Aclidinium bromide, a novel inhaled long-acting anticholinergic

A review of data presented at the European Respiratory Society 2007

Per-Olof Andersson
Executive Director, Research & Development
Almirall, Barcelona, Spain
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 M₃ receptors and rapid plasma clearance
    - Bronchodilator effects of aclidinium 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 aclidinium bromide in guinea pig isolated trachea in vitro
    - Bronchodilator/bronchoprotective effects of aclidinium bromide, a novel long-acting anticholinergic: a Phase I study
Presentation 1:
Aclidinium bromide, a novel muscarinic receptor antagonist combining long residence at $M_3$ receptors and rapid plasma clearance

Amadeu Gavaldà, Montserrat Miralpeix, Israel Ramos, Dolors Vilella, Sonia Sentellas, Joan Albertí, Hamish Ryder, Jordi Beleta

Almirall, Barcelona, Spain
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 M₃ receptors
  - reduced residence at M₂ 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
Assessment of the potency and duration of action of aclidinium bromide in guinea pig isolated trachea *in vitro*

Montserrat Miralpeix, Amadeu Gavaldà, Esteban Morcillo, Julio Cortijo, Jaume Puig, Hamish Ryder, Jordi Beleta

Almirall, Barcelona, Spain
Objectives 2

- To assess the potency, onset and duration of action of aclidinium bromide in isolated guinea pig trachea preparations
  - Potency (pA₂) – 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
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.
Bronchodilator/bronchoprotective effects of aclidinium bromide, a novel long-acting anticholinergic: a Phase I study

Vanessa J Schelfhout,1 Guy F Joos,1 Esther Garcia Gil,2 Eric Massana Montejo,2

1Department of Respiratory Diseases, Ghent University Hospital
Ghent, Belgium

2Almirall
Barcelona, Spain

Presented 17 September 2007
Objectives 3

- To assess the activity, safety, tolerability profile and pharmacokinetics of single doses of aclidinium 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

Guy F Joos,1 Vanessa J Schelfhout,1 Frank Kanniess,2 Andrea Ludwig-Sengpiel,2 Esther Garcia Gil,3 Eric Massana Montejo3

1Department of Respiratory Diseases, Ghent University Hospital
   Ghent, Belgium

2Pulmonary Research Institute, Hospital Grosshansdorf
   Germany

3Almirall
   Barcelona, Spain

Presented 17 September 2007
To assess the pharmacodynamics, pharmacokinetics, safety and tolerability of single doses of aclidinium 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 aclidinium 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
Aclidinium: 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