This press release replaces the originally published on 03/09/2012

Eklira® Genuair® provides meaningful and sustained bronchodilation from the first dose. Patients prefer the Genuair® inhaler over HandiHaler®

- **Eklira® Genuair® (aclidinium bromide) showed a clinically meaningful and statistically significant improvement in' bronchodilation vs placebo along a 6 week study**
- **Eklira also demonstrated statistically significant improvement in night, morning and daytime Chronic Obstructive Pulmonary Disease (COPD) symptoms vs placebo**
- **The Genuair® inhaler was associated with significantly higher patient preference and satisfaction and fewer critical inhaler use errors vs HandiHaler®**

Barcelona, Spain – September 3rd 2012 – Almirall S.A. (ALM.MC) today announced positive results for two phase IIIb studies with Eklira® Genuair® (aclidinium bromide), its COPD maintenance treatment in its novel inhaler delivery system.

The first study (NCT01462929 at clinicaltrials.gov) assessed the efficacy, safety and tolerability of inhaled aclidinium 400µg (corresponding to 322µg of aclidinium) twice daily compared to placebo and tiotropium 18µg once daily, in 414 patients with stable moderate to severe chronic obstructive pulmonary disease (COPD, which includes chronic bronchitis or emphysema), over a 6-week period.

In the study, aclidinium met the primary endpoint (change from baseline in normalized FEV_1 AUC 0-24h at 6- weeks) showing a clinically meaningful and statistically significant improvement ($p<0.0001$) vs placebo. The benefits of this 24-hour bronchodilation vs placebo were seen from the first day of treatment with aclidinium and tiotropium ($p<0.0001$).

Also, aclidinium showed a good safety and tolerability profile with a comparable incidence of treatment emergent side effects across treatment arms (aclidinium 27.5%; placebo 25.9%, tiotropium 29.7%).

COPD symptoms were additional measurements within the study, in which aclidinium demonstrated statistically significant improvements in the individual morning symptoms. Only aclidinium demonstrated a significant improvement in the severity of night-time symptoms vs placebo ($p<0.01$).

"The reliable bronchodilation and symptom improvements demonstrated by Eklira® Genuair® (aclidinium) during the day and at night provide a new valuable treatment option to COPD patients. The Genuair® inhaler delivers this in an easy to use device, which patients prefer and can handle easily", said Bertil Lindmark, Chief Scientific Officer at Almirall.

A second study (NCT01385696 at clinicaltrials.org), which is being presented at ERS as a poster (P2177) on September 3rd, was conducted in 130 randomised COPD patients, evaluating device preference, satisfaction and critical errors showed that a significantly higher proportion of patients expressed a preference for the Almirall's Genuair® inhaler vs HandiHaler® **(*)** (79.1% vs 20.9% respectively; $p<0.0001$) which was consistent with findings observed in the first study

reported above. Patients were also more satisfied using the Genuair® than HandiHaler® ($p<0.0001$). Importantly, critical errors were significantly less frequent with Genuair® ($p<0.0001$), with only 10.5% of patients making one or more critical errors versus 26.7% for HandiHaler®.

Aclidinium was approved in the USA and in Europe in July 2012 for the maintenance treatment of COPD. In Europe, it will be marketed by Almirall under the trade name Eklira® Genuair® and by Menarini under the name Bretaris® Genuair®.

Additionally, a Phase III clinical development programme of a fixed dose combination of aclidinium plus formoterol twice daily is currently underway, also using the Genuair® device.

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Endpoint Definitions

- **FEV1** - Forced expiratory volume in one second, or the amount of air that can be exhaled in the first second following an inhalation.

- **Normalized AUC (0-12 hours, 12-24 hours) FEV1** - Average area under the FEV1 curve over 12 hours, from dosing in the morning until pre-dose twelve hours later (0-12 hours), and from dosing in the evening through the night until pre-dose the next morning (12-24 hours), respectively.

About the first study - NCT01462929
This was a six-week treatment, prospective, multiple dose, randomised, double-blind (open with tiotropium), double-dummy, placebo and active comparator controlled, parallel multicentre clinical trial. It assessed the efficacy and safety of twice daily inhaled aclidinium bromide 400µg (equivalent to 322µg of aclidinium) compared to placebo and to once daily tiotropium 18µg, in 414 patients with moderate to severe COPD at 49 trial centres across Europe.

Patients were randomised to one of three treatment arms using a randomisation ratio of 2:2:1 (aclidinium bromide 400µg, tiotropium 18µg or placebo).

Lung function was measured by means of serial spirometry over a 24h-period on day 1 and after 6 weeks of treatment. The presence and severity of COPD symptoms during morning and night time periods were assessed daily by a 9-item questionnaire developed by the sponsor and through the “The Exacerbations of Chronic Pulmonary Disease (EXACT) Tool-Respiratory Symptoms” questionnaire.

About the second study (device preference) - NCT01385696 at clinicaltrials.
This was a two-week clinical device study of 130 patients with a randomised cross-over multinational and multicentre design. The study compared Almirall’s Genuair® versus HandiHaler®, both containing placebo.

During the study period, patients had two clinic visits. On their first visit they were provided with instructions to be read, were trained with a demonstration and were then asked to try how they would use the inhaler up to five times. Error rates were recorded.

After 2 weeks of daily practise with both inhaler, patients returned to the clinic and were requested to demonstrate the use of the inhalers in order to assess error rates, device preference and satisfaction. Critical errors were defined as those that compromise the potential benefit of the treatment such as those that impedes drug deposition in the lungs or delivery of sufficient dose.

(*) HandiHaler® is the inhaler device of Boehringer Ingelheim used to deliver their long acting muscarinic antagonist tiotropium. HandiHaler® is a registered trademark of Boehringer Ingelheim GmbH

About Eklira® Genuair®

Aclidinium is a novel, long-acting inhaled muscarinic antagonist (sometimes referred to as an anticholinergic) that has a long residence time at M3 receptors and a shorter residence time at M2 receptors. When given by inhalation, aclidinium leads to bronchodilation by inhibiting airway smooth muscle contraction. Aclidinium is rapidly hydrolysed in human plasma to two major inactive metabolites.

Aclidinium is administered to patients using the novel, user-friendly, multidose dry powder inhaler (MDPI), Genuair®. This inhaler was designed with a “click and colour” feedback system which, through a 'coloured control window' and an audible click, indicates that the patient used the inhaler correctly. It also incorporates significant safety features such as a visible dose indicator, an anti-double-dosing mechanism and an end-of-dose lock-out system to prevent use of an empty inhaler.

Aclidinium is being developed worldwide and has been recently approved in the USA by the FDA where it will be marketed by Forest Laboratories and marketed under the name of Tudorza™ Pressair™. In Japan the product is in development in partnership with Kyorin and with Daewoong in Korea. Almirall holds the rights for the rest of the world.

Eklira® Genuair® and Bretaris® Genuair® are trademarks owned by Almirall, S.A.

About COPD

COPD is a chronic (persistent) lung disease that affects your ability to breathe. It is a term used for a number of conditions including chronic bronchitis (persistent cough with mucus) and emphysema (destruction of the lungs over time)[i]. For patients who have COPD, airflow is obstructed due to stiffening of lung tissue, making it hard to move air in and out of the lungs [i]. In clinical practice, COPD is defined by its characteristically low airflow on lung function tests[ii].

The World Health Organization (WHO) has described COPD as a global epidemic, and it is estimated that 64 million people suffer from COPD worldwide in 2004. More than 3 million people died of the condition in 2005, which is equal to 5% of all deaths globally that year. Total deaths from COPD are projected to increase by more than 30% in the next 10 years without interventions to cut risks, particularly exposure to tobacco smoke. [iii]

The most common symptoms of COPD are breathlessness, an increased effort to breathe, heaviness or a ‘need for air’, excessive mucus, and a chronic cough. Some people feel like they are gasping for breath. Not everyone has all of these symptoms and some people have different combinations of symptoms to other people. These symptoms get worse when exercising, when you have a respiratory infection or during an exacerbation (a period of time when there is a sudden increase in symptoms and the disease is worse).[i]

About Almirall

Almirall is an international pharmaceutical company based on innovation and committed to health. Headquartered in Barcelona, it researches, develops, manufactures and commercialises its own R&D and licensed drugs with the aim of improving people’s health and wellbeing. Almirall focuses its research resources on respiratory, gastrointestinal, dermatology and pain. Almirall’s products are currently present in over 70 countries in the five continents. It has direct presence in Europe and Mexico through 12 affiliates.

For further information please visit the website at: www.almirall.com

References

[i] European Federation of Allergy and Airway Disease Patient Association. Available from http://www.efanet.org/copd/what_is_copd.html [Accessed June 2012]

[ii] Nathell, L.; Nathell, M.; Malmberg, P.; Larsson, K. (2007). "COPD diagnosis related to different guidelines and spirometry techniques". Respiratory research 8 (1): 89

[iii] World Health Organisation. Global Alliance Against Chronic Respiratory Diseases. http://www.who.int/mediacentre/factsheets/fs315/en/index.html (accessed August 28, 2012)