Aclidinium bromide, a novel inhaled long-acting anticholinergic

A review of data presented at the European Respiratory Society 2007

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Presented 17 September 2007

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_3 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

Presented 17 September 2007

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

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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_3 receptors
  - reduced residence at M_2 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 aclidinium 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 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

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Objectives 4

- 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