CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

202450Orig1s000

CROSS DISCIPLINE TEAM LEADER REVIEW

Cross-Discipline Team Leader Review

Date	June 11, 2012
From	Susan Limb, MD
Subject	Cross-Discipline Team Leader Review
NDA/BLA # Supplement#	NDA 202-450/ SN000
Applicant	Forest Laboratories
Date of Submission	June 23, 2011
PDUFA Goal Date	July 23, 2012
Proprietary Name / Established (USAN) names	Tudorza Pressair (aclidinium bromide inhalation powder)
Dosage forms / Strength	Aclidinium bromide 400 mcg BID
Proposed Indication(s)	Maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD)
Recommended:	Approval

1. Introduction

Forest Laboratories submitted a 505(b)(1) New Drug Application (NDA) 202-450 on June 23, 2011, for aclidinium bromide inhalation powder 400 mcg twice daily, proposed for the long-term, maintenance treatment of bronchospasm associated with COPD, including chronic bronchitis and emphysema. Aclidinium bromide is a new molecular entity and is categorized as an anticholinergic agent. Due to its duration of action and its specific action on muscarinic receptors, aclidinium bromide belongs to the subclass of long-acting antimuscarinics (LAMA). Aclidinium bromide is supplied as a dry powder inhalation formulation administered by the Almirall inhaler device. The proposed tradename is Tudorza Pressair®.

The application was initially submitted on June 23, 2011, and was filed as a standard review. The Applicant submitted an amendment on March 15, 2012, containing corrected tables and datasets pertaining to a key secondary efficacy variable, the St. George's Respiratory Questionnaire (SGRQ). Since the SGRQ data provide an important alternative assessment of efficacy that is independent of spirometry, the submission was considered to be a major amendment, and the review clock was extended by three months.

Throughout this memo, the drug product for this application will be referred to as aclidinium. The memo provides an overview of the application, with a focus on the size of the safety database and its adequacy to address safety concerns associated with anticholinergic agents as a drug class. The memo will cover the entire review period and address the recommendations from each of the individual review disciplines.

2. Background

Several drug classes are available for the relief of airflow obstruction in patients with COPD. These include anticholinergic agents, beta-adrenergic agonists, combination products containing anticholinergic and beta-adrenergic agonists, combination products containing long-acting beta-adrenergic agonists and corticosteroids, and PDE-4 inhibitors. With the exception of PDE-4 inhibitors, these are inhalation products.

Anticholinergic agents and the treatment of COPD

Aclidinium is a new molecular entity that belongs to the anticholinergic class of drugs, specifically, an M3 muscarinic antagonist. The binding of M3 muscarinic receptors blocks acetylcholine-mediated bronchoconstriction. Inhaled anticholinergics are widely used in the US and worldwide. In the US, a short-acting anticholinergic, ipratropium bromide, has been approved as a bronchodilator for patients with COPD since 1986. A long-acting anticholinergic, tiotropium bromide (Spiriva Handihaler), has been available in the US since 2004. Common anticholinergic adverse effects include dry mouth, constipation, and urinary retention. More recently, safety concerns regarding increased risk of stroke, cardiovascular death, and myocardial infarction (MI) associated with inhaled anticholinergic use have been raised following a meta-analysis of 17 clinical trials in COPD.[1] These concerns are echoed in the experience with an alternate tiotropium formulation delivered by the Respimat device, which is not approved in the US. Three, 1-year, placebo-controlled trials of tiotropium Respimat showed a numerical imbalance in all-cause mortality over placebo, without any consistent cause of death. However, interpretation of these results is limited by the lack of pre-specification of safety endpoints and retrospective vital status assessment. At the time of this memorandum, the manufacturer of tiotropium Respimat is conducting a large, prospective safety trial to further evaluate the risk.

In contrast with the meta-analysis and the tiotropium Respimat trials, a large, 4-year, randomized, controlled trial (Understanding Potential Long-Term Impacts on Function with Tiotropium; UPLIFT) with pre-specified safety endpoints did not show any increased mortality risk with Spiriva Handihaler compared to placebo.[2] With 17,721 patient-years of exposure, the UPLIFT study doubled the size of the tiotropium safety database. The UPLIFT results were discussed at a previous PADAC meeting held on November 19, 2009. Given the strength of the UPLIFT study design and findings, the committee members and the Division subsequently concluded that the current data do not support an increased risk of stroke, myocardial infarction, or death associated with Spiriva Handihaler.[3] However, the safety signal for the tiotropium Respimat formulation remains unresolved at this time, and cardiovascular adverse events and stroke remain safety issues of interest for this class of drugs.

Relevant regulatory history

Forest (and the previous owner of the IND, Almirall Prodespharma) studied several different doses and dosing regimens for aclidinium in its development program. The

[1] Singh S, Loke YK, Furberg CD. JAMA 2008; 300: 1439-50.
[2] Tashkin DP, Celli B, Senn S, et al. N Engl J Med 2008; 359: 1543-54.
[3] Michele TM, Pinheiro S, Iyasu S. N Engl J Med 2010; 363:1097-99.

following timeline highlights the major regulatory interactions to discuss the clinical program that occurred during development:

- **September 30, 2003, Pre-IND meeting:** The Division and Forest/Almirall discussed the appropriate use of trough FEV1 for evaluation of bronchodilator efficacy. While trough FEV1 is considered useful for evaluating the dosing interval, the Division expressed reservation regarding its use as a primary efficacy variable and noted that peak FEV1 and FEV1 AUC were more traditional variables. The discussion also addressed the use of various secondary endpoints, included measurements of dyspnea using the Mahler Baseline and Transitional Dyspnea Index (BDI/TDI) and the Borg Scale for dyspnea during exercise. In response, the Division highlighted the need for validation of the instruments and determination of the minimum clinically meaningful difference (MCID).
- **April 26, 2005, End-of-Phase-2 meeting:** Forest proposed evaluating a dose of 200 mcg once daily in Phase 3 trials, as well as pursuing a COPD exacerbation claim. The Division suggested including a second higher dose of 400 mcg in the Phase 3 program and noted that the clinical relevance of the COPD exacerbation definition used would be a review issue. Forest also projected a safety database of approximately 1800 patients with moderate to severe COPD, of which 1204 would be exposed for at least 4 weeks to the therapeutic dose and 1020 for 52 weeks. The Division deemed the safety database to be reasonable but noted that additional studies may be required depending on the safety profile observed. In addition, the Division raised concerns that the Mahler BDI/TDI was not an acceptable instrument for supporting a dyspnea claim.
- **March 3, 2009, Pre-NDA meeting:** Forest provided an overview of two placebo-controlled, 1-year trials that evaluated aclidinium bromide 200 mcg once daily for the treatment of COPD. The Division questioned the clinical relevance of a 60 ml treatment difference in trough FEV1, despite the statistical significance of the findings. The Division noted that this treatment difference was much lower than the 150 ml difference observed in the original dose-ranging study and recommended exploration of higher doses and more frequent dosing intervals. Forest proposed conducting two additional Phase 3 long-term safety trials of aclidinium 200 mcg BID and 400 mcg BID. A total of 131 patients for 6 months and 105 patients for 1 year to the 200 mcg BID dose and 343 patients for 6 months and 105 patients for 1 year to the 400 mcg BID dose would be exposed. The Division responded that the adequacy of these patient numbers to support registration of the higher dose would depend on the quality of the safety data and the nature of the adverse events observed.
- **February 25, 2011, Second pre-NDA meeting:** Forest provided an overview of a new Phase 3 program evaluating aclidinium 400 mcg BID, with a projected total of 509 and 103 patients exposed for 6 months and 1 year, respectively. Forest stated that the safety studies were ongoing and that the majority of the 1 year data would not be available at the time of NDA submission but would be submitted separately as an update during the NDA review period. The Division responded that the NDA should be complete at the time of submission and stated that it was at Forest's discretion to decide which efficacy and safety data were necessary to

support the application. The Division also requested an analysis of Major Adverse Cardiac Events (MACE) in addition to the planned summary of safety.

- **June 23, 2011, NDA submission**
- **March 15, 2012, Submission of major amendment**

3. CMC/Device

The recommended action from a CMC perspective is Approval. There are no outstanding issues from a CMC perspective at this time.

- **General product quality considerations**

Aclidinium is formulated as an inhalation powder, comprised of a mixture of micronized aclidinium bromide and α-lactose monohydrate, which functions as a carrier. The mixture is delivered by the Almirall inhaler device (proposed proprietary name (b) (4) a non-refillable, breath-actuated, multi-dose, device-metered, dry powder inhaler (DPI) device. Each inhaler delivers at least 60 nominal doses, and each actuation meters 13 mg of the powder containing 400 mcg of aclidinium and delivering approximately 375 mcg of aclidinium from the mouthpiece (based on in vitro testing at a flow rate of 63 L/min in average for 2 seconds). Based on characterization data, the full dose can be delivered with a minimum of 35 L/min flow rate. The inhaler is sealed in an aluminum pouch and packaged in a cardboard carton. Stability data support a shelf-life of 24 months with a labeled storage statement of "Store at 25ºC (77ºF); excursions permitted from 15º to 30ºC (59º - 86ºF)." The Product Quality Microbiology review recommends approval of the product, which is a non-sterile dry powder.

In addition to routine bench testing for device ruggedness, the Applicant sampled partially used devices from the clinical trials and all complaint/malfunctioning devices. The rate of malfunctioning devices was low and did not indicate any systematic problems with device design. Patient use did not appear to influence the functionality of the device.

- **Facilities review/inspection**

The drug substance is manufactured by (b) (4) and micronized by (b) (4) The Almirall inhaler device is manufactured by (b) (4) The drug product is manufactured by Forest Laboratories (Dublin, Ireland). The drug substance and device DMFs were deemed adequate. Manufacturing and testing facilities have been deemed Acceptable by the Office of Compliance.

- **Other notable issues (resolved or outstanding)**

No postmarketing commitments or requirements are requested from a CMC perspective. The initial CMC review noted a need for revision of drug product specifications for dose content uniformity (DCU) and aerodynamic particle size distribution, which the applicant has adequately addressed during the course of the review.

The CMC review also noted that the integrated dose indicator in the inhaler may potentially confuse patients. The device was designed to deliver at least 60 doses (64 ± 4 doses) and as such locks out after a variable number of doses, 60 doses or more. (b) (4)

Following discussion, the Applicant has redesigned the dose counter for improved legibility and revised the instructions for use so that patients would be advised to discard the inhaler after the dose counter reaches "0" or after lock-out, whichever comes first.

4. Nonclinical Pharmacology/Toxicology

The recommendation from the Nonclinical Pharmacology/Toxicology review is Approval. There are no outstanding issues from a pharmacology/toxicology perspective at this time.

Forest submitted results from a full preclinical program, including single dose toxicology, subchronic toxicology, chronic toxicology, reproductive toxicology, genotoxicity, and carcinogenicity studies. The program included studies in which animals were dosed with the drug via inhalation to assess both local and systemic toxicities. Repeat-dose inhalation toxicity studies of up to 3 months' duration in the mouse, 6 months in the rat, and 39 weeks in the dog were conducted. Most of the observed effects in these studies could be related to the pharmacological action of an anticholinergic, including increased heart rate, mydriasis, decreased tear production, and/or tremor.

Studies for genotoxicity, reproductive toxicity, and carcinogenicity did not show any major findings of concern. Aclidinium was positive in the Ames bacterial mutation assay and in the mouse lymphoma assay, but negative in the in vivo mouse micronucleus assay and the in vivo/in vitro unscheduled DNA synthesis assay in male rats. Two-year carcinogenicity studies in mice and rats did not indicate any statistically significant test article-related tumor findings. Reproductive and developmental toxicity studies showed impairment of several fertility and reproductive performance indices and an increased incidence of additional liver lobes and decreased fetal body weights when aclidinium was administered by the oral route, but no structural alterations were observed in rats and rabbits when aclidinium was administered by inhalation. Aclidinium is designated as Pregnancy Category C.

5. Clinical Pharmacology/Biopharmaceutics

The application is deemed acceptable from a Clinical Pharmacology perspective. No issues are outstanding at this time.

Forest submitted results from a comprehensive clinical pharmacology program that included studies to assess protein binding and metabolism, pharmacokinetics after single and multiple inhaled doses, pharmacokinetics in COPD patients, effect of renal impairment, and QTc effect. Studies in hepatic impairment were not conducted as aclidinium is metabolized via chemical and enzymatic hydrolysis. In vitro studies indicated that aclidinium and its major metabolites do not inhibit CYP enzymes. Given these results and the low plasma levels achieved at clinically relevant doses, aclidinium is not anticipated to interact with co-administered drugs, and formal drug-drug interaction studies were not conducted.

Inhaled aclidinium at a dose of 400 mcg has an approximate absolute bioavailability of <5% in healthy volunteers and reaches maximum plasma concentrations approximately 0.08 hours after inhalation when administered twice daily. Based on the chemical structure, minimal GI absorption is expected to occur. The estimated effective half-life is 5 to 8 hours, and systemic exposure is dose-proportional across the dose range of 200 to 800 mcg. No clinically significant differences were observed with renal impairment or age, and no dose adjustment is recommended for these subgroups. Cross-study comparison suggests that COPD patients exhibit a lower Cmax and higher AUC than healthy patients.

6. Clinical Microbiology

Clinical microbiology is not applicable for this NDA.

7. Clinical/Statistical – Efficacy

Overview of the clinical program

As noted in the regulatory history, Forest initially conducted a clinical program to develop an aclidinium 200 mcg QD regimen. As this dose is not currently proposed for marketing, the discussion of the clinical efficacy and safety data focuses on the clinical trials that support the proposed 400 mcg BID dose. The following table summarizes the main dose-ranging and efficacy and safety trials included in the clinical development program for aclidinium 400 mcg BID (Table 1). (For the sake of brevity, the trials are referred to by the last two digits of the protocol number, e.g., Trial 23 refers to LAS-MD-CL23.) The program included two crossover-design, pharmacodynamic trials (Trials 23 and 29) to evaluate the nominal dose and dosing frequency, and three main efficacy and safety trials. The efficacy trials were randomized, placebo-controlled, parallel-group trials with double-blind treatment periods of 12 or 24 weeks. Patients enrolled in the two 12-week trials (Trial 33 and Trial 38 Part A) were subsequently given the option of rolling over into a corresponding open-label, extension trial (Trial 36 or Trial 38 Part B). An additional, 1-year safety trial, Trial 35, was also conducted. Of note, Trial 35 and Trial

38 Part B were completed after NDA submission. As a result, updated safety information from these two trials was submitted in October 2011 during the review period.

Table 1 Aclidinium 400 mcg BID clinical development program

Trial *Year completed*	Design	N	Treatment	Endpoint	Sites
Dose-ranging trials					
LAS-MD-CL23 (M/34273/23) *2009*	R, DB, PC, AC, XO, 15-day treatment	30	A 400 mcg BID[1] Tiotropium 18 mcg QD Placebo	FEV AUC_{0-12h}	2 sites (Germany)
LAS-MD-CL29 (M/34273/29) *2010*	R, DB, PC, AC, XO, 7-day treatment	79	A 400 mcg BID A 200 mcg BID A 100 mcg BID Formoterol 12 mcg BID Placebo	FEV AUC_{0-12h}	11 sites (Germany, Belgium)
Placebo-controlled, efficacy and safety trials					
LAS-MD-33 (M/34273/33) *2009*	R, DB, PC, 12 weeks	190 184 186	A 400 mcg BID A 200 mcg BID Placebo	Trough FEV1	99 sites (US, Canada)
LAS-MD-CL34 (M/34273/34) *2010*	R, DB, PC, 24 weeks	269 277 273	A 400 mcg BID A 200 mcg BID Placebo	Trough FEV1	100 sites (W and E Europe, S Africa, Peru)
LAS-MD-38 Part A (M/34273/38) *2010*	R, DB, PC, 12 week	177 183 182	A 400 mcg BID A 200 mcg BID Placebo	Trough FEV1	103 sites (US, Canada)
Long-term safety trials					
LAS-MD-35 *2011*	R, DB, 52 weeks	291 311	A 400 mcg BID A 200 mcg BID	Long-term safety	US, Canada
LAS-MD-36 (extension of LAS-MD-33) *2010*	R, DB, 52 weeks	153[2] 138[2]	A 400 mcg BID A 200 mcg BID	Long-term safety	77 sites (US, Canada)
LAS-MD-38 Part B (extension of LAS-MD-38 Part A) *2011*	R, single-arm, OL, 40 weeks	448[2]	A 400 mcg BID	Long-term safety	US, Canada

1 A = aclidinium
2 These patients were previously enrolled in the placebo-controlled efficacy trials.

Forest also conducted a 6-week trial (Trial 26) to evaluate the effect of aclidinium 200 mcg QD on exercise tolerance and proposed inclusion of this information in the product label. In addition to some limitations inherent to the trial design and endpoint selection, these results were not replicated and do not support the proposed dose of aclidinium 400 mcg BID. Therefore, this trial and its results are not discussed further.

Dose selection

As mentioned previously, the aclidinium development program initially evaluated once-daily dosing. Two Phase 3 clinical trials were conducted that showed suboptimal efficacy with a dose of 200 mcg QD. Subsequently, Forest conducted two additional dose-ranging trials, Trial 23 and Trial 29, to evaluate a higher nominal dose given twice daily. Both trials were crossover trials with 15-day and 7-day treatment periods, respectively, and included tiotropium or formoterol for benchmark comparison. The dose-ranging trials supported a BID dosing interval, and the 400 mcg dose demonstrated a greater change in trough FEV1 and serial FEV1 measurements compared to lower nominal doses of 100 mcg and 200 mcg (Figure 1 and Figure 2). Although some differences were observed in the second 12-hour interval, aclidinium 400 mcg generally performed in a similar range as the active comparators, tiotropium and formoterol.

Figure 1 Change from baseline in FEV1 over 24 hours postdose on Day 15 (Trial 23)

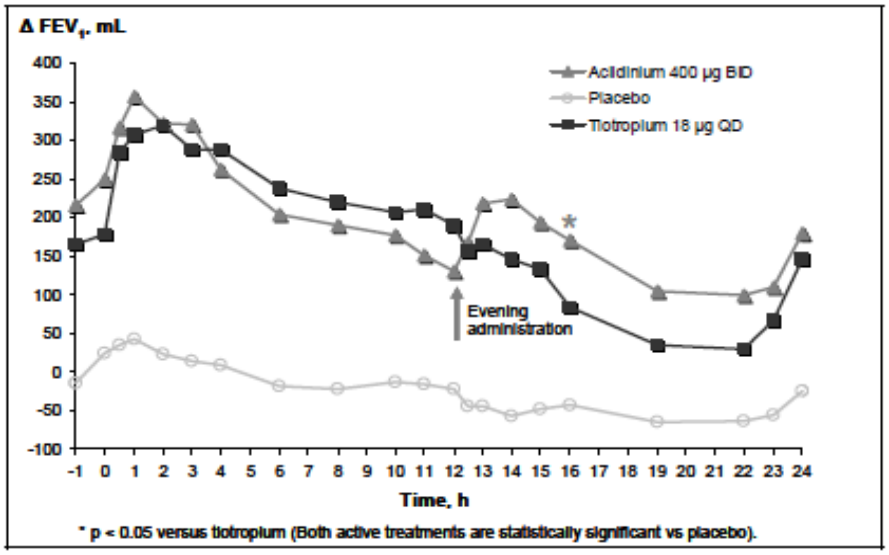
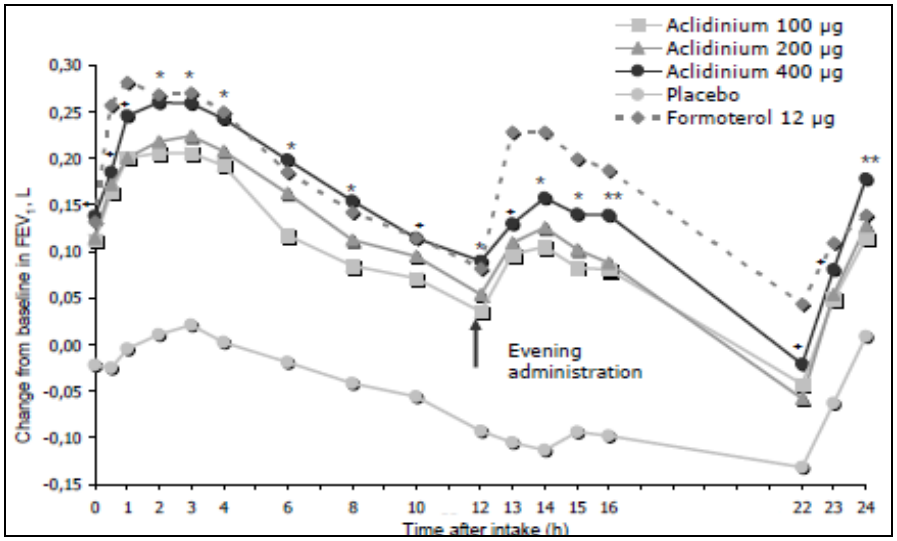


Figure 2 Change from baseline in FEV1 over 24 hours postdose on Day 7 (Trial 29)



Based on these results and the previous experience with aclidinium at a lower nominal dose and less frequent dosing frequency, the selection of aclidinium 400 mcg BID for further evaluation in the Phase 3 program appeared reasonable.

Trial design

- *Efficacy and safety trials: Trials 33, 34, and 38A*

The main efficacy and safety trials, Trials 33, 34, and 38A, were similar in design. All three trials were multicenter, randomized, double-blind, placebo-controlled comparing aclidinium 400 mcg BID, aclidinium 200 mcg BID, and placebo in patients with stable, moderate to severe COPD. Patients 40 years or older were required to have a post-salbutamol FEV1/FVC ratio <70%, an FEV1 ≥30% and <80%, and a smoking history of at least 10 pack-years. Patients with a history of COPD exacerbation requiring hospitalization within 3 months prior to screening or history of other significant co-morbid conditions, such as unstable cardiovascular disease, were excluded.

After an initial screening period, patients entered a 2-week run-in period for assessment of disease stability. Qualified patients were then randomized to the double-blind treatment period of 12 or 24 weeks' duration, depending on the trial. The change from baseline in morning trough FEV1 at Week 12 was designated as the primary efficacy endpoint. Other efficacy variables included peak FEV1 and St. George's Respiratory Questionnaire (SGRQ), rescue medication usage, and COPD exacerbations. A subset of approximately 20% of patients also underwent 12-hour serial spirometry at various intervals and at the end of the double-blind treatment period. Treatment compliance was assessed via diary entries and dose counter checks at interval clinical visits. Safety assessments included adverse events (AEs), physical exams, clinical laboratory parameters, vital signs, ECGs, and in a subset of patients, Holter monitoring.

During the trial, patients were permitted to use short-acting beta-agonists (SABA) as rescue medication as well as inhaled corticosteroids, prednisone (up to 10 mg/day), or oral sustained-release theophylline as maintenance medications if at a stable dose prior to study entry. The use of a placebo control for up to 6 months was considered ethically acceptable given the availability of rescue SABA and permitted use of other maintenance medications in conjunction with close clinical monitoring for exacerbation symptoms. The informed consent forms described the possibility of receiving placebo and noted that alternative treatments for COPD were available.

- *Safety trials: Trials 36, 38B, and 35*

Following completion of the placebo-controlled phase of Trials 33 and 38A, patients were eligible to enroll in the uncontrolled safety extension trials, Trials 36 and 38B, respectively. In Trial 36, patients who had received aclidinium 400 mcg or 200 mcg during the placebo-controlled phase were maintained on the same dose; patients who had been allocated to placebo were re-randomized 1:1 to one of the two aclidinium doses. Study treatments otherwise remained double-blinded for the duration of the 52-week extension. In Trial 38B, all patients who elected to participate received aclidinium 400 mcg for the duration of the 40-week extension treatment period.

Trial 35 was a dedicated, randomized, double-blind, 52-week safety trial. Patients received either aclidinium 400 mcg or 200 mcg. Entry criteria were similar to those described for the pivotal efficacy and safety trials.

Efficacy findings

Across the treatment groups in the three trials, completion rates ranged from 80% to 93%, with the lowest completion rates observed in the placebo arm in each trial, followed by the aclidinium 200 mcg arm. Lack of efficacy was cited more frequently as a reason for discontinuation in the placebo and aclidinium 200 mcg arms compared to aclidinium 400 mcg. The results discussed below reflect analyses performed with the intent-to-treat (ITT) population unless otherwise noted.

- *Spirometry*

All three efficacy trials demonstrated a statistically significant increase from baseline morning trough FEV1 compared to placebo at Week 12 or 24 (Table 2). The effect size for aclidinium 400 mcg ranged from 72 ml to 124 ml across the three trials at Week 12, and the treatment effect appeared to persist when assessed at Week 24 in Trial 34. Aclidinium 200 mcg also demonstrated a statistically significant difference from placebo, although the magnitude of the treatment difference (51 to 86 ml) was smaller than the effect size observed for the 400 mcg dose.

Table 2 Change from baseline in trough FEV1 (LOCF)							
Treatment	**N**	**Baseline (L)**	**Timepoint**	**Change from baseline (L)**	**Difference from placebo**	**95% CI**	**P**
Trial 34							
A 400	269	1.447	*Week 12*	0.058	0.105	(0.07, 0.14)	<0.001
A 200	277	1.453		0.030	0.077	(0.04, 0.12)	<0.001
Placebo	273	1.419		-0.047			
A 400	269	1.447	*Week 24*	0.055	0.128	(0.08, 0.17)	<0.001
A 200	277	1.453		0.026	0.099	(0.06, 0.14)	<0.001
Placebo	273	1.419		-0.073			
Trial 33							
A 400	190	1.328	*Week 12*	0.099	0.124	(0.08, 0.16)	<0.001
A 200	184	1.308		0.061	0.086	(0.04, 0.13)	<0.001
Placebo	185	1.383		-0.025			
Trial 38A							
A 400	177	1.255	*Week 12*	0.064	0.072	(0.03, 0.12)	<0.001
A 200	182	1.387		0.043	0.051	(0.01, 0.09)	0.019
Placebo	182	1.418		-0.008			

A = aclidinium

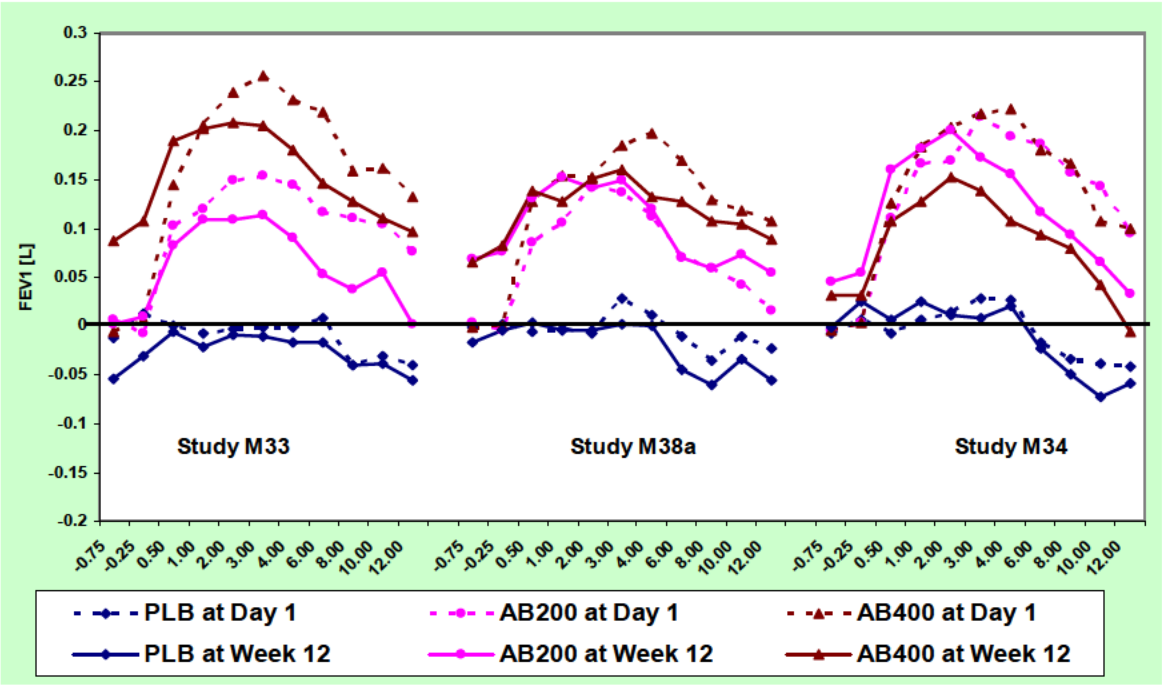
P-value, LS mean, and LSMD obtained from ANCOVA model with change from baseline in trough FEV1 as response, with treatment group and sex as factors and baseline trough FEV1 and age as covariates.

The application includes exploratory subgroup analyses by gender, ethnicity, age, COPD severity, bronchodilator reversibility, concomitant ICS use, and smoking status. While certain analyses were limited by sample size (e.g., ethnic subgroups), the results were generally similar to the efficacy results observed for the population as a whole.

As trough FEV1 reflects bronchodilation at only the end of the dosing interval, other spirometric parameters, such as peak FEV1 and serial FEV1, were of interest to support the bronchodilation claim. For aclidinium 400 mcg, the raw mean peak FEV1 (the maximum FEV1 measurement from 0 to 3 hours post-dose) ranged from 1.60 to 1.75 L In Trials 33 and 34 and was relatively constant from Day 1 to Week 12. Similar raw mean peak FEV1 values were reported for aclidinium 200 mcg. By comparison, the raw peak FEV1 values for the placebo group in these two trials ranged from 1.44 to 1.55 L. Trial 38A had discrepant results, with lower raw peak FEV1 values reported for the aclidinium 400 mcg arm compared to placebo. Forest attributes this discrepancy to worse disease severity in the aclidinium treatment arms as measured by FEV1 and GOLD staging at baseline. The reason for this discrepancy is hard to confirm, but this explanation is certainly plausible.

Serial spirometry was collected in a subset of patients to characterize the FEV1 response over the entire 12-hour dosing interval (Figure 3). Greater bronchodilation was observed for aclidinium 400 mcg BID over placebo at all timepoints. While a dose response was not observed in Trial 34, numerical separation between aclidinium 400 mcg and 200 mcg was observed in Trials 33 and 38A.

Figure 3 12-hour serial FEV1 (Trials 33, 38A, and 34)



- *St. George's Respiratory Questionnaire (SGRQ)*

The change from baseline in the SGRQ total symptom score was assessed as another efficacy variable. Baseline total symptom scores were similar across the treatment arms (Table 3). Greater decreases in total score were observed for aclidinium compared to placebo and were generally supportive of efficacy, but only Trial 34 demonstrated a treatment difference between aclidinium 400 mcg and placebo that exceeded the minimum clinical important difference (MCID) threshold of a 4-unit change.

Table 3 Change from baseline in SGRQ total symptom score

Treatment	N	Mean baseline	Change from baseline (Wk 12)	Difference from placebo	P	Change from baseline (Wk 24)	Difference from placebo	P
Trial 34								
A 400	269	47.9	-6.5	-4.1	<0.001	-7.4	-4.6	<0.001
A 200	275	46.4	-5.5	-3.2	0.002	-6.6	-3.8	<0.001
Placebo	271	45.1	-2.4			-2.3		
Trial 33								
A 400	189	48.5	-4.6	-2.5	0.019			
A 200	180	45.6	-4.8	-2.7	0.013			
Placebo	181	45.3	-2.0					
Trial 38A								
A 400	172	50.6	-5.4	-1.1	0.43			
A 200	178	47.9	-6.0	-1.7	0.22			
Placebo	178	48.8	-4.3					

SE=standard error. 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 SGRQ and age as covariates.

- *COPD exacerbations*

COPD exacerbations were categorized by severity and defined as increased COPD symptoms of at least 2 consecutive days requiring one of the following: 1) increased rescue medications (mild exacerbation); 2) treatment with antibiotics and/or corticosteroids (moderate exacerbation), or 3) hospitalization or emergency room treatment (severe exacerbation). While this definition relies on individual investigator discretion and may be impacted by local practice standards, the exacerbation data are useful as supplementary evidence of efficacy. Exacerbation results from the six-month trial, Trial 34, suggested a dose-dependent decrease in exacerbations with aclidinium treatment (Table 4). Results from the three-months studies were less consistent, although this variability may be due in part to a low background rate of exacerbations overall.

Table 4 Number (%) patients with at least one COPD exacerbation

	Treatment	N	Any exacerbation N (%)	Mild exacerbation N (%)	Moderate Exacerbation N (%)	Severe Exacerbation N (%)
6-month treatment period	**Trial 34**					
	A 400	269	38 (14)	6 (2)	31 (12)	2 (1)
	A 200	277	44 (16)	9 (3)	33 (12)	3 (1)
	Pbo	273	56 (21)	14 (5)	35 (13)	10 (4)
3-month treatment period	**Trial 33**					
	A 400	190	12 (6)	1 (<1)	10 (5)	2 (1)
	A 200	184	16 (9)	5 (3)	13 (7)	1 (1)
	Pbo	185	22 (12)	6 (3)	15 (8)	1 (1)
	Trial 38A					
	A 400	177	19 (11)	3 (2)	13 (7)	3 (2)
	A 200	183	14 (8)	3 (2)	8 (4)	3 (2)
	Pbo	182	19 (10)	-	14 (8)	5 (3)

Source: Individual complete study reports provided by Forest in June 2011 NDA submission

- *Other efficacy endpoints*

Rescue medication use was assessed as secondary efficacy variable. According to the individual study report for Trial 34, use of daily rescue medication decreased by a mean of -1.2 puffs/day in the aclidinium 400 mcg arm, compared to -0.9 puffs/day in the aclidinium 200 mcg arm and -0.3 puffs/day in the placebo group. Similar differences were observed in Trial 33 but not in 38A between active and placebo groups.

Forest used the Baseline Dyspnea Index (BDI) and Transition Dyspnea Index (TDI) to assess dyspnea and has proposed inclusion of dyspnea information in the product label as a secondary claim. Measurement of dyspnea in clinical trials is challenging, and there are currently no agreed-upon validated instruments. The limitations of the BDI/TDI patient-reported outcome instruments were previously discussed with Forest at the April 2005 End-of-Phase 2 meeting and were the subject of more extensive discussion at a previous Advisory Committee meeting for another inhalation product.[4] While results for the BDI and TDI were generally numerically supportive, the clinical relevance of the results is difficult to interpret and, therefore, the results are not discussed further here.

[4] Pulmonary Allergy Drugs Advisory Committee Meeting, September 2002, Meeting Minutes

Efficacy conclusions
Replicate, statistically significant differences between aclidinium 400 mcg BID and placebo were demonstrated for the primary efficacy endpoint of 12-hour post-dose AM trough FEV1 after 12 weeks of treatment. Secondary endpoints provided additional support, including peak FEV1, serial FEV1 measurements, patterns of rescue medication usage, and COPD exacerbation data. Based on these results, the application supports the efficacy of aclidinium for the proposed indication.

8. Safety

Overview of the safety database
The safety database for aclidinium 400 mcg is comprised primarily of the three efficacy and safety trials, the two extension trials, and the dedicated one-year safety trial, Trial 35. These pivotal trials are supplemented by several short-term Phase 2 trials and safety information from the QD program. The trial designs for the main trials are described in the preceding section. The safety population for aclidinium 400 mcg BID includes a total of 1471 COPD patients exposed to at least one dose or more of aclidinium 400 mcg BID. At the time of NDA submission, a total of 462 patients had been exposed for at least 6 months, and 97 patients had been exposed for ≥1 year. Following the October 21, 2011, safety update, these numbers were increased to 733 and 329 patients, respectively, following completion of the long-terms safety trials, Trials 35 and 38B. For comparison, the original clinical program for tiotropium included a total of 1152 patients exposed for ≥200 days and 562 patients exposed ≥330 days.

Overall, the mean age was 63 years, and the safety population was approximately 45% female, 91% White, and 7% Black. Approximately half the patients were current smokers. The long-term safety data is based on patients in the US and Canada.

Forest provided an Integrated Summary of Safety which pooled patients into 3 major categories: Group 1A, Group 1B, and Group 1C. Group 1A was comprised of patients who participated in the placebo-controlled phase of the Phase 3 efficacy trials. Group 1B was intended to address long-term safety and included all patients who participated in any of the Phase 3 trials. Group 1C consisted of patients from short-term Phase 2 studies. The Division's clinical review focused on the Phase 3 patients but was concerned that the 1B grouping did not represent true long-term exposure, since patients from Group 1A who had not continued in the extension trials were still included in the sample. For this reason, the Division requested a second analysis of long-term data limited to those patients in the extension trials, Trials 36 and 38B, and the one-year safety study, Trial 35, along with AE incidence rates adjusted for time of exposure. Forest expressed concern that this pooling strategy may be flawed as Trial 38B was open-label and included only the 400 mcg BID dose. Forest submitted a third long-term safety analysis, separating Trial 38B from the other two safety trials. To resolve these differences, the Division's clinical review evaluated results from the three long-term safety analyses to see if the

different pooling strategies impacted the safety assessment. For the most part, the results appeared fairly comparable, so this memorandum focuses on the analyses as requested by the Division unless otherwise noted.

Deaths

Given a relatively older and chronically sick population, deaths are expected in a COPD program. A total of 17 deaths were reported in the aclidinium BID program: 8 deaths in the placebo-controlled trials and 9 in the long-term safety trials (Table 5). In the placebo-controlled trials, 4 deaths were reported in the aclidinium 400 mcg arm, compared to 2 deaths in the aclidinium 200 mcg and placebo arms each. The long-term trials, 6 and 3 deaths occurred in the aclidinium 400 and 200 mcg arms, respectively. The causes of death varied. Some cases appeared unlikely to be related to aclidinium (e.g. lung cancer, sepsis occurring a month after discontinuation, etc.,) but in other cases, causality could neither be confirmed nor ruled out.

Table 5 Summary of all deaths in the aclidinium BID program

	Trial	Age/ Sex	Time to death (days)	On-Treatment*	Cause of Death (preferred term)
Placebo-control trials	***Placebo***				
	34	78/M	33	Yes	Road traffic accident
	38A	49/M	48	Yes	Death
	Aclidinium 200				
	34	52/M	165	No	Completed suicide
	34	71/M	105	Yes	Myocardial infarction
	Aclidinium 400				
	33	65/M	23	Yes	Lung cancer metastatic
	34	56/F	91	Yes	Cardiac failure acute
	34	76/M	32 days after d/c	No	Sepsis
	38A	56/M	55	Yes	Cardio-respiratory arrest
Long-term safety trials	***Aclidinium 200***				
	35	68/M	366	Yes	Biliary sepsis
	35	63/F	228	No	Lung neoplasm malignant
	36	56/M	107	Yes	Multiple drug overdose accidental
	Aclidinium 400				
	35	73/F	103	No	Pneumonia
	35	72/M	281	Yes	Subarachnoid hemorrhage
	36	70/F	270	Yes	Esophagitis
	38B	48/F	180	Yes	Cardiac Arrest
	38B	51/F	282	Yes	Cardiac arrest
	38B	51/M	97	Yes	Cardio-respiratory arrest

* On-treatment defined as occurring within 30 days of last dose of investigational product.

Deaths attributed to a cardiovascular event or cardiorespiratory arrest were of particular interest. Of the 10 deaths in the aclidinium 400 mcg group, four were cited as cardiac arrest and one as acute cardiac failure, whereas 1 case of myocardial infarction was reported in patients who received aclidinium 200 mcg and no cases for placebo (although a cardiovascular cause cannot be ruled out in the 2 placebo cases). Given the high prevalence of cardiovascular disease in a COPD population and the limitations of sample size, the significance of these findings, if any, is uncertain. A more detailed discussion of

both fatal and non-fatal cardiovascular-related adverse events follows in a subsequent section.

For comparison, in the aclidinium QD program, the incidence of on-treatment death was similar between placebo and acidinium 200 mcg (0.7% and 0.6%, respectively), but the range of total daily doses was lower than the doses evaluated in the aclidinium BID program.

Serious adverse events (SAE)[5]and discontinuations due to adverse events
In the placebo-controlled trials, the overall incidence rate of serious adverse events was greater in the placebo group (105 events/1000 patient-years) compared to aclidinium 200 (70 events/1000 patient-years) and 400 mcg (76 events/1000 patient-years). A wide range of events were reported and most events occurred in just 1 or 2 patients. COPD cited as an SAE was an exception, with a higher incidence reported in the placebo arm (89 events/1000 patient-years) compared to aclidinium (45-50 events/1000 patient-years). In the long-term trials, a higher incidence of SAEs was reported overall for aclidinium 400 mcg compared to the 200 dose (89 versus 76 events/1000 patient-years), but the actual numbers were low and most events occurred in 1 or 2 patients, making it difficult to confirm any dose-dependence. SAEs related to AEs of interest specific to the drug class are discussed further below.

In the placebo-controlled trials, the rate of discontinuation due to an adverse event was highest in the placebo group and similar in the aclidinium groups, and the most commonly cited AE leading to discontinuation was COPD. Other AEs cited occurred in a few patients each, and no safety signal was apparent in the pattern of discontinuations. Similar results were observed in the long-term safety trials.

Cardiovascular adverse events
As discussed earlier, cardiovascular adverse events have been raised as an AE of specific interest for anticholinergic products. Forest conducted an analysis of major adverse cardiac events (MACE) and an analysis based on standard MedDRA queries (SMQ).

The MACE score is defined as the total number of cardiovascular deaths, nonfatal myocardial infarctions, and nonfatal strokes. Table 6 and Table 7 present the summary results of the original adjudication submitted in the application. More recently in January 2012, Forest readjudicated the deaths and reversed their decision on one of the two aclidinium 400 mcg cardiovascular deaths identified in the first adjudication. As there was prior consensus, and no substantial justification was provided for the decision to conduct a second adjudication, the relevance of this change is unclear, and results of the original adjudication are presented here.

[5] Serious Adverse Drug Experience is defined in 21 CFR 312.32 as any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience (defined in the same regulation as any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred), inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect.

Table 6 MACE score: Placebo-controlled trials						
	Placebo N=641 ET=190.6		Aclidinium 200 N=644 ET=199.4		Aclidinium 400 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

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 7 MACE score: Long-term safety trials				
	Aclidinium 200 N=448 ET=340.6		Aclidinium 400 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

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.

While these results do not indicate an increased overall MACE score for aclidinium, the strength of this assessment is limited by the relatively limited sample size and a low background event rate. With these caveats in mind, the small imbalance for cardiovascular deaths seen in both the placebo-controlled trials and long-term trials does not rise to the level of a clear safety signal, but it does introduce some uncertainty regarding the safety of aclidinium 400 mcg BID.

The cardiovascular SMQ analysis included search criteria for ischemic heart disease, supraventricular tachyarrhythmias, cardiac failure, and bradyarrhythmia (including conduction defects and sinus node function disorders). As with the MACE analysis, some imbalances were noted but the overall numbers were low, making the clinical relevance of these findings difficult to interpret as well (Table 8 and Table 9).

Table 8 Cardiovascular AE SMQ analysis, Placebo-controlled trials						
SMQ Category	**Placebo N=641 ET=190.6**		**Aclidinium 200 µg N=644 ET=199.4**		**Aclidinium 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

Table 9 Cardiovascular AE SMQ analysis, Long-term safety trials				
SMQ Category	**Aclidinium 200 µg N=448 ET=340.6**		**Aclidinium 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

Other cardiac safety parameters assessed in the program included serial ECGs and Holter monitoring in a subset of patients, as well as an earlier thorough QT study, which did not indicate a QT prolongation effect. ECG data did not suggest an increased risk of arrhythmia, both in terms of mean changes and individual outliers. Likewise, 24-hour Holter monitoring at Week 12 from a subset of patients in Trials 33 and 38A did not indicate any specific safety signals.

Other adverse events of interest

Other adverse events of interest included stroke, pneumonia, and symptoms associated with anticholinergic syndrome. Forest conducted an SMQ analysis of central nervous system hemorrhages and cerebrovascular conditions. Overall rates were low and did not indicate an increased risk associated with aclidinium. Similar analysis of preferred terms related to pneumonia (pneumonia bacterial, pneumonia, lobar pneumonia, and pneumonia streptococcal/pneumococcal) and other respiratory-related AEs (respiratory failure, bronchitis, and bronchospasm) also did not indicate any increased risk. Comparison of AEs associated with anticholinergic use, such as dry mouth, constipation, and urinary retention, did not indicate any clear dose dependence between the aclidinium 200 mcg and 400 mcg arms. A specific analysis of intestinal obstruction, esophageal stenosis, and small intestinal obstruction was also unrevealing.

Common adverse events
In terms of common adverse events, the overall rate was similar across the treatment arms of the placebo controlled trials (50-54%; Table 10). Similar events were observed in the long-term safety trials, and rates were fairly similar between the two doses.

Table 10 Common adverse events in ≥3% patients and occurring at a frequency greater than placebo, Placebo-controlled trials

Preferred term	Placebo N=641 ET=190.6		Aclidinium 200 µg N=644 ET=199.4		Aclidinium 400 µg N=636 ET=198.4	
	n (%)	Incidence Rate	n (%)	Incidence Rate	n (%)	Incidence Rate
Patients with at least 1 AE	344 (54)	1805	321 (50)	1609	319 (50)	1608
Headache	32 (5)	168	43 (7)	216	42 (7)	212
Nasopharyngitis	25 (4)	131	40 (6)	201	35 (6)	176
Cough	14 (2)	74	17 (3)	85	19 (3)	96
Diarrhea	9 (1)	47	12 (2)	60	17 (3)	86

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 application included subgroup analysis of AEs by age, gender, race, and COPD severity. The overall rate of adverse events was slightly higher in the oldest age bracket, patients ≥70 years, but the distribution of AEs was similar to the profile observed in younger patients. No clinically relevant differences by gender or baseline disease severity were observed, and subgroup analysis by race was limited by the low number of non-White patients.

Other safety parameters
Other safety assessments performed in the clinical program included laboratory parameters and vital signs. While some clinically relevant derangements were observed in a few individuals, the overall distribution was similar across placebo and active treatment arms in the placebo-control trials and between aclidinium dose levels in the long-term safety trials.

Safety conclusions
Adverse events were generally low in incidence, but the overall long-term safety database for aclidinium 400 mcg BID was relatively modest compared to other COPD development programs. In this context, a small imbalance in cardiovascular deaths was observed for aclidinium 400 mcg, and subsequent additional data from long-term exposure suggests a possible dose-dependence. Whether these results represent a spurious finding or a potential safety signal is difficult to discern and warrants further investigation. This issue is of importance given the concern for possible increased mortality that has been raised with other inhalational anticholinergic agents. Therefore, the clinical review recommends a postmarketing trial to address cardiovascular risk specifically. The CDTL review concurs with this recommendation. The proposed postmarketing requirement (PMR) trial is described in further detail below.

9. Advisory Committee Meeting

A meeting of the Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was convened on February 23, 2012, to discuss the application. The major issues for discussion were the adequacy of the efficacy data to support the proposed indication, the adequacy of the safety database for making an informed benefit-risk assessment, and the benefit-risk assessment for aclidinium 400 mcg twice daily for its proposed indication. The following questions for discussion and voting were posed to the committee:

1. Discuss the efficacy data for aclidinium considering the following
    - The bronchodilatory effect of aclidinium
    - The effect of aclidinium on other efficacy endpoints

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 COPD? **(Voting question)**
    - *If not, what further data should be obtained?*

3. Discuss the overall safety profile of aclidinium considering the following
    - The size of the safety database
    - The duration of exposure

4. Has the safety of aclidinium been adequately assessed for the proposed indication? **(Voting question)**
    - *If not, what further data should be obtained?*

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? **(Voting Question)**
    - *If not, what further data should be obtained?*

In general, the panel members concurred that there were sufficient data to support the efficacy of aclidinium 400 mcg for the proposed indication, and voted unanimously on Question #2 in favor of aclidinium (14 yes, 0 no). Several members stated that data on COPD exacerbations would be helpful for determining how best to use aclidinium. In terms of safety, the majority of the panel felt that the safety database was generally adequate, but several members voiced concerns regarding the need for further information in patients at risk for cardiovascular disease. The vote on Question #3 reflected this mix of opinions (10 yes, 3 no, 1 abstention). The final vote on Question #5 regarding the overall risk-benefit assessment was consistent with the views and votes expressed previously, with the majority stating that there were sufficient data to support of aclidinium 400 mcg twice daily for the maintenance treatment of bronchospasm (12 yes, 2 no).

10. Pediatrics

COPD is considered a disease specific to adults. For this reason, the requirement for pediatric studies under the Pediatric Research Equity Act (PREA) were waived. The Pediatric Research Committee (PeRC) concurred with the waiver.

11. Other Relevant Regulatory Issues

The Applicant conducted the clinical trials using Good Clinical Practices and provided the required financial disclosure information for investigators, which did not suggest a conflict of interest that would have impacted the overall conclusions of the review. A DSI audit was requested of two study sites that enrolled a higher number of patients: Dr. Anthony D'Urzo in Toronto, Canada and Dr. Susanne Mindt-Prüfert in Hamburg, Germany. The conclusion of the DSI was that the data appeared to be reliable.

12. Labeling

This section provides a high level overview of labeling, which remains pending at the time of this memorandum. The proposed tradename is Tudorza Pressair, which has been found acceptable by DMEPA. Consults from OPDP and OSE were received and included in the labeling process. Carton and container labeling were also reviewed. Regarding the package insert, the following are high level revisions that were made to the product label:

- Section 6: Addition of long-term safety data
- Section 14: Inclusion of dose-ranging information
- Section 14: Presentation of analysis based on observed data without imputation
- Section 14: (b) (4)

13. Recommendations/Risk Benefit Assessment

- **Recommended Regulatory Action**

The recommended regulatory action is Approval.

- **Risk Benefit Assessment**

Replicate, statistically significant differences between aclidinium 400 mcg BID and placebo were demonstrated for the primary efficacy endpoint of 12-hour post-dose AM trough FEV1 after 12 weeks of treatment. Secondary endpoints provided additional support, including peak FEV1, serial FEV1 measurements, patterns of rescue medication usage, and COPD exacerbation data. Adverse events were generally low in incidence,

but the overall long-term safety database for aclidinium 400 mcg BID is relatively modest compared to other COPD development programs. In this context, a small imbalance in cardiovascular deaths was observed for aclidinium 400 mcg, and subsequent additional data from long-term exposure suggests a possible dose-dependence. Whether these results represent a spurious finding or a potential safety signal is difficult to discern and warrants further investigation. This issue is of particular importance given the concern for possible increased mortality that has been raised with other inhalational anticholinergic agents.

- **Recommendation for Postmarketing Risk Evaluation and Management Strategies**

No postmarketing risk evaluation and management strategies are recommended.

- **Recommendation for other Postmarketing Requirements and Commitments**

Given a potential increase in cardiovascular-related adverse events associated with aclidinium, a postmarketing safety trial to further assess the risk of cardiac events is recommended as follows:

FDAA Post-marketing Requirement

Conduct a postmarketing clinical trial with Tudorza Pressair in patients with COPD to evaluate the risk of major adverse cardiac events.

- *Protocol submission:* *November 2012*
- *Study Completion:* *September 2017*
- *Final Report Submission:* *June 2018*

The need for a PMR trial has been discussed with the Applicant. The Applicant submitted a preliminary proposal on April 9, 2012, for a randomized, placebo-controlled, double-blind, parallel group trial in approximately 4000 patients with moderate to severe COPD and a history of one COPD exacerbation within one year of screening. The trial duration will be determined by the number of cardiovascular events, with a minimum treatment period of one year to a maximum of three years. Patients will be randomized to receive aclidinium 400 mcg BID or placebo. Short-acting beta-agonist (SABA) will be available as rescue medication, and inhaled corticosteroids (ICS), long-acting beta-agonists (LABA), ICS/LABA combination products, systemic steroids, and/or PDE4 inhibitors will be permitted background medication. Other anti-muscarininc agents will be prohibited. The trial will be powered to assess two co-primary endpoints: the time to first major cardiac event and the rate of COPD exacerbations during the first year of treatment. While the general proposal appears reasonable, the details of the protocol remain subject to further discussion. Two major issues for consideration in the trial design include the enrichment of the trial population with patients at increased cardiovascular risk and the potential ethical concerns of withholding LAMA during the treatment period, particularly in those patients who were on a LAMA at screening.

- **Recommended Comments to Applicant**

There are no additional comments for the Approval Letter.

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/s/

SUSAN L LIMB
06/11/2012