Aclidinium bromide, a novel, long-acting anticholinergic in Phase III development for maintenance treatment of COPD

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4 preclinical and 4 clinical presentations

4 preclinical posters

1. In vitro characterization of aclidinium bromide, a novel long-acting anticholinergic: effects on isolated human bronchi

2. Aclidinium bromide, a novel anti-muscarinic, reverses cholinergic-induced bronchoconstriction with a fast onset of action and a long-lasting effect in guinea pigs

3. Aclidinium bromide, a novel long-acting anticholinergic, is rapidly inactivated in plasma

4. The preclinical cardiovascular safety profile of aclidinium bromide, a novel long-acting anticholinergic drug

4 clinical posters

5. Pharmacokinetics and safety of aclidinium bromide, a novel long-acting, inhaled anticholinergic, in healthy subjects

6. Low systemic exposure to aclidinium bromide, a novel long-acting anticholinergic, after multiple doses

7. Aclidinium bromide, a novel long-acting anticholinergic, does not affect QT interval in healthy subjects

8. Once-daily administration of aclidinium bromide, a novel, long-acting anticholinergic: a Phase II, dose-finding study
Conclusions:
ATS 2008 preclinical presentations

- Aclidinium is a **potent anticholinergic** that has a long-lasting action *in vitro* and *in vivo*

- This profile suggests that in the clinical setting aclidinium may provide sustained bronchodilation suitable for **once-daily dosing**

- Aclidinium is **rapidly hydrolyzed** in plasma to two major metabolites that do not contribute to the bronchodilator effect of aclidinium

- The **potential for systemic side effects is reduced** due to the rapid inactivation of aclidinium in plasma and the inert nature of the major metabolites

- Aclidinium has a favorable cardiovascular safety profile in animal models at plasma concentrations at least 100-fold greater than those observed in humans. These results suggest a **low potential for cardiovascular side effects** in the clinical setting
Presentation 5: 
Pharmacokinetics and safety of aclidinium bromide, a novel long-acting, inhaled anticholinergic, in healthy subjects

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2Almirall, Barcelona, Spain
Objectives 5

This Phase I, placebo-controlled study assessed the pharmacokinetics, safety, tolerability, and maximum tolerated dose (MTD) of single doses of aclidinium in healthy male subjects.

MTD was defined as the highest dose that does not cause at least 50% of subjects to experience function-limiting adverse events (AEs) or does not elicit a medically unacceptable, drug-related serious AE.

Ferrer et al, ATS 2008: poster F52
Results summary 5

- Aclidinium in the dose range of 600-6000 µg was well tolerated.

- No AEs were judged to be treatment related for doses up to 1800 µg.
  - AEs were mild to moderate in severity and the overall incidence for aclidinium was comparable to placebo.
  - There were no serious AEs.

- The MTD could not be established.
  - Even at the highest dose assessed very few subjects reported AEs, demonstrating an excellent tolerability profile in this study.

Ferrer et al, ATS 2008: poster F52
Results summary 5 cont

● Aclidinium was only detectable in plasma up to 1 hour post-dose for the 600 µg, 1200 µg, and 1800 µg doses in the majority of subjects

○ This limited and transient systemic exposure suggests a low potential for anticholinergic systemic adverse events (intended clinical dose is 200 µg/day)

● Pharmacokinetic parameters showed dose proportionality for doses up to 4800 µg

Ferrer et al, ATS 2008: poster F52
Presentation 6:
Low systemic exposure to aclidinium bromide, a novel long-acting anticholinergic, after multiple doses

G de Miquel, A Schrödter, B Miletzki, M Gurniak, C Serra, JM Jansat

1Almirall, Barcelona, Spain
2FOCUS Clinical Drug Development GmbH, Neuss, Germany
Objectives 6

This Phase I, randomized, placebo-controlled, single-blind, cross-over trial assessed the safety, tolerability, and pharmacokinetics of aclidinium 200-800 µg after multiple doses (5 consecutive days) were administered by dry powder inhaler in healthy subjects.

de Miquel et al, ATS 2008: poster F53
Results summary 6

- Multiple doses of aclidinium (200-800 µg) were found to be well tolerated
  - This dose range studied was up to 4-times the anticipated therapeutic dose for COPD
- Aclidinium 200 µg and 400 µg were undetectable in plasma
- Aclidinium has a low potential for side effects resulting from its low and transient systemic availability

de Miquel et al, ATS 2008: poster F53
Presentation 7:
Aclidinium bromide, a novel long-acting anticholinergic, does not affect QT interval in healthy subjects

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²Almirall, Barcelona, Spain
Objectives 7

This Phase I, double-blind, randomized, parallel group study evaluated the effect on QT interval as well as overall cardiovascular safety of single and multiple doses of aclidinium 200 μg and 800 μg versus placebo and versus open-label moxifloxacin 400 mg daily in 272 healthy subjects.

Lasseter et al, ATS 2008: poster F54
Results summary 7

- Aclidinium, at doses up to 4-times (i.e. up to 800 µg) the therapeutic dose, demonstrated no effect on QT interval compared with placebo.

- ECG parameters were not affected by aclidinium administration.

- Aclidinium was well tolerated and no subjects withdrew due to adverse events.

Lasseter et al, ATS 2008: poster F54
Results summary 7 cont
Mean change in individual heart rate corrected QT interval (QTci) in healthy subjects

Lasseter et al, ATS 2008: poster F54
Presentation 8:
Once-daily administration of aclidinium bromide,
a novel, long-acting anticholinergic:
a Phase II, dose-finding study

P Chanez,1 S Burge,2 R Dahl,3 J Creemers,4 R Lamarca,5 E Garcia Gil5

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2Birmingham Heartlands Hospital, Birmingham, UK
3Aarhus University Hospital, Aarhus, Denmark
4Cathrina Ziekenhuis, Eindhoven, The Netherlands
5Almirall, Barcelona, Spain
Objectives 8

- This Phase II, double-blind, randomized, parallel group study assessed the efficacy, safety and tolerability of aclidinium compared with placebo in order to establish the optimal dose of aclidinium for use in Phase III studies.

- The study contained an open-label tiotropium treatment arm to allow an exploratory comparison with aclidinium.
Bronchodilatory effects of aclidinium were sustained over 24 hours.

On Day 29, trough FEV₁ was statistically significantly greater with aclidinium 200 µg, 400 µg and tiotropium 18 µg compared with placebo (primary endpoint).

On Day 1, aclidinium 100, 200 and 400 µg and tiotropium 18 µg produced statistically significant increases in FEV₁ compared with placebo 30 minutes post-dose (the first assessment) and these increases were maintained over the first 6 hours post-dose (secondary endpoint).
### Results summary 8 cont

**Mean change from baseline in trough FEV$_1$ on Day 29**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Acldinium</th>
<th>Tio</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>25 µg</td>
<td>50 µg</td>
</tr>
<tr>
<td><strong>No. patients</strong></td>
<td>64</td>
<td>65</td>
<td>65</td>
</tr>
<tr>
<td><strong>LSMean, mL</strong></td>
<td>Ref.</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td><strong>95% CI</strong></td>
<td>Ref.</td>
<td>-67, 145</td>
<td>-70, 141</td>
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LSMean = least squares mean  
Ref. = reference group for between-treatment comparisons  
CI = confidence interval

*p<0.05 versus placebo

Chanez et al, ATS 2008: poster F23
Results summary 8 cont

Aclidinium 100, 200 and 400 µg significantly increased FEV₁ over 6 h post-dose on Day 1

\[
\text{Least squares mean } \text{FEV}_1 (\text{mL})
\]

- Placebo
- Aclidinium 25 µg
- Aclidinium 50 µg
- Aclidinium 100 µg
- Aclidinium 200 µg
- Aclidinium 400 µg
- Tiotropium 18 µg

\[p<0.05 \text{ for aclidinium 100, 200 and 400 µg and tiotropium versus placebo from 30 minutes to 6 hours post-dose (secondary endpoint)}\]

Chanez et al, ATS 2008: poster F23
The minimum effective dose of aclidinium in patients with moderate to severe COPD was 100 µg.

Aclidinium 25-400 µg was well tolerated in patients with COPD in this study.

Based on the results of this study, aclidinium 200 µg was selected for further development.
Conclusions:
ATS 2008 clinical presentations

- Phase I and II clinical studies consistently demonstrate that aclidinium produces bronchodilation for at least 24 hours.

- Aclidinium showed no effect on prolongation of QT interval.

- Aclidinium was well tolerated with minimal anticholinergic side-effects, this is likely to be due to the low and transient systemic exposure.

- Aclidinium 200 µg was the dose selected to move into Phase III.
Aclidinium bromide: moving forward

- Phase III trials on track, top-line results available second half of 2008
- Combination products development ongoing
Thank you