2 SYNOPSIS

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**
Title of Study: A MULTIPLE DOSE, DOUBLE BLIND, DOUBLE-DUMMY, TWO-WEEK 3 WAY CROSS-OVER, PLACEBO CONTROLLED CLINICAL TRIAL TO ASSESS THE EFFICACY AND SAFETY OF TWICE DAILY INHALED ACLIDINIUM BROMIDE 400 µg COMPARED TO PLACEBO AND TO AN ACTIVE COMPARATOR IN PATIENTS WITH STABLE MODERATE TO SEVERE CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)		
Investigators: Coordinating Investigator: Other Principal Investigator:		
Study centres:		
Publication (reference): None		
Studied period (years): Date study initiated (first screening): 09 March 2009 Date study finalised (last patient last visit): 01 July 2009[1] [1] Treatment with IMP was completed on 27 June 2009, while the study was considered completed when the last follow-up call was performed (01 July 2009).	**Phase of development:** IIa	
Objectives: - To evaluate the efficacy of inhaled aclidinium bromide 400 µg BID in moderate to severe COPD patients - To assess the safety and tolerability of multiple doses of inhaled aclidinium bromide 400 µg BID in the same target population		
Methodology: The study consisted of 3 periods of 15 treatment days each, separated by a washout period of 9 to 15 days. At each period, patients received one of the 3 treatments: aclidinium bromide 400 µg BID, tiotropium 18 µg QD or placebo. Depending on the treatment arm the patient was assigned to in each period, patients received the following:		

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Treatment arm[1]		**Morning administration**	**Evening administration**
A:	Aclidinium bromide 400 µg BID	Aclidinium bromide 400 µg + placebo to tiotropium	Aclidinium bromide 400 µg
T:	Tiotropium 18 µg QD	Placebo to aclidinium bromide + tiotropium 18 µg	Placebo to aclidinium bromide
P:	Placebo	Placebo to aclidinium bromide + placebo to tiotropium	Placebo to aclidinium bromide

BID = *bis in die* (twice a day); QD = *quaque die* (every day)
[1] Patients received each of the three treatment arms (one per period)

After a Screening evaluation, eligible patients had at least a 5-day run-in period (and a maximum of 9 days) to assess patient's clinical stability. At the end of the run-in period, those patients still fulfilling inclusion/exclusion criteria were assigned to one of the six treatment sequences according to a randomisation schedule in a (1:1:1:1:1:1) ratio:

Sequence	**Period 1**	**Period 2**	**Period 3**
1	A	P	T
2	A	T	P
3	T	A	P
4	T	P	A
5	P	A	T
6	P	T	A

A = aclidinium bromide 400 µg BID; T = tiotropium 18 µg QD; P = placebo
BID = *bis in die* (twice a day); QD = *quaque die* (every day)

After the Screening Visit, there were 6 more visits (Visits 1 to 6 [V1 to V6]) and a Follow-up Visit (phone contact). At each visit (V1 to V6), patients were confined to the clinical pharmacology research unit (CPRU) for approximately 25 h (from 08:00 on the visit day to 09:00 on the following day). At the beginning of each period, patients were provided with two boxes of study medication (differentiated between morning and evening use).
For each treatment period, patients received the first dose of study medication at the CPRU at 09:00 (±1 h) on Day 1, at least 10 min after last baseline spirometric measurement. The last dose at each treatment period was administered at the CPRU on Day 15 at 21:00 (±1 h).
Follow-up contact with the patient was made 4 to 6 days after the last IMP administration or after premature discontinuation. This consisted of a telephone call in order to assess adverse events. A clinic visit might have been arranged if warranted in the opinion of the Investigator.

Number of subjects (planned and analysed):

Planned:	30
Screened:	41
Randomised:	30
Completed study:	27
Evaluated for safety:	30
Evaluated for efficacy (ITT):	30
Evaluated for efficacy (PP):	27

ITT = Intention-to-treat; PP = Per-Protocol

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Diagnosis and main criteria for inclusion:

- Adult male and female patients aged ≥40 years with stable moderate to severe COPD (GOLD guidelines)
- Post-salbutamol forced expiratory volume in one second (FEV_1) <80% and ≥30% of predicted normal value and post-salbutamol FEV_1 / forced vital capacity (FVC) <70%
- Current or ex−smokers of ≥10 pack-years
- Patients with no history or current diagnosis of asthma
- No evidence of an exacerbation within 6 weeks prior to the Screening Visit
- No evidence of clinically significant respiratory and/or cardiovascular conditions or laboratory abnormalities
- No contraindication to use of anticholinergic drugs such as known symptomatic prostatic hypertrophy, bladder neck obstruction or narrow-angle glaucoma.

Test product , dose and mode of administration, batch number, expiry date:

Name:	Aclidinium bromide
Administration route:	Oral inhalation using Genuair® multi-dose dry powder inhaler
Dosage form:	Dry powder for inhalation
Dose and regimen:	400 µg, one puff at 09:00 (±1 h) and at 21:00 (±1 h)
Batch number:	K1-69
Expiry date:	October 2010

Duration of treatment:

There were 3 periods of 15 treatment days.

The total duration of the study for each patient was approximately 11 to 12 weeks (including Screening and Follow-up Visits). There was at least a 5-day run-in period with a maximum of 9 days, followed by 3 periods of 15 treatment days separated by a washout period of 9 to 15 days and a Follow-up Visit (phone contact) that was performed 4 to 6 days after last treatment day.

Reference therapies, doses and modes of administration, batch numbers, expiry dates:

Name:	Tiotropium
Administration route:	Oral inhalation using Handihaler® single-dose dry powder inhaler
Dosage form:	Dry powder in hard gelatine capsule form inserted in a Handihaler®
Dose and regimen:	18 µg, one puff at 09:00 (±1 h)
Batch number:	087F0145
Expiry date:	December 2009
Name:	Placebo to aclidinium bromide
Administration route:	Oral inhalation using Genuair® multi-dose dry powder inhaler
Dosage form:	Dry powder for inhalation
Dose and regimen:	Placebo, one puff at 09:00 (±1 h) and at 21:00 (±1 h)
Batch number:	DPI022
Expiry date:	October 2010
Name:	Placebo to tiotropium
Administration route:	Dry powder (lactose) in hard gelatine capsule form inserted in a Handihaler®
Dosage form:	Dry powder for inhalation
Dose and regimen:	Placebo, one puff at 09:00 (±1 h)
Batch number:	086F0144
Expiry date:	December 2009

Criteria for evaluation:

Pharmacodynamics/Efficacy:

Primary:

- Change from baseline in normalised FEV_1 area under the curve over the 12-h period immediately after morning IMP administration, normalised AUC_{0-12}, at Day 15 on treatment

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Secondary:
- Change from baseline in normalised FEV_1 AUC_{0-12} at Day 1 on treatment
- Change from baseline in normalised FVC AUC_{0-12} at Days 1 and 15 on treatment
- Change from baseline in normalised FEV_1 and FVC AUC_{0-24} at Days 1 and 15 on treatment
- Change from baseline in normalised FEV_1 and FVC AUC_{12-24} at Days 1 and 15 on treatment
- Change from baseline in morning and evening pre-dose FEV_1 and FVC at Days 1 and 15 on treatment
- Change from baseline in morning and evening peak FEV_1 and FVC at Days 1 and 15 on treatment
- Change from baseline in FEV_1 and FVC at each specific time-point at Days 1 and 15 on treatment
- Change from baseline in day and night use of relieve medication recorded by the patient (number of puffs) at Weeks 1 and 2 on treatment
- Change from baseline in COPD symptom scores at Weeks 1 and 2 on treatment

AUC_{0-12} = area under the curve from 0 to 12 hours; AUC_{0-24} = area under the curve from 0 to 24 hours; AUC_{12-24} = area under the curve from 12 to 24 hours

Safety:
Adverse events (AEs), serious adverse events (SAEs), 12-lead ECG parameters, blood pressure parameters, laboratory parameters (standard haematology, biochemistry and urinalysis) and pregnancy results.

Other:
Convenience of devices assessment, exposure to study medication, medication taken during the run-in and concomitant medication, number (%) of withdrawals and reasons for withdrawal.

Statistical methods:
The analysis of all the efficacy variables was performed on the ITT population. In addition, the primary efficacy variable was also analysed using the PP Population to assess the robustness of the findings from the ITT Population. All the safety outcomes were analysed using the Safety population.
All variables of efficacy were analyzed using Analysis of Covariance (ANCOVA) models for crossover designs. Sequence, period and treatment were included in the model as fixed effects, patient was a random effect and baseline FEV_1 was included as a covariate.
Safety and tolerability data, demographic variables, baseline characteristics and concomitant medication were summarised by means of the appropriate descriptive statistics by treatment or overall.

SUMMARY – CONCLUSIONS

Efficacy Results:
- Twice-daily doses of aclidinium bromide 400 µg BID induced a marked bronchodilatory effect compared to placebo that was evident from post-morning administration on Day 1, was sustained over time and was well preserved until the end of the entire treatment period, i.e. 24 h after morning administration on Day 15 (see tables below).
- The change from baseline in normalised AUC_{0-12h} FEV_1 on Day 15 was higher after treatment with aclidinium bromide (0.236 L) and tiotropium (0.260 L) than that after placebo (0.015 L). Similarly, the changes from baseline in normalised AUC_{0-24h} FEV_1 were 0.226 L, 0.178 L and –0.006 L, respectively, and the changes from baseline in normalised AUC_{12-24h} FEV_1 were 0.174, 0.096 L and –0.032 L, respectively.
- The differences in the change from baseline in normalised AUC values of FEV_1 between both aclidinium bromide and tiotropium versus placebo were clinically and statistically significant at Day 15 on treatment:

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

Change from baseline in FEV_1 at Day 15 (vs placebo)	Aclidinium bromide		Tiotropium		Aclidinium vs tiotropium	
	LSmean	p-value	LSmean	p-value	LSmean	p-value
$AUC_{0-12/12h}$	0.221	<0.0001	0.244	<0.0001	-0.023	0.5723
$AUC_{0-24/24h}$	0.232	<0.0001	0.185	<0.0001	0.048	0.1038
$AUC_{12-24/12h}$	0.207	<0.0001	0.129	0.0003	0.078	0.0202

$AUC_{0-12/12h}$ = normalised AUC_{0-12h}; $AUC_{0-24/24h}$ = normalised AUC_{0-24h};
$AUC_{12-24/12h}$ = normalised AUC_{12-24h}

- Aclidinium bromide 400 µg BID has shown a bronchodilatory profile that was similar to tiotropium in the first 12 h and slightly higher than that after tiotropium over the last 12 h after 15 days of treatment as demonstrated by statistically significant differences in FEV_1 $AUC_{12-24/12h}$ and comparable $AUC_{0-12/12h}$ and $AUC_{0-24/12h}$ (see table above).
- The differences in the change from baseline in normalised AUC values of FEV_1 between both aclidinium bromide and tiotropium versus placebo were clinically and statistically significant at Day 1:

Change from baseline in FEV_1 at Day 1 (vs placebo)	Aclidinium bromide		Tiotropium		Aclidinium vs tiotropium	
	LSmean	p-value	LSmean	p-value	LSmean	p-value
$AUC_{0-12/12h}$	0.214	<0.0001	0.163	<0.0001	0.052	0.0411
$AUC_{0-24/24h}$	0.235	<0.0001	0.162	<0.0001	0.073	0.0080
$AUC_{12-24/12h}$	0.262	<0.0001	0.161	<0.0001	0.101	0.0017

$AUC_{0-12/12h}$ = normalised AUC_{0-12h}; $AUC_{0-24/24h}$ = normalised AUC_{0-24h};
$AUC_{12-24/12h}$ = normalised AUC_{12-24h}

- Aclidinium bromide 400 µg BID provided similar bronchodilation on Day 1 compared to Day 15 in all parameters assessed (see tables above). The bronchodilation provided by tiotropium was lower on Day 1 compared to Day 15. These results might suggest that the pharmacodynamic steady state is reached after the first day of treatment with aclidinium bromide, whereas at least 1 week is needed to reach this state after tiotropium, as defined in its Summary of Product Characteristics (SmPC).
- The treatment difference between aclidinium bromide and tiotropium in the change from baseline in all FEV_1 AUC on Day 1 reached statistical significance, favouring aclidinium bromide, ranging from 0.052 L in the $AUC_{0-12/12h}$ (p=0.0411) to 0.101 L in the $AUC_{12-24/12h}$ (p=0.0017).
- In addition, aclidinium bromide has provided a clinically and statistically significant bronchodilation at morning pre-dose FEV_1 at Day 15 on treatment compared with placebo (0.186 L; p<0.0001) and the magnitude of this improvement was slightly higher than that in the tiotropium group, although this difference was not statistically significant (treatment difference of 0.036 L; p =0.2560). The magnitude of the improvement with tiotropium compared to placebo (0.150 L) is consistent with previous clinical trials.
- Similar results to those obtained for FEV_1 were obtained for the FVC at Days 1 and 15 on treatment.
- A statistically significant improvement in COPD symptoms breathlessness, cough and night time symptoms compared to placebo over the 15 days on treatment was only demonstrated for treatment with aclidinium bromide. No improvements were observed in sputum production.
- In addition, the proportion of patients taking relieve medication was lower following aclidinium

Name of Sponsor / Company: AstraZeneca **Name of Finished Product:** N.A. **Name of Active Ingredients:** Aclidinium bromide	**Individual Study Table Referring to Part of the Dossier** **Volume:** **Page:**	**(For National Authority Use only)**

bromide compared with tiotropium and placebo. Moreover, the daily use of relieve medication (number of puffs taken) after treatment with aclidinium bromide was statistically significantly lower versus placebo (–2.0 puffs/day) as well as at day time, but not statistically significant, versus tiotropium.

Additional Results:

- Most patients (60%) preferred one of the 2 inhalers used in this study and most of these patients preferred the Genuair® device "definitely" (30%) or "somewhat" (20%) compared with 7% and 3% of the patients, respectively, who preferred the Handihaler®.

Safety Results:

- Administration of aclidinium bromide 400 µg BID for 15 days was safe and generally well tolerated in patients with stable moderate to severe COPD patients. A drug-response relationship could not be observed in any of the different safety and tolerability outcomes evaluated.
- The incidence of TEAEs in the aclidinium bromide group was similar to that after placebo (24.1% vs. 26.7%) and both of them were higher than the incidence in the tiotropium group (10.7%). COPD exacerbation (after placebo administration) and diarrhoea (after aclidinium bromide administration) were the most commonly reported TEAE (reported by at least two patients).
- The percentage of TEAEs considered by the Investigator to be related to IMP was low and similar in aclidinium and placebo (15.4% vs. 22.2%). These events included pruritus and cough after aclidinium bromide, and dyspnoea and oropharyngeal pain after placebo.
- There was one SAE (severe COPD exacerbation), which led to the discontinuation of the patient, and 2 additional withdrawals due to TEAEs (COPD exacerbation and atrial fibrillation), all of which occurred in the treatment period with placebo administration and were considered not related to IMP.
- The TEAEs were mild (48%) or moderate (44%) in intensity, 2 TEAEs (pneumonia and COPD exacerbation) were severe (8%).
- There was no clinically relevant abnormality in any safety laboratory parameter or blood pressure.
- ECGs were globally judged by the Investigator as being normal or abnormal without clinical relevance except for 2 abnormalities that were clinically relevant according to the Investigator: one in the aclidinium bromide group (ectopic atrial rhythm 2 h post-dose at Day 1) and another in the placebo group (atrial fibrillation before administration of placebo at Day 15).

CONCLUSIONS:

DATE OF REPORT:
22 April 2010