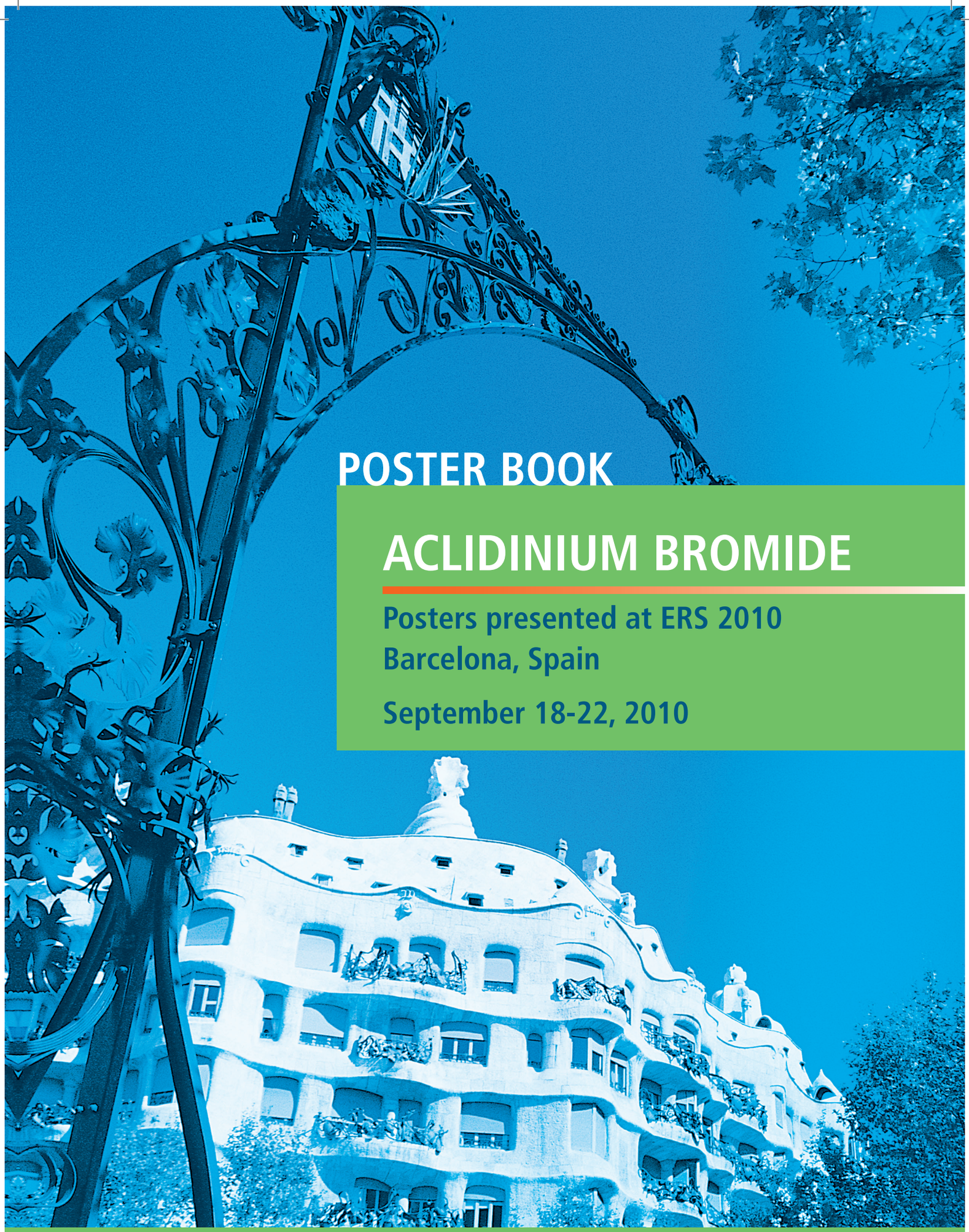

POSTER BOOK

ACLIDINIUM BROMIDE

Posters presented at ERS 2010
Barcelona, Spain

September 18-22, 2010

Contents

Clinical posters

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Genuair® inhaler posters

Absolute bioavailability of inhaled aclidinium bromide and safety and tolerability of aclidinium bromide administered intravenously in healthy subjects

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Introduction

- Aclidinium bromide is a novel, long-acting muscarinic antagonist currently in Phase III development as a maintenance treatment for COPD.
- Aclidinium bromide exhibits long residence time at M_3 receptors, with a shorter residence time at M_2 receptors, and is rapidly hydrolysed in human plasma to two inactive metabolites.[1-4]
- Clinical studies in COPD patients have demonstrated a favourable tolerability profile and sustained bronchodilation with aclidinium bromide.[5,6] At single doses up to 6000 µg, aclidinium bromide via dry powder inhaler was well tolerated and the maximum tolerated dose (MTD) could not be established.[2]
- Objectives of this two-part study were:
  - To evaluate the safety and tolerability of single ascending doses of intravenous (IV) aclidinium bromide in healthy male subjects (Part I).
  - To estimate the absolute bioavailability of aclidinium bromide administered by inhalation via the Genuair® inhaler (Part II).

Methods

Study design

- Healthy male subjects (n=24) were randomised to one of two treatment groups (1:1) in this two-part Phase I study.
- Part I: Three-period, single-blind, placebo-controlled study (n=12) of alternating, single-ascending IV doses of aclidinium bromide (Table 1A).
  - Subjects were randomised to 1 of 2 treatment groups (Group A or B) and treated with a single aclidinium bromide dose or placebo via IV infusion over a 5-minute period (Table 1A).
- Part II: Open-label, single-dose, two-period crossover study (n=12) of IV and inhaled administration of aclidinium bromide 200 µg (Table 1B).
  - Subjects were randomised to 1 of 2 treatment groups (Group C or D) and participated in both treatment periods.
  - Aclidinium bromide was administered by IV infusion over 5 minutes (Period I) and as a single inhalation (Period II).
- Subjects resided at the clinical research unit from the morning prior to dosing (Day -1) to the morning of Day 3 (48 hours post-dose) of each treatment period. All subjects were assessed via telephone 7 days after study completion.

Table 1. Study design and dosing regimen

A. Part I

	Period I	Period II	Period III
Treatment group A (n=6)	IV aclidinium bromide 25 µg (n=4), IV placebo (n=2)	IV aclidinium bromide 100 µg (n=4), IV placebo (n=2)	IV aclidinium bromide 300 µg (n=4), IV placebo (n=2)
Treatment group B (n=6)	IV aclidinium bromide 50 µg (n=4), IV placebo (n=2)	IV aclidinium bromide 200 µg (n=4), IV placebo (n=2)	IV aclidinium bromide 400 µg (n=4), IV placebo (n=2)

B. Part II

	Period I	Period II
Treatment group C (n=6)	Inhaled aclidinium bromide 200 µg	IV aclidinium bromide 200 µg
Treatment group D (n=6)	IV aclidinium bromide 200 µg	Inhaled aclidinium bromide 200 µg

All treatment periods were separated by washout periods of ≥7 days.

Study population

Inclusion criteria

- Healthy, non-smoking males aged 18 to 45 years, with normal physical examination, vital signs, pulse rate, and blood pressure
- Body mass index of 18-30 kg/m^2

Exclusion criteria

- Evidence of sensitivity or allergic reaction to muscarinic antagonists
- Clinically significant or relevant cardiovascular conditions, laboratory tests, or electrocardiogram (ECG) parameters
- History of alcohol or substance abuse
- History of orthostatic hypotension, syncope, or vasovagal attacks
- Any clinical condition that may affect the absorption, distribution, metabolism, or excretion of aclidinium bromide
- Concomitant medications

Pharmacokinetic assessments

- Blood samples for pharmacokinetic assessments were taken pre-dose, at 5, 15, 30, 45 minutes, and at 1, 1.5, 2, 4, 6, 8, 10, 12, 16 (Part II only), 24, and 48 (Part II only) hours post-dose.
- In Part II, urine was collected pre-dose and at 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-36, and 36-48 hours post-dose (inhalation and IV administration) to measure the urinary concentration of aclidinium and its metabolites.
- The lower limit of quantitation (LLOQ) for the plasma measurements was 5 pg/mL for aclidinium bromide, 5 pg/mL for the alcohol metabolite, and 100 pg/mL for the acid metabolite.
- The LLOQ for the urine measurements was 20 pg/mL for aclidinium bromide, 250 pg/mL for the alcohol metabolite, and 2000 pg/mL for the acid metabolite.

Safety assessments

- Safety and tolerability were assessed via adverse events (AEs), vital signs, ECGs, clinical laboratory tests, and physical examinations.
- The maximum tolerated dose was defined as the dose level that caused function-limiting AEs in at least 50% of subjects or that elicited a medically unacceptable, drug-related serious AE in ≥1 subject.

Statistical analysis

- Pharmacokinetic (PK) analyses were performed on all subjects who received aclidinium bromide and completed the study (PK analysis population).
- Pharmacokinetic calculations included $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}6h}$, C_{max}, t_{max}, and $t_{½}$; CL and V_z for aclidinium bromide and its two inactive metabolites (acid metabolite and alcohol metabolite); and absolute bioavailability (F) for aclidinium bromide.
- Urinary pharmacokinetic calculations included amount of aclidinium, acid or alcohol metabolite excreted in urine, percentage of dose excreted in urine (fe), and renal clearance (CL_R).
- Demographic and safety data were analysed using descriptive statistics for all subjects who received one dose of aclidinium (safety population).

Results

Baseline characteristics

- Of 24 randomised subjects, 22 completed the study. Mean (SD) ages were 29 (6.6) and 31 (8.8) years in Part I and Part II, respectively.
- Baseline demographics and clinical characteristics were similar between treatment groups.

Part I

Plasma pharmacokinetics of aclidinium following IV administration

- Maximum plasma concentration (C_{max}) occurred at a median t_{max} of 5-6 minutes (0.08-0.11 hours) after the start of the IV infusion at each dose level (Table 2).
- After C_{max}, plasma levels of aclidinium declined rapidly at all dose levels; most concentrations measured beyond 45 minutes after IV start were close to the LLOQ (5.0 pg/mL).
- Exposure ($AUC_{0\text{-}t}$) and maximum systemic exposure (C_{max}) increased proportionally with increasing dose in the 50 to 300 µg range, and appeared to plateau at the 300 µg IV dose.

Table 2. Mean plasma pharmacokinetic parameters of aclidinium bromide following single IV administration: Part I PK analysis population

Parameter	Aclidinium bromide (IV) 25 µg (n=3)	50 µg (n=4)	100 µg (n=4)	200 µg (n=4)	300 µg (n=3)	400 µg (n=4)
$AUC_{0\text{-}t}$ (pg.h/mL)	247.5 (37.1)	307.9 (36.0)	857.5 (25.2)	1537.7 (36.8)	2285.8 (21.0)	2365.9 (29.7)
$AUC_{t_{last}\text{-}\infty}$ (pg.h/mL)	NC	NC	NC	1545.4 (37.0)	2296.1 (21.1)	2539.2 (30.2)[a]
C_{max} (pg/mL)	1536.3 (36.6)	2009.0 (34.7)	5873.3 (26.8)	10605.9 (32.4)	15363.2 (27.4)	17282.4 (30.4)
t_{max} (h)	0.08 (0.08-0.13)	0.10 (0.10-0.17)	0.11 (0.08-0.15)	0.08 (0.08-0.08)	0.10 (0.08-0.10)	0.08 (0.08-0.08)
$t_{1/2}$ (h)	NC	NC	NC	0.83 (80.7)	1.02 (80.6)	1.35 (92.2)[a]
λ_z (1/h)	NC	NC	NC	1.83 (114.7)	0.98 (57.1)	0.81 (60.2)[a]
CL (L/h)	NC	NC	NC	140.4 (28.4)	135.2 (23.9)	169.7 (35.7)[a]
V_z (L)	NC	NC	NC	140.0 (56.0)	185.3 (66.6)	302.4 (79.1)[a]

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max}, for which median (min-max) are presented.
IV, intravenous; NC, not calculated; PK, pharmacokinetic
[a]n=3

Plasma pharmacokinetics of acid and alcohol metabolites following IV aclidinium administration

- Following IV aclidinium, maximum concentrations of the acid metabolite appeared slightly later (mean t_{max}: 8-15 minutes) than for aclidinium bromide; median t_{max} for the alcohol metabolite was 5-6 minutes (Table 3).
- The mean apparent elimination half-life of the acid metabolite was similar across the 50 to 400 µg IV aclidinium bromide dose range ($t_{½}$ range: 3.50-4.22 hours); the elimination half-life across the same range was shorter ($t_{½}$ range: 1.10-2.76 hours) for the alcohol metabolite (Table 3).

Table 3. Mean plasma pharmacokinetic parameters of acid and alcohol metabolites: Part I PK analysis population

Parameter	Aclidinium bromide (IV) 25 µg (n=3)	50 µg (n=4)	100 µg (n=4)	200 µg (n=4)	300 µg (n=3)	400 µg (n=4)
Acid metabolite						
$AUC_{0\text{-}t}$ (pg.h/mL)	819.7 (16.5)	3215.5 (22.2)	6787.0 (7.1)	14180.9 (19.0)	19453.4 (23.2)	27806.7 (22.9)
$AUC_{0\text{-}\infty}$ (pg.h/mL)	1207.0 (11.0)	3798.5 (19.3)	7463.2 (7.5)	15692.5 (18.0)	21766.1 (21.9)	30510.5 (21.1)
C_{max} (pg/mL)	495.9 (12.4)	1432.4 (16.9)	2662.4 (20.5)	6255.7 (8.7)	8801.4 (24.0)	11218.5 (15.3)
t_{max} (h)	0.25 (0.13-0.25)	0.13 (0.10-0.25)	0.13 (0.10-0.27)	0.25 (0.25-0.25)	0.25 (0.10-0.28)	0.25 (0.25-0.25)
$t_{½}$ (h)	2.27 (10.2)	3.50 (27.3)	3.62 (7.8)	3.90 (14.4)	4.04 (12.4)	4.22 (17.0)
λ_z (1/h)	0.31 (9.8)	0.21 (26.4)	0.19 (7.8)	0.18 (14.1)	0.17 (11.6)	0.17 (16.8)
Alcohol metabolite						
$AUC_{0\text{-}t}$ (pg.h/mL)	137.5 (39.9)	330.5 (28.7)	656.0 (16.3)	1460.3 (14.7)	2156.8 (21.4)	2646.1 (17.8)
$AUC_{0\text{-}\infty}$ (pg.h/mL)	NC	340.2 (28.3)	711.5 (13.6)[a]	1485.1 (14.5)	2180.7 (20.9)	2675.4 (17.8)
C_{max} (pg/mL)	377.8 (32.4)	1090.4 (20.3)	2178.3 (25.0)	4877.7 (16.7)	7244.5 (47.2)	9737.7 (21.7)
t_{max} (h)	0.08 (0.08-0.13)	0.10 (0.10-0.17)	0.11 (0.08-0.15)	0.08 (0.08-0.08)	0.10 (0.08-0.10)	0.08 (0.08-0.08)
$t_{½}$ (h)	NC	1.10 (14.2)	2.17 (24.5)[a]	2.79 (17.7)	2.48 (18.0)	2.76 (12.2)
λ_z (1/h)	NC	0.64 (14.8)	0.33 (23.0)[a]	0.25 (18.6)	0.29 (19.0)	0.25 (12.2)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max}, for which median (min-max) are presented.
IV, intravenous; NC, not calculated; PK, pharmacokinetic
[a]n=3

Part II

Plasma pharmacokinetics of aclidinium following inhalation and IV administration

- The absolute bioavailability (F) of inhaled aclidinium 200 µg was low at a mean of <5% (Table 4), with values for individual subjects ranging from 1.6% to 9.1%.
- Aclidinium appeared rapidly in plasma following aclidinium 200 µg inhalation, with maximum plasma concentrations occurring at a median t_{max} of 5 minutes (0.09 hours) post-dose (Table 4); the IV aclidinium pharmacokinetic profile was similar in Part II compared with Part I (Tables 2 and 4).

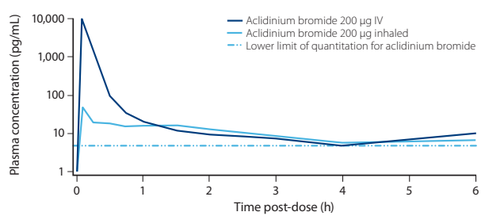
Table 4. Mean plasma and urinary pharmacokinetic parameters of aclidinium bromide: Part II PK analysis population

Parameter	Aclidinium bromide 200 µg (inhaled) (n=12)	200 µg (IV) (n=12)
F (%)[a]	4.37 (52.1)	NC
$AUC_{0\text{-}6}$ (pg.h/mL)	71.1 (52.8)	1744.1 (40.4)
$AUC_{0\text{-}\infty}$ (pg.h/mL)	76.8 (43.5)[b]	1816.3 (53.7)[c]
C_{max} (pg/mL)	52.7 (63.8)	9882.4 (39.4)
t_{max} (h)	0.09 (0.05-0.35)	0.10 (0.08-0.13)
$t_{½}$ (h)	2.64 (43.8)[b]	0.68 (129.3)[c]
λ_z (1/h)	0.30 (40.0)[b]	2.62 (63.4)[c]
CL (L/h)	NC	146.2 (59.8)[c]
V_z (L)	NC	94.9 (80.9)[c]
Ae (ng)	329.5 (33.7)	5448.0 (19.5)
fe (%)	0.16 (33.7)	2.72 (19.5)
CL_R (mL/min)[a]	87.0 (39.4)	60.3 (43.7)

Arithmetic mean (CV%) data are presented for all parameters with the exception of t_{max}, for which median (min-max) are presented.
F, absolute bioavailability; Ae, amount of unchanged drug excreted in urine; CL_R, renal clearance; fe, dose excreted in urine; IV, intravenous; NC, not calculated; PK, pharmacokinetic
[a]Based on $AUC_{0\text{-}6h}$; [b]n=5; [c]n=6

- Aclidinium bromide concentrations declined rapidly in plasma following aclidinium inhalation (Figure 1); most concentrations measured beyond ~1 hour were close to the LLOQ.

Figure 1. Mean plasma concentration of aclidinium bromide (semi-logarithmic scale): Part II PK analysis population

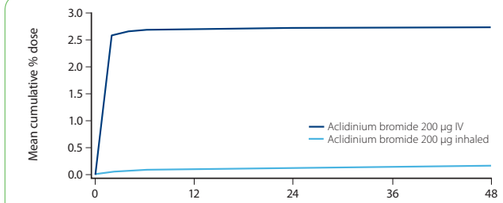


IV, intravenous; PK, pharmacokinetic

Urinary pharmacokinetics of aclidinium bromide

- The amount of unchanged aclidinium excreted in urine was low when measured up to 48 hours post-dose for both inhaled aclidinium (0.16%) and IV aclidinium (2.72%), a 17-fold difference (Figure 2).
- Excretion of the acid metabolite in urine was moderate when measured up to 48 hours post-dose after inhalation (16%) and IV administration (26%) of aclidinium.
- Excretion of the alcohol metabolite in urine following inhalation of aclidinium was approximately one-third that of IV administration (8% vs 25%, respectively).
- Renal clearance of aclidinium and the acid metabolite was similar for the two aclidinium formulations; the alcohol metabolite was 2.5-3.3 times higher following aclidinium inhalation vs IV administration.

Figure 2. Mean cumulative urinary excretion (%) of aclidinium bromide: Part II PK analysis population



IV, intravenous; PK, pharmacokinetic

Safety

- The MTD was not determined in this study.
- Laboratory values, vital signs, and ECG parameters did not show clinically relevant changes.
- Of the 24 subjects in the safety population, 20 reported 51 treatment-emergent adverse events (TEAEs) mild to moderate in intensity; none were serious or led to discontinuation. The most common TEAEs were infusion site pain (n=9), headache (n=4), puncture site pain (n=3), application site rash (n=2), and erythema (n=2).
- There was no dose relationship in the frequency or kinds of AEs in Part I. The IV dose of aclidinium bromide 200 µg led to a higher incidence of AEs compared to the inhalation dose in Part II (66.6% vs 49.9%).
- No anticholinergic AEs were reported, despite the high dose of aclidinium bromide administered in Part I.

Conclusions

- **Absolute bioavailability of aclidinium was low (<5%) following a single 200 µg inhaled dose.**
- **Aclidinium appeared rapidly in plasma following inhalation and was rapidly cleared from the body after both inhaled and IV administration.**
- **Urinary excretion of unchanged aclidinium was very low (0.16% for inhaled and 2.72% for IV).**
- **Single ascending doses of aclidinium bromide 25 µg to 400 µg administered by IV and single inhaled doses of aclidinium 200 µg were safe and well tolerated in this study.**
- **Based on results from this study, aclidinium demonstrates a favourable pharmacokinetic profile and a low potential for adverse events associated with systemic exposure.**

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Abstract

Absolute bioavailability of inhaled aclidinium bromide and safety and tolerability of aclidinium bromide administered intravenously in healthy subjects

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Introduction

Aclidinium bromide is a long-acting muscarinic antagonist in development for COPD treatment. The maximum tolerated dose (MTD) following intravenous (IV) administration of aclidinium bromide (Part I), and absolute bioavailability after inhalation (Part II) were studied.

Methods

Healthy male subjects (N=24) were randomised (1:1) in each Part: I. 3-period crossover, placebo-controlled, single-ascending, alternating IV doses of aclidinium bromide (25–400 µg); II. open-label, 2-period crossover, single-alternating IV and inhaled doses of aclidinium bromide (200 µg). A washout of ⩾7 days separated treatment periods. MTD was determined after Part I assessments. Pharmacokinetic data were collected in both Parts.

Results

Following IV or inhaled aclidinium, t_{max} was 5–6 min for all doses. After C_{max}, aclidinium was rapidly cleared from plasma and exposure grew proportionally with dosage. Aclidinium absolute bioavailability was <5% following a single inhaled 200 µg dose. Urinary excretion of unchanged aclidinium was very low with a greater amount of inactive metabolites excreted compared to aclidinium. Inhaled and IV aclidinium was recovered in urine as aclidinium or metabolites within 12 hrs post-dose. The MTD following IV administration was not reached; all single IV (25–400 µg) and inhaled doses (200 µg) were well tolerated.

Conclusion

Aclidinium absolute bioavailability was low following a single inhaled dose. Aclidinium appeared rapidly in plasma following IV administration and was rapidly excreted. Urinary excretion of aclidinium was very low and the MTD was not reached; IV and inhaled doses were safe and well tolerated.

Pharmacokinetics and safety of aclidinium bromide in young and elderly patients with COPD

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Introduction

- The prevalence of chronic obstructive pulmonary disease (COPD) increases with age.[1] As elderly patients tend to have reduced kidney function compared with younger patients,[2] the pharmacokinetics of COPD drugs should be examined across different age groups.
- Aclidinium bromide is a novel, long-acting muscarinic antagonist in clinical development for the treatment of COPD.
- Clinical studies have shown that aclidinium has long-lasting bronchodilatory activity and a favourable safety profile.[3,4] Moreover, aclidinium is rapidly hydrolysed in human plasma to two major inactive alcohol and acid metabolites, suggesting a reduced potential for systemic side effects.[5,6]
- This study assessed the pharmacokinetics of aclidinium (200 µg and 400 µg) and its two metabolites in young and elderly patients with COPD.

Methods

Study design and treatment

- This was an open-label, two-period, multiple-dose study in young (aged 40–59 years) and elderly (aged ≥70 years) patients with stable moderate to severe COPD.
- Patients received once-daily aclidinium 200 µg (single inhalation) for 3 days. After a 7-day washout, patients received once-daily aclidinium 400 µg (two consecutive 200 µg inhalations) for 3 days.
- Aclidinium was administered via the Genuair® inhaler, a novel, multidose dry powder inhaler.

Assessments

- On Days 1 and 3 of treatment with aclidinium 200 µg and 400 µg, blood and urine samples were collected at regular intervals.
- The concentrations of aclidinium and its metabolites in plasma and urine were determined by liquid chromatography tandem mass spectrometry. The lower limit of quantification (LLOQ) in plasma was 5 pg/mL for aclidinium and the alcohol metabolite, and 100 pg/mL for the acid metabolite. In urine, the LLOQ was 0.2 ng/mL for aclidinium, 0.25 ng/mL for the alcohol metabolite and 2 ng/mL for the acid metabolite.
- Safety assessments included adverse events (AEs), physical examination, vital signs, 12-lead electrocardiograms (ECGs) and laboratory data.

Statistical analysis

- Pharmacokinetic parameters for aclidinium and its two main metabolites were calculated after a single administration (Day 1) and at steady state (Day 3).
- All data were analysed using descriptive statistics.

Results

Patients

- In total, 12 young and 12 elderly patients were recruited, all of whom completed the study.
- Baseline demographic and clinical characteristics are shown in Table 1.

Pharmacokinetics

Aclidinium

- The mean plasma concentration-time profiles of aclidinium were similar for young and elderly patients at each dose and day (Figure 1). The plasma exposure at the 400 µg inhaled dose was approximately two-fold higher than the 200 µg dose.
- Plasma and urine pharmacokinetic parameters for aclidinium were similar between young and elderly patients at each dose and day (Table 2).

Metabolites

- Plasma and urine pharmacokinetic parameters for the alcohol and acid metabolites are provided in Table 3.

Safety

- AEs, which were mostly mild to moderate in intensity, occurred at a low incidence in both age groups at both dose levels (Table 4).
- No serious AEs or deaths occurred during the study.
- There were no clinically relevant changes on physical examination, vital signs, ECG parameters or laboratory assessments across the age and dose groups.

Table 1. Baseline demographic and clinical characteristics

	Young patients (n=12)	Elderly patients (n=12)	All patients (n=24)
Age, mean (SD) years	53 (5.1)	73 (2.9)	63 (10.9)
Male, n (%)	6 (50.0)	10 (83.3)	16 (66.7)
Caucasian, n (%)	12 (100)	12 (100)	24 (100)
BMI, mean (SD) kg/m^2	26.0 (4.82)	26.3 (4.05)	26.1 (4.35)
Current smoker, n (%)	10 (83.3)	4 (33.3)	14 (58.3)
Smoking history, mean (SD) pack-years	55.1 (27.90)	69.4 (42.40)	62.3 (35.86)
Pre-bronchodilator FEV_1, mean (SD) L	1.46 (0.57)	1.31 (0.38)	1.39 (0.48)
Post-bronchodilator FEV_1, mean (SD) % of predicted value	55.2 (14.75)	57.0 (13.43)	56.1 (13.83)
Post-bronchodilator FEV_1/FVC ratio, mean (SD) %	47.5 (11.71)	50.2 (12.21)	48.8 (11.77)
Creatinine clearance, mean (SD) mL/min	111.5 (35.3)	79.3 (26.1)	95.4 (34.5)

BMI, body mass index; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; SD, standard deviation

Figure 1. Mean plasma concentration-time profiles following an inhaled dose of aclidinium 200 µg or 400 µg on Days 1 and 3 in young and elderly patients with COPD

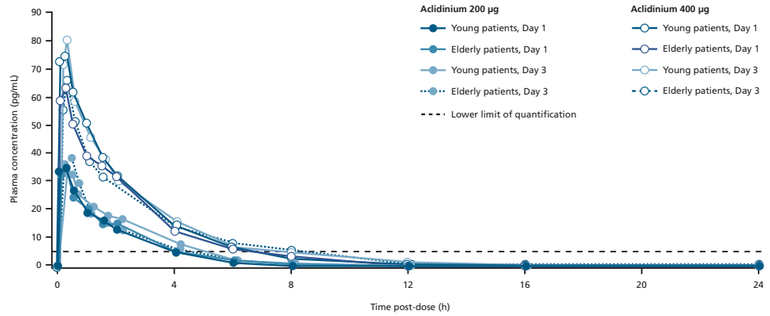

Table 2. Pharmacokinetic parameters for aclidinium after a single dose (Day 1) and at steady state (Day 3) in young and elderly patients with COPD

	Aclidinium dose	Young patients (n=12)		Elderly patients (n=12)	
		Day 1	Day 3	Day 1	Day 3
Plasma					
Day 1 AUC, pg.h/mL	200 µg	79.9 (48.6)	NA	97.3 (67.4)	NA
	400 µg	193.9 (51.7)	NA	192.6 (48.0)	NA
Day 1 AUC_τ; Day 3 AUC_{ss}^{tau}, pg.h/mL	200 µg	75.4 (49.0)	103.1 (45.4)	92.0 (69.5)	94.7 (37.5)
	400 µg	193.5 (51.4)	199.6 (36.4)	171.3 (56.7)	191.1 (47.4)
Day 1 C_{max}; Day 3 C_{max}^{ss}, pg/mL	200 µg	39.0 (46.2)	37.8 (44.1)	38.3 (62.4)	40.1 (56.0)
	400 µg	82.3 (32.0)	86.1 (31.6)	71.1 (58.2)	67.8 (44.7)
Day 2 C_{min}; Day 3 C_{min}^{ss}, pg/mL	200 µg	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)
	400 µg	<5.00 (0.00)	<5.00 (0.00)	<5.00 (0.00)	<5.00 (29.86)
Day 3 Ca_{ss}^{tau}, pg/mL	200 µg	NA	4.30 (45.40)	NA	3.94 (37.45)
	400 µg	NA	8.32 (36.40)	NA	7.96 (47.38)
t_{max}, h	200 µg	0.17 (0.08–0.50)	0.19 (0.08–1.00)	0.25 (0.10–2.00)	0.25 (0.08–0.50)
	400 µg	0.17 (0.08–1.00)	0.25 (0.08–1.03)	0.25 (0.08–1.50)	0.25 (0.08–0.50)
$t_{1/2}$, h	200 µg	1.71 (37.12)	2.20 (20.18)	1.73 (39.16)	2.26 (29.92)
	400 µg	1.92 (29.03)	2.31 (32.20)	1.97 (29.00)	3.16 (34.38)
Urine					
$fe_{(0\text{-}24)ss}$, %	200 µg	0.10 (46.25)	0.14 (58.47)	0.07 (50.01)	0.09 (54.71)
	400 µg	0.12 (50.37)	0.13 (47.47)	0.08 (40.95)	0.09 (39.24)
CL_R, mL/min	200 µg	50.4 (43.2)	50.6 (56.3)	37.2 (68.5)	37.2 (45.5)
	400 µg	47.1 (48.9)	50.2 (56.6)	38.9 (47.9)	34.9 (43.9)

Data reported as mean (coefficient of variation %) except for t_{max} which is reported as median (range)
AUC, area under the concentration time curve from time zero to infinity; AUC_τ, area under the concentration time curve over a 24-hour dosing interval; AUC_{ss}^{tau}, area under the concentration time curve over a 24-hour dosing interval at steady state; C_{max}, maximum observed plasma concentration; C_{max}^{ss}, maximum observed plasma concentration at steady state; C_{min}, minimum observed plasma concentration; C_{min}^{ss}, minimum observed plasma concentration at steady state; Ca_{ss}^{tau}, average plasma concentration at steady state; t_{max}, time of maximum observed plasma concentration; $t_{1/2}$, apparent plasma terminal elimination half-life; CL_R, renal clearance; $fe_{(0\text{-}24)ss}$ percentage of dose excreted in urine from 0 to 24 hours; NA, not applicable

Table 3. Pharmacokinetic parameters for aclidinium metabolites after a single dose (Day 1) and at steady state (Day 3) in young and elderly patients with COPD

	Aclidinium dose	Metabolite	Young patients (n=12)		Elderly patients (n=12)	
			Day 1	Day 3	Day 1	Day 3
Plasma						
Day 1 AUC, pg.h/mL	200 µg	Alcohol	209.1 (64.8)	NA	372.4 (79.9)	NA
		Acid	7819.8 (34.4)	NA	9123.8 (38.8)	NA
	400 µg	Alcohol	380.5 (63.4)	NA	733.8 (61.7)	NA
		Acid	16530 (40.6)	NA	21734 (29.9)	NA
Day 1 AUC_τ; Day 3 AUC_{ss}^{tau}, pg.h/mL	200 µg	Alcohol	165.6 (59.7)	216.8 (56.7)	327.5 (65.2)	366.4 (57.1)
		Acid	7369.8 (35.0)	8569.5 (52.6)	8479.9 (38.2)	11382 (40.8)
	400 µg	Alcohol	382.8 (57.2)	443.0 (41.3)	628.7 (52.3)	742.6 (59.4)
		Acid	15359 (41.6)	18196 (40.0)	20317 (30.2)	22458 (22.0)
Day 1 C_{max}; Day 3 C_{max}^{ss}, pg/mL	200 µg	Alcohol	34.0 (58.9)	34.1 (41.5)	37.6 (46.3)	41.0 (59.9)
		Acid	805.9 (36.2)	844.0 (57.4)	829.2 (30.4)	1029.5 (41.1)
	400 µg	Alcohol	66.2 (43.3)	61.4 (35.2)	79.2 (51.8)	80.5 (39.3)
		Acid	1669.8 (44.7)	1812.0 (48.5)	1942.6 (31.0)	2058.7 (26.3)
Day 2 C_{min}; Day 3 C_{min}^{ss}, pg/mL	200 µg	Alcohol	<5.00 (0.00)	<5.00 (0.00)	<5.00 (107.53)	<5.00 (86.21)
		Acid	<100.00 (33.61)	<100.00 (55.75)	<100.00 (58.73)	100.18 (48.56)
	400 µg	Alcohol	<5.00 (56.09)	<5.00 (46.55)	7.40 (108.72)	10.70 (105.92)
		Acid	128.20 (58.33)	170.43 (43.50)	176.31 (35.79)	233.67 (32.66)
Day 3 Ca_{ss}^{tau}, pg/mL	200 µg	Alcohol	NA	9.03 (56.73)	NA	15.27 (57.08)
		Acid	NA	357.06 (52.63)	NA	474.24 (40.75)
	400 µg	Alcohol	NA	18.46 (41.32)	NA	30.94 (59.44)
		Acid	NA	758.15 (40.03)	NA	935.74 (21.98)
t_{max}, h	200 µg	Alcohol	1.00 (0.25–4.00)	0.50 (0.25–2.00)	0.50 (0.25–6.00)	1.25 (0.25–8.00)
		Acid	4.00 (1.50–4.02)	4.00 (1.50–6.00)	4.00 (1.50–6.00)	4.00 (2.00–6.00)
	400 µg	Alcohol	0.25 (0.25–2.00)	0.25 (0.25–4.00)	1.25 (0.25–8.00)	1.50 (0.25–6.00)
		Acid	4.00 (1.50–4.00)	4.00 (1.50–6.00)	4.00 (2.00–8.00)	4.00 (2.00–6.00)
$t_{1/2}$, h	200 µg	Alcohol	4.51 (79.53)	4.53 (42.24)	5.83 (41.99)	7.18 (46.35)
		Acid	5.35 (28.5)	6.41 (37.78)	5.42 (32.50)	8.69 (54.64)
	400 µg	Alcohol	4.66 (44.41)	8.16 (50.62)	7.77 (35.00)	11.66 (33.13)
		Acid	5.86 (30.45)	10.21 (44.22)	5.43 (17.36)	11.58 (39.81)
Urine						
$fe_{(0\text{-}24)ss}$, %	200 µg	Alcohol	3.71 (31.48)	5.03 (52.68)	4.15 (57.04)	5.52 (58.55)
		Acid	9.99 (41.86)	12.01 (60.92)	9.29 (48.27)	12.67 (43.08)
	400 µg	Alcohol	4.37 (55.06)	4.98 (39.23)	4.69 (52.84)	6.09 (71.61)
		Acid	11.48 (43.19)	12.85 (43.55)	11.20 (37.94)	13.16 (38.16)
CL_R, mL/min	200 µg	Alcohol	499.0 (46.2)	558.9 (57.9)	279.6 (39.6)	319.4 (41.6)
		Acid	23.0 (42.9)	22.5 (39.6)	18.2 (29.6)	20.6 (44.1)
	400 µg	Alcohol	448.9 (42.0)	454.1 (48.5)	285.4 (30.8)	308.0 (34.2)
		Acid	25.6 (34.1)	23.9 (30.9)	18.1 (25.0)	19.5 (30.3)

Data reported as mean (coefficient of variation %) except for t_{max} which is reported as median (range)
AUC, area under the concentration time curve from time zero to infinity; AUC_τ, area under the concentration time curve over a 24-hour dosing interval; AUC_{ss}^{tau}, area under the concentration time curve over a 24-hour dosing interval at steady state; C_{max}, maximum observed plasma concentration; C_{max}^{ss}, maximum observed plasma concentration at steady state; C_{min}, minimum observed plasma concentration; C_{min}^{ss}, minimum observed plasma concentration at steady state; Ca_{ss}^{tau}, average plasma concentration at steady state; t_{max}, time of maximum observed plasma concentration; $t_{1/2}$, apparent plasma terminal elimination half-life; CLR, renal clearance; $fe_{(0\text{-}24)ss}$ percentage of dose excreted in urine from 0 to 24 hours; NA, not applicable

Table 4. Number of adverse events reported by ≥2 patients by patient age and dose

Adverse event (preferred term)	Aclidinium 200 µg		Aclidinium 400 µg	
	Young patients (n=12)	Elderly patients (n=12)	Young patients (n=12)	Elderly patients (n=12)
Any	13	4	13	4
Fatigue	3	2	9	1
Headache	4	1	1	2
Dyspnoea	2	0	1	0

Conclusions

- **Once-daily doses of aclidinium 200 µg and 400 µg (administered as two consecutive 200 µg inhalations) are safe and well tolerated in young and elderly patients with COPD.**
- **Aclidinium showed linear and time-independent pharmacokinetics, with a similar profile in young and elderly patients at each dose level after administration of a single dose and at steady state.**
- **Although exposure to the alcohol and acid metabolites was somewhat higher in elderly patients, this is not considered to be clinically relevant as these metabolites are inactive at a wide array of receptors and enzymes, including muscarinic receptors.[5]**
- **These findings suggest that no dose adjustment of aclidinium is required when treating elderly patients with COPD.**

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Abstract

Pharmacokinetics and safety of aclidinium bromide in young and elderly patients with COPD

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Introduction

Aclidinium bromide is a novel, long-acting muscarinic antagonist in development for the treatment of chronic obstructive pulmonary disease (COPD). This study investigated the pharmacokinetics of aclidinium at two doses in young and elderly patients with stable moderate to severe COPD.

Methods

In this open-label, two-period, multidose study, 12 young (aged 40–50 years) and 12 elderly (aged ⩾70 years) patients were treated with aclidinium via Genuair®, a novel, multidose dry powder inhaler. Patients received aclidinium 200 µg (one inhalation) once-daily for 3 days, followed by a washout. Patients then received aclidinium 400 µg (2 x 200 µg inhalations) once-daily for 3 days. Pharmacokinetic (PK) analyses were carried out on plasma and urine on Days 1 and 3 of both treatment periods. Safety evaluations included adverse events (AEs).

Results

The PK profiles of aclidinium in plasma and urine were similar in both age groups. Concentrations of aclidinium in plasma after 400 µg were two-fold higher than those observed with the 200 µg dose. PK data are shown in the table. Aclidinium 200 µg and 400 µg were well tolerated in both age groups; the incidence of treatment-emergent AEs was low and no safety concerns arose.

Table. Pharmacokinetics of aclidinium bromide 200 µg and 400 µg in young and elderly patients.

	Aclidinium dose	Young patients (n=12)		Elderly patients (n=12)	
		Day 1	Day 3	Day 1	Day 3
Plasma					
$AUC_{(0\text{-}t)}$ (pg.h/mL)	200 µg	59.9 (58.7)	81.6 (59.1)	75.5 (83.9)	73.6 (49.8)
	400 µg	175.5 (54.7)	177.6 (40.3)	152.0 (59.3)	164.6 (55.0)
C_{max} (Day 1)	200 µg	39.0 (46.2)	37.8 (44.1)	38.3 (62.4)	40.1 (56.0)
C_{max}^{ss} (Day 3)	400 µg	82.3 (32.0)	86.1 (31.6)	71.1 (58.2)	67.8 (44.7)
t_{max} (h)	200 µg	0.17 (0.08-0.50)	0.19 (0.08-1.00)	0.25 (0.10-2.00)	0.25 (0.08-0.50)
	400 µg	0.17 (0.08-1.00)	0.25 (0.08-1.03)	0.25 (0.08-1.50)	0.25 (0.08-0.50)
$t_{1/2}$ (h)	200 µg	1.71 (37.12)	2.20 (20.18)	1.73 (39.16)	2.26 (29.92)
	400 µg	1.92 (29.03)	2.31 (32.20)	1.97 (29.00)	3.16 (34.38)
Urine					
$fe_{(0\text{-}24h)}$ (%)	200 µg	0.10 (46.25)	0.14 (58.47)	0.07 (50.01)	0.09 (54.71)
	400 µg	0.12 (50.37)	0.13 (47.47)	0.08 (40.95)	0.09 (39.24)
CL_R (mL/min)	200 µg	50.4 (43.2)	50.6[a] (56.3)	37.2[b] (68.5)	37.2[a] (45.5)
	400 µg	47.1 (48.9)	50.2 (56.6)	38.9 (47.9)	34.9[a] (43.9)

Data reported as mean (coefficient of variation %) except for t_{max}, where data is reported as mean (range); fe, percentage of dose excreted in urine; C_{max}^{ss}, maximium observed plasma concentration at steady state; CL_R, renal clearance; [a]n=11; [b]n=10.

Conclusion

Aclidinium 200 µg and 400 µg were well tolerated in young and elderly patients and exhibited a linear and time-independent PK profile. No dose adjustment is necessary for elderly patients.

Aclidinium bromide improves resting lung function in patients with moderate to severe COPD

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Introduction

- Lung hyperinflation is associated with diminished exercise capacity, dyspnoea and increased mortality in patients with chronic obstructive pulmonary disease (COPD).[1,2] Treatment with long-acting bronchodilators, including anticholinergic drugs, has been shown to improve lung hyperinflation.[3,4]
- Aclidinium bromide is a long-acting inhaled muscarinic antagonist currently in Phase III development for the maintenance treatment of COPD.

Objective

- The main purpose of this study was to examine the effect of once-daily aclidinium 200 µg on lung hyperinflation in patients with COPD.
- Here we report the effects of aclidinium on bronchodilation, resting lung hyperinflation, dyspnoea, quality of life (QoL), and safety and tolerability.

Methods

Study design

- This was a Phase III, randomised, double-blind, placebo-controlled, multicentre trial.
- After a 14-day run-in period, patients were randomised (1:1) to receive aclidinium 200 µg or placebo, administered once-daily for 6 weeks via the Genuair® inhaler, a novel, multidose dry powder inhaler.

Study population

Inclusion criteria

- Patients with a clinical diagnosis of COPD aged ⩾40 years and with a smoking history of ⩾10 pack-years
  - Post-bronchodilator forced expiratory volume in 1 second (FEV_1)/ forced vital capacity (FVC) ratio of <70%
  - FEV_1 ⩾30% and <80% of predicted value
- Functional residual capacity (FRC) ⩾120% of predicted value
- Baseline Dyspnoea Index focal score ⩽7

Exclusion criteria

- History or current diagnosis of asthma, rhinitis or atopy
- Any other clinically relevant respiratory or cardiovascular condition, including laboratory test and electrocardiogram (ECG) abnormalities, and contraindications to clinical exercise testing
- Respiratory tract infection or COPD exacerbation within 6 weeks pre-screening, or hospitalisation for acute COPD exacerbation within 3 months pre-screening
- Cycled ⩾20 minutes during the constant work-rate tests performed during the run-in period

Endpoints

- Change from baseline in FEV_1, FVC, inspiratory capacity (IC), FRC, IC/total lung capacity (TLC), residual volume (RV) and vital capacity (VC) at 2 hours post-dose on Day 1 and at trough (pre-dose) and 2 hours post-dose at Weeks 3 and 6
- Change from baseline in dyspnoea at Weeks 3 and 6, measured using the Baseline Dyspnoea Index/ Transitional Dyspnoea Index
- Use of daily rescue medication (levalbuterol/ salbutamol puffs) throughout the study period
- Change from baseline in QoL at Week 6, measured using the Chronic Respiratory Questionnaire – Self Administered Standardised
- Safety and tolerability were evaluated using adverse event (AE) reporting, physical examinations, vital signs, ECGs and clinical laboratory tests.

Statistical analysis

- Efficacy endpoints were analysed using analysis of covariance.

Results

Patients

- In total, 181 patients with moderate to severe COPD were randomised to aclidinium (n=86) or placebo (n=95), of which 81 and 78 patients, respectively, completed the study.
- Baseline demographic and clinical characteristics were similar between the treatment groups (Table 1).

Table 1. Baseline demographic and clinical characteristics

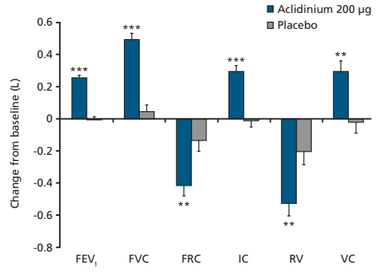
Characteristics	Aclidinium 200 µg (n=86)	Placebo (n=95)
Age, years	64 (10)	66 (8)
Male, n (%)	52 (61)	53 (56)
Caucasian, n (%)	83 (97)	92 (97)
BMI, kg/m²	26.2 (4.6)	26.6 (4.7)
Current smoker, n (%)	38 (44)	31 (33)
Smoking history, pack-years	57 (25)	54 (21)
Pulmonary function		
Pre-bronchodilator FEV_1, L	1.18 (0.44)	1.29 (0.43)
Post-bronchodilator FEV_1, % predicted	49 (11)	52 (14)
Post-bronchodilator FVC, L	3.28 (1.03)	3.14 (0.85)
Post-bronchodilator FEV_1/FVC ratio, %	44.7 (9.8)	47.4 (9.9)
FRC, L	5.12 (1.23)	4.85 (1.24)
FRC, % predicted	159 (30)	152 (33)
IC,† L	1.96 (0.67)	1.97 (0.54)
TLC, L	6.85 (1.56)	6.68 (1.47)
RV, L	4.27 (1.25)	4.10 (1.27)
VC,† L	2.74 (1.21)	2.63 (1.09)

Data are presented as mean (SD) unless otherwise stated
†Measured during the run-in period (Day -10)
BMI, body mass index; FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; SD, standard deviation; TLC, total lung capacity; VC, vital capacity

Efficacy

- Two hours after administration of study medication, changes from baseline in FEV_1, FVC, FRC, IC, RV and VC were all significantly greater in patients receiving aclidinium compared with placebo at Week 6 (Figure 1). Similar results were observed at Day 1 and Week 3.

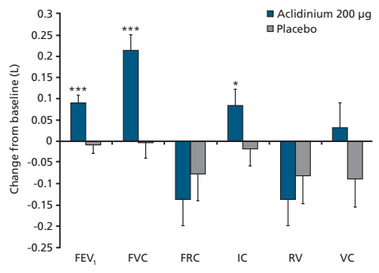
Figure 1. Resting lung function and volume at Week 6 (2 hours post-dose)



Data presented as least squares mean change from baseline (standard error)
FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; VC, vital capacity
**p<0.01; ***p<0.0001

- At Week 6, aclidinium significantly improved trough FEV_1, FVC, and IC compared with placebo (p<0.0001, p<0.0001, p=0.0142, respectively; Figure 2). Similar results were observed at Week 3.

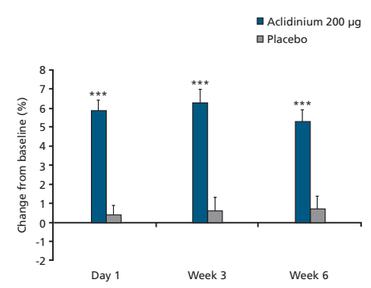
Figure 2. Resting lung function and volume at Week 6 (trough)



Data presented as least squares mean change from baseline (standard error)
FEV_1, forced expiratory volume in one second; FRC, functional residual capacity; FVC, forced vital capacity; IC, inspiratory capacity; RV, residual volume; VC, vital capacity
*p<0.05; ***p<0.0001 vs placebo

- Trough FRC, RV and VC showed a trend towards improvement with aclidinium versus placebo at Week 6, but the treatment differences did not achieve statistical significance (p=0.4456, p=0.5054, p=0.1089, respectively; Figure 2). At Week 3, the results for trough FRC and RV were similar; however, there was a significant improvement (p=0.03) observed for VC in patients treated with aclidinium, compared with placebo.
- Change from baseline in trough IC/TLC was significantly greater in patients receiving aclidinium compared with placebo at Day 1 and Weeks 3 and 6 (Figure 3).

Figure 3. Change from baseline in trough IC/TLC



Data presented as least squares mean change from baseline (standard error)
IC, inspiratory capacity; TLC, total lung capacity
***p<0.0001

- Significant improvements in dyspnoea were observed with aclidinium versus placebo at Weeks 3 and 6 (Table 2), with placebo-adjusted improvements in mean Transitional Dyspnoea Index focal scores of 1.19 (p=0.005) and 1.71 (p=0.0004), respectively.

Table 2. Treatment differences (aclidinium-placebo) in change from baseline in dyspnoea status at Week 3 and Week 6

TDI dimension	Week 3	Week 6
Change in functional impairment	0.30 (0.00, 0.59)	0.54 (0.28, 0.89)
Change in magnitude of task	0.42 (0.14, 0.71)	0.57 (0.24, 0.91)
Change in magnitude of effort	0.40 (0.08, 0.72)	0.53 (0.17, 0.89)
Focal score	1.19 (0.36, 2.02)	1.71 (0.79, 2.64)

Data presented as least squares mean (95% confidence intervals)
TDI, Transitional Dyspnoea Index

- Aclidinium also reduced the use of daily rescue medication throughout the treatment period compared with placebo; the adjusted mean decreases from baseline were -0.89 and -0.75 puffs, respectively; however, the treatment difference was not significant (p=0.73).
- There were no significant differences between aclidinium and placebo in the change from baseline in Chronic Respiratory Questionnaire – Self Administered Standardised scores at Week 6.

Safety

- The incidence of AEs was similar in each study arm (Table 3); most AEs were of mild or moderate intensity.
- In total, five patients experienced serious AEs; two patients in the aclidinium group and three in the placebo group. None of the SAEs was considered to be treatment-related. Eleven patients discontinued the study due to AEs; three in the aclidinium group and eight in the placebo group. There were no deaths reported during the study.

Table 3. Number of patients (%) with adverse events

Adverse event	Aclidinium 200 µg (n=86)	Placebo (n=95)
Any event	49 (57.0)	44 (46.3)
Events occurring in >3% patients in either treatment arm		
Headache	5 (5.8)	7 (7.4)
COPD exacerbation	2 (2.3)	7 (7.4)
Cough	5 (5.8)	3 (3.2)
Upper respiratory tract infection	5 (5.8)	2 (2.1)
Nasopharyngitis	4 (4.7)	2 (2.1)
Pharyngolaryngeal pain	3 (3.5)	1 (1.1)
Back pain	3 (3.5)	3 (3.2)
Dyspepsia	3 (3.5)	1 (1.1)
Dyspnoea	1 (1.2)	3 (3.2)
Urinary tract infection	2 (2.3)	4 (4.2)
Sinus congestion	0 (0.0)	4 (4.2)

COPD, chronic obstructive pulmonary disease

- No clinically relevant changes were observed in vital signs, ECGs or laboratory parameters.

Conclusions

- **In this study, once-daily aclidinium 200 µg improved resting lung hyperinflation, demonstrated by the significant improvements in trough IC and trough IC/TLC, and a positive trend for FRC, at study end. The magnitude of the improvement in resting IC reported here is similar to that reported in a 6-week tiotropium study.[5]**
- **Once-daily aclidinium 200 µg also produced statistically significant and clinically relevant improvements in lung function parameters from Day 1 until Week 6, indicating that aclidinium was efficacious on its first day of administration and that this was sustained until the end of the study.**
- **Once-daily aclidinium 200 µg significantly improved dyspnoea, compared with placebo. The use of rescue medication was also reduced in the aclidinium group compared with placebo, albeit non-significantly.**
- **Aclidinium was safe and well tolerated in this study and may be a valuable new treatment for COPD.**

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Acknowledgements

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Poster presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 18-22 September 2010

Abstract

Aclidinium bromide improves resting lung function in patients with moderate to severe COPD

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Introduction

This study was designed to assess the effects of aclidinium bromide, a novel long-acting muscarinic antagonist, on resting lung function at the end of the dosing interval, dyspnoea and quality of life in patients with chronic obstructive pulmonary disease (COPD).

Methods

This multicentre, double-blind study compared aclidinium 200 µg once-daily with placebo once-daily for 6 weeks. After a 14-day run-in, patients were randomised (1:1) to aclidinium or placebo. Spirometry and body plethysmography were assessed before (trough) and after treatment. Dyspnoea (BDI/TDI), use of rescue medication, quality of life (Chronic Respiratory Questionnaire–Self Administered Standardised [CRQ-SAS]) and safety were also assessed.

Results

In total, 181 patients (mean age 64.8 years) received aclidinium (n=86) or placebo (n=95). At Week 6, aclidinium significantly improved several lung function parameters (trough FEV_1, FEV_1, trough FVC, trough IC, trough IC/TLC and FRC) vs placebo (Table). Aclidinium improved dyspnoea, with mean TDI scores of 1.190 units (p=0.0050) and 1.714 units (p=0.0004), at Weeks 3 and 6, respectively. No treatment differences were observed for use of rescue medication or CRQ-SAS scores. Aclidinium was well tolerated; no safety concerns arose.

Table. Change from baseline (LS mean) and treatment differences (aclidinium–placebo) at Week 6 in resting lung function assessments.

Efficacy measure	Change from baseline, LS mean (SE)		Treatment difference	p value*
	Aclidinium bromide 200 µg	Placebo		
Trough FEV_1 (L)	0.090 (0.0181)	-0.010 (0.0182)	0.101 (0.0232)	p<0.0001
FEV_1 (L)	0.254 (0.0193)	-0.007 (0.0195)	0.261 (0.0249)	p<0.0001
Trough FVC (L)	0.213 (0.0368)	-0.006 (0.0374)	0.219 (0.0477)	p<0.0001
FVC (L)	0.493 (0.0381)	0.045 (0.0387)	0.448 (0.0493)	p<0.0001
Trough IC (L)	0.083 (0.0321)	-0.019 (0.0321)	0.102 (0.0412)	p=0.0142
IC (L)	0.292 (0.0388)	-0.012 (0.0394)	0.303 (0.0501)	p<0.0001
Trough FRC (L)	-0.138 (0.0608)	-0.076 (0.0643)	-0.062 (0.0813)	p=0.4456
FRC (L)	-0.418 (0.0638)	-0.135 (0.0675)	-0.283 (0.0854)	p=0.0011
Trough IC/TLC	0.014 (0.0059)	-0.003 (0.0063)	0.017 (0.0079)	p=0.0367
Trough RV (L)	-0.136 (0.0617)	-0.081 (0.0653)	-0.055 (0.0824)	p=0.5054
RV (L)	-0.530 (0.0750)	-0.206 (0.0793)	-0.324 (0.1001)	p=0.0015
Trough VC (L)	0.032 (0.0583)	-0.089 (0.0584)	0.121 (0.0751)	p=0.1089
VC (L)	0.295 (0.0655)	-0.024 (0.0665)	0.319 (0.0846)	p=0.0002

LS mean, least squares mean; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IC, inspiratory capacity; FRC, functional residual capacity; TLC, total lung capacity; RV, residual volume; VC, vital capacity.
*p value denotes statistical significance of the treatment difference (aclidinium–placebo).

Conclusion

Aclidinium provided clinically significant bronchodilation and improvements in IC and dyspnoea and may be a valuable new treatment for COPD.

fold

Efficacy and safety of twice-daily aclidinium bromide compared with tiotropium and placebo in patients with moderate to severe COPD

Rainard Fuhr,[1] Helgo Magnussen,[2] Anna Ribera Llovera,[3] Anne-Marie Kirsten,[2] Meritxell Falqués,[3] Cynthia Caracta,[4] Esther Garcia Gil[3]

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Introduction

- Chronic obstructive pulmonary disease (COPD) is a highly prevalent lung disease characterised by gradual loss of lung function and airflow limitation that is not fully reversible.[1]
- The high morbidity and mortality rates associated with COPD, and the availability of only one long-acting anticholinergic for COPD treatment, necessitate the investigation of additional therapeutic options.
- Aclidinium bromide is a new, potent, long-acting muscarinic antagonist being investigated for the maintenance treatment of COPD.
- Clinical trials of aclidinium bromide in patients with COPD have demonstrated sustained bronchodilation and a favourable tolerability profile.[2,3]
- The objective of this Phase IIa study was to assess the efficacy, safety, and tolerability of aclidinium bromide 400 µg BID in moderate to severe COPD patients.

Methods

Study design

- This was a multicentre, randomised, double-blind, double-dummy, placebo- and active comparator-controlled, 3-period crossover trial.
- Patients (n=30) were randomised (1:1:1) to receive aclidinium bromide 400 µg BID, tiotropium 18 µg QD, or placebo; each treatment arm consisted of three 15-day treatment periods separated by a 9- to 15-day washout period.
- Patients were evaluated at screening (for inclusion), at baseline following a 5- to 9-day run-in period, on Days 1 and 15 during each treatment period (6 visits total), and at follow-up.

Study population

Inclusion criteria

- Male and non-pregnant, non-lactating female patients aged ≥40 years
- Post-bronchodilator forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%
- Post-bronchodilator FEV_1 ≥30% and <80% of predicted
- Current or ex-smokers with a smoking history of ≥10 pack-years

Exclusion criteria

- History or current diagnosis of asthma
- Other clinically relevant respiratory or cardiovascular conditions
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if hospitalised) prior to screening
- Clinically relevant abnormalities in laboratory values, electrocardiogram (ECG), or physical examination

Study endpoints

Primary endpoint

- Change from baseline in normalised FEV_1 area under the curve for the 12 hours immediately following morning dose administration (AUC_{0-12}) on Day 15

Secondary endpoints

- Change from baseline in normalised FEV_1 AUC_{0-12} on Day 1
- Change from baseline in normalised FEV_1 AUC_{0-24} and FEV_1 AUC_{12-24} on Days 1 and 15
- Change from baseline in normalised morning pre-dose and peak FEV_1 on Days 1 and 15
- Change from baseline in FEV_1 at each specific time point on Days 1 and 15

Safety

- Adverse events (AEs), 12-lead ECGs, and blood pressure and laboratory parameters

Statistical analysis

- All patients who took at least one dose of trial medication, had a baseline FEV_1 measurement, and had at least one post-dose FEV_1 measurement were included in the intention-to-treat (ITT) population, which was used to analyse all efficacy variables.
- All patients who took at least one dose of study medication were included in the safety population, which was used to perform safety analyses.
- Descriptive statistics were used to summarise safety outcomes. The analysis of covariance model for crossover designs was used to analyse efficacy outcomes.

Results

Baseline demographics

- Demographic and baseline characteristics of the 30 randomised subjects (n=27 completed) are presented in Table 1.

Table 1. Demographic and baseline characteristics (safety population)

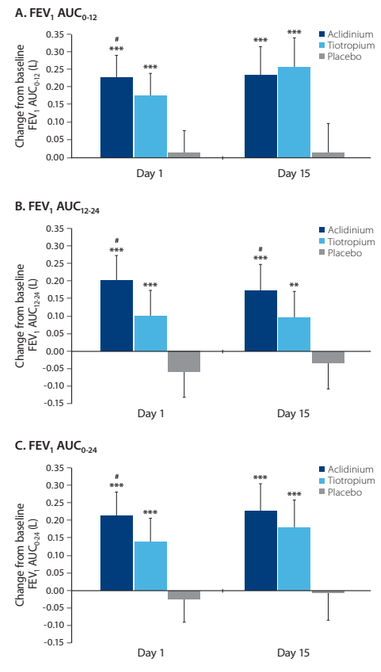
Characteristic	
Age, mean (SD), years	58.4 (7.9)
Male, n (%)	19 (63.3)
White, n (%)	30 (100.0)
BMI, mean (SD), kg/m^2	26.1 (4.4)
Current smoker, n (%)	19 (63.3)
Smoking history, mean (SD), pack-years	41.1 (15.9)
Baseline FEV_1 at screening, mean (SD), L	1.47 (0.47)
Post-bronchodilator FEV_1, mean (SD), L	1.7 (0.5)
Post-bronchodilator FEV_1, mean (SD), % of predicted value	55.8 (13.7)
Post-bronchodilator FEV_1/FVC ratio, mean (SD), %	46.2 (10.3)
Bronchodilator reversibility, mean (SD), %	18.2 (11.9)

BMI, body mass index; SD, standard deviation

Efficacy

- Normalised FEV_1 AUC_{0-12} at Day 15 was significantly increased in patients with stable moderate to severe COPD treated with aclidinium (0.24 L) and tiotropium (0.26 L) compared with placebo (0.02 L) (p<0.0001 for both; Figure 1A).
  - At Day 1, normalised FEV_1 AUC_{0-12} was significantly greater for both aclidinium and tiotropium versus placebo (p<0.001 for both) and for aclidinium versus tiotropium (p<0.05; Figure 1A).
- Normalised FEV_1 AUC_{12-24} and AUC_{0-24} (Days 1 and 15) were significantly greater for both aclidinium and tiotropium versus placebo (p<0.001 for all).
  - Compared with tiotropium, aclidinium produced a significantly greater increase in normalised FEV_1 AUC_{12-24} on Days 1 and 15 (Figure 1B) and on Day 1 for FEV_1 AUC_{0-24} (Figure 1C).

Figure 1. Change from baseline in normalised FEV_1 AUC_{0-12}, AUC_{12-24}, and AUC_{0-24} on Day 1 and Day 15



Data reported as change from baseline ± SE.
***p<0.0001, **p<0.001 vs placebo; #p<0.05 vs tiotropium bromide

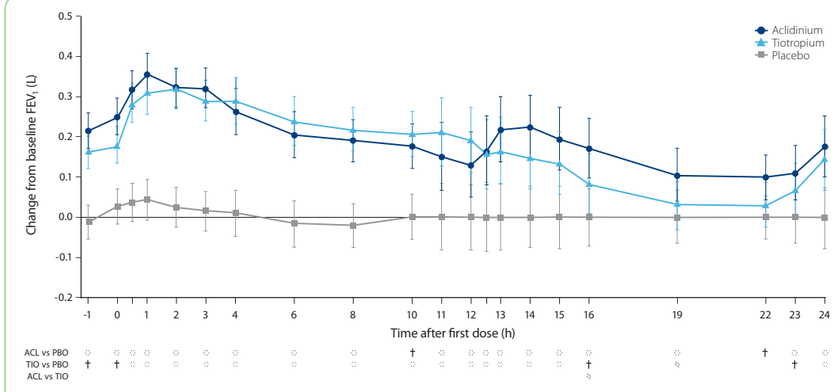
- FEV_1 morning pre-dose and peak values on Days 1 and 15 were significantly higher for both aclidinium and tiotropium treatment versus placebo (Table 2). Aclidinium treatment did not significantly differ from tiotropium treatment at any measurement.

Table 2. Change from baseline in morning FEV_1 measurements

	Aclidinium bromide		Tiotropium bromide		Placebo	
Parameter	Day 1	Day 15	Day 1	Day 15	Day 1	Day 15
Morning pre-dose FEV_1, L	0.163**	0.143**	0.099*	0.107**	-0.022	-0.043
Morning peak FEV_1, L	0.362**	0.408**	0.314**	0.382**	0.144	0.131

*p<0.05, **p<0.0001 vs placebo
Morning pre-dose FEV_1 is defined as the average of values for 23h and 24h after morning IMP administration on Days 1 and 15.

Figure 2. Change from baseline in FEV_1 on Day 15 (LS mean ± SE; ITT population)



*p<0.001; †p<0.01; ‡p<0.05
Baseline value was measured as the average of the two values measured just prior to the first dose administration at Day 1 of each treatment period (time points: -1h and 0h before dosing).
ACL, aclidinium bromide; TIO, tiotropium bromide; PBO, placebo

- Aclidinium bromide maintained a bronchodilatory effect compared with placebo over a 24-hour period on Day 15 (Figure 2).
  - Compared with placebo, aclidinium bromide significantly increased mean change from baseline in FEV_1 for all time points on Day 1 (p<0.001) and Day 15 (p<0.01).
  - Compared with placebo, tiotropium bromide significantly increased mean change from baseline in FEV_1 for all time points on Days 1 and 15 except 22 hours post-dose.

Safety

- Aclidinium 400 µg BID was generally safe and well tolerated.
- Treatment-emergent AEs (TEAEs) were reported by 3 patients (11%) taking tiotropium bromide, 7 patients (24%) taking aclidinium bromide, and 8 patients (27%) taking placebo.
- The most common AEs were diarrhoea (n=2 in the aclidinium group) and COPD exacerbations (n=3 in the placebo group).
- Three subjects withdrew due to TEAEs during treatment with placebo. One withdrawal was for a serious AE (severe COPD exacerbation), two were due to moderate COPD exacerbation and mild atrial fibrillation; none were considered related to treatment.
- There were no clinically relevant changes in laboratory results or blood pressure during the study.

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Conclusions

- **Aclidinium 400 µg twice-daily provides bronchodilation over 24 hours that is statistically superior and clinically meaningful compared with placebo.**
- **In this study, improvements in Day 1 normalised FEV_1 AUC_{0-12}, FEV_1 AUC_{12-24}, and FEV_1 AUC_{0-24} with aclidinium indicate that optimal bronchodilation is achieved as early as the first day of treatment and is sustained over time.**
- **Aclidinium treatment resulted in significantly greater improvements than tiotropium in normalised FEV_1 AUC_{0-12} and FEV_1 AUC_{0-24} on Day 1 and in normalised FEV_1 AUC_{12-24} on Day 1 and Day 15.**
- **Treatment with twice-daily aclidinium was safe and well tolerated.**

Acknowledgements

This study was supported by Almirall SA, Barcelona, Spain, and Forest Laboratories, Inc., New York, NY, USA.

Poster presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 18-22 September, 2010

Abstract

Efficacy and safety of twice-daily aclidinium bromide compared with tiotropium and placebo in patients with moderate to severe COPD

Rainard Fuhr,[1] Helgo Magnussen,[2] Anna Ribera Llovera,[3] Anne-Marie Kirsten,[2] Meritxell Falques,[3] Cynthia Caracta,[4] Esther Garcia Gil[3]

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Introduction

The efficacy and safety of twice-daily aclidinium bromide, a novel, long-acting, muscarinic antagonist was assessed in patients with moderate to severe COPD.

Methods

In this Phase IIa randomised, double-blind, double-dummy, crossover trial, patients with moderate to severe COPD received aclidinium 400 µg BID, tiotropium 18 µg QD and placebo for 15 days, with a 9–15 day washout between treatment periods. Treatments were administered via the Genuair® and HandiHaler® dry-powder inhalers. The primary endpoint was mean change from baseline in FEV_1 $AUC_{0\text{-}12/12h}$ on Day 15. Secondary endpoints were $AUC_{12\text{-}24/12h}$, $AUC_{0\text{-}24/24h}$, morning pre-dose, and peak FEV_1. Safety was assessed via adverse events (AEs), ECGs, blood samples and vital signs.

Results

Thirty patients were randomised, and 27 completed the study. Mean change from baseline in FEV_1 $AUC_{0\text{-}12/12h}$ was significantly greater for aclidinium and tiotropium over placebo (Table). FEV_1 $AUC_{12\text{-}24/12h}$, FEV_1 $AUC_{0\text{-}24/24h}$, morning pre-dose FEV_1 and peak FEV_1 were also significantly greater for aclidinium and tiotropium over placebo. Compared to tiotropium, FEV_1 $AUC_{12\text{-}24/12h}$ was significantly greater for aclidinium. Active treatments were safe and well tolerated.

Table. Mean change from baseline to Day 15 (mL).

Mean ± SE	Aclidinium 400 µg BID	Tiotropium 18 µg QD	Placebo
FEV_1 $AUC_{0\text{-}12/12h}$	236.2±69.2**	259.7±69.6**	15.5±69.9
FEV_1 $AUC_{12\text{-}24/12h}$	174.2±70.3**†	96.5±70.4*	-32.5±70.5
FEV_1 $AUC_{0\text{-}24/24h}$	226.1±62.8**	178.1±62.9**	-6.4±63.0
Morning pre-dose FEV_1	142.9±78.5**	106.7±78.6**	-43.0±78.3
Peak FEV_1	407.9±56.5**	382.0±57.0**	130.5±56.0

*$P<0.001$, **$P<0.0001$ vs placebo; †$P<0.05$ vs tiotropium; results obtained from an ANCOVA model (ITT population). BID, twice daily; FEV, forced expiratory volume; QD, once daily.

Conclusion

Aclidinium 400 µg BID provides bronchodilation over 24 hours with clinically meaningful improvements greater than placebo, and comparable to tiotropium 18 µg QD.

Twice-daily aclidinium bromide in COPD patients: efficacy and safety results from ACCORD COPD I

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Introduction

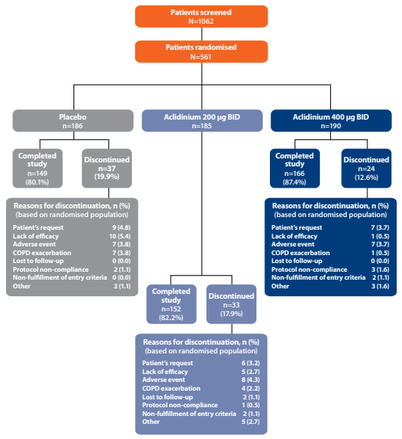
- Chronic obstructive pulmonary disease (COPD) is a highly prevalent lung disease characterised by gradual loss of lung function and airflow limitation that is not fully reversible.[1] As cholinergic tone is the major reversible component of airflow obstruction, therapy with anticholinergics can be effective in the treatment of COPD.[2]
- The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines recommend the use of long-acting bronchodilators, including anticholinergics, for the maintenance treatment of COPD.[1]
- Currently, only one long-acting anticholinergic is available for COPD treatment; therefore, the investigation of additional therapeutic options is necessary.
- Aclidinium bromide is a novel, long-acting muscarinic antagonist that is in development for the maintenance treatment of COPD.
- Previous clinical trials have demonstrated that treatment with aclidinium provides sustained bronchodilation and has a favourable tolerability profile in patients with COPD.[3,4]
- The objective of this Phase III study was to assess the efficacy, safety, and tolerability of aclidinium 200 µg and 400 µg administered BID via the Genuair® inhaler in patients with moderate to severe COPD.

Methods

Study design

- This was a 12-week, multicentre, randomised, double-blind, placebo-controlled, parallel-group trial evaluating twice-daily aclidinium 200 µg and 400 µg BID.
- Patients (N=561) were randomised (1:1:1) to aclidinium (200 or 400 µg BID) or placebo (Figure 1).
- Patients were evaluated at screening (for inclusion), at baseline following a 2-week run-in period, then every 4 weeks up to Week 12, and during follow-up 2 weeks after completion of treatment.

Figure 1. Study flow chart



Study population

Inclusion criteria

- Male and female patients aged ≥40 years
- Diagnosis of moderate to severe stable COPD
- Forced expiratory volume in 1 second (FEV_1)/forced vital capacity (FVC) ratio <70%
- FEV_1 ≥30% and <80% of predicted
- Current or ex-smokers with a smoking history of ≥10 pack-years

Exclusion criteria

- History or current diagnosis of asthma
- Respiratory infection or COPD exacerbation within 6 weeks (3 months if it resulted in hospitalisation) prior to screening
- Clinically significant or relevant cardiovascular conditions, laboratory tests, electrocardiogram (ECG) parameters, or respiratory conditions (other than COPD)

Allowed concomitant medications

- Salbutamol on an as-needed basis
- Inhaled corticosteroids (CS) and oral or parenteral CS at doses equivalent to 10 mg/day or 20 mg every other day (if stable for 4 weeks before Visit 1)

Study endpoints

Primary endpoint

- Change from baseline in morning pre-dose (trough) FEV_1 at Week 12 as compared to placebo

Secondary endpoint

- Change from baseline in peak FEV_1 at Week 12

Additional endpoints

- Change from baseline in St. George's Respiratory Questionnaire (SGRQ) total score at Weeks 4, 8, and 12
- Change from baseline in Transitional Dyspnoea Index (TDI) focal score at Weeks 4, 8, and 12

Safety

- Safety assessments included adverse events (AEs), clinical laboratory measures, vital signs, and ECGs

Statistical analysis

- All efficacy variables were analysed using the intention-to-treat (ITT) population and safety outcomes were analysed using the safety population.
- All efficacy outcomes were analysed using the ANCOVA model with sex and treatment group as factors and baseline FEV_1 and age as covariates. Safety outcomes were summarised with descriptive statistics.

Results

Baseline demographics

- A total of 561 patients were randomised and 467 patients completed the study (80.1% of the placebo group, 82.2% of aclidinium 200 µg, and 87.4% of aclidinium 400 µg). Baseline demographics and clinical characteristics were comparable between treatment groups (Table 1).

Table 1. Demographic and baseline characteristics (safety population; N=560)

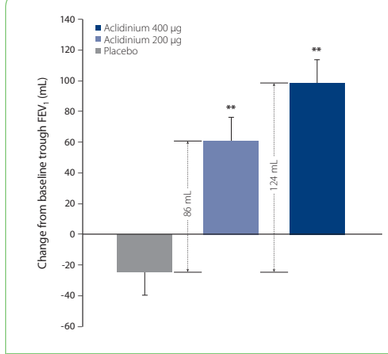
Characteristic	Placebo	Aclidinium 200 µg	Aclidinium 400 µg	Total
Age, mean (SD), years	65.1 (9.2)	63.1 (9.5)	64.9 (9.5)	64.3 (9.4)
Male, n (%)	96 (51.6)	101 (54.9)	100 (52.6)	297 (53.0)
Caucasian, n (%)	175 (94.1)	169 (91.8)	181 (95.3)	525 (93.8)
BMI, mean (SD), kg/m²	27.5 (5.2)	27.3 (5.1)	27.6 (5.0)	27.5 (5.1)
Current smoker, n (%)	87 (46.8)	84 (45.7)	80 (42.1)	251 (44.8)
Smoking history, mean (SD), pack-years	52.7 (28.1)	53.0 (23.3)	57.2 (28.5)	54.3 (26.8)
Pre-bronchodilator FEV_1 at screening, mean (SD), L	1.374 (0.6)	1.352 (0.5)	1.346 (0.5)	1.357 (0.5)
Post-bronchodilator FEV_1, mean (SD), L	1.558 (0.6)	1.543 (0.5)	1.532 (0.5)	1.544 (0.6)
Post-bronchodilator FEV_1, mean (SD), % of predicted value	54.6 (13.5)	52.8 (13.7)	54.1 (12.9)	53.8 (13.4)
Post-bronchodilator FEV_1/FVC ratio, mean (SD), %	52.7 (10.5)	50.9 (10.6)	51.5 (10.2)	51.7 (10.5)
Bronchodilator reversibility, mean (SD), %	17.1 (15.5)	16.7 (15.5)	15.5 (12.0)	16.5 (14.4)
Reversible, n (%)	80 (43.0)	83 (45.1)	77 (40.5)	240 (42.9)

Efficacy

Primary endpoint

- Change from baseline in morning pre-dose (trough) FEV_1 at Week 12 was statistically and clinically significantly greater for both aclidinium 200 and 400 µg BID as compared with placebo (86 mL and 124 mL respectively; p<0.0001 for both, Figure 2).
- In addition, change from baseline in trough FEV_1 at Week 12 was 38 mL greater for aclidinium 400 µg versus the 200 µg dose (p=0.0692).

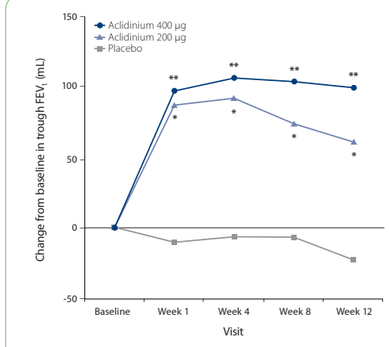
Figure 2. Change from baseline in trough FEV_1 for aclidinium 200 and 400 µg BID versus placebo (ITT population)



**p<0.0001 vs placebo
Data reported as least squares means ± standard error

- Change from baseline in trough FEV_1 was significantly greater for the aclidinium 200 µg and 400 µg treatment groups as compared to placebo for all weeks assessed during the study (p<0.0001 for all, Figure 3)

Figure 3. Change from baseline in trough FEV_1 by visit (ITT population)

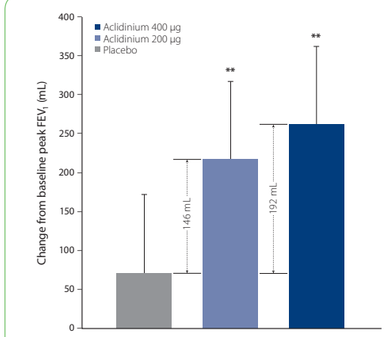


*Aclidinium 200 µg BID vs placebo, p<0.0001; **Aclidinium 400 µg BID vs placebo, p<0.0001

Secondary endpoint

- Following 12 weeks of treatment with aclidinium 200 µg and 400 µg BID, change from baseline in peak FEV_1 was statistically and clinically significantly greater as compared to placebo by 146 mL and 192 mL, respectively (p<0.0001 for both, Figure 4).
- Additionally, the 400 µg dose of aclidinium showed greater improvement over the 200 µg dose by 46 mL (p=0.0409).

Figure 4. Change from baseline in peak FEV_1 for aclidinium 200 µg and 400 µg BID versus placebo (ITT population)



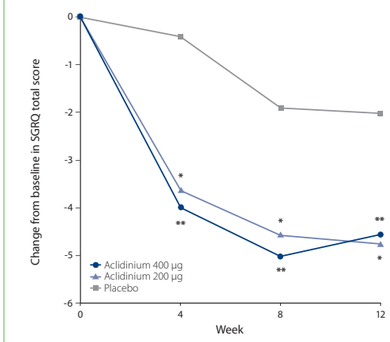
**p<0.0001 vs placebo
Data reported as least squares means ± standard error

Additional endpoints

SGRQ total score

- Both doses of aclidinium showed a statistically significant improvement in change from baseline in SGRQ total score at Weeks 4, 8, and 12 compared to placebo (Figure 5). The improvement was most notable at Week 4 with an adjusted mean difference vs placebo of -3.2 (200 µg dose) and -3.6 (400 µg dose; p<0.001 for both). At study end, the adjusted mean difference vs placebo was -2.7 for the 200 µg dose (p=0.0126) and -2.5 for the 400 µg dose (p=0.0186).

Figure 5. Change from baseline in SGRQ total score at Weeks 4, 8, and 12

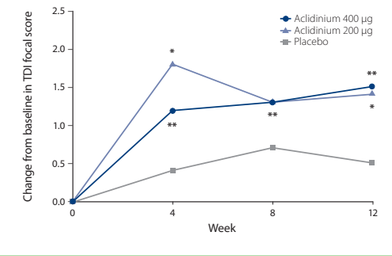


*Aclidinium 200 µg BID vs placebo, p<0.05; **Aclidinium 400 µg BID vs placebo, p<0.05
SGRQ total scores are a sum of symptom, activity, and impact scores.
Range is from 0-100 (100 indicates the worst health status)
Minimal clinically important difference is >4 point difference in SGRQ total score.

TDI focal score

- Treatment with aclidinium 200 µg and 400 µg BID resulted in significant improvement in the change from baseline in TDI focal score at Weeks 4, 8, and 12 as compared to placebo (p<0.05, except at Week 8 for the 200 µg group, p=0.0599; Figure 6). At Week 12, the adjusted mean differences in change from baseline versus placebo were 0.9 for aclidinium 200 µg and 1.0 for aclidinium 400 µg (p<0.01). These results were at or near the minimal clinically important difference (MCID, improvement >1).

Figure 6. Change from baseline in TDI focal score at Weeks 4, 8, and 12



* Aclidinium 200 µg BID vs placebo, p<0.05; **Aclidinium 400 µg BID vs placebo, p<0.05
Minimal clinically important difference is >1 point increase in TDI focal score.

Safety

- Aclidinium 200 µg and 400 µg BID were both well tolerated in patients with moderate to severe COPD.
- The only treatment-emergent adverse event (TEAE) reported by >5% of patients was COPD exacerbation (placebo, 12.4%; 200 µg, 9.2%; 400 µg, 7.4%). The incidence of all other AEs was <4% and was comparable across groups.
- Incidence of systemic anticholinergic effects was low in both aclidinium treatment groups and similar to placebo.
- There was a low incidence of treatment-emergent serious adverse events (SAEs) in all treatment groups (2.2% placebo, 4.3% 200 µg, and 3.2% 400 µg).
- Changes from baseline in laboratory results, vital signs, and ECG parameters were similar across all treatment groups.

Conclusions

- **Treatment with aclidinium 200 µg and 400 µg twice-daily for 12 weeks resulted in statistically and clinically significant improvements in lung function compared to placebo for both trough and peak FEV_1 in moderate to severe COPD patients.**
- **Both aclidinium doses resulted in improvements in patients' quality of life and COPD symptoms as measured by SGRQ and TDI.**
- **Twice-daily treatment with either dose of aclidinium was well tolerated throughout the study, with an incidence of systemic anticholinergic adverse events similar to placebo.**

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Abstract

Twice-daily aclidinium bromide in COPD patients: efficacy and safety results from ACCORD COPD I

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Introduction

This Phase III study evaluated the efficacy and safety of aclidinium bromide (200 µg and 400 µg BID), a long-acting, muscarinic antagonist for the treatment of patients with moderate to severe COPD.

Methods

In this 12-week, double-blind, multicentre, placebo-controlled trial, moderate to severe COPD patients were randomised (1:1:1) to aclidinium (200 or 400 µg BID) or placebo. Efficacy measures were mean change from baseline (±SE) in morning pre-dose (primary) and peak FEV_1 (secondary) at Week 12; additional measures included St George's Respiratory Questionnaire (SGRQ) and the Transitional Dyspnoea Index (TDI). Safety was also assessed.

Results

Of the 561 patients randomised, 467 (83%) completed the study. At Week 12, trough FEV_1 mean change from baseline was significantly ($P<0.0001$) greater than placebo for both 200 µg (86±21 mL) and 400 µg (124±21 mL) aclidinium. Peak FEV_1 was significantly ($P<0.0001$) greater than placebo for both aclidinium doses (Week 12: 200 µg, 146±23 mL; 400 µg, 192±22 mL). Week 12 SGRQ total score was significantly ($P<0.02$) improved vs placebo for aclidinium 200 µg (-2.73±1.1) and 400 µg (-2.54±1.1). TDI focal score was also significantly ($P<0.01$) increased for both aclidinium doses vs placebo (Week 12: 200 µg, 0.9±0.3; 400 µg,1.0±0.3). The only treatment-emergent adverse event (AE) reported by >5% of patients was COPD exacerbation (200 µg, 9.2%; 400 µg, 7.4%; placebo, 12.4%). The incidence of all other AEs was <4% and were comparable across groups.

Conclusion

Aclidinium 200 µg and 400 µg twice-daily significantly improved lung function, dyspnoea and quality of life in patients with moderate to severe COPD and was well tolerated at both doses.

Excretion and metabolism of [^{14}C]-acidinium bromide administered intravenously in healthy subjects

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Introduction

- Aclidinium bromide is a novel, long-acting muscarinic antagonist that is currently being developed for the treatment of COPD.
- Preclinical studies have shown that aclidinium bromide has a longer residence time at M_3 receptors and shorter residence time at M_2 receptors.[1]
- It has also been demonstrated that aclidinium bromide is rapidly hydrolysed in human plasma to two inactive metabolites, limiting the potential for systemic exposure.[2-4]
- In clinical trials with COPD patients, treatment with aclidinium results in sustained bronchodilation and a favourable tolerability profile.[5]
- The objectives of this study were to determine the rates and routes of aclidinium elimination and to identify and characterise its metabolites when administered as a single 400 µg intravenous (IV) dose to healthy male subjects.

Methods

Study design

- This was a Phase I, open-label, single-dose, mass balance study.
- A total of 12 subjects were randomised (1:1) to receive a single dose of aclidinium bromide as either 400 µg [phenyl-U-^{14}C]–aclidinium bromide or 400 µg [glycolyl-U-^{14}C]–aclidinium bromide; treatments were administered intravenously over a 5-minute period and contained approximately 40 µCi of radioactivity.
- The hydrolysis of [phenyl-U-^{14}C]–aclidinium bromide produces ^{14}C-labeled alcohol metabolite and unlabeled acid metabolite, whereas hydrolysis of [glycolyl-U-^{14}C]–aclidinium bromide produces ^{14}C-labeled acid metabolite and unlabeled alcohol metabolite. Therefore, in order to properly determine rates and routes of elimination, [phenyl-U-^{14}C]–aclidinium bromide and [glycolyl-U-^{14}C]–aclidinium bromide were administered to two different groups of healthy subjects.

Study population

Inclusion criteria

- Healthy, non-smoking males aged 18 to 45 years with normal physical examination, vital signs, pulse rate, and blood pressure
- BMI between 18 kg/m^2 and 30 kg/m^2

Exclusion criteria

- Evidence of sensitivity or allergic reaction to muscarinic antagonists
- Clinically significant or relevant cardiovascular conditions, laboratory tests, or electrocardiogram (ECG) parameters
- History of alcohol or substance abuse
- History of orthostatic hypotension, syncope, or vasovagal attacks
- Any clinical condition that could affect the absorption, distribution, metabolism, or excretion of aclidinium
- Concomitant medications within 14 days prior to study drug administration

Assessments

- Blood samples were collected at baseline (pre-dose), 5, 15, 30, and 45 min, at 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 16, 24, 36, 48 hours and at 24-hour intervals thereafter up to 168 hours after the start of infusion.
- Urine was collected pre-dose, 0-2, 2-4, 4-6, 6-8, 8-12, 12-16, 16-24, 24-36, and 36-48 hours post-dose and into 24-hour samples thereafter up to 168 hours.
- Feces were collected in 24-hour intervals during 0-168 hours after dosing.
- Blood, plasma, urine, and feces samples were analysed for radioactivity by HPLC and liquid scintillation counting (LSC).
- Determination of aclidinium and its metabolites in plasma was performed using solid phase extraction (SPE) and liquid chromatography tandem mass spectrometry (LC-MS/MS).
- Safety and tolerability were assessed via adverse events (AEs), vital signs, 12-lead electrocardiograms (ECGs), physical examinations, and clinical laboratory tests.

Statistical analysis

- Pharmacokinetic parameters were calculated using actual sampling times and were derived using noncompartmental analyses with WinNonlin software (version 4.1 or higher).
- The pharmacokinetic analysis population was comprised of subjects in the safety population who received the full dose of study drug and completed the study.
- Rates and routes of aclidinium bromide elimination were assessed along with pharmacokinetic parameters ($AUC_{0\text{-}t}$, C_{max}, t_{max}, and $t_{½}$) for total radioactivity in plasma and whole blood; pharmacokinetic parameters for LAS34850 free acid (acid metabolite) and LAS34823 cation (alcohol metabolite) were assessed in plasma only.
- Because the LC-MS/MS method measured the unlabeled compound rather than the actual concentration of the compound (unlabeled + ^{14}C-labeled), correct analysis of concentrations and pharmacokinetic parameters were only possible for the acid metabolite following 400 µg [phenyl-U-^{14}C]–aclidinium bromide and for the alcohol metabolite following 400 µg [glycolyl-U-^{14}C]–aclidinium bromide.
- Descriptive statistical analysis of demographic and safety data was performed on the safety population (all subjects who received one dose of study treatment).

Results

Baseline demographics

- A total of 12 subjects were randomised and completed the study. The mean age (±SD) of all subjects was 23 ± 4.1 years.
- Baseline demographics and clinical characteristics were similar between treatment groups.

Pharmacokinetic parameters

Plasma

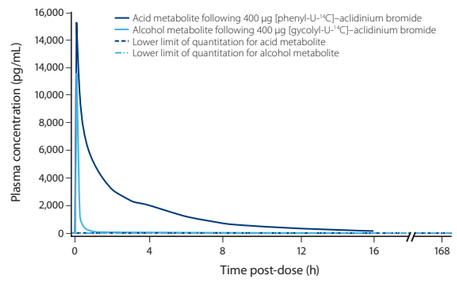
- Following IV administration of 400 mg [phenyl-U-^{14}C]– and [glycolyl-U-^{14}C]–aclidinium bromide, maximum concentrations of aclidinium bromide's two inactive metabolites (acid and alcohol metabolites, respectively) occurred at median t_{max} of approximately 5 minutes (Table 1).
- Plasma levels of the alcohol metabolite were quantifiable (≥5.0 pg/mL) for 16 hours after the start of IV administration; the plasma levels of the acid metabolite were quantifiable (≥100 pg/mL) for 8-16 hours post-dose (Figure 1).

Table 1. Mean pharmacokinetic parameters for the acid and alcohol metabolites following single IV doses of 400 µg [phenyl-U-^{14}C]– and [glycolyl-U-^{14}C]–aclidinium bromide: PK analysis population

	Acid metabolite	Alcohol metabolite
$AUC_{0\text{-}t}$, pg·hr/mL	26500 (11.1)	2340.4 (26.9)
C_{max}, pg/mL	14444 (19.4)	11460 (23.5)
t_{max}, h	0.09 (0.08-0.20)	0.08 (0.08-0.10)
$t_{½}$, h	3.41 (13.1)	2.70 (28.2)

Data are arithmetic mean (coefficient of variation, CV%) except for t_{max}, which is median (minimum-maximum).

Figure 1. Plasma concentration-time profile of aclidinium metabolites



- Plasma radioactivity $AUC_{0\text{-}t}$ and C_{max} were higher following IV [glycolyl-U-^{14}C]–aclidinium bromide than IV [phenyl-U-^{14}C]–aclidinium bromide (increased 8.2- and 1.7-fold, respectively), indicating the clearance of the acid metabolite is probably slower than the clearance of the alcohol metabolite (Table 2).
- Total radioactivity in plasma was quantifiable (≥0.3 ng eq/mL) for 12-16 hours following administration of [phenyl-U-^{14}C]–aclidinium bromide and 36-48 hours following [glycolyl-U-^{14}C]–aclidinium bromide.

Whole blood

- Maximum whole blood concentrations of total radioactivity occurred at a median t_{max} of approximately 5 minutes for [phenyl-U-^{14}C]– and [glycolyl-U-^{14}C]–aclidinium bromide. $AUC_{0\text{-}t}$ and C_{max} values for total radioactivity following [glycolyl-U-^{14}C]–aclidinium bromide were 20.3-fold and 2.0-fold higher, respectively, than those seen with [phenyl-U-^{14}C]–aclidinium bromide (Table 2).
- Total radioactivity was quantifiable (≥0.4 ng.eq/mL) for 1-2 hours following administration of [phenyl-U-^{14}C]–aclidinium bromide and 16-24 hours following [glycolyl-U-^{14}C]–aclidinium bromide.

Table 2. Pharmacokinetic parameters for total radioactivity

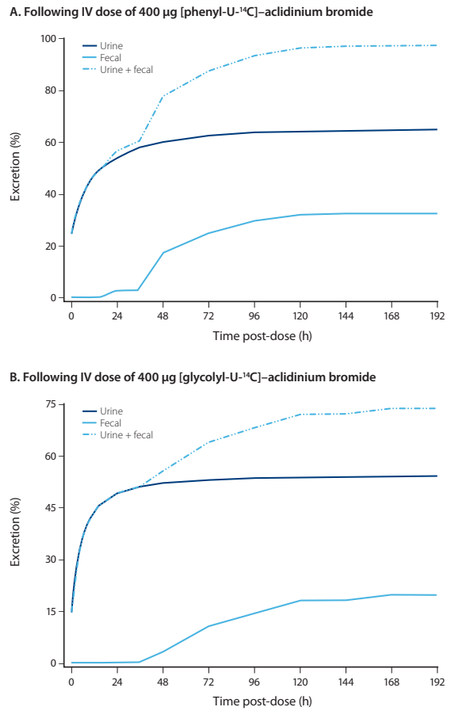
	[Phenyl-U-^{14}C]–aclidinium bromide 400 µg	[Glycolyl-U-^{14}C]–aclidinium bromide 400 µg
Plasma		
$AUC_{0\text{-}t}$, ng eq·h/mL	12.8 (20.3)	105.0 (10.3)
C_{max}, ng eq/mL	24.5 (48.6)	42.2 (18.5)
t_{max}, h	0.09 (0.08-0.20)	0.08 (0.08-0.10)
$t_{½}$, h	8.63 (28.5)	13.3 (22.2)
Whole blood		
$AUC_{0\text{-}t}$, ng eq·h/mL	2.31 (26.9)	46.9 (14.4)
C_{max}, ng eq/mL	10.8 (53.5)	21.4 (15.1)
t_{max}, h	0.09 (0.08-0.20)	0.08 (0.08-0.10)
$t_{½}$, h	1.19 (82.4)	5.53 (13.3)

Data are arithmetic mean (CV%) except for t_{max}, which is median (minimum-maximum).

Mass balance

- The predominant route of excretion for both treatments was renal (Figure 2).
- Most [phenyl-U-^{14}C]–associated radioactivity (93%) was recovered in the first 96 hours post-dose. Within 120 hours post-dose, most [glycolyl-U-^{14}C]–associated radioactivity (72%) was recovered (Figure 2).

Figure 2. Mean cumulative excretion of total radioactivity



IV, intravenous

Metabolite profiles

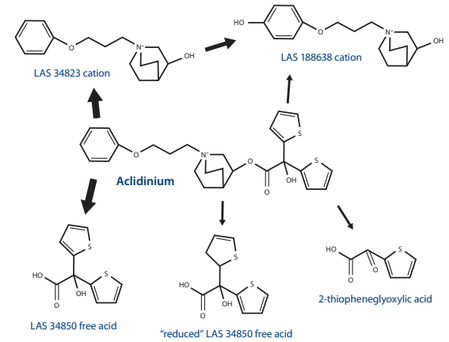
Excreta

- Metabolite profiles were obtained by analysing urine samples from 0 to 24 hours and feces samples from 0 to 96 hours.
- Following IV [phenyl-U-^{14}C]–aclidinium bromide, 1.2% of the dose was excreted unchanged in urine, 41.8% as the p-hydroxy alcohol metabolite and 32.5% as alcohol metabolite. No other metabolites with a significant amount of radioactivity were observed.
- Following IV [glycolyl-U-^{14}C]–aclidinium bromide, 1.7% of the dose was excreted unchanged in urine, 39.5% as the acid metabolite, and 16.8% in equal parts 2-thiophenеglyoxylic acid, "reduced" LAS34850, and an as-yet-unknown species. No other metabolites with a significant amount of radioactivity were observed.
- The proposed metabolic pathway of aclidinium in healthy male subjects is shown in Figure 3.

Plasma

- The highest plasma concentrations of unchanged aclidinium (1.8-5.5 ng eq/mL), the alcohol metabolite (23.8 ng eq/mL), and the acid metabolite (36.4 ng eq/mL) were observed approximately 5 minutes post-dose. The plasma concentration of p-hydroxy LAS34823 metabolite was low and was only 0.045 ng eq/mL of aclidinium bromide. The "reduced" LAS34850 and the unknown metabolite were not detected in plasma.

Figure 3. The proposed metabolic pathway of aclidinium



Safety

- A total of 2 of 12 subjects reported 3 treatment-emergent AEs (TEAEs). These TEAEs included infusion site pain and pain in an extremity and none were serious or led to discontinuation. All TEAEs were mild to moderate in intensity and considered related to [glycolyl-U-^{14}C] treatment.
- No clinically relevant changes in laboratory values, vital signs, or ECG parameters were reported.

Conclusions

- **Aclidinium bromide, administered intravenously, is metabolized rapidly and extensively to its inactive metabolites via hydrolysis directly (hydrolysis alone) or indirectly (metabolic transformation plus hydrolysis).**
- **Only 1.2% of the aclidinium dose was excreted as unchanged drug. The predominant route of excretion was renal for both the alcohol and acid metabolites.**
- **Results from this study suggest that aclidinium has a favourable pharmacokinetic profile and a low potential for adverse events related to systemic exposure.**

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Poster presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 18-22 September, 2010

Abstract

Excretion and metabolism of [^{14}C]-aclidinium bromide administered intravenously in healthy subjects

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Introduction

Aclidinium bromide, a long-acting muscarinic antagonist in development for COPD treatment, is an ester compound rapidly hydrolysed in plasma into inactive alcohol and acid metabolites. Rates and routes of elimination and the metabolite profile following intravenous (IV) administration of [^{14}C]-aclidinium bromide were determined.

Methods

In this Phase I, open-label study, 12 healthy males were randomised (1:1) to receive a single IV 400 µg dose of [phenyl-U-^{14}C]- or [glycolyl-U-^{14}C]-aclidinium bromide (via 5-min infusion) to label alcohol or acid metabolites, respectively. Metabolites were identified in plasma and excreta. Rates and routes of elimination, safety and tolerability were assessed by laboratory measurements, adverse events (AEs), vital signs and 12-lead ECGs over a 9-d period. Pharmacokinetic assessments were evaluated from plasma and whole blood.

Results

Following administration of [phenyl-U-^{14}C]- and [glycolyl-U-^{14}C]-aclidinium, the parent compound was rapidly hydrolysed into its acid and alcohol metabolites. C_{max} of both metabolites was observed 5 min after IV infusion. Primary excretion routes for [phenyl-U-^{14}C]- and [glycolyl-U-^{14}C]-aclidinium were renal (urine: 65% and 54%; feces: 33% and 20%), with 1% excreted as unchanged aclidinium. $AUC_{(0\text{-}t)}$ and C_{max} plasma radioactivity values indicated slower clearance of acid vs alcohol metabolite. Treatment-emergent AEs (3 total) were reported by 2 subjects: infusion site pain (n=2) and mild extremity pain (n=1).

Conclusion

Aclidinium is rapidly hydrolysed into two inactive metabolites that are mainly excreted renally. Aclidinium 400 µg administered intravenously was safe and well tolerated in healthy subjects.

Muscarinic receptor selectivity of aclidinium bromide and glycopyrrolate *in vitro*

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Introduction

- Anticholinergic agents are commonly used to treat chronic obstructive pulmonary disease (COPD) exerting their bronchodilatory effects primarily by blockade of pulmonary M_3 receptors. This effect is often accompanied by the blockade of other muscarinic receptor subtypes, particularly M_2 receptors, which can lead to unwanted side effects.[1,2]
- Since the pharmacological selectivity of anticholinergic drugs may impact on their *in vivo* tolerability, agents with kinetic selectivity for M_3 over M_2 receptors are desirable.
- Aclidinium bromide is a novel, long-acting muscarinic antagonist, currently in clinical development for the maintenance treatment of patients with COPD.
- Preclinical studies have shown aclidinium to be a potent muscarinic receptor antagonist, with a longer residence time at M_3 receptors compared with M_2 receptors.[3] Compared with tiotropium, aclidinium also demonstrates a reduced potential for cardiovascular effects in animal models,[3,4] possibly due to its relatively faster dissociation rate from M_2 receptors and its rapid hydrolysis in plasma.[5]
- This study investigated the effects of glycopyrrolate on M_3 and M_2 *in vitro* systems and compared the results with previously presented data for aclidinium, using tiotropium and ipratropium as comparators, under similar study conditions.[3,6]

Methods*

Affinity for human M_1–M_5 muscarinic receptors

- The affinity (K_i) of each antagonist for muscarinic M_1–M_5 receptors was determined by measuring the displacement of 1-[N-methyl-^{3}H] scopolamine (^{3}H-NMS) from cell membranes expressing human muscarinic receptors.
- M_1, M_2, M_3, M_4 and M_5 receptor membrane preparations (protein concentrations 8.1, 10.0, 4.9, 4.5 and 5.0 µg/well, respectively) were incubated at room temperature with ^{3}H-NMS (0.3 nM for M_1 and M_4; 1 nM for M_2, M_3 and M_5) in the presence of a range of antagonist concentrations (10-5 to 10-14 M) or 1 µM atropine (to measure non-specific binding).
- After a 2- or 6-hour incubation period (M_1–M_4 and M_5, respectively) to ensure that equilibrium was achieved, bound ^{3}H-NMS was separated from free ^{3}H-NMS by filtration, and residual radioactivity was quantified using a scintillation counter.
- K_i values were calculated as described by Cheng and Prusoff.[7]

Dissociation from human M_2 and M_3 muscarinic receptors

- Membranes expressing M_2 and M_3 receptors (final protein concentration 15 µg/mL) were incubated at room temperature with ^{3}H-aclidinium (2.5 nM), ^{3}H-glycopyrrolate (15 and 5 nM for M_2 and M_3, respectively), ^{3}H-tiotropium (2.5 nM) or ^{3}H-ipratropium (10 nM) for 135 minutes. Under these conditions the radioligands reached equilibrium with approximately 90% occupancy of the binding sites.
- Atropine (final concentration 10 µM) was then added to initiate dissociation and to prevent reassociation of the radioligands.
- The amount of radioligand that remained bound at different time points was determined by removing the free radioligands by filtration and quantifying residual radioactivity using a scintillation counter.
- Dissociation half-lives ($t_{1/2}$) were calculated using one-phase exponential decay.[8]

Assessment of potency and duration of action at M_2 and M_3 receptors

M_2 receptors

- Isolated guinea pig left-atria were suspended in an organ bath at 32°C and electrically stimulated to induce M_2 receptor-mediated contraction. Carbachol was added to the stimulated atria to inhibit electrically induced contractions via the M_2 receptor.
- To assess potency at M_2 receptors, increasing concentrations of aclidinium, glycopyrrolate, tiotropium and ipratropium (0.01 to 1000 nM) were added to the carbachol (1 µM)-treated atria every 5 to 10 minutes.
- To measure duration of action at M_2 receptors, antagonists were added to the carbachol (10 µM)-treated atria at a concentration that inhibited 80% of the maximum carbachol-induced relaxation. Once inhibition of tone was stable, the antagonists were washed out and the atria were incubated with carbachol (10 µM) for 240 minutes.

M_3 receptors

- Isolated guinea pig trachea strips were mounted in a superfusion chamber at 37°C and electrically stimulated to induce M_3 receptor-mediated contraction.
- Potency at M_3 receptors was assessed by infusing increasing concentrations of aclidinium, glycopyrrolate, tiotropium and ipratropium (0.01 nM to 1 µM) to the trachea strips every 30 minutes.
- Duration of action at M_3 receptors was examined by incubating stimulated trachea strips with each antagonist at a concentration producing 80–90% inhibition of the electrically stimulated contraction. The antagonists were washed out after 45 minutes to allow the trachea strips to recover the electrically stimulated contraction.

Analysis

- The concentrations required for 50% inhibition (EC_{50}) of the electrically stimulated contraction (M_3 receptors) and maximum carbachol-induced relaxation (M_2 receptors) were calculated using non-linear regression analysis.
- The dissociation half-life ($t_{1/2}$) of each antagonist at M_3 receptors was calculated using non-linear regression analysis. The $t_{1/2}$ for antagonists at M_2 receptors was calculated using one-phase (aclidinium, glycopyrrolate and tiotropium) or two-phase (ipratropium) exponential decay.

Results*

Affinity for human M_1–M_5 muscarinic receptors

- At equilibrium, aclidinium and tiotropium displayed higher affinity for all muscarinic receptor subtypes compared with glycopyrrolate and ipratropium (Table 1).
- Glycopyrrolate appeared to show some preferred affinity for M_3 versus M_2 receptors, but the magnitude of the effect was limited (approximately 3-fold; Table 1).

Table 1. Binding affinity of aclidinium, glycopyrrolate, tiotropium and ipratropium for human M_1, M_2, M_3, M_4 and M_5 receptors

	K_i (nM)				
	M_1	M_2	M_3	M_4	M_5
Aclidinium	0.10 ± 0.00	0.14 ± 0.04	0.14 ± 0.02	0.21 ± 0.04	0.16 ± 0.01
Glycopyrrolate	0.42 ± 0.02	1.77 ± 0.06	0.52 ± 0.04	0.78 ± 0.04	1.29 ± 0.09
Tiotropium	0.13 ± 0.00	0.13 ± 0.04	0.19 ± 0.04	0.30 ± 0.09	0.18 ± 0.06
Ipratropium	1.31 ± 0.15	1.12 ± 0.13	1.24 ± 0.08	1.92 ± 0.18	3.22 ± 0.15

Data are reported as mean ± standard error of the mean; n=3
K_i, affinity

Dissociation from human M_2 and M_3 muscarinic receptors

- Aclidinium dissociated from M_2 and M_3 receptors faster than tiotropium and slower than glycopyrrolate and ipratropium (Figures 1a and b; Table 2).
- The kinetic selectivity for M_3 over M_2 receptors (M_3/M_2 ratio) was similar for all four antagonists (Table 2).

Table 2. Dissociation half-lives of ^{3}H-aclidinium, ^{3}H-glycopyrrolate, ^{3}H-tiotropium and ^{3}H-ipratropium from human M_2 and M_3 receptors

	M_2 $t_{1/2}$ (h)	M_3 $t_{1/2}$ (h)	Relative half-life at M_3 receptor	M_3/M_2 ratio
Aclidinium	4.69 ± 0.29	29.24 ± 0.61	62	6.2
Glycopyrrolate	1.07 ± 0.20	8.10 ± 0.45	17	7.3
Tiotropium	15.11 ± 1.57	62.19 ± 2.96	132	4.1
Ipratropium	0.08 ± 0.01	0.47 ± 0.02	1	5.9

Data are reported as mean ± standard error of the mean; n=3
$t_{1/2}$, dissociation half-life

Assessment of potency and duration of action at M_2 and M_3 receptors

M_2 receptors

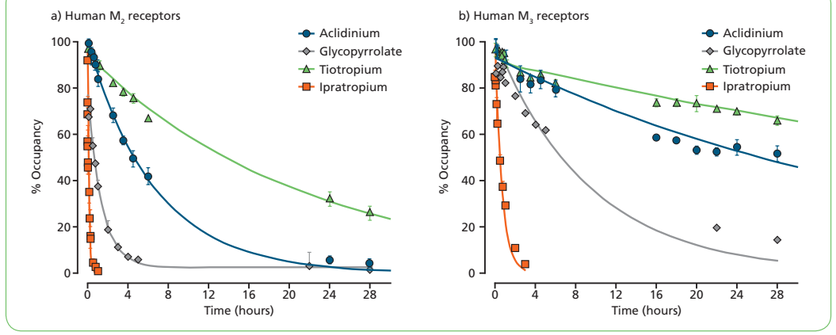
- Tiotropium displayed greater potency at left-atria M_2 receptors compared with aclidinium, glycopyrrolate and ipratropium (Table 3).

Table 3. *In vitro* potency and duration of action of aclidinium, glycopyrrolate, tiotropium and ipratropium at M_2 receptors (guinea pig atria) and M_3 receptors (guinea pig trachea)

	M_2 receptors		M_3 receptors	
	EC_{50} (nM)[a]	$t_{1/2}$ (min)	EC_{50} (nM)[a]	$t_{1/2}$ (min)
Aclidinium	17.4 ± 1.1	102	5.3 ± 1.6	>480
Glycopyrrolate	17.3 ± 1.2	30	4.2 ± 0.3	>480
Tiotropium	11.8 ± 1.1	184	3.0 ± 0.6	>480
Ipratropium	19.9 ± 1.14	4	3.0 ± 0.4	42

[a]Data are reported as mean ± standard error of the mean; n=3–13
EC_{50}, concentrations required for 50% inhibition; $t_{1/2}$, dissociation half-life

Figure 1. Dissociation of ^{3}H-aclidinium, ^{3}H-glycopyrrolate, ^{3}H-tiotropium and ^{3}H-ipratropium from human M_2 and M_3 receptors



M_3 receptors

- In isolated left-atria, glycopyrrolate had a shorter offset time at M_2 receptors compared with aclidinium and tiotropium, but a longer offset time compared with ipratropium.

M_3 receptors

- All four muscarinic antagonists showed similar potency at M_3 receptors in the isolated trachea strip assay (Table 3).
- Aclidinium, glycopyrrolate and tiotropium had similar offset times at M_3 receptors and were of a greater magnitude than that observed for ipratropium (Table 3).

Conclusions

- **Aclidinium, glycopyrrolate, tiotropium and ipratropium are potent muscarinic antagonists that display similar kinetic selectivity for M_3 over M_2 receptors.**
- **In isolated organ studies, aclidinium and glycopyrrolate have similar relative potency at M_3 and M_2 receptors. The slight preference for M_3 versus M_2 receptors observed for glycopyrrolate in the membrane binding experiments does not translate into improved relative potency at M_3 and M_2 receptors compared with aclidinium.**
- **Compared with the other antagonists tested, tiotropium has the greatest potency at M_2 receptors.**
- **Aclidinium and tiotropium have a longer dissociation half-life from the M_3 receptor than glycopyrrolate, suggesting a longer bronchodilatory effect in humans.**

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Acknowledgements

This study was supported by Almirall S.A., Barcelona, Spain.

*Methods and results for aclidinium, tiotropium and ipratropium are as previously reported.[3,6]

Poster presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 18-22 September 2010

Abstract

Muscarinic receptor selectivity of aclidinium bromide and glycopyrrolate *in vitro*

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Introduction

Muscarinic antagonists induce bronchodilation mainly through the blockade of pulmonary M_3 receptors, an effect often accompanied by the unwanted blockade of M_2 receptors. Here we report the effects of aclidinium bromide and glycopyrrolate on M_2 and M_3 receptors *in vitro*. Tiotropium and ipratropium were included as comparators.

Methods

M_1 to M_5 muscarinic receptor affinity was determined by displacement of 1-[N-methyl-^{3}H] scopolamine binding to CHO cell membranes expressing human muscarinic receptors. Dissociation from M_2 and M_3 receptors was measured using ^{3}H-aclidinium, ^{3}H-glycopyrrolate, ^{3}H-tiotropium and ^{3}H-ipratropium. Guinea-pig trachea and rat atria were used to assess *in vitro* potency and offset times for each drug.

Results

Aclidinium and tiotropium showed higher muscarinic receptor affinity than ipratropium or glycopyrrolate. Tiotropium (62.2 h) and aclidinium (29.2 h) had the greatest dissociation half-life at M_3 receptors, compared with glycopyrrolate (8.1 h) and ipratropium (0.47 h). Kinetic selectivity (M_3/M_2 ratio) was similar for all compounds. Potency (EC_{50}) at M_3 receptors ranged from 3.0–5.3 nM. Aclidinium, tiotropium and glycopyrrolate had offset times of $>$8 h at M_3 receptors vs 0.7 h for ipratropium. EC_{50} at M_2 receptors was greater for tiotropium (12 nM) than for aclidinium (17 nM), ipratropium (20 nM) or glycopyrrolate (17 nM). For each drug, offset time was proportional to the dissociation half-life at M_2 receptors.

Conclusion

Aclidinium and glycopyrrolate displayed similar selectivity for M_3 and M_2 receptors. Aclidinium had a longer M_3 receptor dissociation half-life than glycopyrrolate *in vitro*, suggesting a longer bronchodilatory effect in humans.

In vivo, aclidinium bromide has longer duration of action and reduced potential to induce dry mouth, compared with glycopyrrolate

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Introduction

- Inhaled anticholinergic agents are frequently used to treat chronic obstructive pulmonary disease (COPD). Such agents should ideally be potent, long-acting bronchodilators with low systemic availability thereby limiting the potential for unwanted anticholinergic effects. Several current inhaled anticholinergic agents, including ipratropium and tiotropium, have been associated with systemic side effects including dry mouth.[1,2]
- Aclidinium bromide is a novel, inhaled, long-acting muscarinic antagonist, currently in development for the treatment of patients with COPD.
- Preclinical studies have shown that aclidinium has high affinity for muscarinic receptors with a longer residence time at M_3 receptors compared with M_2 receptors.[3] Additionally, aclidinium is rapidly hydrolysed in human plasma to two inactive metabolites. These characteristics suggest aclidinium may provide a sustained bronchodilatory effect with a reduced potential for systemic anticholinergic effects.[3,4]
- Here we report the results of two *in vivo* studies:
  - Study 1 was designed to assess the onset, potency and duration of action of glycopyrrolate in guinea pigs, compared with data previously obtained for aclidinium, tiotropium and ipratropium using identical assays and conditions.[3]
  - Study 2 investigated the effects of either glycopyrrolate or aclidinium on salivation in rats, using tiotropium as a comparator.[5]

Methods*

Study 1: Assessment of onset, potency and duration of action in anaesthetised guinea pigs

- Aclidinium, glycopyrrolate, tiotropium, ipratropium (1–1000 µg/mL) or vehicle were administered to male Dunkin-Hartley guinea pigs (400–600 g) by nebulisation for two 1-minute periods separated by an interval of 5 minutes.
- At selected points after exposure to the antagonists (1, 2, 4, 6, 18 and 24 hours), guinea pigs were anaesthetised, artificially ventilated, and their tracheas were cannulated and connected to a flow and pressure transducer to record airway resistance.
- Bronchoconstriction was induced by an intravenous administration of a single bolus dose of acetylcholine (30 µg/kg), and the inhibitory effect of the antagonists was tested in comparison to vehicle.
- Onset of action was defined as the time to achieve maximal inhibition of bronchoconstriction (t_{max}). Potency was defined as the concentration of antagonist required to induce 50% inhibition (EC_{50}) of bronchoconstriction, determined from a sigmoidal dose-response curve constructed using inhibition values at t_{max}. Duration of action, defined as the time taken to achieve 50% recovery of the maximal inhibitory effect achieved by the antagonist ($t_{1/2}$), was derived from time-course bronchoconstriction inhibition curves using one-phase exponential decay.

Study 2: Salivation studies in conscious rats

- Aclidinium (0.1–1000 µg/kg, s.c.), glycopyrrolate (0.1–10 µg/kg, s.c.), tiotropium (0.1–100 µg/kg, s.c.) or vehicle were administered to male Wistar rats (180–260 g; fasted for 18 hours).
- After 30 minutes, pilocarpine (0.5 mg/kg) was administered via the caudal vein.
- The presence of any excess saliva (sialorrhoea) was recorded for the following 15 minutes by gently pressing filter paper on the animal's mouth.
- For each antagonist, the proportion of salivating animals was compared with vehicle-treated animals by Fischer's exact test. ED_{50} values (the dose of test compound inhibiting pilocarpine-induced salivation in 50% of rats) were calculated by non-linear regression.

Results*

Study 1: Onset, potency and duration of action in guinea pigs

- Aclidinium, glycopyrrolate and ipratropium achieved maximal inhibition of bronchoconstriction at 2 hours post-administration, compared with 4 hours for tiotropium (Table 1).[3]
- The four antagonists showed similar potency at the time of maximal effect (Table 1).
- The duration of action was longer for tiotropium ($t_{1/2}$ = 64 hours) and aclidinium ($t_{1/2}$ = 29 hours) compared with glycopyrrolate and ipratropium ($t_{1/2}$ = 13 hours and $t_{1/2}$ = 8 hours, respectively; Figure 1).[3]
- At the concentrations selected, all four antagonists achieved an inhibitory effect on bronchoconstriction of 97–98% at 1 hour post-administration (Figure 1).

Study 2: Salivation studies in conscious rats

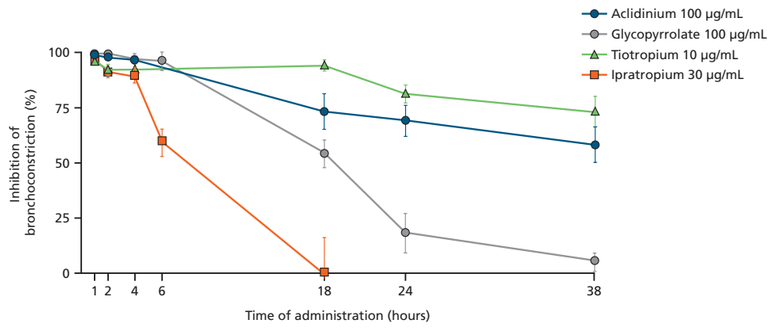
- Aclidinium inhibited pilocarpine-induced salivation to a lesser extent than tiotropium (ED_{50} [µg/kg] = 38 and 0.88, respectively; Figure 2a).[5]
- Glycopyrrolate inhibited pilocarpine-induced salivation to the same extent as tiotropium (ED_{50} [µg/kg] = 0.74 and 0.72, respectively; Figure 2b).

Table 1. Onset of action and potency of aclidinium, glycopyrrolate, tiotropium and ipratropium in reversing acetylcholine-induced bronchoconstriction in guinea pigs[3]

	EC_{50}, µg/mL (95% CI)				
	1 hour	2 hours	4 hours	18 hours	24 hours
Aclidinium	5.9 (3.7–9.4)	2.5 (1.7–3.5)	2.9 (1.8–4.7)	12.4 (4.1–37.6)	23.1 (9.3–57.3)
Glycopyrrolate	7.2 (4.1–12.8)	3.8 (2.5–5.7)	8.8 (5.2–14.8)	68.7 (39.6–119.2)	242.3 (162.0–362.2)
Tiotropium	2.4 (1.4–3.8)	3.9 (2.0–7.6)	1.4 (0.7–2.5)	1.4 (0.7–2.9)	3.3 (2.0–5.2)
Ipratropium	6.9 (4.0–11.7)	3.4 (1.9–5.9)	7.3 (4.0–13.4)	689.7 (337.1–1411.0)	NA

CI, confidence interval; EC_{50}, concentration required to induce 50% inhibition; NA, not available

Figure 1. Duration of action of aclidinium, glycopyrrolate, tiotropium and ipratropium in reversing acetylcholine-induced bronchoconstriction in guinea pigs[3]



Data are mean ± standard error of the mean; n=4–9

Figure 2a. Effects of aclidinium and tiotropium on pilocarpine-induced salivation in conscious male Wistar rats[5]

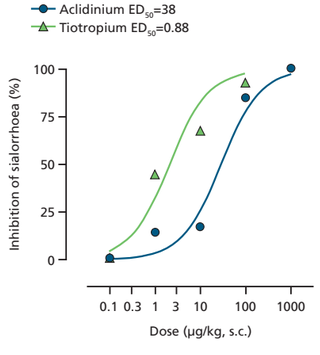
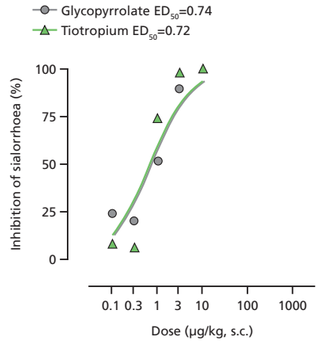


Figure 2b. Effects of glycopyrrolate and tiotropium on pilocarpine-induced salivation in conscious male Wistar rats



Conclusions

- **The onset of bronchodilatory effect for aclidinium in guinea pigs is similar to that of glycopyrrolate and ipratropium and faster than that of tiotropium.**
- **At the time of maximal effect, aclidinium, glycopyrrolate, tiotropium and ipratropium are equipotent inhibitors of bronchoconstriction in guinea pigs.**
- **Aclidinium has a longer duration of action in anaesthetised guinea pigs compared with glycopyrrolate and ipratropium but a shorter duration of action than tiotropium.**
- **The lower potency of aclidinium compared with glycopyrrolate on the inhibition of salivation in conscious rats suggests a lower propensity for dry mouth in the clinical setting.**

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Acknowledgements

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*Methods and results for aclidinium, tiotropium and ipratropium are as previously reported.[3,5]

Poster presented at the European Respiratory Society Annual Congress, Barcelona, Spain, 18-22 September 2010

Abstract

In vivo, aclidinium bromide has longer duration of action and reduced potential to induce dry mouth, compared with glycopyrrolate

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Introduction

The ideal muscarinic antagonist for the treatment of chronic obstructive pulmonary disease (COPD) should be a potent, long-acting bronchodilator with low systemic availability; thus limiting the potential for unwanted effects such as dry mouth. Aclidinium bromide is a novel, long-acting, inhaled muscarinic antagonist being developed as a treatment for COPD. Here we report the *in vivo* bronchodilatory activity of aclidinium and glycopyrrolate, as well as their propensity to induce dry mouth. Tiotropium and ipratropium were included as comparators.

Methods

The onset, potency and duration of action (DoA) of inhaled aclidinium, glycopyrrolate, tiotropium and ipratropium (1–1000 µg/mL) were assessed in anaesthetised guinea-pigs with acetylcholine-induced bronchoconstriction. The effect of aclidinium, glycopyrrolate and tiotropium (0.1–1000 µg/kg; s.c.) on pilocarpine-induced salivation was determined in conscious rats.

Results

Maximum bronchodilation occurred 2 h after administration of aclidinium, glycopyrrolate and ipratropium, compared with 4 h for tiotropium. At maximal effect, potency was similar for all four drugs. Aclidinium and tiotropium had the longest DoA ($t_{1/2}$=29 h and 64 h, respectively) compared with glycopyrrolate ($t_{1/2}$=13 h) and ipratropium ($t_{1/2}$=8 h). Aclidinium inhibited salivation to a lesser extent than tiotropium and glycopyrrolate (ED_{50}=37, 0.74 and 0.88 µg/kg, respectively).

Conclusion

In vivo, aclidinium was a potent bronchodilator with a longer DoA than glycopyrrolate. Aclidinium had less potential to inhibit salivation than tiotropium and glycopyrrolate, suggesting a reduced propensity for dry mouth.

Different inhalation volumes do not impact on the aerodynamics of aclidinium bromide delivered using the Genuair®* inhaler

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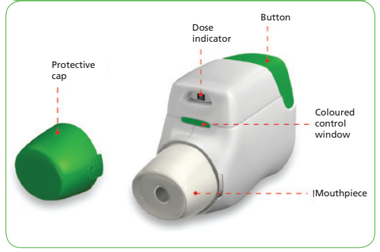
Almirall

Forest Laboratories, Inc.

Introduction

- Accurate and consistent delivery of inhaled medication is an important consideration for the effective treatment of chronic obstructive pulmonary disease (COPD).
- Regulatory authorities of different countries require inhaled drugs to be tested at different inhalation volumes prior to granting marketing approval. *In vitro* testing requirements for Europe and the United States are 4 litres[1] and 2 litres,[2] respectively.
- The Genuair® inhaler (Figure 1) is a breath-actuated, multidose dry powder inhaler (MDPI) with advanced fluid and particle dynamics, that ensure effective deagglomeration and drug delivery, even at low inhalation flow rates and volumes.[3]

Figure 1. Design and features of the Genuair® inhaler



- The Genuair® inhaler has demonstrated highly reproducible dose delivery across a range of inhalation formulations,[4] thus confirming the high aerodynamic precision of this inhaler observed *in vitro*.[5]
- Aclidinium bromide administered via the Genuair® inhaler is currently in clinical development for the maintenance treatment of patients with COPD.
- This study evaluated whether differences in inhalation volume affect the dose content uniformity and fine particle dose of aclidinium delivered via the Genuair® inhaler. The stability of the aerodynamic performance and aclidinium particle size distribution, including fine particle dose, was also assessed.

Methods

- Aerodynamic assessments evaluated the effects of inhalation volume (2 L versus 4 L) on the total delivered dose, fine particle dose and particle size distribution of aclidinium, delivered using the Genuair® inhaler.
- Two formulations (50 µg and 400 µg) of aclidinium were tested at a pressure drop of 4 kPa using identical flow rates (~65 L/min) through a sample collection tube and an Andersen Cascade Impactor, respectively.
- Solutions were analysed using an isocratic high performance liquid chromatography system with ultraviolet detection and a C18 column.
- A range of flow rates (25, 35, 45, 55, ~65 (4 kPa), 75, 85 and 90–95 L/min) were also evaluated using both inhalation volumes on three pilot-scale (PS) batches of aclidinium 200 µg; samples were taken from three consecutive dosages using two inhalers for each batch.
- Stability was assessed by repeating aerodynamic assessments on three PS and three laboratory-scale (LS) batches of aclidinium 200 µg, which were stored for two and three years, respectively, under various environmental conditions (25–40°C and 60–75% relative humidity).
- The specification limits were:
  - ±15% of the label claim (LC) dose of aclidinium
  - A fine particle dose of 40–85 µg aclidinium.
- Investigations were performed according to the European Pharmacopoeia, United States Pharmacopeia and the Food and Drug Administration requirements.

Results

Effect of inhalation volume on aclidinium dose content uniformity

- The mean total dose and fine particle dose of aclidinium (50 µg and 400 µg) were consistent for both inhalation volumes (Figure 2).
- Mean aerodynamic particle size distribution was not affected by inhalation volume for both the 50 µg and 400 µg formulations, with similar stage-to-stage profiles obtained for each inhalation volume (Figure 3).

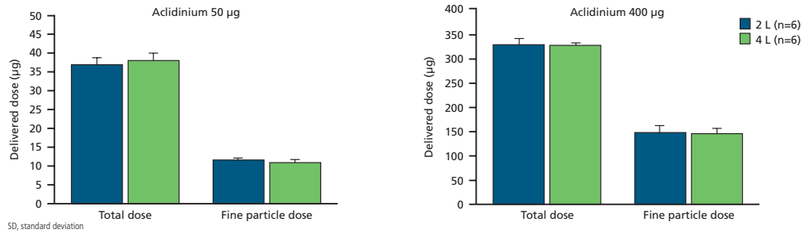
Effect of flow rate and inhalation volume on aclidinium dose content uniformity

- The mean total dose and fine particle dose of PS batches of aclidinium (200 µg) across a range of flow rates were not significantly affected by the different inhalation volumes (Figure 4).
- With the exception of the 25 L/min flow rate and 2 L inhalation volume, the mean total dose remained within ±15% of the LC dose for all flow rates and inhalation volumes.
- With the exception of the 25 L/min flow rate (2 L and 4 L inhalation volumes), the mean fine particle dose delivered remained within specification limits (40–85 µg) for all flow rates and inhalation volumes.

Effect of storage on aclidinium dose content uniformity

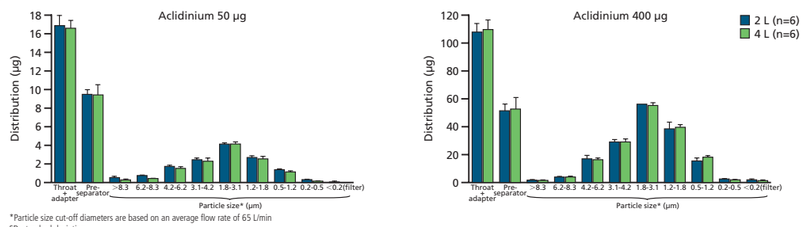
- The mean total dose and fine particle dose of PS and LS batches of aclidinium 200 µg were consistent for both inhalation volumes following storage under various environmental conditions for up to 3 years (Figure 5).
- The mean total dose and fine particle dose remained within the specification limits for all batches and storage conditions.

Figure 2. Effect of inhalation volume on mean (±SD) total dose and fine particle dose of aclidinium delivered with the Genuair® inhaler



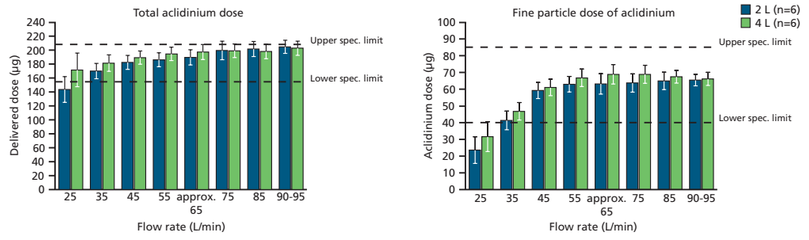
SD, standard deviation

Figure 3. Effect of inhalation volume on mean (±SD) particle size distribution of aclidinium delivered with the Genuair® inhaler



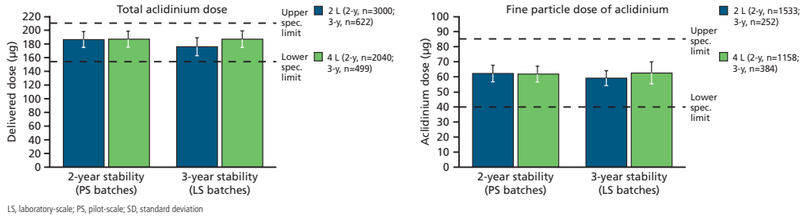
*Particle size cut-off diameters are based on an average flow rate of 65 L/min
SD, standard deviation

Figure 4. Effect of flow rate on mean (±SD) total dose and fine particle dose of aclidinium 200 µg delivered with the Genuair® inhaler using 2 L and 4 L inhalation volumes



SD, standard deviation

Figure 5. Effect of inhalation volume on mean (±SD) total dose and fine particle dose of aclidinium 200 µg delivered with the Genuair® inhaler following storage of up to three years



LS, laboratory-scale; PS, pilot-scale; SD, standard deviation

Conclusions

- **At both inhalation volumes tested, the Genuair® inhaler provides consistent dose delivery and aerodynamic particle size distribution of aclidinium inhalation powder.**
- **Storage of the inhalers for up to 3 years in a range of environmental conditions has no impact on the aerodynamic behaviour of aclidinium at different inhalation volumes.**
- **This MDPI fulfils the requirements of both the EU and US regulatory authorities. No adjustment of the aclidinium inhalation powder formulation is required, based on inhalation volume.**

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*Genuair® is a registered trademark of Almirall S.A.

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Abstract

Different inhalation volumes do not impact on the aerodynamics of aclidinium bromide delivered using the Genuair®* inhaler

Kathrin Block, Beatrix Fyrnys

Almirall Sofotech GmbH, Bad Homburg, Germany

Introduction

Aclidinium bromide is a novel, long-acting muscarinic antagonist in development for the treatment of chronic obstructive pulmonary disease. Genuair®, a novel multidose dry powder inhaler, has advanced aerodynamic features, ensuring effective deaggregation and delivery of the aclidinium inhalation powder. This study evaluated whether differences in inhalation volume and duration of storage impact on the aerodynamics of this novel inhaler.

Methods

Aclidinium 50 µg and 400 µg were used to assess clinically relevant doses. The aerodynamic assessments included: determination of delivered dose; particle size distribution; and fine particle dose at identical flow rates and inhalation volumes of 2 L or 4 L. To investigate the impact of storage, 3 laboratory-scale batches and 3 pilot-scale batches of aclidinium 200 µg, stored for up to 3 years and 2 years, respectively, were also aerodynamically assessed at inhalation volumes of 2 L or 4 L.

Results

For each volume, the delivered dose and fine particle dose were consistent in both aerodynamic and stability tests. Stability was unaffected by storage.

Inhalation volume	Aerodynamic assessment				3-year stability		2-year stability	
	50 µg		400 µg		200 µg		200 µg	
	DD	FPD	DD	FPD	DD	FPD	DD	FPD
2 L	36.9±1.8	11.6±0.4	329.6±12.6	148.2±13.8	175.9±13.0	59.1±4.9	186.3±12.0	62.2±5.5
2 L	38.0±1.9	10.9±0.8	328.3±5.2	145.9±11.3	3172.9±13.6	62.5±7.5	186.9±12.3	61.8±5.2

DD, delivered dose; FPD, fine particle dose.
Results are in µg, presented as mean±standard deviation.
Aerodynamic assessment, n=6; 3- and 2-year stability, n=252–3000.

Conclusion

The novel design and technologically advanced features of the Genuair® inhaler ensured consistent, effective deaggregation of the aclidinium inhalation powder. Inhalation volume and storage conditions had no impact on delivered dose or particle size distribution.

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Delivered dose and fine particle dose of aclidinium bromide 200 µg* via the Genuair®† inhaler are independent of flow rate within the working range of the device

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Introduction

- The Genuair® inhaler is a novel, breath-actuated multidose dry powder inhaler designed for the effective delivery of inhaled drugs, such as aclidinium bromide, a long-acting muscarinic antagonist currently under investigation as a maintenance therapy for chronic obstructive pulmonary disease (COPD).[1-3]
- As the accurate and consistent delivery of inhaled medication is important when treating patients with COPD, it is vital that the delivered dose (DD) and fine particle dose (FPD) of drugs delivered via the inhaler are consistent over a range of flow rates.
- The aim of this study was to evaluate the impact of different flow rates on the aerodynamic performance of different formulations and different production batches of aclidinium inhalation powder delivered through the Genuair® inhaler.
- In addition, correlations between the pressure drop across the Genuair® inhaler and the inspiratory flow rate of different formulations and different production batches of aclidinium inhalation powder were evaluated.

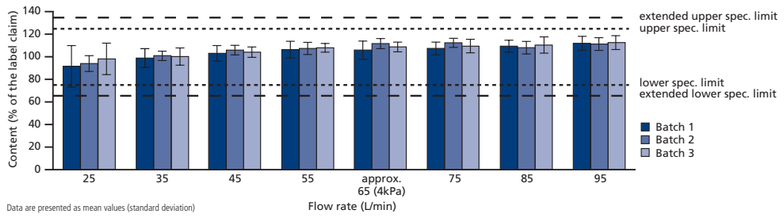
Methods

- Three Phase III and three commercial-scale production batches of Genuair® inhalers containing aclidinium 200 µg, as well as three production batches of Genuair® inhalers containing aclidinium 400 µg, were randomly selected for flow-rate dependency testing.
- The inhalers were tested across a range of flow rates through a sample collection tube and an Andersen Cascade Impactor, respectively. The DD and FPD of aclidinium were evaluated using an isocratic high performance liquid chromatography system with ultraviolet detection and a C18 column.
- The pressure drop (across the inhaler) and the corresponding flow rate were simultaneously measured at a defined pressure point using an aerodynamic test system consisting of a mass flow meter, a differential pressure sensor, a flow control valve and vacuum pumps.
  - For the Phase III and commercial-scale production batches of inhalers (aclidinium 200 µg), two inhalers from each of three different batches were tested three times across the range of flow rates.
  - For the batches of aclidinium 400 µg inhalers, two inhalers from each of three different batches were tested once across the range of flow rates.

Results

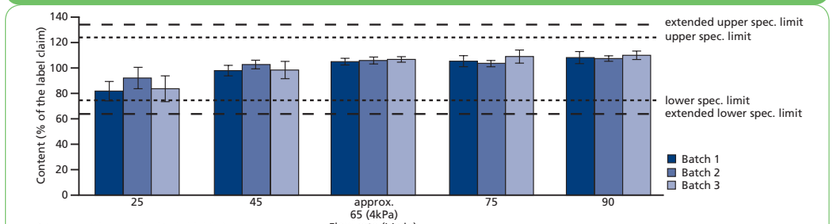
- For the three Phase III and three commercial-scale production batches of inhalers, the DD of aclidinium 200 µg was highly reproducible between the batches, over the range of flow rates tested (Figures 1 and 2). Similar results were observed for the batches containing aclidinium 400 µg (Figure 3).
- The FPD of aclidinium 200 µg was similar between the Phase III and commercial-scale production formulations. Low levels of intra-batch variation in FPD were also observed, irrespective of flow rate. The batches of inhalers containing aclidinium 400 µg showed similar results, with low levels of intra-batch variation (Table 1).

Figure 1. Delivered dose from the Phase III aclidinium 200 µg batches



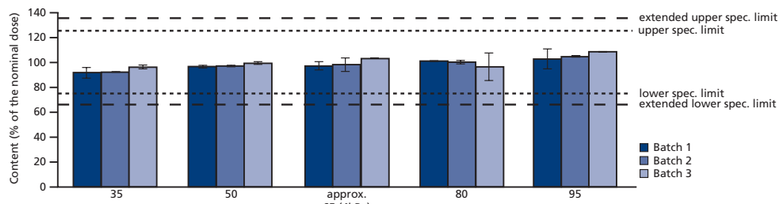
Data are presented as mean values (standard deviation)

Figure 2. Delivered dose from the commercial-scale aclidinium 200 µg batches



Data are presented as mean values (standard deviation)

Figure 3. Delivered dose from the aclidinium 400 µg batches



Data are presented as mean values (standard deviation)

Table 1. Fine particle dose (µg) in different batches of Genuair® inhaler

Aclidinium 200 µg Phase III batches								
Flow rate, L/min	**25**	**35**	**45**	**55**	**65[a]**	**75**	**85**	**95**
Fine particle dose (µg)								
Batch 1	33.1 (8.1)	47.1 (5.5)	62.9 (5.1)	65.9 (3.8)	66.5 (5.0)	66.1 (4.2)	66.4 (3.6)	65.4 (4.3)
Batch 2	26.4 (6.9)	44.3 (3.6)	58.4 (4.2)	64.2 (4.8)	66.8 (3.4)	67.0 (3.3)	66.5 (2.1)	64.5 (2.9)
Batch 3	35.4 (9.6)	48.6 (6.4)	61.8 (5.4)	70.0 (6.0)	73.0 (7.3)	73.3 (6.5)	69.5 (4.8)	68.5 (4.0)

Aclidinium 200 µg commercial-scale batches					
Flow rate, L/min	**25**	**35**	**65[a]**	**75**	**90**
Fine particle dose (µg)					
Batch 1	25.0 (3.1)	56.3 (4.1)	61.8 (1.4)	62.8 (2.1)	65.1 (3.1)
Batch 2	28.5 (5.4)	59.1 (3.3)	67.3 (2.1)	67.3 (3.5)	68.6 (3.6)
Batch 3	29.3 (2.1)	54.8 (2.6)	62.4 (1.8)	63.3 (2.1)	61.1 (2.7)

Aclidinium 400 µg batches					
Flow rate, L/min	**35**	**50**	**65[a]**	**80**	**95**
Fine particle dose (µg)					
Batch 1	113.2 (3.5)	161.9 (3.3)	164.0 (5.1)	155.2 (5.3)	162.6 (8.4)
Batch 2	92.5 (20.5)	137.8 (10.4)	148.2 (10.6)	145.3 (4.3)	150.8 (2.4)
Batch 3	113.5 (6.7)	146.5 (7.3)	149.1 (12.3)	143.8 (14.1)	147.0 (0.4)

[a]Approximately 65 L/min, equivalent to 4kPa

Data are presented as mean values (standard deviation)

- All batches of the aclidinium 200 µg and 400 µg formulations showed a strong correlation between the pressure drop across the Genuair® inhaler and the inspiratory flow rate (Figures 4–6).

Figure 4. Correlation between the pressure drop across the Genuair® inhaler and flow rate for Phase III batches of aclidinium 200 µg

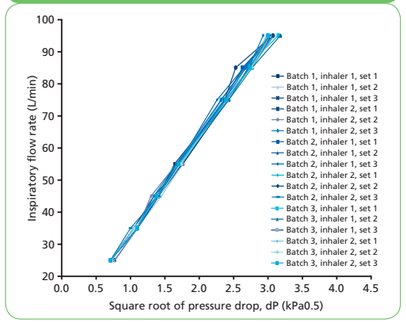


Figure 5. Correlation between the pressure drop across the Genuair® inhaler and flow rate for commercial-scale batches of aclidinium 200 µg

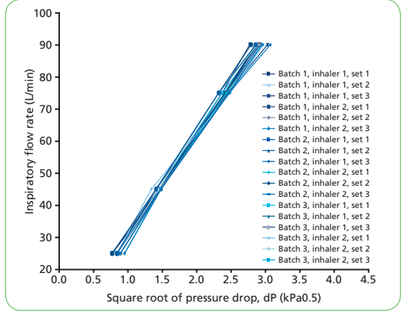
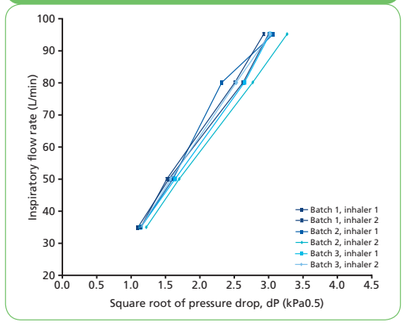


Figure 6. Correlation between the pressure drop across the Genuair® inhaler and flow rate for batches of aclidinium 400 µg



Conclusions

- The DD and FPD of aclidinium 200 µg and 400 µg were largely independent of different flow rates.
- There is a strong correlation between the inspiratory flow rate and the square root of the corresponding pressure drop across the Genuair® inhaler, irrespective of the aclidinium formulation tested.
- Excellent accuracy and consistency of the Genuair® inhaler was demonstrated by the low variability observed within and between the different batches for each formulation examined.
- The average peak inspiratory flow rate of patients with moderate to severe COPD when using the Genuair® inhaler was 92 L/min.[4] Accordingly, the flow rate data presented herein demonstrates that the Genuair® inhaler will provide consistent dose delivery of aclidinium, including FPD, to patients with moderate or severe COPD.

References

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Acknowledgements

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*This e-communication contains additional data that were not available at the time of abstract submission. Results from batches of inhalers containing aclidinium 400 µg are presented alongside the aclidinium 200 µg data.

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Abstract

Delivered dose and fine particle dose of aclidinium bromide 200 µg via the Genuair®* inhaler are independent of flow rate within the working range of the device

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Introduction

The Genuair® inhaler, a novel multidose dry powder inhaler, has advanced aerodynamic features, including an integrated trigger threshold mechanism (at approximately 40 L/min) that provides the patient with inhalation feedback via an audible click. This study evaluated the impact of different flow rates on the aerodynamic behaviour of aclidinium bromide 200 µg inhalation powder delivered using the Genuair® inhaler.

Methods

Six pilot-scale batches (3 Phase III batches and 3 commercial-site batches) of Genuair® inhalers were tested according to European Pharmacopoeia/USP/FDA requirements. Aerodynamic assessments included determination of delivered dose (DD) and fine particle dose (FPD) over a range of flow rates (25–95 L/min).

Results

The DD of aclidinium 200 µg was consistent between the batches over the flow range tested; the percentage of the DD was independent of flow rate within the working range of the device for all batches tested (Table). The FPD of aclidinium bromide 200 µg was also independent of flow rate above 40 L/min (device trigger threshold).

Table: Delivered dose (%) and fine particle dose (µg) in batches of Genuair® inhaler.

	Flow rate, L/min							
Phase III batches	**25**	**35**	**45**	**55**	**65[a]**	**75**	**85**	**95**
Delivered dose, %								
Batch 1	91.6 (18.4)	99.1 (8.3)	103.2 (7.0)	106.5 (7.5)	106.1 (8.0)	107.5 (5.7)	109.5 (5.3)	112.0 (6.2)
Batch 2	94.2 (7.0)	101.0 (4.2)	106.1 (4.3)	107.5 (5.4)	111.8 (4.5)	112.5 (4.0)	108.2 (5.5)	111.4 (5.6)
Batch 3	98.3 (13.9)	100.3 (7.6)	104.2 (4.6)	108.1 (3.9)	108.9 (4.4)	109.7 (6.0)	110.6 (7.1)	112.7 (6.2)
Fine particle dose (µg)								
Batch 1	33.1	47.1	62.9	65.9	66.5	66.1	66.4	65.4
Batch 2	26.4	44.3	58.4	64.2	66.8	67.0	66.5	64.5
Batch 3	35.4	48.6	61.8	70.0	73.0	73.3	69.5	68.5

	Flow rate, L/min				
Commercial-site batches	**25**	**45**	**65[a]**	**75**	**90**
Delivered dose, %					
Batch 1	82.3 (7.7)	98.5 (4.0)	105.6 (2.7)	105.9 (4.4)	108.8 (4.7)
Batch 2	92.6 (8.4)	103.3 (3.5)	106.5 (2.8)	104.0 (2.5)	108.0 (2.1)
Batch 3	84.2 (10.3)	99.0 (6.8)	107.3 (2.3)	109.5 (5.1)	110.6 (3.3)
Fine particle dose (µg)					
Batch 1	25.0	56.3	61.8	62.8	65.1
Batch 2	28.5	59.1	67.3	67.3	68.6
Batch 3	29.3	54.8	62.4	63.3	61.1

[a]Approximately 65 L/min, equivalent to 4kPa.
Data are presented as mean values (standard deviation): 40 L/min=trigger threshold.

Conclusion

The study established the consistent aerodynamic behaviour of aclidinium 200 µg powder delivered using the Genuair® inhaler under a range of inhalation flow rates.

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