

# Aclidinium bromide, a novel inhaled long-acting anticholinergic

## A review of data presented at the European Respiratory Society 2007

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# Aclidinium bromide data presentation at the European Respiratory Society (ERS) Congress 2007

- A novel, inhaled, long-acting bronchodilator in Phase III clinical development for the maintenance treatment of COPD
- 4 communications at the ERS 2007 congress
  - 2 oral presentations:
    - Aclidinium bromide, a novel muscarinic receptor antagonist combining long residence at M<sub>3</sub> receptors and rapid plasma clearance
    - Bronchodilator effects of acclidinium bromide, a novel long-acting anticholinergic, in COPD patients: a Phase IIa study
  - 2 thematic posters:
    - Assessment of the potency and duration of action of acclidinium bromide in guinea pig isolated trachea in vitro
    - Bronchodilator/bronchoprotective effects of acclidinium bromide, a novel long-acting anticholinergic: a Phase I study

Presentation 1:  
Aclidinium bromide, a novel muscarinic  
receptor antagonist combining long  
residence at M<sub>3</sub> receptors and rapid  
plasma clearance

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Israel Ramos, Dolors Vilella, Sonia Sentellas,  
Joan Albertí, Hamish Ryder, Jordi Beleta

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# Objectives 1

- To determine the human *in vitro* pharmacological characteristics of aclidinium
  - muscarinic receptor ( $M_1$ ,  $M_2$ ,  $M_3$ ,  $M_4$ ) binding profile
  - $M_2$  and  $M_3$  receptor dissociation rate
  - human plasma stability
- To compare the *in vitro* profile of aclidinium with those of tiotropium and ipratropium

# Results Summary 1

- The combination of:
  - persistent blockade of M<sub>3</sub> receptors
  - reduced residence at M<sub>2</sub> receptors
  - and a rapid elimination from plasma

in the same molecule confers to aclidinium a unique *in vitro* profile

- This profile is suggestive of prolonged bronchodilation in the absence of unwanted side effects upon administration by inhalation

Presentation 2  
Assessment of the potency and duration of  
action of acclidinium bromide in guinea pig  
isolated trachea *in vitro*

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## Objectives 2

- To assess the potency, onset and duration of action of aclidinium bromide in isolated guinea pig trachea preparations
  - Potency ( $pA_2$ ) – concentration response curves in the presence of acetylcholine and carbachol
  - Onset of action – time to achieve inhibition of carbachol contraction
  - Duration of action – recovery of tracheal tone
- To compare the *in vitro* profile of aclidinium with those of tiotropium and ipratropium

## Results Summary 2

- Aclidinium demonstrates potent anticholinergic activity in isolated guinea pig trachea with  $pA_2$  values similar to tiotropium and ipratropium
- The rate of onset of aclidinium is similar to ipratropium and faster than tiotropium
- The duration of action of aclidinium, measured as recovery of tracheal tone, is significantly longer than ipratropium and shorter than tiotropium

Presentation 3  
Bronchodilator/bronchoprotective effects of  
aclidinium bromide, a novel long-acting  
anticholinergic: a Phase I study

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## Objectives 3

- To assess the activity, safety, tolerability profile and pharmacokinetics of single doses of acclidinium bromide (50 µg, 300 µg and 600 µg) vs placebo in healthy subjects

## Results Summary 3

- Aclidinium is superior to placebo in improving specific airway resistance. This effect was more clearly observed with the 300 µg and 600 µg doses
- A significant effect was observed at the earliest time point (1 hour) and maintained over 24 hours for the 300 µg and 600 µg doses
- Undetectable plasma levels may account for the favourable safety and tolerability profile of aclidinium in this study

Presentation 4  
Bronchodilator effects of aclidinium bromide,  
a novel long-acting anticholinergic,  
in COPD patients: a Phase IIa study

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## Objectives 4

- To assess the pharmacodynamics, pharmacokinetics, safety and tolerability of single doses of acclidinium bromide (100 µg, 300 µg and 900 µg) vs placebo in patients with moderate to severe COPD

## Results Summary 4

- Single doses of inhaled aclidinium bromide (100, 300 and 900 µg) had a significant, rapid and long-acting bronchodilatory effect in patients with COPD
- Bronchodilatory effects of aclidinium (300 µg and 900 µg) were observed at 15 minutes post-dose (earliest time point), and were sustained for at least 24 hours
- Aclidinium was safe and well tolerated and no patients withdrew due to adverse events. Specifically no anticholinergic side-effects were observed
- Undetectable plasma levels may account for the favourable safety and tolerability profile of aclidinium in this study

## Conclusions:

### ERS 2007 Aclidinium Presentations

- Aclidinium is a **potent anticholinergic** that has long-lasting action *in-vitro* and rapid plasma clearance
- Early clinical studies demonstrate acclidinium produces bronchodilation for at least 24 hours suggestive of **once daily dosing**
- Aclidinium has a **fast onset** of action
- Aclidinium was **safe and well tolerated** with no anticholinergic side-effects, likely due to the **low systemic exposure**
- Manuscripts in development for all these data

# Acridinium: Moving Forward

- Phase III trials on track, top-line results available second half of 2008
- Expected EU, US filings on track for 2009
- Combination products development ongoing
- Next presentation of key data planned for ATS 2008
  - Further preclinical characterisation
  - Phase IIb – 28 day dose finding
  - Clinical cardiovascular safety (QTc)
  - Further clinical data