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

Data presented at the American Thoracic Society (ATS) 2008

Per-Olof Andersson
Executive Director, Research & Development
Almirall, Barcelona, Spain

Lawrence S. Olanoff
President and Chief Operating Officer
Forest Laboratories, Inc., New York, USA

Aclidinium bromide data presented at the American Thoracic Society (ATS) Congress 2008

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

Aclidinium bromide data presented at the American Thoracic Society (ATS) Congress 2008

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

P Ferrer,[1] JM Jansat,[2] E Garcia Gil[2]

[1]Centre Hospitalier de la Polynésie française, Papeete, French Polynesia
[2]Almirall, 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

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

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

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

G de Miquel,[1] A Schrödter,[2] B Miletzki,[2] M Gurniak,[2] C Serra,[1] JM Jansat[1]

[1]Almirall, Barcelona, Spain
[2]FOCUS 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

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

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

KC Lasseter,[1] J Aubets,[2] E Garcia Gil[2]

[1]PharmaNet Development Group, Miami, FL, USA
[2]Almirall, Barcelona, Spain

Objectives 7

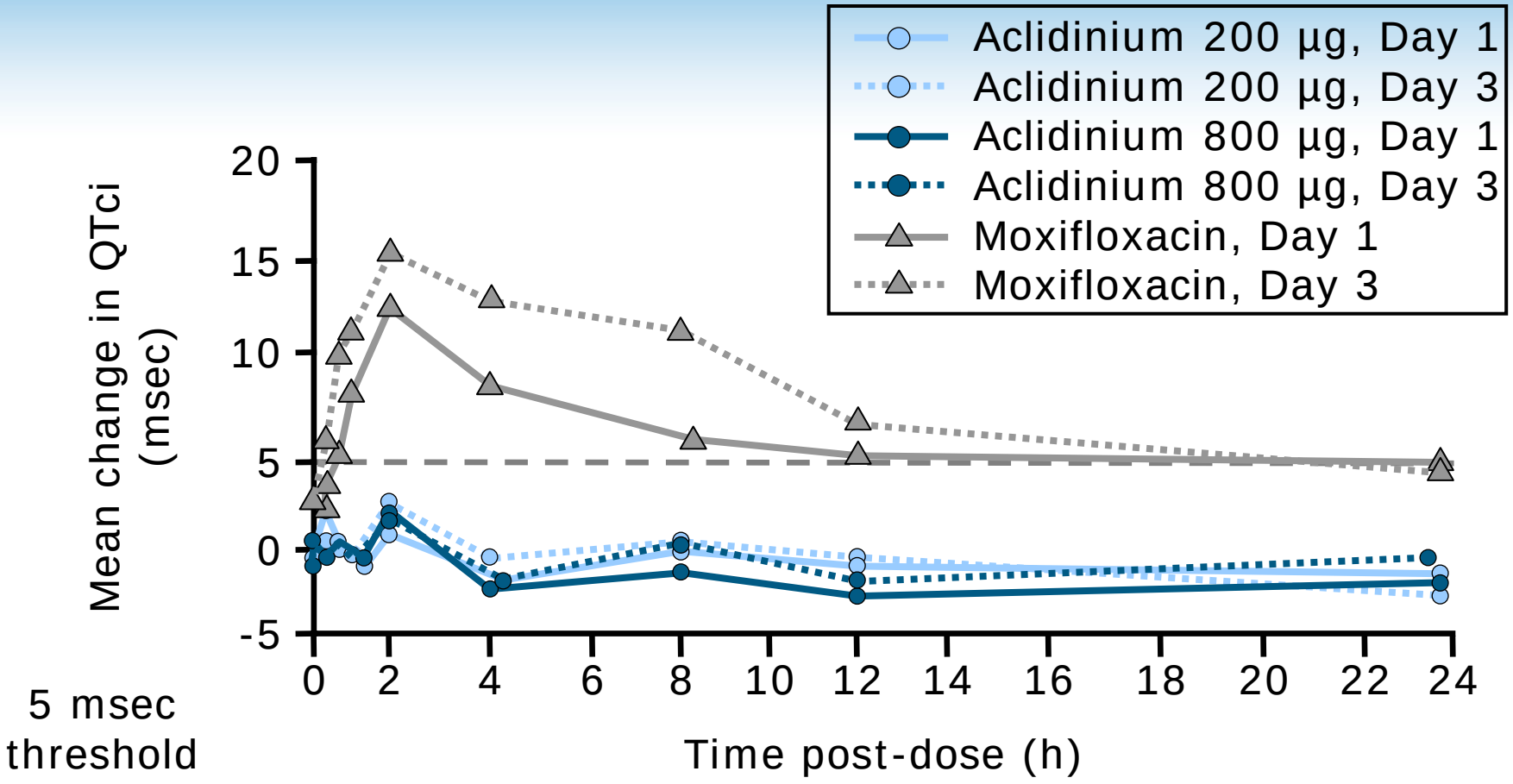
- This Phase I, double-blind, randomized, parallel group study evaluated the effect on QT interval as well as overall cardiovascular safety of single and multiple doses of aclidinium 200 μg and 800 μg versus placebo and versus open-label moxifloxacin 400 mg daily in 272 healthy subjects

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

Results summary 7 cont

Mean change in individual heart rate corrected QT interval (QTci) in healthy subjects



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 Gil[5]

[1]Université de la Méditerranée AP-HM, Marseille, France
[2]Birmingham Heartlands Hospital, Birmingham, UK
[3]Aarhus University Hospital, Aarhus, Denmark
[4]Cathrina Ziekenhuis, Eindhoven, The Netherlands
[5]Almirall, 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

Results summary 8

- Bronchodilatory effects of aclidinium were sustained over 24 hours
- On Day 29, trough FEV_1 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 FEV_1 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

		Aclidinium					Tio
	Placebo	25 µg	50 µg	100 µg	200 µg	400 µg	18 µg
No. patients	64	65	65	69	66	67	64
LSMean, mL	Ref.	39	36	83	148*	128*	161*
95% CI	Ref.	-67, 145	-70, 141	-22, 187	42, 253	22, 233	55, 267

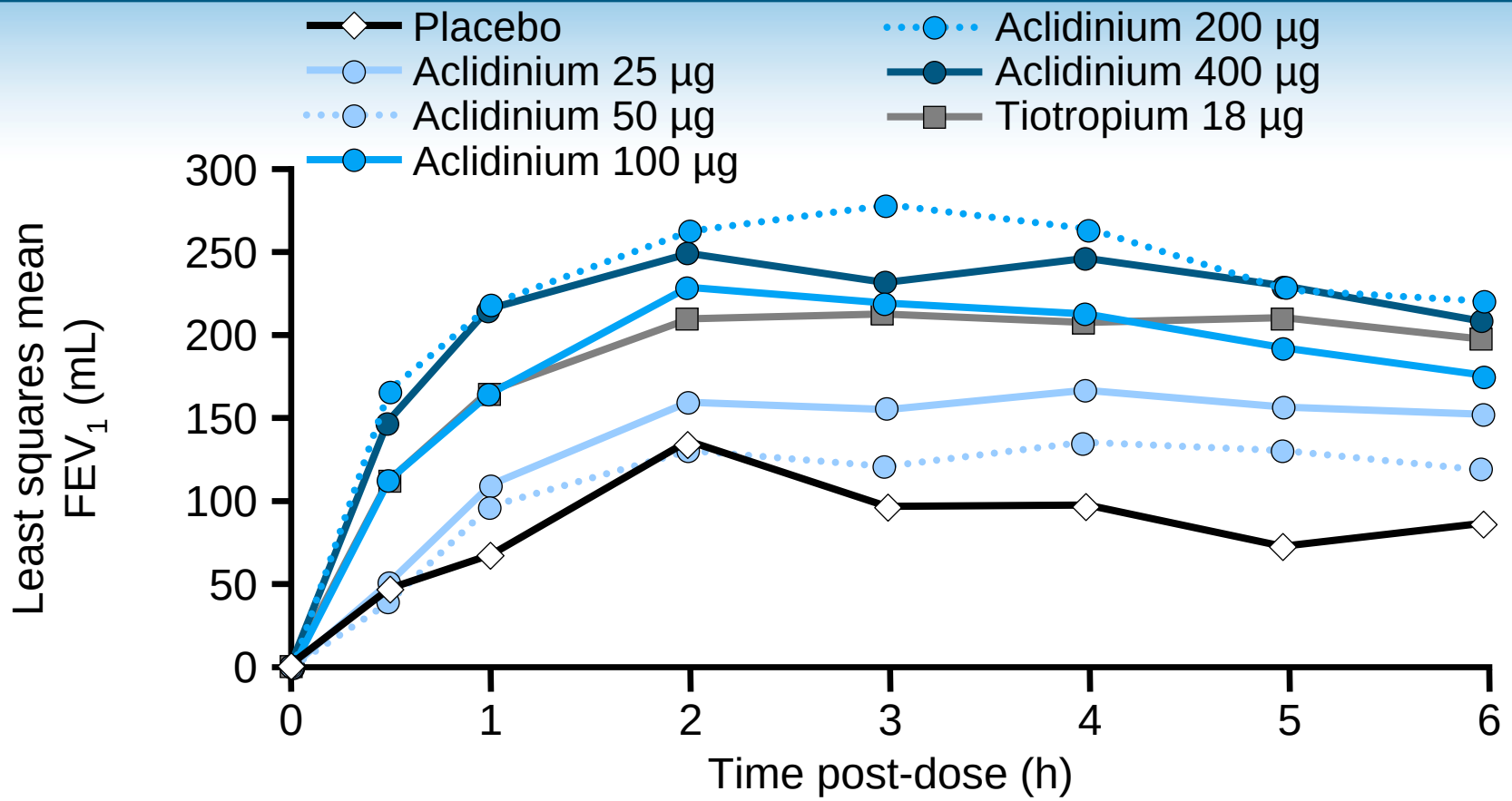
LSMean = least squares mean
Ref. = reference group for between-treatment comparisons
CI = confidence interval

*p<0.05 versus placebo

Chanez et al, ATS 2008: poster F23

Results summary 8 cont

Aclidinium 100, 200 and 400 µg significantly increased FEV_1 over 6 h post-dose on Day 1



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

Results summary 8 cont

- 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