Aclidinium and formoterol fixed dose combination for COPD submitted for registration in Europe

- New twice-daily combination of aclidinium/formoterol successfully achieved the primary endpoints in the phase III pivotal trials and has demonstrated superior improvement in lung function by combining two proven bronchodilators with complementary modes of action

Barcelona, November 4th, 2013 - Almirall, S.A. (ALM.MC) announced today the submission of the Marketing Authorisation Application (MAA) to the European Medicines Agency (EMA) for the fixed combination of aclidinium bromide (LAMA) and formoterol fumarate (LABA– Long Acting β_2-Agonist) for the treatment of Chronic Obstructive Pulmonary Disease (COPD).

The regulatory submission is based on efficacy and safety data from two pivotal Phase III studies (ACLIFORM/COPD and AUGMENT/COPD) -run in 25 countries worldwide- which were completed this year. Additional Long term safety studies (LAC-MD-32 and LAC-MD-36) complete a robust safety clinical data package including more than 4.000 patients in the program.

"*The success of this Phase III program supports the potential of aclidinium/formoterol as a new treatment option for COPD patients who could benefit from the enhanced bronchodilation of two complementary, proven therapies",* said Professor Alvar Agusti, Director of the Institut Clínic del Tòrax, Hospital Clínic, Universitat de Barcelona, Spain. *"The reliable bronchodilation and symptoms' improvements during the day and at night demonstrated by the combination provide* a new *highly efficacious and safe treatment option",* he added.

In these studies, the combination of aclidinium/formoterol 400/12 µg met the co-primary endpoints showing statistically significant lung function improvement compared with each individual component. Therefore, it successfully met the required regulatory "Combination Rule" for testing two or more drugs combined in a single dosage form. Also, improvements in COPD-related symptoms such as breathlessness (the main symptom in COPD) and in disease-related quality of life endpoints showed positive outcomes with aclidinium/formoterol 400/12 µg. Additionally, the combination showed to be well-tolerated in the two pivotal studies. The combination of a LAMA and a LABA, which act through different mechanisms of action, results in additive efficacy compared to that achieved with either bronchodilator alone.

Dr. Bertil Lindmark, Chief Scientific Officer at Almirall said: *"With the MAA submission of aclidinium/formoterol, we have reached another important strategic milestone in the development of innovative treatments geared towards improving the quality of life in patients with COPD. Moreover, it confirms Almirall's potential to build an innovative worldwide respiratory franchise around our Genuair® device and aclidinium bromide (Eklira®/Bretaris®)".*

Aclidinium/formoterol is an Almirall inhaled COPD investigational product that combines two already approved and marketed bronchodilators, delivered twice daily in the Genuair® inhaler device.

About aclidinium/formoterol

Aclidinium bromide /formoterol fumarate (400/12µg and 400/6µg) are investigational fixed dose combinations of two approved long-acting bronchodilators with different mechanisms of action and similar pharmacodynamic profiles. Aclidinium bromide is a long-acting cholinergic (or muscarinic) antagonist (LAMA) that produces bronchodilation by inhibiting the muscarinic M3

receptor in the airway smooth muscle. Formoterol fumarate is a long-acting beta-agonist (LABA) that stimulates the B2-receptors in the bronchial smooth muscle resulting in bronchodilation. Both individual components, aclidinium bromide (Elkira®/Bretaris®) and formoterol fumarate are approved for the maintenance treatment of COPD in Europe and the United States.

Aclidinium/formoterol was administered using a multiple-dose dry powder inhaler, Genuair®, which delivers 60 doses of aclidinium bromide/formoterol powder for inhalation. The Genuair® inhaler has a colored control window which confirms successful inhalation of the full dose and a dose indicator to let patients know approximately how many doses remain in the inhaler. The Genuair® locks out after last available dose is administered.

Aclidinium/formoterol has been filed for EMA (European Medicines Agency) evaluation as a potential treatment for COPD patients who could benefit from two bronchodilators administered in a single multi-dose inhaler.

About Phase III Studies

AUGMENT and ACLIFORM/COPD were two almost identical 24-week randomized double-blind trials evaluating the 400/6µg and 400/12µg fixed dose combinations of aclidinium bromide/formoterol fumarate compared with aclidinium bromide 400µg, formoterol fumarate 12µg and placebo administered BID through the Genuair® inhalers in patients with moderate to severe COPD. Augment was conducted in 1,692 patients in the USA, Australia and New Zealand; and ACLIFORM/COPD in 1,729 patients, in 22 countries including Europe, Korea and South Africa.

LAC-MD-32 a stand-alone one-year long term safety study, and **LAC-MD-36** a six-month extension of AUGMENT/COPD, both confirmed the good safety and tolerability profile of aclidinium/formoterol FDC 400/12 µg and provided additional data on persistence of efficacy. These two studies support the selection of aclidinium/formoterol FDC 400/12 µg as the optimal fixed combination dose for the maintenance treatment of COPD.

COPD: Impact on Patient's Quality Of Life

COPD (sometimes referred to as chronic bronchitis and emphysema) is a progressive and an often life threatening disease caused by an abnormal inflammatory response of the lungs to harmful gases, resulting in airways obstruction that is not fully reversible. It is a preventable disease but there is no cure and so the main goal of treatment is to control symptoms and slow disease progression[i].

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 they are gasping for breath. These symptoms get worse when exercising, in case of a respiratory infection or during an exacerbation – periods of time when there is a sudden increase in symptoms and the disease is worse - and they occur throughout the 24h a day[3]. COPD affects the ability to breathe and is a progressive disease, which means that COPD gets worse over time. Daily activities may become more difficult as the disease worsens. There are significant unmet needs in the treatment of COPD and new therapies may be of value.

In the European Union, approximately 200,000–300,000 people die each year in Europe because of COPD. Patients experiencing frequent exacerbations are at risk of increased morbidity and mortality, a faster decline in lung function, and poorer health status.

COPD also impacts adversely on economic productivity. In the EU, approximately 41,300 lost work days per 100,000 people are due to COPD every year and productivity losses due to COPD amount to a total of €28.5 billion annually[2]. This disease is associated as well with significant economic burden. In European Union, the total direct costs of respiratory disease are estimated to be about 6% of the total health care budget, with COPD accounting for 56% (38,6 billion Euros) of this respiratory disease[4].

About Almirall

Almirall is a pharmaceutical company committed to provide valuable medicines through our own R&D efforts, which exceeded 23% on sales in 2012, together with external partnerships, licenses and collaborations. Through seeking innovative medicines we aim to become a relevant player in respiratory and dermatology diseases with also a strong interest in gastroenterology and pain. With more than 3,000 employees in 22 countries, Almirall generated total revenues of 900 million euros in 2012.

The company was founded in 1943 and is headquartered in Barcelona, Spain. The stock is traded in the Spanish stock exchange (ticker: ALM).

For more information please visit www.almirall.com

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[1]-European Lung Foundation 2003. European Lung White Book

[2]-European Lung Foundation – 2012

[3] Partridge MR, Karlsson N, Small IR. Patient insight into the impact of chronic obstructive pulmonary disease in the morning: an internet survey. Curr Med Res Opin. 2009, 25 (8):2043-2048

[4]Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for Diagnosis, Management, and Prevention of COPD. 2013.