 26)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

**Table 59. Cardiovascular SMQ Results: BID Long-Term Safety Trials, Safety Population**

SMQ Category	Acidinium 200 µg N=448 ET=340.6		Acidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Ischemic Heart Disease	11 (2.5)	32.3	22 (2.5)	34.2
Myocardial Infarction	5 (1.1)	14.7	8 (0.9)	12.4
Other Ischemic Heart Disease	8 (1.8)	23.5	17 (1.9)	26.4
Supraventricular Tachyarrhythmias	4 (0.9)	11.7	6 (0.7)	9.3
Bradyarrhythmia	18 (4.0)	52.8	12 (1.3)	18.6
Conduction defects	16 (3.6)	47.0	12 (1.3)	18.6
Cardiac failure	2 (0.4)	5.9	8 (0.9)	12.4

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 49-51 (Table 28)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

For the BID Group 1A trials, results for the cardiovascular SMQ analyses are generally balanced between the placebo and aclidinium 200 µg treatment groups for Myocardial Infarction and Other Ischemic Heart Disease, as well as for Supraventricular Tachyarrhythmias; the incidence of these events is lower for the aclidinium 400 µg treatment group. There is a notable imbalance for the SMQ bradyarrhythmia/conduction defects/sinus node disorder, which was reported at a frequency of n=10 (1.6%) for the aclidinium 400 µg treatment arm, versus n=5 (0.8%) for the placebo treatment arm and n=6 (0.9%) for the aclidinium 200 µg treatment arm. A notable imbalance is also observed for the cardiac failure SMQ, which was reported at a frequency of n=5 (0.8%) for the aclidinium 400 µg treatment arm, versus n=2 (0.3%) for the placebo treatment arm and n=1 (0.2%) for the aclidinium 200 µg treatment arm. For the BID Long-Term Safety trials, the results for each of the SMQs are either roughly comparable between the aclidinium 200 µg and 400 µg treatment groups, or higher for the lower dose, with the exception of cardiac failure, which demonstrates an imbalance favoring the aclidinium 200 µg treatment group.

The Applicant conducted further analyses to evaluate the imbalances noted for cardiac failure and bradyarrhythmias/conduction defects/sinus node disorders. Regarding the

cardiac failure SMQ, the Applicant concluded the observed imbalance for the BID Group 1A trials was driven by the results of Trial M/34273/34. Regarding the imbalance in the bradyarrhythmias/conduction defects/sinus node disorders SMQ for the BID Group 1A trials, the Applicant concluded that the imbalance was driven by the results for conduction defects. Patients treated with aclidinium in these trials experienced a variety of conduction defects, including atrioventricular block, QT prolongation, left bundle branch block, and right bundle branch block. The Applicant noted that these events were all considered to be nonserious, and did not result in other serious cardiac events.

As is the case for the MACE analysis, the ability to interpret these data is limited by size of the database, particularly that of the long-term database. The imbalance in cardiac failure observed in both the BID Group 1A and BID Long-Term Safety trials may warrant further exploration.

### **Stroke**

The potential association between anticholinergics and stroke has been previously discussed in the literature.<sup>50</sup> Most recently, FDA provided a Follow-Up<sup>51</sup> to an Early Communication regarding the safety of tiotropium marketed as Spiriva Handihaler. In this update, FDA communicated its conclusion that the available data, including results from the UPLIFT trial, do not support an association between the use of Spiriva HandiHaler (tiotropium) and an increased risk for stroke. A summary of the FDA's conclusions regarding the safety of tiotropium may also be found in the medical literature.<sup>52</sup>

To explore the potential association between aclidinium and stroke, the Applicant conducted a SMQ for "central nervous system hemorrhages and cerebrovascular conditions." This is consistent with the Division's recommendations during the preNDA interaction for the twice daily program.

### ***Stroke Assessment based on Standard MedDRA Query (SMQ)***

Results for the SMQ of central nervous system hemorrhages and cerebrovascular conditions, conducted for the placebo-controlled trials, twice-daily Program (BID Group 1A), are provided in Table 60. Results for the BID Long-Term Safety trials are provided in Table 61.

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<sup>50</sup> Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease. *JAMA* 2008; 300(12):1439-1450.

<sup>51</sup> Follow-Up to the October 2008 Updated Early Communication about an Ongoing Safety Review of Tiotropium (marketed as Spiriva HandiHaler), January 14, 2010. Available at: <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHealthcareProfessionals/ucm197429.htm>; accessed October 25, 2011.

<sup>52</sup> Michele TM, Pinheiro S, Iyasu S. The safety of tiotropium – the FDA's conclusions. *NEJM* 2010;363(12):1097-9.

**Table 60. Cerebrovascular SMQ Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with SMQ: central nervous system hemorrhages and cerebrovascular conditions	3 (0.5)	15.7	1 (0.2)	5.0	1 (0.2)	5.0

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 62 (Table 29)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

**Table 61. Cerebrovascular SMQ Results: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with SMQ: central nervous system hemorrhages and cerebrovascular conditions	3 (0.7)	8.8	9 (1.0)	14.0

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 53 (Table 31)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

For the BID Group 1A trials, there were more events identified by the central nervous system hemorrhages and cerebrovascular conditions SMQ for the placebo treatment group as compared to the acclidinium 200 µg and 400 µg treatment groups. For the BID Long-Term Safety trials, the incidence rate for the cerebrovascular SMQ is 14.0 per 1000 PY for the acclidinium 400 µg treatment group, and exceeds that of the acclidinium 200 µg treatment group (8.8 per 1000 PY). The overall number of events is low, making it difficult to draw conclusions from these data.

### **Pneumonia**

To explore the potential association between acclidinium and pneumonia, the Applicant provided an adverse event analysis collapsing terms for pneumonia. This is consistent with the Division's recommendations during the preNDA interaction for the twice daily program.

### ***Assessment of Pneumonia based on Applicant's Preferred Term Search***

Results for the analysis of pneumonia-related preferred terms, conducted for the placebo-controlled trials, twice-daily Program (BID Group 1A), are provided in Table 62. Results for the BID Long-Term Safety trials are provided in Table 63.

**Table 62. Pneumonia Preferred Term Analysis Results: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ETT=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 pneumonia-related TEAE	5 (0.8)	26.2	4 (0.6)	20.1	2 (0.3)	10.1

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 65 (Table 32)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

**Table 63. Pneumonia Preferred Term Analysis Results: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 pneumonia-related TEAE	14 (3.1)	41.1	21 (2.4)	32.6

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 55 (Table 34)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

Based on the Applicant's analyses of collapsed preferred terms for BID Group 1A, the percentage of patients with at least one pneumonia-related TEAE was lower for the acclidinium 200 µg and 400 µg treatment arms, compared to placebo. While the percentage of patients with pneumonia was higher in the BID Long-Term Safety trials (2.4-3.1%), compared to the BID Group 1A trials (0.3-0.8%), there was no dose response observed.

### **Anticholinergic Adverse Events**

Given acclidinium's mechanism of action, the Applicant conducted an evaluation for adverse events consistent with anticholinergic effects.

### ***Assessment of Potential Anticholinergic Adverse Events based on Standard MedDRA Query and Additional Preferred Terms (SMQ + PT)***

The Applicant's analysis of potential anticholinergic adverse events included a SMQ for anticholinergic syndrome, along with an analysis of additional related PTs. Results for

the SMQ+PT analysis of potential anticholinergic adverse events, conducted for the placebo-controlled trials, twice-daily Program (BID Group 1A), are provided in Table 64. Results for the BID Long-Term Safety trials are provided in Table 65.

**Table 64. TEAEs consistent with Anticholinergic Syndrome: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6		Acclidinium 200 µg N=644 ET=199.4		Acclidinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
<b>Gastrointestinal disorders</b>	10 (1.6)	52.5	11 (1.7)	55.2	5 (0.8)	25.2
Dry Mouth	4 (0.6)	21.0	7 (1.1)	35.1	5 (0.8)	25.2
Constipation	6 (0.9)	31.5	4 (0.6)	20.1	0	0
<b>Renal and urinary disorders</b>	2 (0.3)	10.5	0	0	3 (0.5)	15.1
Dysuria	1 (0.2)	5.2	0	0	2 (0.3)	10.1
Urinary Retention	0	0	0	0	1 (0.2)	5.0
Urinary Incontinence	1 (0.2)	5.2	0	0	0	0
<b>Cardiac Disorders</b>	4 (0.6)	21.0	8 (1.2)	40.1	6 (0.9)	30.2
Supraventricular tachycardia	2 (0.3)	10.5	2 (0.3)	10.0	2 (0.3)	10.1
Tachycardia	0	0	1 (0.2)	5.0	2 (0.3)	10.1
Ventricular tachycardia	1 (0.2)	5.2	1 (0.2)	5.0	2 (0.3)	10.1
Palpitations	1 (0.2)	5.2	4 (0.6)	20.1	1 (0.2)	5.0
Sinus tachycardia	1 (0.2)	5.2	0	0	1 (0.2)	5.0
<b>Eye Disorders</b>	0	0	3 (0.5)	15.0	0	0
Blindness transient	0	0	1 (0.2)	5.0	0	0
Dry eye	0	0	1 (0.2)	5.0	0	0
Vision blurred	0	0	1 (0.2)	5.0	0	0
Visual acuity reduced	0	0	1 (0.2)	5.0	0	0
<b>Other disorders</b>	34 (5.3)	178.4	40 (6.2)	200.6	29 (4.6)	146.2

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 68 (Table 35)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

**Table 65. TEAEs consistent with Anticholinergic Syndrome: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
<b>Gastrointestinal disorders</b>	18 (4.0)	52.8	26 (2.9)	40.4
Constipation	13 (2.9)	38.2	13 (1.5)	20.2
Dry Mouth	4 (0.9)	11.7	11 (1.2)	17.1
Dysphagia	1 (0.2)	2.9	3 (0.3)	4.7
<b>Renal and urinary disorders</b>	2 (0.4)	5.9	3 (0.3)	4.7

Dysuria	2 (0.4)	5.9	1 (0.1)	1.6
Urinary incontinence	0	0	1 (0.1)	1.6
Urinary retention	0	0	1 (0.1)	1.6
<b>Cardiac Disorders</b>	6 (1.3)	17.6	6 (0.7)	9.3
Palpitations	1 (0.2)	2.9	4 (0.4)	6.2
Sinus tachycardia	0	0	1 (0.1)	1.6
Ventricular tachycardia	0	0	1 (0.1)	1.6
Supraventricular tachycardia	2 (0.4)	5.9	0	0
Tachycardia	4 (0.9)	11.7	0	0
<b>Eye Disorders</b>	3 (0.7)	8.8	7 (0.8)	10.9
Dry eye	2 (0.4)	5.9	2 (0.2)	3.1
Vision blurred	1 (0.2)	2.9	2 (0.2)	3.1
Accommodation Disorder	0	0	1 (0.1)	1.6
Angle closure glaucoma	0	0	1 (0.1)	1.6
Glaucoma	0	0	1 (0.1)	1.6
<b>Other disorders</b>	38 (8.5)	111.6	73 (8.2)	113.3

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 58 (Table 37)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate (IR)= $n/ET \times 1000$ .

For the BID Group 1A trials, there were only a few TEAEs reported for two or more patients with an imbalance favoring placebo as compared to either of the acridinium treatment arms: dry mouth (0.6%, 1.1%, and 0.8% for placebo, 200 µg, and 400 µg, respectively), palpitations (0.2%, 0.6%, 0.2% for placebo, 200 µg, and 400 µg, respectively). For each of these TEAEs, however, no dose response was observed, and the overall numbers of events were fairly low. For the BID Long-Term Safety trials, potential anticholinergic TEAEs reported for two or more patients and more commonly reported for the higher acridinium dose (based on incidence rate) were dry mouth (17.1 per 1000 PY and 11.7 per 1000 PY for the 400 µg and 200 µg treatment groups, respectively), dysphagia (4.7 per 1000 PY and 2.9 per 1000 PY for the 400 µg and 200 µg treatment groups, respectively), palpitations (6.2 per 1000 PY and 2.9 per 1000 PY for the 400 µg and 200 µg treatment groups, respectively), and blurred vision (3.1 per 1000 PY and 2.9 per 1000 PY for the 400 µg and 200 µg treatment groups, respectively). This adverse event profile is reassuring.

### **Intestinal Obstruction**

The UPLIFT trial demonstrated a statistically significant association between tiotropium bromide inhalation powder (Spiriva HandiHaler) and intestinal obstruction, although the absolute number of events was low;<sup>53</sup> intestinal obstruction is listed in the post-marketing adverse event section of the product label. The underlying mechanism of this class, with the potential for anticholinergic effects, makes a relationship to intestinal obstruction plausible. Given this context, the Agency requested an analysis of events

<sup>53</sup> Division's November 19, 2009, Advisory Committee briefing materials, dated October 21, 2009, and available at:

<http://www.fda.gov/downloads/advisorycommittees/committeesmeetingmaterials/drugs/pulmonary-allergydrugsadvisorycommittee/ucm190463.pdf>, accessed October 27, 2011.

related to intestinal obstruction, which was provided by the Applicant. There were no intestinal obstruction-related TEAEs identified for the BID Group 1A trials; results for the BID Long-Term Safety trials are provided in Table 66.

**Table 66. Intestinal Obstruction-related TEAEs: BID Long-Term Safety Trials, Safety Population**

	Acridinium 200 µg N=448 ET=340.6		Acridinium 400 µg N=891 ET=644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 intestinal obstruction-related TEAE	2 (0.4)	5.9	1 (0.1)	1.6
Intestinal obstruction	0	0	1 (0.1)	1.6
Esophageal stenosis	1 (0.2)	2.9	0	0
Small intestinal obstruction	1 (0.2)	2.9	0	0

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 61 (Table 40)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

The overall frequency of intestinal obstruction-related events is low, limiting the interpretability of the data.

## 7.4 Supportive Safety Results

### 7.4.1 Common Adverse Events

#### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

The overall incidence of TEAEs and TEAEs by preferred term in 2% or more patients in any treatment group for the BID Group 1A trials are provided in Table 67.

**Table 67. Overall Incidence of TEAEs and TEAEs by Preferred Term in ≥ 2% Patients in Any Treatment Group: BID Placebo-Controlled Trials (BID Group 1A), Safety Population**

	Placebo N=641 ET=190.6	Acridinium 200 µg N=644 199.4	Acridinium 400 µg N=636 198.4

	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 TEAE	344 (53.7)	1805	321 (49.8)	1609	319 (50.2)	1608
COPD	100 (15.6)	524.7	77 (12.0)	386.1	75 (11.8)	378.1
Headache	32 (5.0)	167.9	43 (6.7)	215.6	42 (6.6)	211.7
Nasopharyngitis	25 (3.9)	131.2	40 (6.2)	200.6	35 (5.5)	176.4
Cough	14 (2.2)	73.5	17 (2.6)	85.2	19 (3.0)	95.8
Diarrhea	9 (1.4)	47.2	12 (1.9)	60.2	17 (2.7)	85.7
Hypertension	16 (2.5)	83.9	8 (1.2)	40.1	10 (1.6)	50.4
Back Pain	12 (1.9)	63.0	18 (2.8)	90.2	8 (1.3)	40.3
Bronchitis	13 (2.0)	68.2	5 (0.8)	25.1	7 (1.1)	35.3

Source: Applicant's Submission dated December 12, 2011, Section 5.3.5.3.28, pg. 77 (Table 41)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as 100 x (n/N). Incidence Rate (IR)=n/ET\*1000.

For the BID Group 1A trials the overall percentage of patients with at least 1 TEAE was somewhat higher for the placebo treatment group (53.7%) as compared to the acclidinium treatment groups (49.8% and 50.2% for the 200 µg and 400 µg treatment arms, respectively). The most common TEAE was COPD exacerbation, which was more often reported for patients in the placebo treatment group (15.6%) as compared to those in the acclidinium treatment groups (12.0% and 11.8% the 200 µg and 400 µg treatment arms, respectively). TEAEs in ≥ 2% patients (in any treatment group), and demonstrating a dose response include: cough (2.2%, 2.6%, and 3.0% for the placebo, 200 µg and 400 µg treatment arms, respectively), and diarrhea (1.4%, 1.9%, and 2.7% for the placebo, 200 µg and 400 µg treatment arms, respectively). Diarrhea is unexpected, given the underlying mechanism of acclidinium.

### Long-term Safety Trials, Twice-Daily Program (BID Long-Term Safety Trials)

The overall incidence of TEAEs and TEAEs by preferred term in 2% or more patients in any treatment group for the BID Long-Term Safety trials are provided in Table 68.

**Table 68. Overall Incidence of TEAEs and TEAEs by Preferred Term in ≥ 2% Patients in Any Treatment Group: BID Long-Term Safety Trials, Safety Population**

	Acclidinium 200 µg N=448 ET=340.6		Acclidinium 400 µg N=891 644.2	
	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 TEAE	300 (67.0)	880.9	593 (66.6)	920.5
COPD	95 (21.2)	278.9	172 (19.3)	267.0
Nasopharyngitis	24 (5.4)	70.5	46 (5.2)	71.4
Upper Respiratory Tract Infection	20 (4.5)	58.7	42 (4.7)	65.2
Sinusitis	22 (4.9)	64.6	35 (3.9)	54.3

Headache	15 (3.3)	44.0	28 (3.1)	43.5
Cough	19 (4.2)	55.8	26 (2.9)	40.4
Urinary Tract Infection	13 (2.9)	38.2	26 (2.9)	40.4
Back Pain	9 (2.0)	26.4	24 (2.7)	37.3
Bronchitis	11 (2.5)	32.3	23 (2.6)	35.7
Nausea	17 (3.8)	49.9	22 (2.5)	34.1
Arthralgia	10 (2.2)	29.4	20 (2.2)	31.0
Hypertension	12 (2.7)	35.2	20 (2.2)	31.0
Diarrhea	7 (1.6)	20.6	19 (2.1)	29.5
Peripheral Edema	8 (1.8)	23.5	19 (2.1)	29.5
Dyspnea	13 (2.9)	38.2	16 (1.8)	24.8
Insomnia	9 (2.0)	26.4	15 (1.7)	23.3
Pneumonia	13 (2.9)	38.2	14 (1.6)	21.7
Constipation	13 (2.9)	38.2	13 (1.5)	20.2
Rash	9 (2.0)	26.4	12 (1.3)	18.6
Blood Glucose Increased	11 (2.5)	32.3	9 (1.0)	14.0
Dizziness	10 (2.2)	29.4	9 (1.0)	14.0
Abdominal Pain	9 (2.0)	26.4	7 (0.8)	10.9
Gastroesophageal Reflux Disease	11 (2.5)	32.3	7 (0.8)	10.9
Fall	10 (2.2)	29.4	6 (0.7)	9.3
Fatigue	9 (2.0)	26.4	3 (0.3)	4.7

Source: Applicant's Submission dated January 6, 2012, Section 5.3.5.3.28, pg. 63-64 (Table 43)

Note: N=number of patients in the Safety Population; ET=total exposure time in years; n=number of patients in the specific category. Percentages are calculated as  $100 \times (n/N)$ . Incidence Rate (IR)= $n/ET \times 1000$ .

For the BID Long-Term Safety trials, the overall incidence rate of TEAEs is somewhat higher for the acclidinium 400 µg treatment group (920.5 per 1000 PY) as compared to the acclidinium 200 µg treatment group (880.9 per 1000 PY), but the incidence rate of COPD exacerbations is higher for the lower acclidinium treatment dose (278.9 per 1000 PY for the 200 µg treatment group as compared to 267.0 per 1000 PY for the 400 µg treatment group). Nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis, arthralgia, diarrhea, and peripheral edema are more commonly reported for the higher acclidinium dose (based on incidence rate).

#### 7.4.2 Laboratory Findings

##### **MEAN CHANGE**

Mean changes in laboratory values for the BID Group 1A trials is provided in Table 69 and for the BID Group 1B trials in Table 70.

##### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 69. Mean Change in Laboratory Values: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter	Placebo	Acclidinium 200 µg	Acclidinium 400 µg
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	N=641	N=644	N=636
	Change from BL Mean (SD)	Change from BL Mean (SD)	Change from BL Mean (SD)
<b>Hematology</b>			
Hemoglobin (G/L)	-1.75 (8.9)	-1.77 (8.1)	-1.52 (7.4)
Hematocrit (L/L)	0.00 (0.03)	0.01 (0.03)	0.01 (0.03)
RBC count (10 <sup>12</sup> /L)	-0.04 (0.30)	-0.04 (0.3)	-0.03 (0.3)
WBC count (10 <sup>9</sup> /L)	-0.10 (1.8)	-0.05 (1.8)	0.03 (1.8)
Platelet count (10 <sup>9</sup> /L)	-9.62 (45.7)	-12.83 (41.9)	-8.45 (44.8)
<b>Chemistry: Hepatic Measures</b>			
Albumin (G/L)	-0.62 (3.0)	-0.81 (2.7)	-0.61 (2.7)
Alkaline phosphatase (U/L)	-2.65 (13.6)	-1.07 (13.1)	0.01 (13.0)
ALT (U/L)	-0.21 (10.8)	0.49 (11.3)	-0.07 (12.8)
AST (U/L)	-0.20 (9.1)	0.34 (10.2)	-0.09 (9.5)
Bilirubin (UMOL/L)	-0.21 (3.1)	-0.19 (4.3)	-0.24 (3.3)
GGT (U/L)	0.30 (31.5)	2.83 (32.9)	1.28 (30.9)
LDH (U/L)	-0.72 (25.0)	1.51 (25.4)	1.41 (23.7)
Total protein (G/L)	-1.28(4.0)	-1.29 (4.0)	-1.03 (3.7)
<b>Chemistry: Renal Function and Electrolytes</b>			
BUN (MMOL/L)	0.13 (1.6)	0.05 (1.5)	0.14 (1.7)
Creatinine (UMOL/L)	0.83 (12.6)	0.12 (10.5)	0.01 (10.8)
Sodium (MMOL/L)	-0.39 (3.0)	-0.37 (2.8)	-0.34 (2.8)
Potassium	-0.02 (0.5)	-0.05 (0.5)	-0.02 (0.5)
Chloride (MMOL/L)	-0.09 (2.9)	0.04 (2.8)	0.04 (2.8)
<b>Chemistry: Other</b>			
Glucose (MMOL/L)	-0.03 (1.6)	0.23 (1.4)	0.08 (1.7)
Total Cholesterol (MMOL/L)	-0.06 (0.7)	-0.09 (0.7)	-0.08 (0.7)
Triglycerides (MMOL/L)	0.07 (1.1)	0.05 (1.2)	0.02 (0.8)
Uric Acid (UMOL/L)	0.90 (59.8)	2.46 (53.8)	6.15 (59.9)
Creatine Kinase (U/L)	-2.94 (92.2)	-10.38 (121.8)	-3.24 (68.5)
Calcium (MMOL/L)	-0.02 (0.1)	-0.02 (0.1)	-0.01 (0.1)
Phosphorus (MMOL/L)	0.01 (0.2)	0.01 (0.2)	0.01 (0.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 108-109 (Table 3.1.1.1-1)

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=γ-glutamyl transferase; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

In general, mean changes in laboratory values were small and balanced across treatment groups. Exceptions include: GGT, LDH, and Uric Acid. For GGT, mean change for the acridinium treatment groups exceeded that for placebo, although not in a dose-dependent fashion. There were no comparable imbalances in other laboratory values that typically accompany changes in GGT, such as alkaline phosphatase, ALT, AST, or bilirubin. There was an imbalance in LDH, with a similar increase in both the acridinium treatment groups as compared to placebo; the nonspecific nature of LDH limits the interpretability of this finding. An imbalance with a dose-dependent pattern is

noted for uric acid, however, the magnitude of change is small and not likely to be of clinical significance.

**Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 70. Mean Change in Laboratory Values: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter	Acridinium 200 µg N=568	Acridinium 400 µg N=1005
	Change from BL Mean (SD)	Change from BL Mean (SD)
<b>Hematology</b>		
Hemoglobin (G/L)	-0.82 (8.5)	-0.56 (9.7)
Hematocrit (L/L)	0.00 (0.03)	-0.01 (0.03)
RBC count (10 <sup>12</sup> /L)	-0.05 (0.3)	-0.07 (0.3)
WBC count (10 <sup>9</sup> /L)	-0.07 (1.9)	-0.04 (1.7)
Platelet count (10 <sup>9</sup> /L)	-13.00 (48.6)	-13.15 (50.1)
<b>Chemistry: Hepatic Measures</b>		
Albumin (G/L)	-1.01 (3.0)	-0.97 (3.0)
Alkaline phosphatase (U/L)	-1.27 (11.9)	-1.54 (14.3)
ALT (U/L)	-0.39 (8.6)	0.11 (16.6)
AST (U/L)	0.15 (7.6)	0.92 (29.8)
Bilirubin (UMOL/L)	-0.33 (3.4)	-0.49 (3.3)
GGT (U/L)	1.15 (18.7)	1.96 (32.1)
LDH (U/L)	2.40 (25.6)	1.70 (25.7)
Total protein (G/L)	-1.71 (4.0)	-1.51 (4.2)
<b>Chemistry: Renal Function and Electrolytes</b>		
BUN (MMOL/L)	0.00 (1.7)	-0.03 (1.8)
Creatinine (UMOL/L)	0.96 (15.3)	1.14 (12.5)
Sodium (MMOL/L)	-0.52 (3.1)	-0.41 (3.3)
Potassium	-0.04 (0.5)	-0.01 (0.5)
Chloride (MMOL/L)	-0.12 (2.8)	-0.05 (3.0)
<b>Chemistry: Other</b>		
Glucose (MMOL/L)	0.20 (1.7)	0.13 (2.1)
Total Cholesterol (MMOL/L)	-0.10 (0.7)	-0.10 (0.7)
Triglycerides (MMOL/L)	0.03 (0.8)	0.14 (1.0)
Uric Acid (UMOL/L)	4.98 (53.9)	4.79 (60.9)
Creatine Kinase (U/L)	-11.56 (96.2)	4.91 (180.6)
Calcium (MMOL/L)	-0.04 (0.1)	-0.02 (0.1)
Phosphorus (MMOL/L)	0.01 (0.2)	0.01 (0.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 110 (Table 3.1.1.1-1)

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=γ-glutamyl transferase; LDH=lactate dehydrogenase; RBC=red blood cell; WBC=white blood cell

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

In general, mean changes in laboratory values were small and balanced across treatment groups. Mean changes in GGT and LDH were comparable to that observed for the BID Group 1A trials; in addition, an increase in uric acid is again observed, although without a dose-dependent pattern in these trials.

### **NOTABLE SHIFTS IN LABORATORY VALUES**

Notable shifts in laboratory values for BID are provided in Table 71 for the BID Group 1A trials and in Table 72 for the BID Group 1B trials.

### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 71. Notable Shifts in Laboratory Values: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter	Baseline	Placebo N=641	Acclidinium 200 µg N=644	Acclidinium 400 µg N=636
<b>Hematology</b>				
Hematocrit (L/L)	Low	1/594 (0.2)	0/593	0/593
Platelet count (10 <sup>9</sup> /L)	Low	0/578	2/578 (0.3)	1/574 (0.2)
	Normal	1/578 (0.2)	1/578 (0.2)	1/574 (0.2)
<b>Chemistry</b>				
Creatinine (UMOL/L)	High	0/596	2/607 (0.3)	0/592
GGT (U/L)	Normal	1/594 (0.2)	1/606 (0.2)	3/590 (0.5)
	High	13/594 (2.2)	16/606 (2.6)	12/590 (2.0)
Glucose (MMOL/L)	High	0/595	0/597	1/584 (0.2)
AST (U/L)	Normal	1/577 (0.2)	1/585 (0.2)	1/572 (0.2)
	High	2/577 (0.3)	3/585 (0.5)	0/572
ALT (U/L)	Normal	1/590 (0.2)	0/596	2/583 (0.3)
	High	1/590 (0.2)	3/596 (0.5)	0/583
Total bilirubin (UMOL/L)	Normal	0/595	1/599 (0.2)	0/587
	High	0/595	1/599 (0.2)	0/587
BUN (MMOL/L)	High	0/597	1/607 (0.2)	0/592
Uric acid (UMOL/L)	High	0/597	1/607 (0.2)	1/592 (0.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 120 (Table 3.3.1-1)

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT= γ-glutamyl transferase

In general, notable shifts in laboratory values were balanced across treatment groups. While notable shifts in GGT are observed, the frequency of these changes is comparable between placebo and the acclidinium treatment arms.

**Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 72. Notable Shifts in Laboratory Values: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter	Baseline	Aclidinium 200 µg N=568	Aclidinium 400 µg N=1005
<b><i>Hematology</i></b>			
Platelet count (10 <sup>9</sup> /L)	Low Normal	0/488 1/488 (0.2)	4/788 (0.5) 1/788 (0.1)
White blood cell count (10 <sup>9</sup> /L)	High	1/507 (0.2)	0/818
<b><i>Chemistry</i></b>			
Creatine kinase (U/L)	Normal	0/509	1/810 (0.1)
Creatinine (UMOL/L)	High	2/511 (0.4)	0/814
GGT (U/L)	Normal High	0/511 7/511 (1.4)	3/814 (0.4) 21/814 (2.6)
Glucose (MMOL/L)	Normal High	1/507 (0.2) 0/507	0/807 1/807 (0.1)
Potassium (MMOL/L)	Normal	1/505 (0.2)	0/808
AST (U/L)	Normal High	0/500 2/500 (0.4)	3/802 (0.4) 1/802 (0.1)
ALT (U/L)	Normal High	0/508 1/508 (0.2)	1/809 (0.1) 1/809 (0.1)
BUN (MMOL/L)	Normal	1/511 (0.2)	0/814
Uric acid (UMOL/L)	High	0/511	2/814 (0.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 122 (Table 3.3.2-1)

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT= γ-glutamyl transferase

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

For the BID Group 1B trials, a dose-dependent pattern is seen for shifts in GGT.

***POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY ASSESSMENTS AND LABORATORY-RELATED TEAEs***

Potentially clinically significant (PCS) laboratory assessments and laboratory-related TEAEs are provided in Table 73 and Table 74 for the BID Group 1A trials and in Table 75 and Table 76 for the BID Group 1B trials.

**Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 73. Potentially Clinically Significant Laboratory Assessments with a Frequency of at Least 1% in any Treatment Group: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter	Relationship to Expanded Normal Range	Placebo N=641	Acridinium 200 µg N=644	Acridinium 400 µg N=636
<b>Hematology</b>				
White Blood Cell Count	> 1.15 x ULN	18/583 (3.1)	10/592 (1.7)	17/587 (2.9)
Eosinophils	> 1.15 x ULN	7/600 (1.2)	5/599 (0.8)	8/596 (1.3)
Lymphocytes	> 1.15 x ULN	6/592 (1.0)	8/582 (1.4)	10/579 (1.7)
Monocytes	> 1.15 x ULN	7/601 (1.2)	9/602 (1.5)	5/597 (0.8)
Neutrophils	> 1.15 x ULN	26/575 (4.5)	21/590 (3.6)	17/577 (2.9)
Platelet Count	> 1.15 x ULN	8/580 (1.4)	3/572 (0.5)	3/566 (0.5)
<b>Chemistry</b>				
Alkaline phosphatase	> 1.15 x ULN	4/594 (0.7)	5/599 (0.8)	6/584 (1.0)
Creatine kinase	> 1.15 x ULN	20/555 (3.6)	30/558 (5.4)	27/555 (4.9)
Creatinine	> 1.15 x ULN	4/592 (0.7)	9/591 (1.5)	6/590 (1.0)
GGT	> 1.15 x ULN	22/531 (4.1)	18/533 (3.4)	19/527 (3.6)
Glucose	> 1.15 x ULN	49/518 (9.5)	65/531 (12)	59/513 (12)
Potassium	> 1.05 x ULN	8/588 (1.4)	9/590 (1.5)	10/585 (1.7)
AST	> 1.15 x ULN	20/565 (3.5)	20/569 (3.5)	21/562 (3.7)
ALT	> 1.15 x ULN	15/566 (2.7)	26/572 (4.5)	18/568 (3.2)
Total Bilirubin	> 1.15 x ULN	3/601 (0.5)	7/600 (1.2)	3/595 (0.5)
Triglycerides	> 1.15 x ULN	21/573 (3.7)	20/580 (3.4)	25/567 (4.4)
BUN	> 1.15 x ULN	16/593 (2.7)	4/594 (0.7)	13/593 (2.2)
Uric acid	> 1.15 x ULN	8/587 (1.4)	12/591 (2.0)	15/581 (2.6)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 114 (Table 3.2.1-1)

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT=γ-glutamyl transferase, LDH=lactate dehydrogenase; LLN=lower limit of normal range; ULN=upper limit of normal range

**Table 74. PCS laboratory assessments reported as TEAEs in 2 or more patients: BID Placebo-Controlled Trials, (BID Group 1A)**

Treatment Arm	PCS Laboratory Assessments reported as TEAEs (number of patients)
Placebo	anemia (2), increased creatinine (2), increased glucose (2), hypokalemia (5)
Acridinium 200 µg	bilirubin (2), glucose (3), GGT (2), hyperglycemia (2), hematuria (2), and increased white blood cell count (2)
Acridinium 400 µg	mean red cell volume increased (2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 123

While a number of imbalances (i.e. for creatine kinase, creatinine, glucose, ALT, total bilirubin, and uric acid) in the frequency of potentially clinically significant (PCS) laboratory assessments for placebo versus the acridinium treatment groups are observed, these imbalances are all of modest magnitude, and the overall number of PCS laboratory assessments reported as TEAEs in 2 or more patients is low. While two of the PCS laboratory assessments (increased creatine phosphokinase and increased

white blood cell count, both for patients in the acclidinium 200 µg treatment group) resulted in permanent discontinuation of treatment, the absence of any PCS laboratory assessments among the reported SAEs for the BID Group 1A trials is reassuring.

**Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 75. Potentially Clinically Significant Laboratory Assessments with a Frequency of at Least 1% in any Treatment Group: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter	Relationship to Expanded Normal Range	Acclidinium 200 µg N=568	Acclidinium 400 µg N=1005
<b>Hematology</b>			
White Blood Cell Count	> 1.15 x ULN	17/493 (3.4)	33/879 (3.8)
Eosinophils	> 1.15 x ULN	7/506 (1.4)	11/900 (1.2)
Lymphocytes	< 0.85 x LLN	7/491 (1.4)	6/870 (0.7)
Lymphocytes	> 1.15 x ULN	11/491 (2.2)	16/870 (1.8)
Monocytes	> 1.15 x ULN	8/506 (1.6)	23/898 (2.6)
Neutrophils	> 1.15 x ULN	33/488 (6.8)	45/865 (5.2)
Platelet Count	> 1.15 x ULN	7/485 (1.4)	10/855 (1.2)
<b>Chemistry</b>			
Alkaline phosphatase	> 1.15 x ULN	9/504 (1.8)	11/883 (1.2)
Creatine kinase	> 1.15 x ULN	32/465 (6.9)	56/839 (6.7)
Creatinine	> 1.15 x ULN	10/494 (2.0)	16/872 (1.8)
GGT	> 1.15 x ULN	20/470 (4.3)	38/796 (4.8)
Glucose	< 0.85 x LLN	7/470 (1.5)	11/810 (1.4)
Glucose	> 1.15 x ULN	92/470 (20)	132/810 (16)
LDH	> 1.15 x ULN	7/496 (1.4)	16/868 (1.8)
Potassium	> 1.05 x ULN	16/497 (3.2)	21/886 (2.4)
AST	> 1.15 x ULN	17/485 (3.5)	34/849 (4.0)
ALT	> 1.15 x ULN	20/494 (4.0)	31/849 (3.7)
Total Bilirubin	> 1.15 x ULN	5/508 (1.0)	5/895 (0.6)
Triglycerides	> 1.15 x ULN	23/486 (4.7)	68/851 (8.0)
BUN	> 1.15 x ULN	19/494 (3.8)	23/886 (2.6)
Uric acid	> 1.15 x ULN	9/504 (1.8)	19/871 (2.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 117 (Table 3.2.2-1)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

Key: ALT=alanine aminotransferase; AST=aspartate aminotransferase; BUN=blood urea nitrogen; GGT= γ-glutamyl transferase, LDH=lactate dehydrogenase; LLN=lower limit of normal range; ULN=upper limit of normal range

**Table 76. PCS laboratory assessments reported as TEAEs in 2 or more patients: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Treatment Arm	PCS Laboratory Assessments reported as TEAEs (number of patients)
Acclidinium 200 µg	leukocytosis (3), increased glucose (9), increased GGT (6), increased ALT (4), increased uric acid (2), increased creatine phosphokinase (4), hyperglycemia (4), hypokalemia (3), hyponatremia (2), hematuria (3), and

	proteinuria (2)
Acidinium 400 µg	anemia (3), increased mean red blood cell volume (2), increased glucose (7), increased GGT (7), increased ALT (3), increased AST (3), increased creatinine (2), increased creatine phosphokinase (7), increased LDH (2), increased triglycerides (3), glycosuria (2), hypercholesterolemia (2), hyperglycemia (2), hyperkalemia (2), and hyponatremia (4)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 124

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

Imbalances in the frequencies of potentially clinically significant (PCS) laboratory assessments between the aclidinium treatment groups are observed only for monocytes and triglycerides. The overall number of PCS laboratory assessments reported as TEAEs in 2 or more patients is low; the most frequent PCS laboratory assessment reported as such were increased glucose/hyperglycemia and increased GGT.

Of note, there were three PCS laboratory assessments reported as TEAEs that were classified as SAEs: two events of hyperglycemia (one for a patient receiving aclidinium 200 mcg, and one for a patient receiving aclidinium 400 mcg), and one event of hypoglycemia (for a patient receiving aclidinium 400 mcg). The ISS states that none of these SAEs were the direct cause of permanent discontinuation of treatment. Five TEAEs related to laboratory tests (and not classified as SAEs) resulted in discontinuation of treatment: four for patients receiving aclidinium 200 mcg (eosinophilia, decreased platelet count, increased creatine phosphokinase, and increased GGT), and one for a patient receiving aclidinium 400 mcg (glycosuria)

As is discussed in Section 5.3.2, there were two SAEs of acute renal failure for the aclidinium 400 µg treatment group (and none for the aclidinium 200 µg treatment group) in the BID Long-Term Safety trials. Given this finding, it is useful to examine the frequency of potentially clinical significant (PCS) creatinine values. These were balanced between the two aclidinium treatment groups in the BID Group 1B trials (2.0% and 1.8% for the 200 µg and 400 µg treatment groups, respectively). For the BID Group 1A trials, the frequency was comparable between the placebo and aclidinium 400 µg treatment groups (0.7% and 1.0%, respectively), and higher for the 200 µg treatment group (1.5%). Together, these data do not represent a convincing signal for renal failure or insufficiency.

**OVERALL CONCLUSIONS REGARDING LABORATORY FINDINGS**

Overall, the results for mean changes and notable shifts in laboratory assessments, along with the frequencies of potentially clinically significant laboratory assessments overall and PSC laboratory assessments reported as TEAEs were small in magnitude and balanced across treatment groups for both the BID Group 1A and BID Group 1B trials. Notable exceptions include the results for GGT, uric acid, glucose, and creatine phosphokinase.

### 7.4.3 Vital Signs

#### **MEAN CHANGE**

Mean changes in systolic and diastolic blood pressure are in Table 77 for the BID Group 1A trials and in Table 78 for the BID Group 1B trials.

#### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 77. Mean Change in Systolic and Diastolic Blood Pressure: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter (mmHg)	Placebo N=641		Aclidinium 200 µg N=644		Aclidinium 400 µg N=636	
	Baseline Mean (SD)	Change Mean (SD)	Baseline Mean (SD)	Change Mean (SD)	Baseline Mean (SD)	Change Mean (SD)
Systolic Blood Pressure	129 (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	77.6 (9.5)	-1.0 (9.1)	78.1 (9.6)	-0.5 (9.3)	77.9 (9.3)	-0.6 (9.2)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 126 (Table 4.1.1-1)

#### **Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 78. Mean Change in Systolic and Diastolic Blood Pressure: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter (mmHg)	Aclidinium 200 µg N=568		Aclidinium 400 µg N=1005	
	Baseline Mean (SD)	Change Mean (SD)	Baseline Mean (SD)	Change Mean (SD)
Systolic Blood Pressure	127.3 (15.0)	-0.2 (14.7)	129.0 (14.9)	-1.7 (15.1)
Diastolic Blood Pressure	76.3 (9.1)	-0.1 (9.2)	76.1 (9.5)	-0.3 (9.5)

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 121 (Table 9.1.4-1)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

In general, mean changes in systolic and diastolic blood pressure were small and balanced across treatment groups for both the BID Group 1A and BID Group 1B trials.

#### **POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND TEAEs**

Potentially clinically significant changes in systolic and diastolic blood pressure are provided in Table 79 for the BID Group 1A trials and in Table 80 for the BID Group 1B trials.

**Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 79. Potentially Clinically Significant Changes in Systolic and Diastolic Blood Pressure: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter (mmHg)	Criteria for PCS Change	Placebo N=641 n (%)	Acclidinium 200 µg N=644 n (%)	Acclidinium 400 µg N=636 n (%)
SBP, increase	(≥ 180 and increase from BL ≥ 20) or (≥ 200 if BL < 200)	2/635 (0.3)	5/633 (0.8)	3/623 (0.5)
SBP, decrease	(≤ 90 and decrease from BL ≥ 20) or (≤ 75 if BL > 75)	6/635 (0.9)	4/633 (0.6)	5/623 (0.8)
DBP, increase	(≥ 105 and increase from BL ≥ 15) or (≥ 115 if BL < 115)	2/635 (0.3)	5/633 (0.8)	4/623 (0.6)
DBP, decrease	(≤ 50 and decrease from BL ≥ 15) or (≤ 40 if BL > 40)	1/635 (0.2)	6/633 (1.0)	2/623 (0.3)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 128 (Table 4.2.1-1)

Key: DBP=diastolic blood pressure, PCS=potentially clinically significant, SBP=systolic blood pressure

There were two occurrences of PCS blood pressure measurements (described as “hypertension”) that were also reported as TEAEs, one each for the acclidinium 200 and 400 µg treatment groups. Neither event resulted in discontinuation from the trial.

**Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 80. Potentially Clinically Significant Changes in Systolic and Diastolic Blood Pressure: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter (mmHg)	Criteria for PCS Change	Acclidinium 200 µg N=568 n (%)	Acclidinium 400 µg N=1005 n (%)
SBP, increase	(≥ 180 and increase from BL ≥ 20) or (≥ 200 if BL < 200)	5/555 (0.9)	3/943 (0.3)
SBP, decrease	(≤ 90 and decrease from BL ≥ 20) or (≤ 75 if BL > 75)	5/555 (0.9)	5/943 (0.5)
DBP, increase	(≥ 105 and increase from BL ≥ 15) or (≥ 115 if BL < 115)	4/555 (0.7)	3/943 (0.3)
DBP, decrease	(≤ 50 and decrease from BL ≥ 15) or (≤ 40 if BL > 40)	8/555 (1.4)	12/943 (1.3)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 129 (Table 4.2.2-1)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.  
 Key: DBP=diastolic blood pressure, PCS=potentially clinically significant, SBP=systolic blood pressure

There were three occurrences of PCS blood pressure measurements that were also reported as TEAEs. These included "uncontrolled hypertension" and "hypertension" for the acclidinium 200 µg treatment group, and "hypertensive nephrosclerosis" for the acclidinium 400 µg treatment group. None of these events resulted in discontinuation from the trial.

In general, potentially clinical significant changes in systolic and diastolic blood pressure were infrequent and balanced across treatment groups for both the BID Group 1A trials and the BID Group 1B trials. The overall number of PCS blood pressure measurements reported as TEAEs was low, and no event resulted in trial discontinuation. These data are reassuring.

#### 7.4.4 Electrocardiograms (ECGs)

##### **MEAN CHANGE**

Mean changes in ECG parameters are provided in Table 81 for the BID Group 1A trials and in Table 82 for the BID Group 1B trials.

#### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 81. Mean Changes From Baseline to End of Study for ECG Values: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter	Placebo N=641		Acclidinium 200 µg N=644		Acclidinium 400 µg N=636	
	Baseline Mean (SD)	Mean (SD) Change from BL	Baseline Mean (SD)	Mean (SD) Change from BL	Baseline Mean (SD)	Mean (SD) Change from BL
Heart rate, bpm	73.3 (12.5)	-3.0 (11.0)	73.5 (12.9)	-3.7 (11.1)	73.9 (13.0)	-3.0 (11.6)
PR, msec	164.0 (27.9)	1.4 (15.4)	161.8 (23.7)	2.6 (14.4)	164.7 (26.4)	0.6 (14.6)
QRS, msec	92.8 (13.4)	0.6 (7.6)	92.0 (13.0)	1.9 (8.3)	93.2 (14.5)	0.6 (8.4)
QT, msec	387.1 (31.4)	7.1 (26.0)	386.4 (32.5)	8.7 (26.5)	388.1 (32.2)	7.7 (27.8)

QTcF, msec	411.0 (20.2)	1.7 (16.8)	410.6 (22.1)	2.1 (18.2)	413.2 (21.6)	2.3 (17.9)
RR, msec	844.1 (151.6)	36.2 (134.6)	841.1 (147.8)	44.1 (137.6)	836.7 (147.7)	35.5 (132.0)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 131 (Table 4.4.1.1.1-1)  
 Key: BL=baseline

### **Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 82. Mean Changes From Baseline to End of Study for ECG Values: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter	Acidinium 200 µg N=568		Acidinium 400 µg N=1005	
	Baseline Mean (SD)	Mean (SD) Change from BL	Baseline Mean (SD)	Mean (SD) Change from BL
Heart rate, bpm	72.7 (12.3)	-3.0 (10.3)	72.9 (12.5)	-2.7 (10.9)
PR, msec	163.8 (26.3)	1.7 (14.6)	164.5 (26.8)	1.1 (14.6)
QRS, msec	92.7 (12.7)	1.2 (8.2)	93.2 (14.9)	0.7 (8.5)
QT, msec	389.0 (32.2)	8.4 (25.8)	389.8 (31.9)	8.1 (27.2)
QTcF, msec	412.0 (21.5)	2.8 (17.2)	413.1 (21.6)	3.3 (18.6)
RR, msec	848.9 (145.2)	39.0 (127.9)	847.5 (146.4)	33.8 (130.2)

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 122 (Table 9.1.4-4)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

In general, mean changes in ECG parameters for the small and balanced between treatment groups for both the BID Group 1A and BID Group 1B trials. Exceptions to this include some of the mean changes for the aclidinium 200 µg treatment group, which were somewhat larger in magnitude; this is of unclear significance.

### ***POTENTIALLY CLINICALLY SIGNIFICANT CHANGES AND TEAEs***

The Applicant identified potentially clinically significant (PCS) changes in ECG parameters using two sets of criteria, which employed different thresholds (lower for set 1 and higher for set 2). The frequency of PCS changes (based on the two sets of criteria) in ECG parameters is provided in Table 83 for the BID Group 1A trials and in Table 85 for the BID Group 1B trials. Potentially clinically significant ECG values reported as TEAEs are provided in Table 84 for the BID Group 1A trials and in Table 86 for the BID Group 1B trials.

### **Placebo-controlled Trials, Twice-Daily Program (BID Group 1A)**

**Table 83. Potentially Clinically Significant ECG Values: BID Placebo-Controlled Trials, (BID Group 1A)**

Parameter	Criteria for PCS Value	Placebo N=641 n (%)	Acclidinium 200 µg N=644 n (%)	Acclidinium 400 µg N=636 n (%)
<b>Criteria Set 1</b>				
QT interval, msec	> 480 msec	15/637 (2.4)	16/642 (2.5)	12/632 (1.9)
	Increase ≥ 30 msec	264/637 (41.4)	282/642 (43.9)	268/632 (42.4)
QTcF interval, msec	> 480 msec	4/639 (0.6)	12/640 (1.9)	6/634 (1.0)
	Increase ≥ 30 msec	89/639 (13.9)	120/640 (18.8)	101/634 (15.9)
QRS interval, msec	≥ 100 msec and increase ≥ 25%	7/640 (1.1)	26/642 (3.7)	12/635 (1.9)
PR interval, msec	≥ 200 msec and increase ≥ 25%	5/626 (0.8)	8/629 (1.3)	7/625 (1.1)
Tachycardia event, bpm	≥ 110 bpm and increase ≥ 15%	6/640 (0.9)	4/642 (0.6)	1/635 (0.2)
Bradycardia event, bpm	≤ 50 bpm and decrease ≥ 15%	32/640 (5.0)	39/642 (6.1)	40/635 (6.3)
<b>Criteria Set 2</b>				
QT interval, msec	> 500 msec	4/640 (0.6)	3/642 (0.5)	7/634 (1.1)
	Increase ≥ 60 msec	33/640 (5.2)	57/642 (8.9)	44/634 (6.9)
QTcF interval, msec	> 500 msec	1/640 (0.2)	0/641	2/635 (0.3)
	Increase ≥ 60 msec	3/640 (0.5)	4/641 (0.6)	2/635 (0.3)
QRS interval, msec	≥ 150 msec if baseline < 150 msec	7/640 (1.1)	8/642 (1.3)	6/635 (0.9)
PR interval, msec	≥ 250 msec if baseline < 250 msec	9/626 (1.4)	9/629 (1.4)	6/625 (1.0)
Tachycardia event, bpm	≥ 120 if baseline < 120 bpm	0/640	2/642 (0.3)	1/635 (0.2)
Bradycardia event, bpm	≤ 40 bpm if baseline > 40 bpm	3/640 (0.5)	1/642 (0.2)	0/635

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 134 (Table 4.4.1.2.1-1)

**Table 84. Potentially Clinically Significant ECG Values Reported as TEAEs: BID Placebo-Controlled Trials, (BID Group 1A)**

Preferred Term	Placebo N=641 n (%)	Acclidinium 200 µg N=644 n (%)	Acclidinium 400 µg N=636 n (%)
Number (%) with at least 1 TEAE	23 (3.6)	26 (4.0)	27 (4.2)
Atrioventricular block first degree	1 (0.2)	1 (0.2)	2 (0.3)
Bundle branch block left	0 (0.0)	1 (0.2)	1 (0.2)
Bundle branch block right	0 (0.0)	0 (0.0)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2)	0 (0.0)
Bradycardia	1 (0.2)	0 (0.0)	0 (0.0)
Bradycardia	2 (0.3)	1 (0.2)	0 (0.0)
Sinus bradycardia	0 (0.0)	0 (0.0)	1 (0.2)
Supraventricular tachycardia	2 (0.3)	1 (0.2)	2 (0.3)
Atrial fibrillation	2 (0.3)	3 (0.5)	1 (0.2)
Sick sinus syndrome	0 (0.0)	0 (0.0)	1 (0.2)
Sinus tachycardia	1 (0.2)	0 (0.0)	1 (0.2)
Sinus arrest	1 (0.2)	0 (0.0)	0 (0.0)
Ventricular extrasystoles	2 (0.3)	0 (0.0)	1 (0.2)
Ventricular tachycardia	1 (0.2)	0 (0.0)	1 (0.2)

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 124 (Table 9.1.4-6)

When the ECG data for the BID Group 1A trials is examined using criteria set 1, an imbalance in the frequency of PCS ECG values (where the frequency for acridinium exceeds that for placebo) is noted for the following parameters: QTcF, QRS, PR, bradycardia event. When examined using criteria set 2, an imbalance is only noted for the QT interval (uncorrected). For PCS ECG values reported as TEAEs, no striking imbalance across treatment groups is noted, and the frequency of any individual event is low.

**Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

**Table 85. Potentially Clinically Significant ECG Values: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Parameter	Criteria for PCS Value	Acridinium 200 µg N=568 n (%)	Acridinium 400 µg N=1005 n (%)
<b>Criteria Set 1</b>			
QT interval, msec	> 480 msec	21/564 (3.7)	22/951 (2.3)
	Increase ≥ 30 msec	239/564 (42.4)	401/951 (42.2)
QTcF interval, msec	> 480 msec	11/564 (2.0)	12/953 (1.3)
	Increase ≥ 30 msec	101/564 (17.9)	160/952 (16.8)
QRS interval, msec	≥ 100 msec and increase ≥ 25%	17/566 (3.0)	19/956 (2.0)
PR interval, msec	≥ 200 msec and increase ≥ 25%	5/557 (0.9)	11/936 (1.2)
Tachycardia event, bpm	≥ 110 bpm and increase ≥ 15%	3/566 (0.5)	3/955 (0.3)
Bradycardia event, bpm	≤ 50 bpm and decrease ≥ 15%	34/566 (6.0)	55/956 (5.8)
<b>Criteria Set 2</b>			
QT interval, msec	> 500 msec	4/565 (0.7)	7/955 (0.7)
	Increase ≥ 60 msec	28/565 (5.0)	60/955 (6.3)
QTcF interval, msec	> 500 msec	1/566 (0.2)	4/956 (0.4)
	Increase ≥ 60 msec	2/566 (0.4)	7/956 (0.7)
QRS interval, msec	≥ 150 msec if baseline < 150 msec	10/566 (1.8)	13/955 (1.4)
PR interval, msec	≥ 250 msec if baseline < 250 msec	5/557 (0.9)	10/936 (1.1)
Tachycardia event, bpm	≥ 120 if baseline < 120 bpm	2/566 (0.4)	1/956 (0.1)
Bradycardia event, bpm	≤ 40 bpm if baseline > 40 bpm	1/566 (0.2)	3/956 (0.3)

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 135 (Table 4.4.1.2.2-1)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

**Table 86. Potentially Clinically Significant ECG Values Reported as TEAEs: Long-term Safety Trials, Twice-Daily Program (BID Group 1B)**

Preferred Term	Acclidinium 200 µg N=568 n (%)	Acclidinium 400 µg N=1005 n (%)
Number (%) with at least 1 TEAE	38 (6.7)	49 (4.9)
Atrioventricular block first degree	3 (0.5)	3 (0.3)
Bundle branch block left	6 (1.1)	5 (0.5)
Conduction disorder	0 (0.0)	1 (0.1)
Atrioventricular block second degree	1 (0.2)	0 (0.0)
Bundle branch block right	1 (0.2)	0 (0.0)
Bradycardia	3 (0.5)	0 (0.0)
Tachycardia	2 (0.4)	1 (0.1)
Atrial fibrillation	4 (0.7)	3 (0.3)
Supraventricular tachycardia	2 (0.4)	2 (0.2)
Atrial flutter	0 (0.0)	1 (0.1)
Sinus bradycardia	2 (0.4)	0 (0.0)
Sinus tachycardia	0 (0.0)	1 (0.1)
Wandering pacemaker	1 (0.2)	0 (0.0)
Ventricular extrasystoles	2 (0.4)	1 (0.1)
Ventricular tachycardia	0 (0.0)	3 (0.3)

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 125 (Table 9.1.4-7)

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

The only notable imbalance in PCS ECG values (where the frequency for acclidinium 400 µg exceeds that for acclidinium 200 µg) for the BID Group 1B trials is in QT interval, based on criteria set 2. For PCS ECG values reported as TEAEs, frequency of any individual event was generally low, however, it is noted that 3 events of ventricular tachycardia were reported for the acclidinium 400 µg treatment group, compared to none for the 200 µg treatment group.

### **HOLTER DATA**

Holter monitoring (24-hour, 12-lead) was conducted in a subset of patients participating in trials LAS-MD-33 and LAS-MD-38A, both prior to the initiation of treatment, and again at the conclusion of treatment. Data from the 18-hour time point was analyzed as part of the Applicant's ISS. Table 87 lists new findings present at Week 12 on Holter monitoring.

**Table 87. Holter Data: New Findings at Week 12**

Parameter	Placebo N=172 n (%)	Acclidinium 200 µg N=173 n (%)	Acclidinium 400 µg N=164 n (%)

≥ 30 PVC in 1 hour	2 (1.2)	2 (1.2)	0
Frequent PVCs	9 (5.2)	10 (5.8)	12 (7.3)
Increased nonsustained supraventricular tachycardia episodes	24 (14.0)	44 (25.4)	39 (23.8)
Increased sustained supraventricular tachycardia episodes	0	1 (0.6)	1 (0.6)
Atrial fibrillation	0	1 (0.6)	0
Mobitz I (Wenckebach)2 <sup>nd</sup> degree heart block	0	1 (0.6)	1 (0.6)
2:1 AV Block	0	1 (0.6)	1 (0.6)
RR > 2.0 Sec	2 (1.2)	1 (0.6)	2 (1.2)
Intermittent ectopic atrial rhythm	1 (0.6)	0	2 (1.2)
Intermittent junctional rhythm	0	1 (0.6)	0

Source: Section 5.3.5.3.28 (ISS Volume 1), pg. 140 (Table 4.4.1.6-1)

Note: Based on Applicant's cardiologist's review

Individual events on Holter monitoring were generally infrequent and balanced across treatment arms. Exceptions include frequent PVCs and increased episodes nonsustained supraventricular tachycardia, which both were more common in the aclidinium treatment groups as compared to placebo. There were no episodes of ventricular fibrillation or torsade de pointes reported.

### **THOROUGH QT STUDY**

The aclidinium clinical development program included an evaluation of the potential effect of aclidinium on the QT interval (i.e. a "Thorough QT Study") in healthy volunteers (n=272). Trial M/34273/11 was a randomized, parallel, placebo-controlled (double-blind) and active-controlled (open-label) trial evaluating aclidinium 200 µg, aclidinium 800 µg, and moxifloxacin 400 mg (a positive control), with a treatment duration of 3 days. The results of this trial were evaluated by the Interdisciplinary Review Team for QT Studies Consultation, which concluded that there was no significant QT prolongation effect detected for either of the aclidinium doses evaluated. The review states that the largest upper bounds of the 2-sided 90% confidence interval for the mean difference between aclidinium (200 µg and 800 µg) and placebo were below 10 ms on both day 1 and day 3 of treatment, which is the threshold for regulatory concern. At the same time, the largest lower bound of the two-sided 90% CI for the  $\Delta\Delta\text{QTcF}$  for moxifloxacin was greater than 5 ms for both day 1 and day 3, indicating that assay sensitivity was established.

### **OVERALL CONCLUSIONS REGARDING ECG, HOLTER, AND THOROUGH QT STUDY FINDINGS**

In general, the frequency of individual events was low, and balanced across treatment groups for the BID Group 1A and BID Group 1B ECG data. Exceptions include the occurrence of 3 instances of PCS ventricular tachycardia events reported as TEAEs for the acridinium 400 µg treatment group, compared to none for the 200 µg treatment group. On Holter monitoring, individual events were generally infrequent and balanced across treatment arms, with the exception of frequent PVCs and increased episodes nonsustained supraventricular tachycardia, which were both more common among patients treated with acridinium. Finally, there was no significant QT prolongation effect detected for either of the acridinium doses evaluated in the Thorough QT Study.

#### 7.4.5 Special Safety Studies/Clinical Trials

See Section 7.4.4 for a description Trial M/34273/11 (“Thorough QT Study”).

#### 7.4.6 Immunogenicity

As a small molecule, acridinium is not anticipated to induce an immune response, and immunogenicity was not assessed.

### 7.5 Other Safety Explorations

#### 7.5.1 Dose Dependency for Adverse Events

The twice-daily acridinium program evaluated both the proposed dose, 400 µg, as well as a lower dose, 200 µg. The inclusion of the 200 µg treatment arm allows for an exploration of dose dependency for adverse events and other safety data, which is discussed throughout this review of safety.

#### 7.5.2 Time Dependency for Adverse Events

No specific analysis of time dependency was conducted for adverse events.

#### 7.5.3 Drug-Demographic Interactions

The application includes an exploration of the effects of age, sex, and race on safety.

#### **AGE**

The ISS includes a subgroup analysis of TEAEs based on age (less than 60 years, 60 to less than 70 years, and 70 years and older). The results of the analysis for the BID Group 1A trials are provided in Table 88.

**Table 88. Treatment-Emergent Adverse Events by Preferred Term in ≥ 2% Patients in Any Treatment Group, Stratified by Age: BID Placebo-Controlled Trials, (BID Group 1A)**

Preferred Term, n (%)	Age < 60 years			Age ≥ 60 to < 70 years			Age ≥ 70 years		
	P N=220	A 200 µg N=220	A 400 µg N=197	P N=278	A 200 µg N=276	A 400 µg N=272	P N=143	A 200 µg N=148	A 400 µg N=167
Patients with any TEAE	112 (50.9)	103 (46.8)	96 (48.7)	140 (50.4)	136 (49.3)	131 (48.2)	92 (64.3)	82 (55.4)	92 (55.1)
COPD*	38 (17.3)	29 (13.2)	24 (12.2)	42 (15.1)	36 (13.0)	29 (10.7)	20 (14.0)	12 (8.1)	22 (13.2)
Nasopharyngitis	9 (4.1)	11 (5.0)	14 (7.1)	7 (2.5)	19 (6.9)	11 (4.0)	9 (6.3)	10 (6.8)	10 (6.0)
Headache	19 (8.6)	19 (8.6)	13 (6.6)	9 (3.2)	15 (5.4)	20 (7.4)	4 (2.8)	9 (6.1)	9 (5.4)
Cough	3 (1.4)	2 (0.9)	8 (4.1)	5 (1.8)	7 (2.5)	4 (1.5)	6 (4.2)	8 (5.4)	7 (4.2)
Diarrhea	4 (1.8)	2 (0.9)	4 (2.0)	3 (1.1)	7 (2.5)	6 (2.2)	2 (1.4)	3 (2.0)	7 (4.2)
Hypertension	5 (2.3)	2 (0.9)	3 (1.5)	7 (2.5)	4 (1.4)	6 (2.2)	4 (2.8)	2 (1.4)	1 (0.6)
Back pain	3 (1.4)	9 (4.1)	3 (1.5)	7 (2.5)	5 (1.8)	1 (0.4)	2 (1.4)	4 (2.7)	4 (2.4)
Bronchitis	5 (2.3)	1 (0.5)	2 (1.0)	4 (1.4)	2 (0.7)	2 (0.7)	4 (2.8)	2 (1.4)	3 (1.8)

Source: Section 5.3.5.3.28, pg. 148 (Table 5.1.3.1.1-1)

Key: A=aclidinium; P=placebo

\* The preferred term "COPD" refers to COPD exacerbation.

The overall percentage of patients experiencing at least one TEAE was somewhat higher, across all treatment groups (including placebo), for the oldest patients (≥ 70 years). Individual events with higher percentages reported for the oldest age group included cough, diarrhea, hypertension, back pain, and bronchitis.

Of the thirteen on-treatment deaths reported across the BID program, four occurred in patients 70 years of age and older, two in patients aged 60 years to less than 70 years, and seven in patients less than 60 years of age. There is therefore no apparent association between age and death.

### SEX

The Applicant's analysis of TEAEs by sex for the BID Group 1A trials is summarized in Table 89.

**Table 89. Treatment-Emergent Adverse Events by Preferred Term with in ≥ 2% Patients in Any Treatment Group, Stratified by Sex: BID Placebo-Controlled Trials, (BID Group 1A)**

Preferred Term, n (%)	Males			Females		
	P N=385	A 200 µg N=381	A 400 µg N=371	P N=256	A 200 µg N=263	A 400 µg N=265
Patients with any TEAE	199 (51.7)	173 (45.4)	174 (46.9)	145 (56.6)	148 (56.3)	145 (54.7)

COPD*	59 (15.3)	38 (10.0)	47 (12.7)	41 (16.0)	39 (14.8)	28 (10.6)
Headache	15 (3.9)	20 (5.2)	22 (5.9)	17 (6.6)	23 (8.7)	20 (7.5)
Nasopharyngitis	16 (4.2)	19 (5.0)	21 (5.7)	9 (3.5)	21 (8.0)	14 (5.3)
Cough	9 (2.3)	11 (2.9)	5 (1.3)	5 (2.0)	6 (2.3)	14 (5.3)
Diarrhea	4 (1.0)	5 (1.3)	5 (1.3)	5 (2.0)	7 (2.7)	12 (4.5)
Hypertension	10 (2.6)	3 (0.8)	6 (1.6)	6 (2.3)	5 (1.9)	4 (1.5)
Back pain	4 (1.0)	8 (2.1)	4 (1.1)	8 (3.1)	10 (3.8)	4 (1.5)
Bronchitis	6 (1.6)	5 (1.3)	2 (0.5)	7 (2.7)	0	5 (1.9)

Source: Section 5.3.5.3.28, pg. 150 (Table 5.1.4.1.1-1)

Key: A=aclidinium; P=placebo

\* The preferred term "COPD" refers to COPD exacerbation.

The overall percentage of patients experiencing at least one TEAE was somewhat higher, across all treatment groups (including placebo), for female patients. Females treated with aclidinium (in either the 200 µg or 400 µg treatment arm, or in both aclidinium treatment arms) had higher percentages for all the individual TEAEs reported in ≥ 2% of patients.

Of the thirteen on-treatment deaths reported across the BID program, nine occurred in males, and four in females. This imbalance in death between the genders is of unclear significance; interpretation is limited by the small number of deaths overall.

### **RACE**

The ISS includes a subgroup analysis of TEAEs based on race (Caucasian vs. Non-Caucasian) for the BID Group 1A trials, however, this analysis is limited by a small sample size for Non-Caucasians (n=125) and is not discussed in this review.

### 7.5.4 Drug-Disease Interactions

#### **COPD SEVERITY**

The ISS includes a subgroup analysis of TEAEs based on COPD severity (mild/moderate vs. severe/very severe) for the BID Group 1A trials. The results of the analysis are provided in Table 90.

**Table 90. Treatment-Emergent Adverse Events by Preferred Term in ≥ 2% Patients in Any Treatment Group, Stratified COPD Disease Severity: BID Placebo-Controlled Trials, (BID Group 1A)**

Preferred Term, n (%)	Mild/Moderate			Severe/Very Severe		
	P N=404	A 200 µg N=385	A 400 µg N=381	P N=233	A 200 µg N=253	A 400 µg N=249

Patients with any TEAE	214 (53.0)	193 (50.1)	191 (50.1)	127 (54.5)	123 (48.6)	126 (50.6)
COPD*	56 (13.9)	40 (10.4)	38 (10.0)	44 (18.9)	36 (14.2)	37 (14.9)
Headache	17 (4.2)	29 (7.5)	30 (7.9)	15 (6.4)	14 (5.5)	12 (4.8)
Nasopharyngitis	15 (3.7)	25 (6.5)	21 (5.5)	9 (3.9)	14 (5.5)	14 (5.6)
Cough	8 (2.0)	11 (2.9)	12 (3.1)	6 (2.6)	6 (2.4)	7 (2.8)
Diarrhea	5 (1.2)	7 (1.8)	12 (3.1)	4 (1.7)	5 (2.0)	4 (1.6)
Hypertension	7 (1.7)	4 (1.0)	5 (1.3)	9 (3.9)	4 (1.6)	5 (2.0)
Back pain	6 (1.5)	12 (3.1)	7 (1.8)	6 (2.6)	6 (2.4)	1 (0.4)
Bronchitis	10 (2.5)	2 (0.5)	5 (1.3)	3 (1.3)	3 (1.2)	2 (0.8)

Source: Section 5.3.5.3.28, pg. 156 (Table 5.1.7.1-1)

Key: A=acridinium; P=placebo

\* The preferred term "COPD" refers to COPD exacerbation.

The overall percentage of patients experiencing at least one TEAE was similar for patients with mild/moderate COPD as compared to severe/very severe COPD. The only individual TEAE reported more often for patients with severe/very severe disease was COPD exacerbation, which likely reflects the underlying disease process.

### RENAL DYSFUNCTION

One single-dose (400 µg), open-label, PK and safety trial in the acridinium development program included patients with renal dysfunction. Trial M/34273/08 evaluated acridinium 400 µg in 18 patients with renal insufficiency (mild, moderate, and severe), as well as in 6 subjects with normal renal function. The frequency of any TEAE, by degree of renal impairment, is provided in Table 91.

**Table 91. Overall Frequency of TEAEs, by degree of Renal Impairment: Trial M/34273/08**

	Normal Renal function N=6	Mild Renal Insufficiency N=6	Moderate Renal Insufficiency N=6	Severe Renal Insufficiency N=6
Patients with any TEAE, n (%)	3 (50.0%)	2 (33.3%)	1 (16.7%)	1 (16.7%)

Source: Section 5.3.5.3.28, pg. 145

There is no apparent association between the degree of renal impairment and the frequency of TEAEs, however, the ability to draw conclusions is limited by the small sample size. The proposed product label states that "no clinically significant differences

in acridinium pharmacokinetics were noted” based on renal function, and that dose adjustment is not needed for this population.

### HEPATIC DYSFUNCTION

The application notes that hepatic metabolism plays a minor role in the clearance of acridinium, and so specific evaluations of the impact of hepatic dysfunction on the safety and pharmacokinetics of the proposed product were not performed. This approach appears to be reasonable.

### 7.5.5 Drug-Drug Interactions

The proposed product label indicates that formal drug interaction studies were not performed, given the low likelihood that acridinium would either alter the pharmacokinetics of a co-administered drug or have its pharmacokinetics altered by a co-administered drug, given its main route of metabolism (hydrolysis by esterases).

The Applicant conducted an analysis of TEAEs stratified by the use of concomitant medications (short-acting  $\beta$ -agonists, xanthines, ACE inhibitors, non-steroidal anti-inflammatory rheumatology products, anti-thrombotic agents, drugs for peptic ulcer disease/GERD, lipid modifying agents, inhaled adrenergic agents, and other inhaled drugs for obstructive airway disease) for the BID Group 1A trials, which is summarized in Table 92.

**Table 92. TEAEs, stratified by concomitant medication use: BID Placebo-Controlled Trials, (BID Group 1A)**

Patients with any TEAE	Placebo N=641		Acridinium 200 $\mu$ g N=644		Acridinium 400 $\mu$ g N=636	
	CM No N1 n (%)	CM Yes N1 n (%)	CM No N1 n (%)	CM Yes N1 n (%)	CM No N1 n (%)	CM Yes N1 n (%)
Short-acting $\beta$ -agonists	545 295 (54.1)	96 49 (51.0)	544 272 (50.0)	100 49 (49.0)	536 269 (50.0)	100 50 (50.0)
Xanthines	579 307 (53.0)	62 37 (59.7)	575 289 (50.3)	69 32 (46.4)	577 286 (49.6)	59 33 (55.9)
ACE inhibitors	491 260 (53.0)	150 84 (56.0)	503 256 (50.9)	141 65 (46.1)	485 234 (48.2)	151 85 (56.3)

Anti-inflammatory/ anti-rheumatic drugs, nonsteroidal	500 234 (46.8)	141 110 (78.0)	502 212 (42.2)	142 109 (76.8)	505 238 (47.1)	131 81 (61.8)
Antithrombotic agents	459 232 (50.5)	182 112 (61.5)	465 230 (49.5)	179 91 (50.8)	447 214 (47.9)	189 105 (55.6)
Drugs for peptic ulcer disease and GERD	485 251 (51.8)	156 93 (59.6)	521 258 (49.5)	123 63 (51.2)	507 237 (46.7)	129 82 (63.6)
Lipid modifying agents	483 222 (50.7)	203 122 (60.1)	454 229 (50.4)	190 92 (48.4)	446 224 (50.2)	190 95 (50.0)
Other inhaled drugs for obstructive airways diseases	341 174 (51.0)	300 170 (56.7)	358 176 (49.2)	286 145 (50.7)	359 172 (47.9)	277 147 (53.1)
Inhaled adrenergic drugs	493 262 (53.1)	148 82 (55.4)	494 244 (49.9)	150 77 (51.3)	492 249 (50.6)	144 70 (48.6)

Source: Section 5.3.5.3.28, pg. 164 (Table 5.3.3.1-1)

Key: ACE=angiotensin-converting enzyme; CM=concomitant medication; GERD=gastro-esophageal reflux

In most cases, the frequency of TEAEs was higher for patients in the acridinium 400 µg treatment arm who received a concomitant medication compared to those not receiving concomitant treatment. A similar pattern was seen for patients receiving placebo, but not for patients treated with acridinium 200 µg. The similarity to placebo is reassuring.

## 7.6 Additional Safety Evaluations

### 7.6.1 Human Carcinogenicity

A summary of TEAES reported for the System Organ Class (SOC), “Neoplasms, benign, malignant and unspecified” is provided in Table 93 for the BID Group 1A trials and in Table 94 for the BID Group 1B trials.

**Table 93. TEAEs reported for the System Organ Class, “Neoplasms, benign, malignant and unspecified”: BID Placebo-Controlled Trials, (BID Group 1A)**

	Placebo N=641	Aclidinium 200 µg N=644	Aclidinium 400 µg N=636
<b>Total for SOC, n (%)</b>	5 (0.8)	8 (1.2)	4 (0.6)
<b>Preferred Term, n (%)</b>			
Pancreatic neuroendocrine tumor	0	1 (0.2)	0
Laryngeal cancer	1 (0.2)	0	0
Lip neoplasm	0	0	1 (0.2)
Metastases to CNS	0	0	1 (0.2)
Mycosis fungoides	0	1 (0.2)	1 (0.2)
Lung adenocarcinoma	0	2 (0.3)	0
Benign lung neoplasm	1 (0.2)	0	0
Lung neoplasm	0	2 (0.3)	0
Lung cancer metastatic	0	0	1 (0.2)
Melanocytic nevus	1 (0.2)	1 (0.2)	0
Skin cancer	0	1 (0.2)	1 (0.2)
Basal cell carcinoma	2 (0.3)	0	0

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 444-446 (Table 4.1.1)

n=total number of patients in the category

Key: CNS=central nervous system

**Table 94. TEAEs reported for the System Organ Class, “Neoplasms, benign, malignant and unspecified”: Long-Term Safety Trials, Twice-Daily Program (BID Group 1B)**

	Aclidinium 200 µg N=568	Aclidinium 400 µg N=1005
<b>Total for SOC, n (%)</b>	16 (2.8)	15 (1.5)
<b>Preferred Term, n (%)</b>		
Adrenal adenoma	0	1 (0.1)
Bladder cancer	0	2 (0.2)
Breast cancer	1 (0.2)	1 (0.1)
Breast cancer stage II	0	1 (0.1)
Laryngeal cancer	0	1 (0.1)
Metastases to CNS	0	1 (0.1)
Metastases to liver	0	1 (0.1)
Metastases to mediastinum	0	1 (0.1)
Squamous cell carcinoma	1 (0.2)	1 (0.1)
Lung adenocarcinoma	2 (0.4)	0
Lung squamous cell carcinoma stage unspecified	1 (0.2)	0
Non-small cell lung cancer	1 (0.2)	0
Prostate cancer	1 (0.2)	0
Lung neoplasm	2 (0.4)	1 (0.1)
Lung cancer metastatic	0	1 (0.1)
Lung neoplasm malignant	1 (0.2)	1 (0.1)
Throat cancer	0	1 (0.1)
Small cell lung cancer stage	1 (0.2)	0

unspecified		
Malignant melanoma	2 (0.4)	0
Acrochordon	1 (0.2)	0
Basal cell carcinoma	0	1 (0.1)
Skin cancer	0	1 (0.1)
Squamous cell carcinoma of skin	0	1 (0.1)
Benign neoplasm of thyroid gland	0	1 (0.1)
Transitional cell carcinoma	1 (0.2)	0
Bladder neoplasm	1 (0.2)	0

Source: Section 5.3.5.3.28 (ISS Volume 2), pg. 1519-1522 (Table 4.1.2)

n=total number of patients in the category

Note: These data are for the Applicant's "BID Group 1B" grouping of trials, which is comprised of both the long-term safety trials and their lead-in trials. It does not include data from the 120-day safety update.

Key: CNS=central nervous system

For both the BID Group 1A and BID Group 1B trials, the percentage of patients with events categorized under the "Neoplasms, benign, malignant and unspecified" SOC was greater for the acridinium 200 µg treatment group as compared to the other treatment groups. The higher percentage observed for the 200 µg treatment group, compared to the 400 µg treatment group, suggests against a dose response.

The number of most individual malignancies was low, without any apparent pattern of relationship to treatment. When lung-related malignancies are specifically examined, the pattern is similar to that for the overall SOC: the number of patients with events is highest for the acridinium 200 µg treatment group for both the BID Group 1A (n=1, 4, and 1 for placebo, acridinium 200 µg, and acridinium 400 µg, respectively) and BID Group 1B (n=8, and 3 for acridinium 200 µg, and acridinium 400 µg, respectively) trials. While the reason for the excess of lung-related malignancies in the acridinium 200 µg treatment group is unclear, the pattern of events again suggests against a dose response. In addition, the Applicant conducted two 2-year non-clinical carcinogenicity studies which were negative for neoplastic findings in mice and rats.

### 7.6.2 Human Reproduction and Pregnancy Data

No pregnancies were reported for the BID program; a single pregnancy was reported for a patient treated with placebo in the QD program. The proposed product label categorizes the product as Pregnancy Category C.

### 7.6.3 Pediatrics and Assessment of Effects on Growth

No trials of acridinium have been conducted for the pediatric population. The Applicant requests a waiver of pediatric studies, from birth to 17 years of age, providing the rationale that COPD is a disease exclusive to the adult population. Both the Division and the Pediatric Review Committee (PeRC) find the justification for the waiver to be acceptable.

#### 7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

Single doses of acclidinium up to 6000 µg were evaluated in Trial M/34273/01<sup>54</sup> in healthy males. Repeat doses of acclidinium up to 800 µg twice daily were evaluated in healthy adults in Trial LAS-PK-12. There were no SAEs or deaths reported for either trial.

The Applicant assesses that the drug abuse potential of acclidinium is low, due to a lack of any structural or pharmacologic similarities between the proposed product and any drug known to cause abuse or dependence. No trials specifically evaluating the potential for abuse, withdrawal, or rebound with acclidinium were conducted.

### 7.7 Additional Submissions / Safety Issues

The Applicant provided a 120-Day Safety Update on October 21, 2011. This additional submission included safety information from the long-term safety trials LAS-MD-36 and LAS-MD-38 Part B, which had been ongoing at the time the original NDA was submitted and were completed in the interim. Review of the relevant data from the 120-Day Safety Update is incorporated throughout Section 7. Other notable clinical submissions were provided by the Applicant on December 12, 2011 (response to the Division's December 5, 2011, Information Request asking for an alternative pooling of safety data), January 6, 2012 (response to the Division's January 4, 2012, IR asking for clarification of the data for deaths and a correction of errors found in the December 12, 2011, submission; included the results of a second adjudication of death), February 10, 2012 (response to the Division's February 6, 2012, Information Request asking for clarification of discrepancies between the presentation of data in the Applicant's Advisory Committee Briefing Document and in the NDA submission), February 13, 2012 (brief summary of a proposed phase 4 trial), and April 9, 2012 (draft protocol synopsis of the proposed phase 4 trial).

In addition, on March 15, 2012, the Applicant provided the Division with a submission correcting the SGRQ data for Trial M/34273/34. This submission resulted in an extension of the user fee goal date by three months to July 23, 2012, as described in Section 2.6.

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<sup>54</sup> This trial used a different device (Cyclohaler inhaler) from that proposed for the to-be-marketed product (Almirall inhaler).

## **8 Postmarket Experience**

There has been no postmarket experience with Tudorza Pressair (aclidinium bromide).

## 9 Appendices

### 9.1 Literature Review/References

The application included a listing of references but no systematic literature review.

A PubMed search performed by this Reviewer [search term: acridinium; limits: humans, clinical trial, meta-analysis, randomized controlled trial, English] was conducted (January 11, 2012) yielded 12 references. A brief review of these reports was performed. No new safety signals were identified from these reports.

### 9.2 Labeling Recommendations

A formal review of the proposed trade name Tudorza Pressair by DMEPA concluded that this name is acceptable.

At the time of this review, labeling discussions are pending. Key revisions to the Prescribing Information recommended by the clinical review team are described below:

#### Section 4, Contraindications

- Removal of the (b) (4), as no cases have yet been observed.

#### Section 6, Adverse Reactions

- Subsection 6.1, Clinical Trials Experience
  - Reorganization of the data into two sections: *3-Month to 6-Month Trials* and *Long-term Safety Trials*; the Sponsor will be asked to provide a summary of the safety data for the long-term safety trials.
  - Revision of Table 1: Adverse Reactions, to include all reactions that occurred with a frequency of  $\geq 3\%$  where the frequency in the Tudorza Pressair group exceeded placebo; the original label stipulates that the frequency must exceed placebo by (b) (4).
  - Addition of the terms “diabetes mellitus,” “cardiac failure,” and “cardio-respiratory arrest,” to the list of adverse reactions observed with an incidence of  $<1\%$ .

#### Section 7, Drug Interactions

- Subsection 7.2, Anticholinergics

- Revision of this subsection to make it consistent with the Spiriva HandiHaler (tiotropium bromide) Prescribing Information (PI).

#### Section 12, Clinical Pharmacology

- Subsection 12.2, Pharmacodynamics
  - Deletion of the data from Trial M/34273/29.

#### Section 14, Clinical Studies

- Subsection 14.1, Chronic Obstructive Pulmonary Disease (COPD)
  - Addition of a paragraph on dose selection describing the results from Trial M/34273/29.
  - Deletion of references to the (b) (4)
  - Deletion of the results for (b) (4)
  - Deletion of results for the (b) (4)
  - Deletion of the subsection titled (b) (4)

### 9.3 Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) Meeting was held on February 23, 2012, as aclidinium is a new molecular entity that is unapproved in the United States for any indication. The goal of this meeting was to discuss whether the totality of the data supports the efficacy and safety of aclidinium 400 µg BID for the proposed indication, with a particular focus on the adequacy of the safety database to address safety concerns associated with anticholinergic agents as a drug class. The Applicant presented a summary of medical need, data regarding dose-finding, efficacy, and safety, and concluded with a discussion of risk/benefit and a clinical perspective. The FDA presented an overview of the clinical program, efficacy considerations, safety considerations, and a framework for evaluating risk/benefit.

Five questions (2 Discussion and 3 Voting) were posed to the Committee. A tabulation of votes is provided in Table 95, and a summary of the panel's discussion (in italics) follows below.

**Table 95. Questions and voting results for February 23, 2012, Pulmonary-Allergy Drugs Advisory Committee Meeting**

QUESTIONS	Votes
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	Yes	No	Abstain
1. Discuss the efficacy data for aclidinium considering the following <ul style="list-style-type: none"> <li>The bronchodilatory effect of aclidinium</li> <li>The effect of aclidinium on other efficacy endpoints</li> </ul>	Discussion		
2. Do the efficacy data provide substantial evidence of a clinically meaningful benefit for aclidinium 400 mcg twice daily in the maintenance treatment of bronchospasm associated with Chronic Pulmonary Disease (COPD)? <ul style="list-style-type: none"> <li>If not, what further data should be obtained?</li> </ul>	14	0	0
3. Discuss the overall safety profile of aclidinium considering the following <ul style="list-style-type: none"> <li>The size of the safety database</li> <li>The duration of exposure</li> </ul>	Discussion		
4. Has the safety of aclidinium been adequately assessed for the proposed indication? <ul style="list-style-type: none"> <li>If not, what further data should be obtained?</li> </ul>	10	3	1
5. Do the efficacy and safety data provide substantial evidence to support approval of aclidinium 400 mcg twice daily for the maintenance treatment of bronchospasm associated with COPD?	12	2	0

**Questions to the Committee:**

- (DISCUSSION)** Discuss the efficacy data for aclidinium considering the following
  - The bronchodilatory effect of aclidinium
  - The effect of aclidinium on other efficacy endpoints

*A question was raised as whether a 6 minute walk test could be used as a patient centered measurement. A question was also raised about what would be considered a minimum clinically relevant difference in terms of bronchodilatory effect.*

- (VOTING)** Do the efficacy data provide substantial evidence of a clinically meaningful benefit for aclidinium 400 mcg twice daily in the maintenance treatment of bronchospasm associated with Chronic Obstructive Pulmonary Disease (COPD)?
  - If not, what further data should be obtained?

YES: 14

NO: 0

ABSTAIN: 0

*Overall, the committee's view was that the Applicant's data for the primary endpoint of trough forced expiratory volume in one second (FEV1) demonstrated statistical significance, and that these results were clinically meaningful, or at least of similar magnitude compared to previous COPD development programs. One member noted that appropriate dose-ranging had been conducted. Others commented that the demonstration of an effect at both of the doses evaluated was reassuring, as was the lack of evidence for tachyphylaxis. Comments were made that the results for other measures of efficacy (e.g., the St. George's Respiratory Questionnaire [SGRQ] and COPD exacerbations), while generally not statistically significant, were nonetheless trending in a direction to support the results for the primary endpoint. It was noted that the*

*clinical trials were not powered for these additional endpoints. It was recommended that the Applicant conduct further evaluation of the potential effect of aclidinium on COPD exacerbations, and it was noted that future trials may benefit from the inclusion of a more severe COPD population in order to optimize the ability to detect an effect. Several comments were made regarding the limitations of FEV1-based endpoints and the importance of evaluating patient-centered outcomes.*

3. **(DISCUSSION)** Discuss the overall safety profile of aclidinium considering the following
- The size of the safety database
  - The duration of exposure

*It was noted that while the size of the safety database meets International Conference on Harmonization (ICH) recommendations, a larger long-term safety database would be preferable. Opinions on the duration of exposure needed were mixed, with some members commenting that long-term data is less critical given the availability of long-term safety data for other members of the same drug class, while others highlighted the need for data over an adequate length of time (approximately 1 year) in order to allow for the evaluation of uncommon events. One member commented that the cardiovascular events were the most concerning safety issue, but that their evaluation was limited by the exclusion of patients with significant cardiac disease as well as the incomplete roll-over of patients from the lead-in trials to the extension trials. One member noted the need to account for smoking as a potential confounder of long-term safety data.*

4. **(VOTING)** Has the safety of aclidinium been adequately assessed for the proposed indication?
- *If not, what further data should be obtained?*

YES: 10

NO: 3

ABSTAIN: 1

*Those who abstained felt that the data presented met the standard.*

*Overall, those who voted “yes” felt that the safety had been adequately assessed, adding that the size of the safety database met a minimum standard, that prior experience with this drug class was reassuring, and that the safety profile for aclidinium bromide was consistent with that of tiotropium bromide. A number of members described that their “yes” vote was accompanied by some degree of reluctance. Members commented that additional trials were needed to further evaluate the safety profile of aclidinium bromide, and in particular, the risk of cardiovascular events.*

*Overall, those who voted “no” felt that the safety was not adequately assessed, citing concerns about the size, duration, and composition of the safety database which excluded patients with significant cardiovascular disease. A comment was also made that if the product had a unique*

*benefit over existing therapy, then the safety data might be viewed as adequate; however, since it does not, it was reasonable to require further study prior to approval.*

5. **(VOTING)** Do the efficacy and safety data provide substantial evidence to support approval of aclidinium 400 mcg twice daily for the maintenance treatment of bronchospasm associated with COPD?
- *If not, what further data should be obtained?*

YES: 12

NO: 2

ABSTAIN: 0

*Overall, those who voted “yes” felt that the efficacy and safety data provided evidence to support approval. Members expressed some concerns, however, with one stating that the risk/benefit ratio, while positive, was not strongly so. Another commented that aclidinium bromide ought not to be incorrectly perceived as being the same as tiotropium bromide with regard to safety. Another stated that they would not choose to treat a patient with cardiac disease with aclidinium bromide at this point in time. Multiple members expressed the need for a large phase IV trial of simple design to further evaluate safety, with a focus on cardiovascular adverse events.*

*Overall, those who voted “no” felt that the efficacy and safety data did not provide evidence to support approval. It was recommended that an additional trial be conducted to further evaluate the safety of aclidinium bromide as soon as possible, and that this trial include patients with significant cardiovascular disease.*

*Committee members provided a number of additional recommendations regarding the design of a post-marketing trial. It was recommended that the duration be not less than 12 months, with 24 months or longer being preferable, and that the number of exclusions be kept to a minimum. Multiple members commented that the inclusion of an active comparator would be informative. While some advocated for a three-arm trial (aclidinium, placebo, and active comparator), one member expressed concern about the inclusion of a placebo arm given the existence of products with established efficacy for COPD. Additional comments included a statement advocating the study of patient-centered outcomes including exercise tolerance, an evaluation of the factors associated with an individual’s response to the drug, and the study of potential drug-drug interactions.*

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER R PIPPINS  
05/25/2012

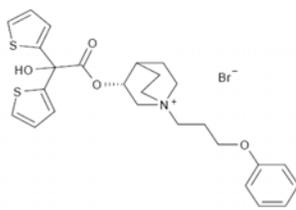
SUSAN L LIMB  
05/28/2012

<b>MEDICAL OFFICER REVIEW</b>			
<b>Division Of Pulmonary and Allergy Drug Products (HFD-570)</b>			
<b>APPLICANT/SPONSOR:</b>	Forest Research Institute, Inc.	<b>PROPOSED</b>	(b) (4) (drug substance)
<b>MEDICAL OFFICER:</b>	Jennifer Rodriguez Pippins, MD, MPH	<b>PROPRIETARY NAME:</b>	Pressair™ (device)
<b>TEAM LEADER:</b>	Susan Limb, MD	<b>USAN NAME:</b>	Acclidinium bromide
<b>DATE:</b>	August 16, 2011	<b>ROUTE:</b>	Oral inhalation
<b>SUBMISSIONS REVIEWED IN THIS DOCUMENT</b>			
<u>Document Date</u>	<u>CDER Stamp Date</u>	<u>Submission</u>	<u>Comments</u>
June 23, 2011	June 23, 2011	NDA 202-450 SD# 1, eCTD# 0	Original NDA; electronic
<b><u>REVIEW SUMMARY:</u></b>			
<p>Forest Research Institute, Inc. (Forest), has submitted a 505(b)(1) New Drug Application (NDA) for acclidinium bromide, a NME. The proposed indication is “the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.” The proposed dose is one oral inhalation of 400 mcg, twice daily.</p> <p>Notable regulatory history includes a pre-NDA meeting (March 3, 2009) during which FDA informed the Applicant that (b) (4). FDA recommended that the Applicant conduct further dose exploration to establish both the nominal dose and dosing frequency. In response to this, the Applicant conducted two Phase 2 dose-ranging trials (M/34273/23 and M/34273/29). The BID clinical development program also includes three phase 3 efficacy and safety trials (M/34273/33, M/34273/34, and M/34273/38 Part A), and three long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B).</p> <p>On initial review, it appears that the results for the primary endpoint, change from baseline in morning predose (trough) FEV1 assessed at 12 weeks, are statistically significant for each of the three efficacy and safety trials; however, the effect size for Trial M/34273/38 Part A was notably smaller than that for Trials M/34273/33 and M/34273/34. The adequacy of the totality of the data will be a review issue.</p> <p>The primary safety database for acclidinium bromide BID includes a total of 2677 individuals in 8 trials. The NDA also provides additional supportive safety information from the QD program.</p> <p>Across the three efficacy and safety trials, the rate of any TEAE, AE leading to withdrawal, and SAE is lower for acclidinium 400 mcg compared to placebo. Overall, there were 6 deaths across these three trials; 2 deaths in the placebo group, one death in the acclidinium 200 mcg group, and 3 deaths in the acclidinium 400 mcg group. The case reports for all deaths will be examined as part of the NDA review.</p> <p>Two of the long-term safety trials are still ongoing. For the one completed trial (LAS-MD-36), the limited sample size and absence of a placebo group limit the interpretability of results. The NDA also includes an analysis of adverse events of interest, including major adverse cardiac events (MACE), as requested by FDA. The overall low number of MACE events makes it difficult to draw conclusions about these data. It is noted that while the MACE score is lower for the acclidinium treatment groups as compared to placebo, there were two cardiovascular deaths across the acclidinium treatment groups, while there were no cardiovascular deaths in the placebo group. The cardiovascular safety profile of the proposed product will be a review issue.</p> <p>On its face, the clinical section organized in a manner to allow substantive review to begin. From a clinical perspective, the NDA is fileable.</p>			
<b>RECOMMENDED REGULATORY ACTION:</b>			
<b>FILEABLE</b> <input checked="" type="checkbox"/>		<b>NOT FILEABLE</b> <input type="checkbox"/>	

## 1. GENERAL INFORMATION

### 1.1 Active Drug

Generic name:	Aclidinium bromide
Chemical name:	1-Azoniabicyclo[2.2.2]octane,3-[(hydroxydi-2-thienylacetyl)oxy]-1-(3-phenoxypropyl)-, bromide, (3 <i>R</i> )-
Proposed Trade name:	(b) (4)
Pharmacologic category:	Selective M3 muscarinic antagonist
Route of administration:	Oral inhalation
Proposed dose:	400 mcg BID
Molecular Formula:	C <sub>26</sub> H <sub>30</sub> NO <sub>4</sub> S <sub>2</sub> Br
Molecular Weight:	564.56
Molecular Structure:	



### 1.2 Background

Forest Research Institute, Inc. (Forest), has submitted a 505(b)(1) New Drug Application (NDA) for acclidinium bromide, a new molecular entity. The proposed indication is “the long-term, maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema.” The proposed dose is one oral inhalation of 400 mcg, twice daily. The submission is electronic.

### 1.3 Regulatory History

A timeline of regulatory proceedings is included below:

- September 30, 2003: Type B Pre-IND Meeting
- November 21, 2003: IND 68,653 submitted
- April 26, 2005: Type B End-of-Phase 2 Meeting
- March 3, 2009: Type B Pre-NDA Meeting (Clinical, Nonclinical),  
Once Daily Dosing Program

FDA informed Forest that while Trial M/34273/30 and Trial M/3473/31 demonstrated statistically significant results for the primary endpoint of trough FEV1 at 12 weeks, the treatment

difference of approximately 60 cc was of uncertain clinical significance. The Agency stated that the dose and dosing interval for the proposed product had not been adequately evaluated, and recommended exploration of higher doses and more frequent dosing regimens.

- May 12, 2009: Type C CMC Teleconference
- January 18, 2011: Type B Pre-NDA CMC Meeting
- February 25, 2011: FDA provided preliminary comments for a Type B Pre-NDA Meeting (Clinical, Nonclinical), Twice Daily Dosing Program; Forest canceled meeting

FDA agreed that the data from Trials LAS-MD-33 and M/34273/34 supported the proposal of a 400 mcg BID dose.

## 2. CLINICAL DEVELOPMENT PROGRAM

The core development program conducted in support of acclidinium 400 mcg BID consists of two phase 2 dose-ranging trials (M/34273/23 and M/34273/29), three phase 3 efficacy and safety trials (M/34273/33, M/34273/34, and M/34273/38 Part A), and three long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B). A summary of the development program is provided in Table 1.

**Table 1. Clinical Development Program (Twice-daily program)**

Trial / Status	Design	Population	n	Treatment Arms	Duration	Key Objectives
<b>P2</b>						
M/34273/23 Completed	R, DB, PC, AC, CO	Moderate-to-severe COPD	30	A 400 mcg BID Tiotropium 18 mcg QD P	15 days	Dose-ranging
M/34273/29 Completed	R, DB, PC, AC, CO	Moderate-to-severe COPD	79	A 400 mcg BID A 200 mcg BID A 100 mcg BID Formoterol 12 mcg BID P	7 days	Dose-ranging
<b>P3</b>						
M/34273/33 Completed	R, DB, PC, PG	Moderate-to-severe COPD	561	A 400 mcg BID A 200 mcg BID P	12 weeks	Efficacy, Safety
M/34273/34 Completed	R, DB, PC, PG	Moderate-to-severe COPD	828	A 400 mcg BID A 200 mcg BID P	24 weeks	Efficacy, Safety
M/34273/38 Part A Completed	R, DB, PC, PG	Moderate-to-severe COPD	544	A 400 mcg BID A 200 mcg BID P	12 weeks	Efficacy, Safety
LAS-MD-35	R, DB, PG	Moderate-to-severe COPD	605 <sup>1</sup>	A 400 mcg BID A 200 mcg BID	52 weeks	Long-term safety

<sup>1</sup> Trial is ongoing; 605 patients included in efficacy evaluation at time of data cutoff

Ongoing						
LAS-MD-36 (extension of LAS-MD-33)	R, DB, PG	Successful completers of LAS-MD-33	291	A 400 mcg BID A 200 mcg BID	52 weeks	Long-term safety
LAS-MD-38 Part B Ongoing (extension of LAS-MD-38 Part A)	R, single-arm, OL	Successful completers of LAS-MD-38 Part A	448 <sup>2</sup>	A 400 mcg BID	40 weeks	Long-term safety

Source: Section 2.7.3; Section 2.5, Table 4.1-1, pg. 23; Section 5.3.5.3.28, Table 1.1.1.1-2, pg. 34

### **Phase 2 Dose-Ranging Trials: M/34273/23 and M/34273/29**

In response to the FDA's feedback received at the March 3, 2009, pre-NDA meeting, the Applicant chose to conduct two additional trials (M/34273/23 and M/34273/29) to explore the dose and dosing interval of acclidinium bromide.

Trials M/34273/23 and M/34273/29 were each randomized, double-blind, placebo- and active-controlled. While the trials were similar in overall design, there were also notable differences, which are summarized in Table 2.

**Table 2. Design of the Phase 2 Dose-Ranging Trials: M/34273/23 and M/34273/29**

	M/34273/23	M/34273/29
Active Comparator	Tiotropium 18 mcg QD	Formoterol 12 mcg BID
Doses of Acclidinium Evaluated	400 mcg BID	400 mcg BID 200 mcg BID 100 mcg BID
Duration of Run-in Period	5-9 days	14 ± 3 days
Duration of Treatment Period	15 days	7 days
Washout Interval	9 days	5 days

Source: Section 2.7.3

The primary endpoint evaluated in both trials was change from baseline in normalized FEV1 area under the curve over the 12-hour period (FEV1 AUC<sub>0-12/12h</sub>) immediately after morning administration of treatment on the last day of the treatment period. Results for the primary endpoint are summarized in Table 3 and Figure 1.

**Table 3. Change from baseline in FEV1 AUC<sub>0-12/12h</sub>, Trial M/34273/23 and Trial M/34273/29**

	LS Mean	p-value
Trial M/34273/23		

<sup>2</sup> Trial is ongoing; 448 patients included in efficacy evaluation at time of data cutoff

(Day 15)		
A 400 mcg vs P	0.221	<0.0001
Tio vs P	0.244	<0.0001
A 400 mcg vs Tio	-0.023	0.572
Trial M/34273/29		
(Day 7)		
A 400 mcg vs P	0.208	<0.0001
A 200 mcg vs P	0.176	<0.0001
A 100 mcg vs P	0.154	<0.0001
F vs P	0.210	<0.0001

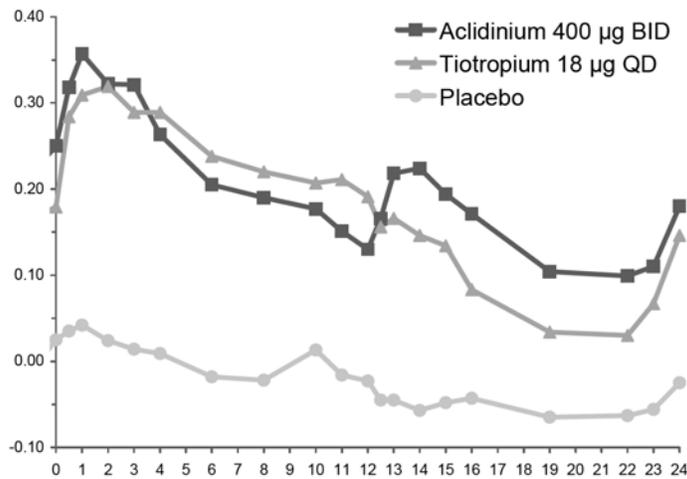
Key: A=acclidinium; F=formoterol 12 mcg BID; P=placebo; Tio=tiotropium 18 mcg QD

Note: p-values are from the Applicant’s ANCOVA analysis

Source: Section 2.7.3, Table 2.2.1-1, pg. 68, and Table 2.2.2-1, pg. 71

Figure 1. Adjusted mean change from baseline in FEV1 at each time point at the End of the Treatment Period, Trial M/34273/23 and Trial M/34273/29

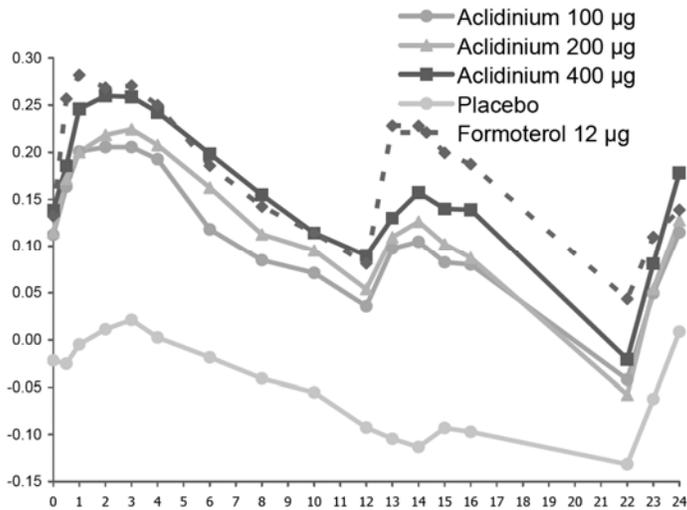
A. Trial M/34273/23 (Day 15)



Note: Based on the Applicant’s ANCOVA analysis.

Source: Source: Section 2.7.3, Figure 2.2.1-1, pg. 69

B. Trial M/34273/29 (Day 7)



Note: Based on the Applicant's ANCOVA analysis.

Source: Source: Section 2.7.3, Figure 2.2.2-1, pg. 73

Reviewer's Comment:

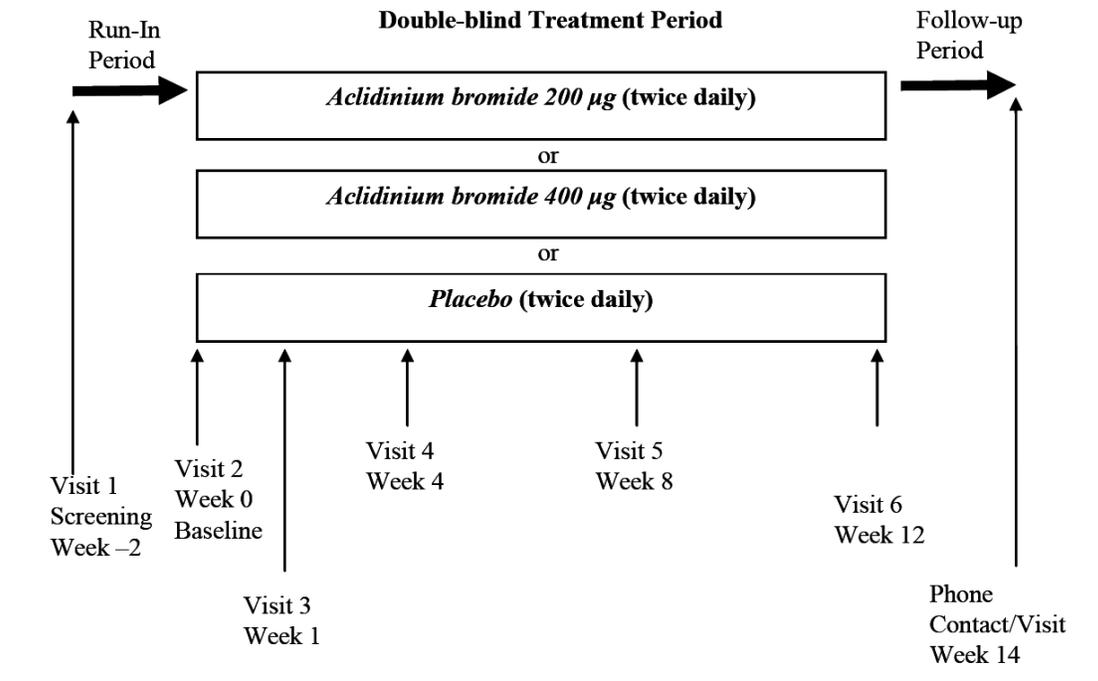
The data from Trial M/34273/23 and Trial M/34273/29 appear to support the proposed dose of acclidinium 400 mcg BID.

**Phase 3 Efficacy and Safety Trials: M/34273/33, M/34273/34, M/34273/38 Part A**

*General Study Design*

The three phase 3 efficacy and safety trials employed a randomized, placebo-controlled, parallel-group design. The trials were similar, each consisting of three periods: run-in, double-blind treatment, and follow-up. The main difference between trials M/34273/33 and M/34273/38 Part A as compared M/34273/34 was the length of the treatment period, which was 12 weeks for the former two trials and 24 weeks for the latter. While Trial M/34273/34 employed a longer treatment period, the primary efficacy endpoint was assessed at 12 weeks, consistent with the other two trials. A summary of the trial designs are provided in Figure 2 (Trial M/34273/33 and M/34273/38 Part A) and Table 4 (Trial M/34273/34).

**Figure 2. General Study Design: Trial M/34273/33 and M/34273/38 Part A**



**Table 4. General Study Design: Trial M/34273/34**

	Run-in	Double-blind treatment							Follow-up (FU)
		Randomisation							
		↓							
<b>Visit no.</b>	1	2	3	4	5	6	7	8	9
<b>Week</b>	-2	0	1	4	8	12	18	24	26
<b>Study day</b>	-14	1	7	29	57	85	127	169	+14
			+/-3	+/-3	+/-3	+/-3	+/-3	+/-3	+/-3

*Treatment arms*

The same three treatment arms were evaluated in each of the three pivotal efficacy and safety trials:

- Acridinium 200 mcg BID
- Acridinium 400 mcg BID
- Placebo

*Primary and Secondary Endpoints*

The primary endpoint for all three trials was the change from baseline in morning predose (trough) FEV1 assessed at 12 weeks.

A summary of secondary and additional variables is provided in Table 5.

**Table 5. Secondary and Additional Variables**

Variable	Trial		
	M/34273/33	M/34273/34	M/34273/38 Part A
Peak FEV1	X	X	X
FEV1 over 12 hours (substudy)	X	X	X
FVC	X	X	X
IC	X	X	X
COPD Exacerbations	X	X	X
SGRQ	X	X	X
Rescue Medication Use	X	X	X
BDI and TDI	X	X	X
Daily Sleep Diary	X		
COPD Night-Time Symptoms Questionnaire (modified Welte)	X		
Night-time and Morning Symptoms Questionnaire		X	
EQ-5D (Health-related QoL)		X	X
EXACT-P PRO		X	
Productivity		X	
COPD Resource Utilization Questionnaire			X

COPD exacerbations were defined as, “an increase in COPD symptoms (eg, dyspnea, cough, sputum volume, sputum purulence) during at least 2 consecutive days” and were classified as mild (self-managed with increased short-acting bronchodilator and/or ICS use), moderate (treated with antibiotics and/or systemic corticosteroids, but no hospitalization required), or severe (requiring overnight stay at hospital or emergency room).

#### Population

The population for each of the three efficacy and safety trials was comprised of adults with moderate-to-severe COPD. Inclusion and exclusion criteria are summarized in Tables 6 and 7.

**Table 6. Inclusion Criteria**

Variable	Trial		
	M/34273/33	M/34273/34	M/34273/38 Part A
<b>Inclusion Criteria</b>			
Male or female outpatients at least 40 years of age	X	X	X
Current or former cigarette smokers with a smoking history of at least 10 pack-years	X	X	X
Stable moderate-to-severe COPD and stable airway obstruction with FEV1/FVC <	X	X	X

70%			
Post-bronchodilator FEV1 ≥ 30% to < 80% of predicted	X	X	X
Able to perform reproducible pulmonary function tests	X	X	X
Females: At least 1 year postmenopausal, surgically sterile, or practicing a medically acceptable method of contraception WOCP: Negative serum βHCG and using either double-barrier contraception or barrier method plus spermicidal agent	X	X	X
Judged to be in otherwise good stable health based on medical history, PE, ECG, and laboratory data	X		X
Able to provide written informed consent	X	X	X

**Table 7. Exclusion Criteria**

Variable	Trial		
	M/34273/33	M/34273/34	M/34273/38 Part A
<b>Exclusion Criteria</b>			
Hospitalized for acute COPD exacerbations within 3 months prior to Visit 1	X	X	X
Any respiratory tract infection or COPD exacerbation in the 6 weeks prior to Visit 1	X	X	X
Clinically significant respiratory disease other than COPD	X	X	X
History or presence of asthma	X	X	X
Chronic use of oxygen therapy ≥ 15 hours a day	X	X	X
BMI ≥ 40 kg/m <sup>2</sup>	X	X	X
Participation in acute pulmonary rehabilitation program within the prior 6 months	X	X	X

Clinically significant cardiovascular conditions <sup>3</sup>	X	X	X
Uncontrolled HIV and/or active hepatitis infection	X	X	X
Clinically relevant abnormalities in laboratory tests, ECG (excluding QTc), PE, or VS (except for those related to COPD)	X	X	X
SBP ≥ 200 mmHg, DBP ≥ 120 mmHg, HR ≥ 105 bpm		X	
QTcB < 470 msec	X	X	X
History or drug or alcohol abuse within the prior 5 years	X	X	X
Physical or mental dysfunction, at the discretion of the Investigator	X	X	X
History of hypersensitivity to inhaled anticholinergics, sympathomimetic amines, or inhaled medication or any component thereof (including report of paradoxical bronchospasm) or history of acute urinary retention, symptomatic benign prostatic hyperplasia, bladder neck obstruction, or narrow-angle glaucoma	X	X	X
Inability to use DPI or pressurized MDI	X	X	X
Treatment with another investigational drug within 30 days or 6 half-lives (whichever is longer) prior to Visit 1	X	X	X
Prior treatment with acclidinium bromide	X	X	X
Pregnancy or lactation	X	X <sup>4</sup>	X
Current diagnosis of cancer (other than basal or squamous cell skin cancer)	X	X	X
Absence of a regular day/night, waking/sleeping cycle (eg, night-shift workers)	X	X	X
Concomitant medication use	X	X	X
Suspected poor compliance	X	X	X

<sup>3</sup> Clinically significant cardiovascular conditions included myocardial infarction during the prior 6 months, newly diagnosed arrhythmia during the prior 3 months, unstable angina, unstable arrhythmia, and/or class III or IV heart failure requiring hospitalization in the prior 12 months

<sup>4</sup> For trial M/34273/34 this was worded as an inclusion criteria, i.e., “non-pregnant, non-lactating females”

Employees or relatives of employees of study center or Applicant	X	X	X
Any other condition, at the discretion of the Investigator	X	X	X

**Safety**

Safety measures evaluated included vital signs, physical examinations, clinical laboratory tests, ECGs, and adverse events. In addition, Holter monitoring was conducted in a subset of patients.<sup>5</sup>

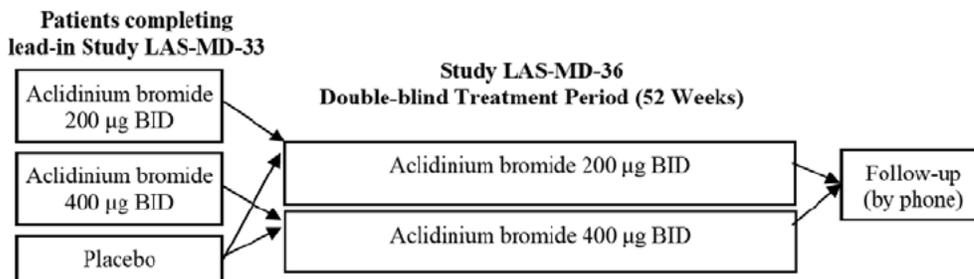
**Long-Term Safety Trials**

The clinical development program in support of acidinium 400 mcg BID includes three long-term safety trials, one of which has been completed (LAS-MD-36), and two of which are ongoing (LAS-MD-35, and LAS-MD-38 Part B). This review focuses on a presentation of the design and results of the completed trial.

*LAS-MD-36*

This long-term safety trial was a randomized, double-blind, parallel group extension trial enrolling patients who had completed Trial LAS-MD-33. There were two treatment arms: acidinium bromide 200 mcg and 400 mcg; patients already receiving active treatment in Trial LAS-MD-33 continued to receive the same treatment during Trial LAS-MD-36; patients receiving placebo in the lead-in trial were randomized (1:1) to receive either acidinium bromide 200 mcg or 400 mcg during the extension trial. The duration of treatment was 52 weeks. Figure 3 provides a schematic of the study design.

**Figure 3. General Study Design: Trial LAS-MD-36**



BID = twice daily.

The Trial included a total of seven visits: Visit 1 occurred at Week 0 (Enrollment), Visits 2-7 occurred at Weeks 1, 12, 24, 36, 48, and 52 (Double-blind Treatment Period). In addition, a follow-up phone contact was conducted two weeks after the completion of treatment.

<sup>5</sup> 24-hour, 12-lead Holter monitoring conducted before Visits 2 and 6 in a subset (30%) of patients at selected centers in each of the three efficacy and safety trials.

Safety assessments included VS, physical examinations, clinical laboratory tests, ECGs, and AEs. In addition to safety, efficacy assessments were also conducted. These included morning predose (trough) FEV1 (primary efficacy assessment), peak FEV1, rescue medication use, FVC, SGRQ, and the EuroQol QOL Questionnaire. A COPD Resource utilization questionnaire was also conducted.

**Reviewer's Comment:**

*The design of Trial LAS-MD-36 is limited by the absence of a placebo comparison arm. All adverse events will be attributed to acclidinium.*

### 3. OVERVIEW OF EFFICACY

This section provides a brief summary of key efficacy findings for the three efficacy and safety trials, M/34273/33, M/34273/34, and M/34273/38 Part A.

#### **Results for the Primary Endpoint**

Results for the primary endpoint, change from baseline in morning predose (trough) FEV1 assessed at 12 weeks are provided in Table 8 and Figure 4.

**Table 8. Change from baseline in morning predose (trough) FEV1 at Week 12, Intent-To-Treat Population**

Treatment Arm	n	Baseline	Change from baseline	Treatment difference from placebo	P-value vs. placebo <sup>6</sup>
<b>M/34273/33</b>					
Acclidinium 400 mcg	190	1.3316	0.1058	0.1318	<0.0001
Acclidinium 200 mcg	184	1.3583	0.0645	0.0905	0.0001
Placebo	185	1.3757	-0.0260	--	--
<b>M/34273/34</b>					
Acclidinium 400 mcg	269	1.508	0.058	0.105	<0.0001
Acclidinium 200 mcg	277	1.514	0.030	0.077	0.0001
Placebo	273	1.500	-0.047	--	--
<b>M/34273/38 Part A</b>					
Acclidinium 400 mcg	177	1.2492	0.0706	0.0800	0.0011
Acclidinium 200 mcg	182	1.3965	0.0450	0.0544	0.0238
Placebo	182	1.4593	-0.0094	--	--

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.1.1, pg. 481-2;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 14.4.1.1, pg. 417-8;

Section 5.3.5.1.3 (LAS-MD-CL34), Table 18, pg. 99

<sup>6</sup> Applicant's MMRM analysis for Trials M/34273/33 and M/34273/38 Part A, and ANCOVA analysis for M/34273/34

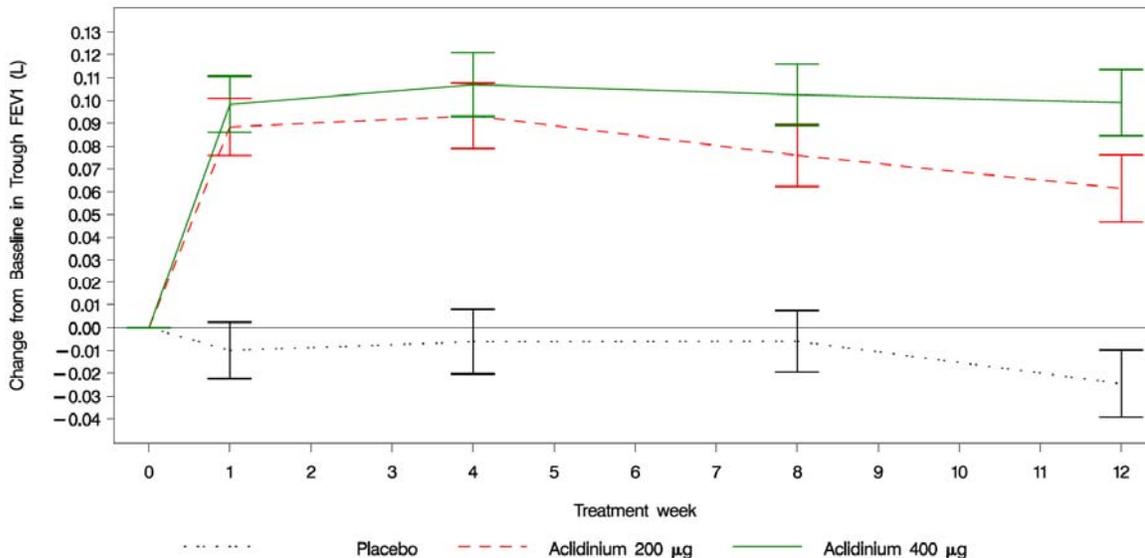
The treatment difference between acclidinium bromide and placebo at Week 24 in Trial M/34273/34 was 0.099 for the 200 mcg dose and 0.128 for the 400 mcg dose; both results were statistically significant at the  $p < 0.0001$  level.

Reviewer's Comment:

While the results of each of the three efficacy and safety trials are statistically significant, the effect size for the acclidinium 400 mcg treatment arm in Trial M/34273/38 Part A is notably smaller (54 mL) compared to that for Trial M/34273/33 and Trial M/34273/34 (132 and 105, respectively). The Applicant attributes this to an imbalance in patients' baseline characteristics including COPD severity. The totality of the efficacy data for the BID program will be reviewed, and the modest effect size of Trial M/34273/38 Part A will be a review issue.

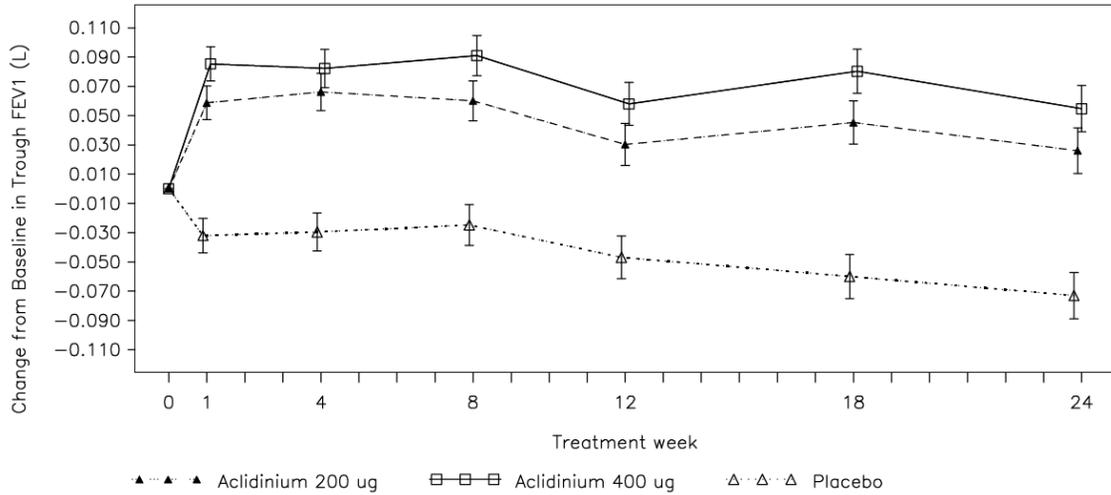
**Figure 4. Change from baseline in morning predose (trough) FEV1 at by Visit (LOCF) over Treatment Period: Least Square Mean (+/- SE), Intent-to-Treat Population**

**A. Trial M/34273/33**



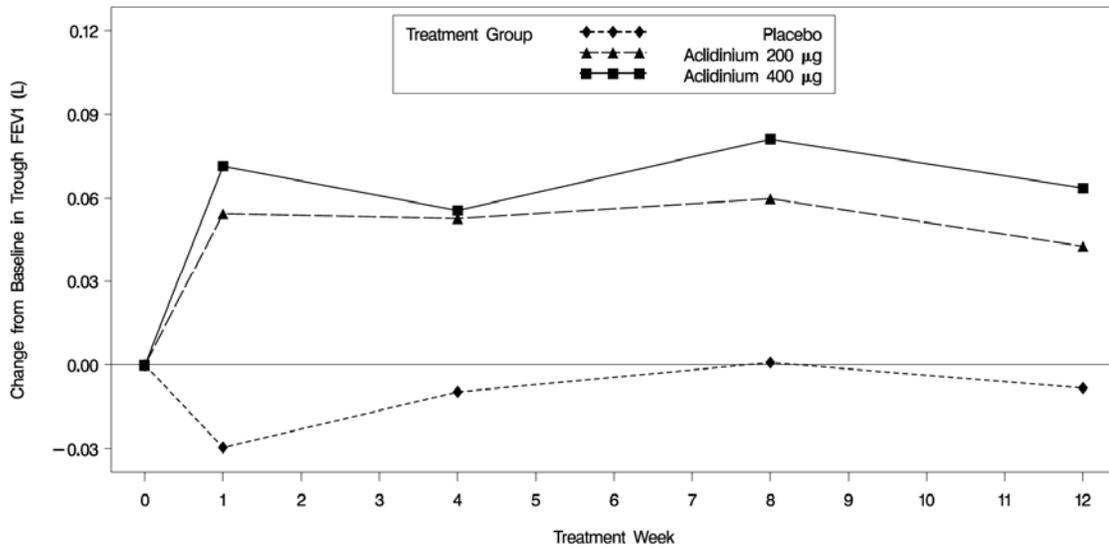
Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Figure 14.4.1.1, pg.483

**B. Trial M/34273/33**



Section 5.3.5.1.3 (LAS-MD-CL34), Figure 4.2, pg. 2771

**C. Trial M/34273/38 Part A**



Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Figure 14.4.1.1, pg. 419

Reviewer's Comment:

*At first glance, the treatment effect for acclidinium 400 mcg BID appears to persist across the duration of the treatment periods.*

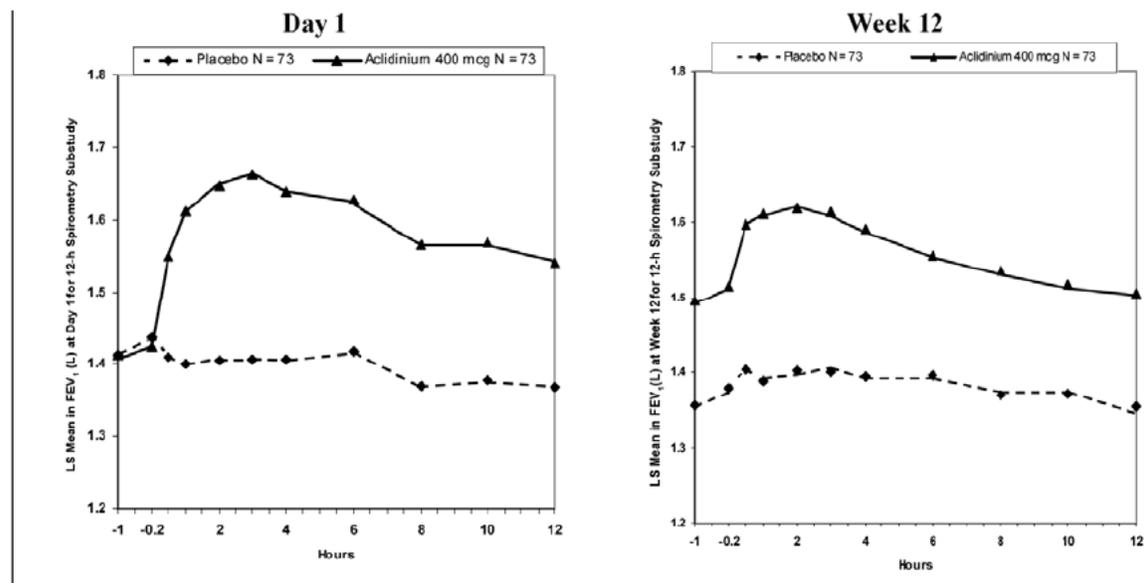
**Results for Selected Secondary Endpoints**

The three efficacy and safety trials evaluated a number of secondary and additional variables, as summarized in Table 5. For the purposes of this filing and planning review, a brief summary of the results for three such variables, FEV1 over 12 hours, COPD exacerbations, and SGRQ, are presented here.

*FEV1 over 12 hours*

The three trials each evaluated FEV1 over 12 hours in a subset of patients. Results for serial FEV1 (measured on Day 1 and Week 12) from Trial M/34273/33 are presented in Figure 5.

**Figure 5. Serial FEV1 over 12 hours, Trial M/34273/33**



Source: Section 1.14.1.2 Annotated Draft Labeling Text, pg. 13

Reviewer’s Comment:

*At first glance, the treatment effect of acclidinium 400 mcg appears to persist over a 12-hour period, both on Day 1 and at Week 12.*

*COPD Exacerbations*

The three trials assessed a number of different parameters related to COPD exacerbations, including: number of patients experiencing exacerbations (Table 9), time to first exacerbation, duration (Figure 6), duration of exacerbations (Table 10) and related withdrawals and hospitalizations (Table 11).

**Table 9. Number (%) of Patients Experiencing COPD Exacerbations During the Study, ITT Population**

Type of Exacerbation	Placebo	Acclidinium 200 mcg	Acclidinium 400 mcg
Trial M/34273/33 <sup>7</sup>			
	n=185	n=184	n=190

<sup>7</sup> For Trial M/34273/33 the Applicant defines COPD exacerbation as one occurring when the patient has been off systemic corticosteroids and antibiotics for at least 14 days. Exacerbations are those reported within the double-blind treatment period.

Any, n (%)	22 (11.9%)	16 (8.7)	12 (6.3)
Mild, n	6	5	1
Moderate, n	15	13	10
Severe, n	1	1	2
Moderate or Severe, n	16	13	11
<b>Trial M/34273/34</b>			
	n=273	n=277	n=269
Any, n (%)	56 (20.5)	44 (15.9)	38 (14.1)
Mild, n	14	9	6
Moderate, n	35	33	31
Severe, n	10	3	2
Moderate or Severe, n	44	36	33
<b>Trial M/34273/38 Part A<sup>8</sup></b>			
	n=182	n=182	n=177
Any, n (%)	19 (10.4)	14 (7.7)	19 (10.7)
Mild, n	0	3	3
Moderate, n	14	8	13
Severe, n	5	3	3
Moderate or Severe, n	19	11	16

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 11.4.1.3.5-1, pg. 164;

Section 5.3.5.1.3 (LAS-MD-CL34), Table 34, pg. 124;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 11.4.1.3.5-1, pg. 155

Reviewer's Comment:

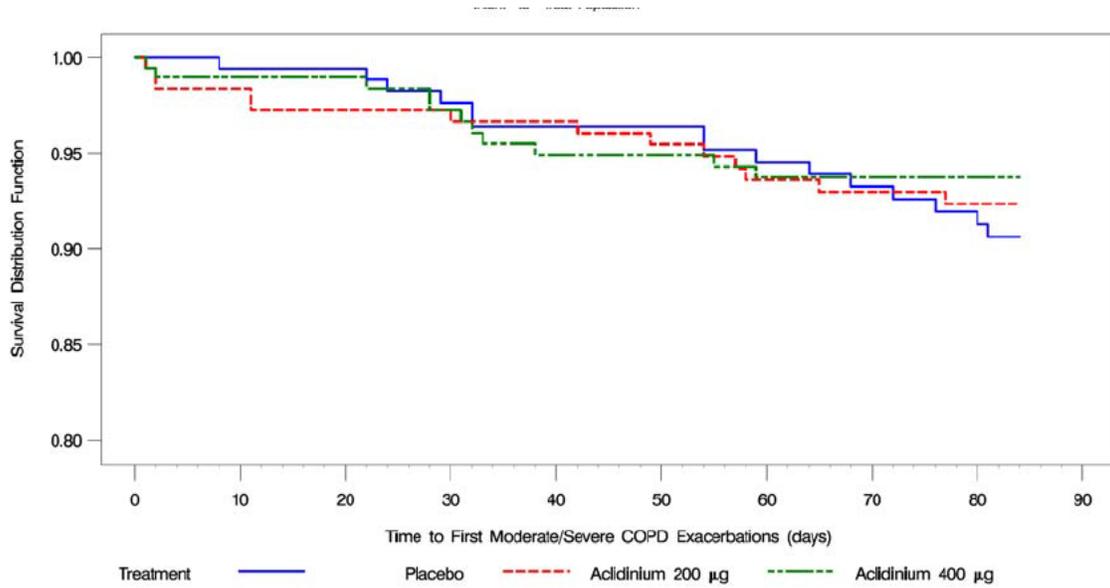
*At first glance, it appears that the percentage of patients experiencing a COPD exacerbation is smaller for the acclidinium 400 mcg bid treatment group as compared to placebo for Trials M/34273/33 and M/34273/34 but not for Trial M/34273/38 Part A.*

**Figure 6. Time to First Moderate/Severe COPD Exacerbation, ITT Population**

**A. Trial M/34273/33**

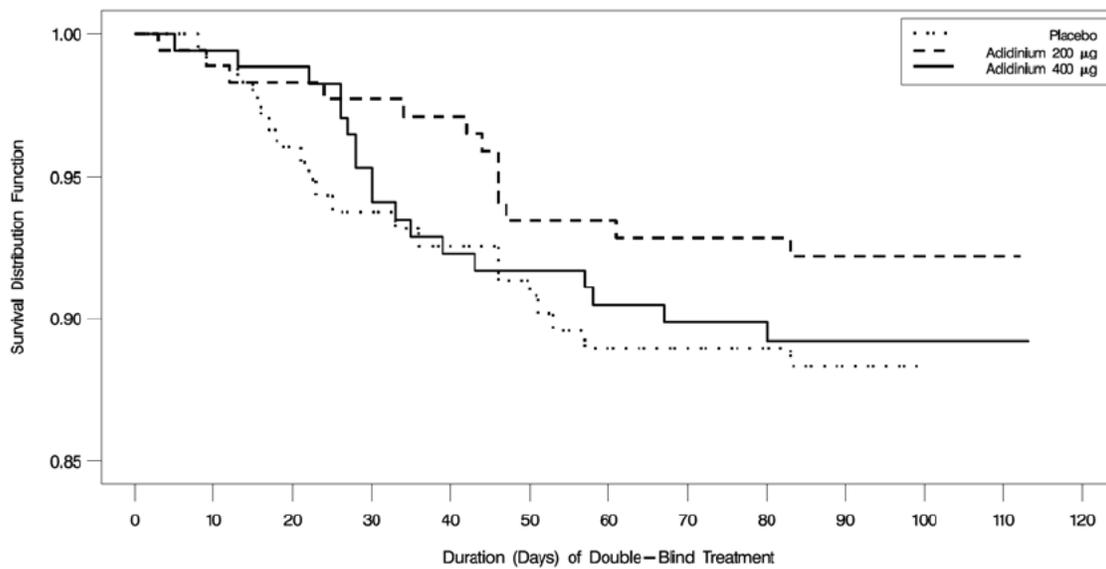
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<sup>8</sup> For Trial M/34273/38 Part A the Applicant defines COPD exacerbation as one occurring when the patient has been off systemic corticosteroids and antibiotics for at least 14 days. Exacerbations are those reported within the double-blind treatment period.



Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Figure 14.4.3.1, pg. 493

**B. Trial M/34273/38 Part A**



Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Figure 14.4.3.1, pg. 432

Table 10. Mean Duration (Days) of Exacerbations, ITT Population

	Placebo	Acclidinium 200 mcg	Acclidinium 400 mcg
<b>Trial M/34273/33</b>	n=185	n=184	n=190
	10.8	12.1	16.3
<b>Trial M/34273/34</b>	n=273	n=277	n=269
	14.9	13.2	11.7
<b>Trial M/34273/38 Part A</b>	n=182	n=182	n=177

	10.3	13.6	8.4
--	------	------	-----

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.3.47a, pg. 1013;

Section 5.3.5.1.3 (LAS-MD-CL34), Table 14.4.22.5, pg. 1289;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 14.4.3.47a, pg. 880

Table 11. Exacerbation-related Withdrawals and Hospitalizations

	Placebo	Acclidinium 200 mcg	Acclidinium 400 mcg
<b>Trial M/34273/33</b>			
	n=185	n=184	n=190
Withdrawals	7	4	1
Hospitalizations	1	1	2
<b>Trial M/34273/34</b>			
	n=273	n=277	n=269
Withdrawals	5	3	4
Hospitalizations	10	3	2
<b>Trial M/34273/38 Part A</b>			
	n=182	n=182	n=177
Withdrawals	4	1	6
Hospitalizations	3	4	1

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.3.471, pg. 1013; pg. 166;

Section 5.3.5.1.3 (LAS-MD-CL34), Table 14.4.22.4, pg. 1288; Table 14.4.22.6, pg. 1291;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 14.4.3.55, pg. 910; Table 14.4.3.57, pg. 912

### SGRQ

The St. George's Respiratory Questionnaire was utilized in each of the three efficacy and safety trials. A comparison of mean SGRQ total score, by treatment group, is presented in Table 12. The percentage of patients achieving at least a 4-point (the minimum clinically important difference [MCID]) reduction from baseline in SGRQ total score, by treatment group, is presented in Table 13.

Table 12. Change from baseline in SGRQ Total Score at Week 12, ITT Population

Treatment Arm	n	Baseline	Change from baseline	Treatment difference from placebo	P-value vs. placebo <sup>9</sup>
<b>M/34273/33</b>					
Acclidinium 400 mcg	190	48.2668	-4.5782	-2.5430	0.0186
Acclidinium 200 mcg	184	45.9232	-4.7663	-2.7311	0.0126
Placebo	185	45.1168	-2.0352	--	--
<b>M/34273/38 Part A</b>					

<sup>9</sup> Applicant's ANCOVA analysis

Acridinium 400 mcg	177	50.4	-5.4	-1.1	0.4288
Acridinium 200 mcg	182	47.6	-6.0	-1.7	0.2216
Placebo	182	49.2	-4.3	--	--

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 14.4.3.43, pg. 1006-1008;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 11.4.1.3.3-1, pg. 149

**Table 13. Percentage of Patients Achieving at Least a 4-Point Reduction from Baseline in SGRQ Total Score, ITT Population**

	Placebo	Acridinium 200 mcg	Acridinium 400 mcg
<b>M/34273/33</b>			
Week 12			
Yes, n (%)	65 (35.9)	89 (49.4)	84 (44.4)
No, n (%)	116 (64.1)	91 (50.6)	105 (55.6)
OR	--	1.745	1.374
p-value vs. placebo	--	0.0103	0.1390
<b>M/34273/34</b>			
Week 12			
Yes, n (%)	106 (39.1)	139 (50.6)	150 (55.8)
No, n (%)	165 (60.9)	136 (49.5)	119 (44.2)
OR	--	1.57	1.91
p-value vs. placebo	--	0.0119	0.0004
Week 24			
Yes, n (%)	107 (39.5)	151 (54.9)	146 (54.3)
No, n (%)	164 (60.5)	124 (45.1)	123 (45.7)
OR	--	1.88	1.77
p-value vs. placebo	--	0.0004	0.0014
<b>M/34273/38 Part A</b>			
Week 12			
Yes, n (%)	69 (38.8)	84 (47.2)	77 (44.8)
No, n (%)	109 (61.2)	94 (52.8)	95 (55.2)
OR	--	1.47	1.28
p-value vs. placebo	--	0.0772	0.2596

Source: Section 5.3.5.1.1 (LAS-MD-33, Volume 1), Table 11.4.1.3.3-2, pg. 158;

Section 5.3.5.1.3 (LAS-MD-CL34), Table 21, pg. 104;

Section 5.3.5.1.1 (LAS-MD-38A, Volume 1), Table 11.4.1.3.3-2, pg. 151

***Reviewer's Comment:***

*While the results for the SGRQ treatment difference between acridinium 400 mcg and placebo are statistically significant only in Trial M/34273/34, in all three trials the trend is in favor of active treatment. The Applicant is not seeking a SGRQ claim.*

#### 4. OVERVIEW OF SAFETY

The primary safety database for acridinium bromide BID includes a total of 2677 individuals (2647 patients with COPD and 30 healthy subjects) in 8 trials. Across the clinical development program, the number patients exposed to acridinium bromide 400 mcg for  $\geq 1$  day,  $\geq 26$  weeks,  $\geq 51$  weeks is 1471, 462, and 97, respectively. Only one of the long-term safety trials (LAS-MD-36) has been completed; two additional long-term safety trials are ongoing. The Applicant proposes to include additional information from the ongoing safety trials at the time of the 120-day safety update.

*Reviewer's Comment:*

*At most, an additional 608 patients exposed to acridinium 400 mcg BID for 40 or more weeks will be added to the long-term safety database with the 120-day update. The adequacy of the safety data to support the proposed indication will be a review issue.*

The NDA also provides additional supportive safety information from the QD program, which included 2905 individuals evaluated in 16 trials. Across these trials, only 91 patients were treated with a dose greater than 200 mcg; none of these 91 patients had a duration of exposure equal to or greater than 84 days.

*Reviewer's Comment:*

*While safety information from the QD program may be informative, particularly if a safety signal is detected, it is not adequate to establish safety for the 400 mcg BID dose.*

This filing and planning review briefly summarizes adverse event data pooled across the three efficacy and safety trials (M/34273/33, M/34273/34, M/34273 38 Part A), as well as from the one completed long-term safety trial.

#### **Safety Findings: Efficacy and Safety Trials M/34273/33, M/34273/34, M/34273 38 Part A**

Table 14 provides an overall summary of adverse events pooled across the three efficacy and safety trials, and Table 15 lists AEs occurring at a frequency of 2% of greater.

**Table 14. Overall Summary of Adverse Events, Trials M/34273/33, M/34273/34, M/34273 38 Part A**

	Placebo n=641	Acridinium 200 mcg n=644	Acridinium 400 mcg N=636
At least 1 TEAE	344 (53.7)	321 (49.8)	319 (50.2)
AE leading to withdrawal	33 (5.1)	27 (4.2)	29 (4.6)
SAE	31 (4.8)	31 (4.8)	28 (4.4)
Death	2 (0.3)	1 (0.2)	3 (0.5)

Source: Section 5.3.5.3.28, Table 2.1.1.1-1, pg. 55

*Reviewer's Comment:*

The rate of any TEAE, AE leading to withdrawal, and SAE is lower for the acclidinium 400 mcg treatment group compared to placebo. Overall, there were 6 deaths across these three trials; 2 deaths in the placebo group, one death in the acclidinium 200 mcg group, and 3 deaths in the acclidinium 400 mcg group. The case reports for all deaths will be examined as part of the NDA review.

**Table 15. TEAEs reported in at least 2% of patients of any treatment, Trials M/34273/33, M/34273/34, M/34273 38 Part A**

Preferred Term	Placebo n=641	Acclidinium 200 mcg n=644	Acclidinium 400 mcg N=636
COPD (i.e. 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)

Source: Section 5.3.5.3.28, Table 2.1.2.2.1-1, pg. 61

### **Safety Findings: Long-term Safety Trial LAS-MD-36**

In Trial LAS-MD-36 the mean duration of exposure was 290.4 and 292.1 days for patients receiving acclidinium bromide 400 mcg and 200 mcg, respectively. Table 16 provides an overall summary of adverse events reported for this trial, and Table 17 lists AEs occurring at a frequency of 3% of greater.

**Table 16. Overall Summary of Adverse Events, LAS-MD-36, Safety Population**

	Acclidinium 200 mcg			Acclidinium 400 mcg			Total N=289 n (%)
	Prior Treatment in LAS-MD-33		Total N=137 n (%)	Prior Treatment in LAS-MD-33		Total N=152 n (%)	
	Placebo N=44 n (%)	200 mcg N=93 n (%)		Placebo N=46 n (%)	400 mcg N=106 n (%)		
Number of patients with TEAEs	35 (79.5)	71 (76.3)	106 (77.4)	35 (76.1)	77 (72.6)	112 (73.7)	218 (75.4)
Number of patients with adverse events leading to dropout	5 (11.4)	14 (15.1)	19 (13.9)	6 (13.0)	8 (7.5)	14 (9.2)	33 (11.4)
Adverse events leading to dropout, excluding COPD exacerbations	4 (9.1)	11 (11.8)	15 (10.9)	6 (13.0)	6 (5.7)	12 (7.9)	27 (9.3)

COPD exacerbations leading to discontinuation	1 (2.3)	3 (3.2)	4 (2.9)	0 (0)	2 (1.9)	2 (1.3)	6 (2.1)
Number of patients with SAEs	7 (15.9)	13 (14.0)	20 (14.6)	7 (15.2)	13 (12.3)	20 (13.2)	40 (13.8)
Number of patients who died	0	1 (1.1)	1 (0.7)	0	1 (0.9)	1 (0.7)	2 (0.7)

Source: Section 5.3.5.2.1 (LAS-MD-36, Volume 1), Table 14.5.1.1, pg. 140

**Reviewer's Comment:**

*The absence of a placebo group limits the interpretability of results from Trial LAS-MD-36. The overall rate of TEAEs appears to be comparable between the acridinium 200 mcg and 400 mcg treatment groups.*

**Table 17. TEAEs reported in at least 3% of patients of any treatment (descending order of frequency by overall total), LAS-MD-36**

Preferred Term	Acridinium 200 mcg			Acridinium 400 mcg			Total N=289 n (%)
	Prior Treatment in LAS-MD-33		Total N=137 n (%)	Prior Treatment in LAS-MD-33		Total N=152 n (%)	
	Placebo N=44 n (%)	200 mcg N=93 n (%)		Placebo N=46 n (%)	400 mcg N=106 n (%)		
Hypertension	2 (4.5)	4 (4.3)	6 (4.4)	0 (0)	3 (2.8)	3 (2.0)	9 (3.1)
Pneumonia	3 (6.8)	3 (3.2)	6 (4.4)	1 (2.2)	2 (1.9)	3 (2.0)	9 (3.1)
Peripheral Edema	0 (0)	3 (3.2)	3 (2.2)	2 (4.3)	3 (2.8)	5 (3.3)	8 (2.8)
Rash	1 (2.3)	2 (2.2)	3 (2.2)	0 (0)	5 (4.7)	5 (3.3)	8 (2.8)
Headache	1 (2.3)	3 (3.2)	4 (2.9)	1 (2.2)	3 (2.8)	4 (2.6)	8 (2.8)
GGT elevation	2 (4.5)	3 (3.2)	5 (3.6)	1 (2.2)	2 (1.9)	3 (2.0)	8 (2.8)
Fall	0 (0)	4 (4.3)	4 (2.9)	2 (4.3)	1 (0.9)	3 (2.0)	7 (2.4)
Bronchitis	0 (0)	1 (1.1)	1 (0.7)	1 (2.2)	4 (3.8)	5 (3.3)	6 (2.1)

Source: Section 5.3.5.2.1 (LAS-MD-36, Volume 1), Table 12.2.2.1.2-1, pg. 146

**Safety Findings: Major Adverse Cardiac Events (MACE)**

During the February 25, 2011, pre-NDA (BID program) interaction FDA indicated that the ISS should include an analysis of Major Adverse Cardiac Events (MACE). The Applicant also conducted an analysis of cardiovascular events of interest based on standard MedDRA queries (SMQs). This filing and planning review briefly summarizes the results of the MACE analysis.

The Applicant defined MACE as a composite of cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. An internal adjudication committee comprised of two licensed physicians (including one licensed cardiologist) assessed all deaths, and grouped them into the following

categories: cardiovascular death, non-cardiovascular death, or insufficient data. MACE scores<sup>10</sup>, by treatment group, are presented for the efficacy and safety trials (M/34273/33, M/34273/34, M/34273 38 Part A) and for the data available from the long-term safety trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B) in Table 18 and 19, respectively.

**Table 18. MACE Score, Efficacy and Safety trials (M/34273/33, M/34273/34, M/34273 38 Part A)**

	<b>Placebo</b> <b>N=641</b> <b>n (%)</b>	<b>Acridinium 200 mcg</b> <b>N=644</b> <b>n (%)</b>	<b>Acridinium 400 mcg</b> <b>N=636</b> <b>n (%)</b>
MACE Score	4 (0.6)	2 (0.3)	2 (0.3)
CV Death	0	1 (0.2)	1 (0.2)
Nonfatal myocardial Infarction	1 (0.2)	0	0
Nonfatal stroke	3 (0.5)	1 (0.2)	1 (0.2)

Source: Section 5.3.5.3.28, Table 2.1.6.1.4-1, pg. 81

Reviewer's Comment:

*The overall low number of events makes it difficult to draw conclusions about these data. It is noted that while the MACE score is lower for the acridinium treatment groups as compared to placebo, there were two cardiovascular deaths across the acridinium treatment groups, while there were no cardiovascular deaths in the placebo group. The cardiovascular safety profile of the proposed product will be a review issue.*

**Table 19. MACE Score, available data from Long-term Safety Trials (LAS-MD-35, LAS-MD-36, LAS-MD-38 Part B)**

	<b>LAS-MD-35</b>		<b>LAS-MD-36</b>		<b>LAS-MD-38 (Part B)</b>
	<b>A 200 mcg</b> <b>N=311</b> <b>n (%)</b>	<b>A 400 mcg</b> <b>N=291</b> <b>n (%)</b>	<b>A 200 mcg</b> <b>N=136</b> <b>n (%)</b>	<b>A 400 mcg</b> <b>N=153</b> <b>n (%)</b>	<b>A 400 mcg</b> <b>N=448</b> <b>n (%)</b>
MACE Score	3 (1.0)	3 (1.0)	2 (1.5)	2 (1.3)	4 (0.9)
CV Death	0	0	0	0	1 (0.2)
Nonfatal Myocardial infarction	1 (0.3)	1 (0.3)	1 (0.7)	1 (0.7)	2 (0.4)
Nonfatal stroke	2 (0.6)	2 (0.7)	1 (0.7)	1 (0.7)	1 (0.2)

<sup>10</sup> The MACE score was defined as the total cardiovascular deaths, nonfatal myocardial infarctions and nonfatal strokes.

Source: Section 5.3.5.3.28, Table 2.1.6.1.4-2, pg. 81

Reviewer's Comment:

*These data are limited by the lack of a placebo comparison group. In addition, trials LAS-MD-35 and LAS-MD-38 Part B are ongoing.*

## 5. ITEMS REQUIRED FOR FILING

See attached Clinical Filing Checklist (Appendix A).

## 6. BRIEF REVIEW OF PROPOSED LABELING

Preliminary review of the proposed label raises the following issues:

- Section 14 Clinical Studies, proposed text:

(b) (4)

Reviewer's Comment:

*How to best describe the results from Trial M/34273/38 Part A, which included a notably smaller effect size compared to Trials M/34273/33 and M/34273/34 will be a review issue.*

- Section 14 Clinical Studies, proposed text:

(b) (4)

Reviewer's Comment:

(b) (4)

## 7. DSI REVIEW/AUDIT

Given that this is an NME, a DSI review is requested. The following two sites are recommended for audit:

- 1) Site 2203, Trial M/34273/33

This site is selected due to a large effect size, unusually low (0%) dropout rate, and a (relatively) large number of subjects.

- 2) Site 4042, Trial M/34273/34

This site is selected due to a high (47%) dropout rate.

## 8. PEDIATRIC DEVELOPMENT PLAN

Forest requests a waiver of pediatric trials, from birth to 17 years of age, providing the rationale that COPD is an adult-specific disease.

### Reviewer's Comment:

*The Applicant's request appears to be reasonable.*

## 9. RECOMMENDATION

The application is fileable.

## 10. COMMENTS FOR THE SPONSOR

1. As stated in the pre-NDA meeting responses dated February 25, 2011, adequate safety data to support the application is expected at the time of NDA filing. We will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action. In general, we note that long-term exposure to the proposed 400 mcg BID dose of aclidinium is relatively small in comparison to other COPD development programs. The adequacy of the safety data to support the proposed indication will be a review issue and may impact approvability of the proposed product.

2.  (b) (4)

**Appendix A. Clinical Filing Checklist**

**NDA/BLA Number: 202-450      Applicant: Forest Research Institute, Inc.      Stamp Date: June 23, 2011**

**Drug Name: acridinium bromide      NDA/BLA Type: 505(b)(1)**

On initial overview of the NDA/BLA application for filing:

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
<b>FORMAT/ORGANIZATION/LEGIBILITY</b>					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	X			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	X			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	X			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	X			
5.	Are all documents submitted in English or are English translations provided when necessary?	X			
6.	Is the clinical section legible so that substantive review can begin?	X			
<b>LABELING</b>					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	X			
<b>SUMMARIES</b>					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	X			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	X			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	X			
11.	Has the applicant submitted a benefit-risk analysis for the product?	X			
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
<b>DOSE</b>					



	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	studies, if needed)?				
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	X			
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure <sup>11</sup> ) been exposed at the dose (or dose range) believed to be efficacious?	X			
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			X	
23.	Has the applicant submitted the coding dictionary <sup>12</sup> used for mapping investigator verbatim terms to preferred terms?	X			<b>MEDRA, versions 13.1</b>
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	X			
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	X			
<b>OTHER STUDIES</b>					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?			X	
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included ( <i>e.g.</i> , label comprehension, self selection and/or actual use)?			X	
<b>PEDIATRIC USE</b>					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	X			<b>Pediatric waiver requested, birth to 17 years of age</b>
<b>ABUSE LIABILITY</b>					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?			X	
<b>FOREIGN STUDIES</b>					
30.	Has the applicant submitted a rationale for assuming the	X			

<sup>11</sup> For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

<sup>12</sup> The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	<b>Content Parameter</b>	<b>Yes</b>	<b>No</b>	<b>NA</b>	<b>Comment</b>
	applicability of foreign data in the submission to the U.S. population?				
<b>DATASETS</b>					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	X			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	X			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	X			
34.	Are all datasets to support the critical safety analyses available and complete?	X			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	X			
<b>CASE REPORT FORMS</b>					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	X			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			X	
<b>FINANCIAL DISCLOSURE</b>					
38.	Has the applicant submitted the required Financial Disclosure information?	X			
<b>GOOD CLINICAL PRACTICE</b>					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	X			Confirmed for Trials M/34273/33, M/34273/34, M/34273/38 Part A, and LAS-MD-36

**IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? \_\_\_ X \_\_\_**

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

### COMMENTS FOR THE SPONSOR

1. As stated in the pre-NDA meeting responses dated February 25, 2011, adequate safety data to support the application is expected at the time of NDA filing. We will not be able to conduct a substantive review of information submitted at the 120-day safety update; as a result, this additional data has limited capacity to support a regulatory action. In general, we note that long-term exposure to the proposed 400 mcg BID dose of acclidinium is relatively small in comparison to other COPD development programs. The adequacy of the safety data to support the proposed indication will be a review issue and may impact approvability of the proposed product.

2.  (b) (4)

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Reviewing Medical Officer

Date

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Clinical Team Leader

Date

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**This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.**  
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/s/  
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JENNIFER R PIPPINS  
08/23/2011

SUSAN L LIMB  
08/23/2011