

## Positive Results from Pioneering Salford Lung Study in Asthma Published in The Lancet, and Presented at European Respiratory Congress

### Relvar Ellipta was superior to usual care treatment in improving asthma control for patients in Salford Lung Study.

LONDON & BRISBANE, Calif.--(BUSINESS WIRE)-- GlaxoSmithKline plc (LSE/NYSE: GSK) and Innoviva, Inc. (NASDAQ: INVA) today announced positive results from the Salford Lung Study (SLS) in asthma have been simultaneously published in *The Lancet* journal and presented at the European Respiratory Society (ERS) International Congress in Milan.

The innovative study, which reported headline results in May 2017, showed that initiation of once-daily Relvar Ellipta (fluticasone furoate 'FF'/vilanterol 'VI' or 'FF/VI', called Breo Ellipta in the U.S.) 92/22mcg or 184/22mcg was superior to usual care in achieving a consistent improvement in patient's asthma control over the 12 month study duration, measured by the Asthma Control Test (ACT), compared with patients who continued to take their usual care medicines. Improvement was defined as an ACT total score  $\geq 20$  or an increase from baseline of  $\geq 3$ . Statistically significant findings were also seen at 12, 40 and 52 weeks.

The study was designed to explore the effectiveness of an asthma medicine when used with minimal intervention in a broad group of people with asthma, closely reflecting how typical asthma patients are managed in everyday clinical care. For the primary endpoint at 24 weeks, a significantly higher percentage of patients with symptomatic asthma and initiated on treatment with FF/VI achieved better control of their asthma (71%), compared with patients continuing usual care treatment (56%), (odds ratio 2.00, 95% CI 1.70, 2.34;  $p < 0.001$ ). Usual care treatment included inhaled corticosteroids (ICS) administered as monotherapy or as ICS/LABA (Long Acting Beta Agonist) combinations. This improvement in asthma control for FF/VI was also consistently seen whether patients were on ICS or ICS/LABA as usual care.

Secondary analyses showed that, in addition to better asthma control, patients initiated with FF/VI also achieved higher quality of life scores (as measured by the Asthma Quality-of-Life Questionnaire, AQLQ), and lower impact on their ability to work and take part in activity (as measured by the Work Productivity and Activity Impairment Questionnaire, WPAI):

- 1 Patients who initiated with FF/VI had a statistically significantly higher AQLQ total score compared with patients initiated on usual care (increase from baseline of  $\geq 0.5$ ; OR 1.79 (95% CI 1.55-2.06);  $p < 0.0001$ ).
- 1 Patients initiated with FF/VI reported a greater decrease in work impairment on the WPAI Questionnaire compared with those continuing with usual care (-6.7% vs. -4.0%, difference -2.8% (95% CI - 4.4 to -1.1),  $p < 0.0001$ ) and a greater decrease in activity impairment (-10.4% vs. -5.9%, difference -4.5% (CI -5.9 to -3.2)  $p < 0.0001$ ).
- 1 There were numerical differences in asthma exacerbations, but these were not statistically significant, FF/VI 2% reduction versus usual care (95% CI -9 to 12,  $p=0.6969$ ).
- 1 There were no differences in annual rate of asthma-related primary care contacts in the total population. In the group initiated on FF/VI, there was an increase in annual rate of all primary care contacts versus usual care (9.7% increase, 95% CI 4.6% to 15.0%).
- 1 There were no differences in all secondary healthcare contacts (1.0% increase, -8.2 - 9.5).
- 1 The number of salbutamol inhalers (rescue medication) was lower in the group initiated with FF/VI than usual care (difference -0.8, 95% CI -1.1 to -0.5);  $p < 0.0001$ .

Safety was also assessed and the safety profile of FF/VI in the Salford Lung Study was consistent with the product label for FF/VI. In the study for the intent-to-treat (ITT) population, the incidence of serious adverse events (SAE) was the same in both arms (FF/VI 13% and usual care 13%).

Lead Investigator, Ashley Woodcock, Professor of Respiratory Medicine and Clinical Director for Respiratory Medicine, University Hospital of South Manchester and University of Manchester said: "Living with asthma can have a significant effect on people's day to day life, from sleeping well at night, to doing exercise, and going to work or school. Unfortunately, people with asthma often don't realise improvements can be made to these parts of their lives. That's why research, such as the Salford Lung Studies, are important tools to help the medical community manage asthma in a way that has a positive impact for people living with this debilitating condition. We're delighted the Lancet has published the results of what I believe to be a pioneering study."

This innovative open-label, randomised study, was carried out in 4,233 patients treated by their own General Practitioner in everyday clinical practice. The study had minimal exclusion criteria, minimal intervention, and involved a broad demographic of patients. As such 90% of screened patients were included in the study, making it more representative of everyday clinical practice than traditional randomised control trials.

Professor Neil Barnes, Global Medical Head, Respiratory Franchise at GSK said: "The Salford Lung Study Programme is the first of its kind. Whilst we set out to measure the effectiveness of our medicine, Relvar/Breo, in everyday clinical practice, we also wanted to find a way for doctors to more accurately assess how people live and manage their condition on a day to day basis. Through this unique study, we saw a meaningful impact on the daily lives of people managing asthma with FF/VI compared with usual care. Importantly, the results were consistent across the whole 12 months of the study, and when compared to patients continuing either ICS or ICS/LABA as their usual care."

Michael W. Aguiar, President and Chief Executive Officer of Innoviva said: "We are pleased with the results of the Salford Lung Study in asthma that are being presented and published today showing that Relvar Ellipta was superior to usual care treatment in improving asthma control. The Salford Lung Study is important as one of the first clinical effectiveness studies of its kind, providing interesting insights into the management of asthma in clinical care."

## Study Design

The Salford Lung Study is a Phase III multi-centre, open label randomised controlled trial (RCT). The objective of this study was to compare the effectiveness and safety profile of initiating treatment with FF/VI with usual asthma maintenance therapy over a 52 week period. All suitable patients with asthma at 74 primary care sites in and around Salford and South Manchester, UK, were identified from practice databases and invited to participate in the study by their own GP. The primary endpoint of the study was measured at week 24 in the primary effectiveness analysis population.

In total, 4,233 patients with asthma who were taking an inhaled corticosteroid (ICS) with or without a long acting beta<sub>2</sub>-agonist (LABA) were randomised to receive either FF/VI or to continue on their existing asthma maintenance therapy (usual care). Usual care was prescribed by the patient's GP and included ICS either alone or in combination with a LABA. In the usual care arm 36% of patients were on an ICS alone and 64% were on an ICS/LABA combination at the time of commencing study medication.

The Salford Lung Study had minimal exclusion criteria and involved a broad demographic of patients which allowed a high proportion of patients screened for inclusion into the study, to enter the study (90%). At baseline patients had a mean age of 49.8 (min 18 years) and were split by gender (males vs. female 41/59%). To enrol in the study, patients were required to have a GP diagnosis of asthma as their primary respiratory disease and be receiving maintenance therapy with an ICS with or without LABA for at least 4 weeks prior to visit. At baseline 72% of patients had uncontrolled asthma with an ACT total score of 5 to 19.

Patients were followed for a period of 52 weeks in a normal clinical practice setting using their electronic medical record (EMR), linking primary care, secondary care and pharmacy data to collect study data. Throughout the duration of the study physicians were allowed to modify or switch treatment at any point as this would happen in normal clinical practice, the only exception being a switch from usual care to FF/VI.

At weeks 12, 24, and 40 patients were telephoned to enquire about whether they had experienced any serious adverse events or non-serious adverse drug reactions. On these telephone calls patients were asked to provide responses to the ACT. At month 12 a face to face visit was carried out. The Standardised Asthma Quality of Life Questionnaire (AQLQ[S]) was also conducted at week 24 and week 52 by telephone.

The study team was able to monitor all hospital admissions, outpatient and emergency department visits, as well as data from primary care (including all healthcare contacts, out-of-hours activity and prescriptions of antibiotics or oral steroids) via the electronic health records.

The Intent-to-Treat (ITT) population is defined as all patients who have been randomised and received at least one prescription of study medication (e.g., FF/VI or usual asthma maintenance therapy). The primary effectiveness analysis (PEA) population is defined as all ITT patients who have an ACT total score of < 20 at baseline (Randomisation Visit).

The odds ratio expressed in the results is calculated as the ratio of the odds of achieving better asthma control as a patient initiated with Relvar Ellipta and the odds of achieving better asthma control as a patient continuing on usual care. This value is adjusted for any imbalances between the treatment arms in certain key characteristics.

The study design protocol paper can be found on [clintrials.gov](https://www.clintrials.gov).

## The Asthma Control Test (ACT)

The ACT is a well-recognised instrument that is used globally in asthma management and referenced in treatment guidelines to assess asthma control. It is self-administered utilising 5 questions to assess asthma control during the past 4 weeks on a 5-point categorical scale (1 to 5). By answering all five questions, a patient with asthma can obtain a score that may range between 5 and 25, with higher scores indicating better control.

An ACT total score of 5 to 19 suggests that a patient's asthma is poorly or not well controlled. A score of 20 to 25 suggests that a patient's asthma is likely to be well controlled. The total score is calculated as the sum of the scores from all 5 questions, provided all scores are non-missing; if any individual scores are missing then the overall score will be set to missing. A change of 3 points is clinically meaningful for the patient.

## About the Study

The Salford Lung Study is intended to enable healthcare professionals and decision makers to more fully assess the potential value of FF/VI by providing data collected in a normal clinical practice setting, which is representative of how healthcare professionals and patients may use the medicine in everyday life. It will add to the existing data set from double blind randomised clinical trials (RCTs) for the medicine which, while critical to establishing the safety and efficacy of a medicine, are conducted in a highly controlled environment and enrol a more highly selected patient population than would be expected in everyday clinical care.

The study is made possible through a unique collaboration between GSK, North West e-Health (NWEH), The University of Manchester, Salford Royal NHS Foundation Trust, University Hospital of South Manchester (UHSM), NHS Salford and GPs and community pharmacists in Salford, Trafford and South Manchester.

The Salford Lung Study in COPD reported findings in May 2016. This is the second of the two Salford Lung Studies to report.

## About asthma

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma affects 358 million people worldwide. Despite medical advances, more than half of patients continue to experience poor control and significant symptoms impacting their daily life.

The causes of asthma are not completely understood but likely involve an interaction between a person's genetic make-up and the environment. Key risk factors are inhaled substances that provoke allergic reactions or irritate the airways.

## About Relvar Ellipta (fluticasone furoate + vilanterol)

Relvar Ellipta is a once-daily dual combination treatment comprising fluticasone furoate, an inhaled corticosteroid and vilanterol, a long-acting beta<sub>2</sub>-agonist, in a single inhaler, the Ellipta.

Relvar Ellipta is indicated in Europe in the regular treatment of patients aged 12 and over with asthma, where use of a combination product (long-acting β<sub>2</sub>-agonist, LABA, and inhaled corticosteroid, ICS) is appropriate: Patients not adequately controlled on both ICS and 'as-needed' short-acting β<sub>2</sub>-agonist (SABA).

Full EU prescribing information is available at: [EU Prescribing Information for Relvar Ellipta](#).

## Important safety information for Relvar Ellipta in Europe

FF/VI is contraindicated in patients with hypersensitivity to either fluticasone furoate, vilanterol, or any of the excipients.

FF/VI should not be used to treat acute asthma symptoms or an acute exacerbation in COPD, for which a short-acting bronchodilator is required. Increasing use of short-acting bronchodilators to relieve symptoms indicates deterioration of control and patients should be reviewed by a physician.

Patients should not stop therapy with FF/VI in asthma or COPD, without physician supervision since symptoms may recur after discontinuation.

Asthma-related adverse events and exacerbations may occur during treatment with FF/VI. Patients should be asked to

continue treatment but to seek medical advice if asthma symptoms remain uncontrolled or worsen after initiation of treatment with FF/VI.

Paradoxical bronchospasm may occur with an immediate increase in wheezing after dosing. This should be treated immediately with a short-acting inhaled bronchodilator. FF/VI should be discontinued immediately, the patient assessed and alternative therapy instituted if necessary.

Cardiovascular effects, such as cardiac arrhythmias e.g. supraventricular tachycardia and extrasystoles may be seen with sympathomimetic medicinal products including FF/VI. Therefore fluticasone furoate/vilanterol should be used with caution in patients with severe cardiovascular disease.

For patients with moderate to severe hepatic impairment, the 92/22 mcg dose should be used and patients should be monitored for systemic corticosteroid-related adverse reactions. FF/VI 184/22 mcg is not indicated for patients with COPD. There is no additional benefit of the 184/22 mcg dose compared to the 92/22 mcg dose and there is a potential increased risk of pneumonia and systemic corticosteroid-related adverse reactions.

An increase in the incidence of pneumonia has been observed in patients with COPD receiving FF/VI. There was also an increased incidence of pneumonias resulting in hospitalisation. In some instances these pneumonia events were fatal.

The incidence of pneumonia in patients with asthma was common at the higher dose. In a previous study of FF/VI in asthma the incidence of pneumonia in patients with asthma taking FF/VI 184/22 mcg was numerically higher compared with those receiving FF/VI 92/22 mcg or placebo.

Hyperglycaemia: There have been reports of increases in blood glucose levels in diabetic patients and this should be considered when prescribing to patients with a history of diabetes mellitus.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses prescribed for long periods. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include Cushing's syndrome, Cushingoid features, adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

FF/VI should be administered with caution in patients with pulmonary tuberculosis or in patients with chronic or untreated infections. Data from large asthma and COPD clinical trials were used to determine the frequency of adverse reactions associated with FF/VI.

Very common adverse reactions (occurring in > 1/10 patients) with FF/VI were headache and nasopharyngitis. Common adverse reactions (occurring in > 1/100 to < 1/10 patients) were pneumonia, upper respiratory tract infection, bronchitis, influenza, candidiasis of mouth and throat, oropharyngeal pain, sinusitis, pharyngitis, rhinitis, cough, dysphonia, abdominal pain, arthralgia, back pain, fractures, and pyrexia and muscle spasms. Extrasystoles were observed as an uncommon adverse reaction (occurring in > 1/1,000 to < 1/100 patients). Rare adverse reactions (occurring in > 1/10,000 to < 1/1,000) were hypersensitivity reactions (including anaphylaxis, angioedema, rash and urticaria), anxiety, tremor, palpitations, tachycardia and paradoxical bronchospasm. With the exception of pneumonia and fractures, the safety profile was similar in patients with asthma and COPD. During clinical studies, pneumonia and fractures were more frequently observed in patients with COPD.

**Relvar Ellipta is known as Breo Ellipta in the United States.** Breo Ellipta is licensed in the US for:

- l The once-daily treatment of asthma in patients aged 18 years and older.

Long-acting beta2-adrenergic agonists (LABA), such as vilanterol, one of the active ingredients in Breo Ellipta, increase the risk of asthma-related death. Available data from controlled clinical trials suggest that LABA increase the risk of asthma-related hospitalization in pediatric and adolescent patients. Therefore, when treating patients with asthma, physicians should only prescribe Breo Ellipta for patients not adequately controlled on a long-term asthma control medication, such as an inhaled corticosteroid, or whose disease severity clearly warrants initiation of treatment with both an inhaled corticosteroid and a LABA. Once asthma control is achieved and maintained, assess the patient at regular intervals and step down therapy (e.g., discontinue Breo Ellipta) if possible without loss of asthma control and maintain the patient on a long-term asthma control medication, such as an inhaled corticosteroid. Do not use BREO ELLIPTA for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

- l Breo Ellipta is NOT indicated for the relief of acute bronchospasm.

Full US prescribing information, including BOXED WARNING and Medication Guide is available at [us.gsk.com](http://us.gsk.com) or [US Prescribing Information for Breo Ellipta](#).

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**Innoviva** - Innoviva is focused on bringing compelling new medicines to patients in areas of unmet need by leveraging its significant expertise in the development, commercialization and financial management of bio-pharmaceuticals. Innoviva's portfolio is anchored by the respiratory assets partnered with Glaxo Group Limited (GSK), including RELVAR<sup>®</sup>/BREO<sup>®</sup> ELLIPTA<sup>®</sup> and ANORO<sup>®</sup> ELLIPTA<sup>®</sup>, which were jointly developed by Innoviva and GSK. Under the agreement with GSK, Innoviva is eligible to receive associated royalty revenues from RELVAR<sup>®</sup>/BREO<sup>®</sup> ELLIPTA<sup>®</sup>, ANORO<sup>®</sup> ELLIPTA<sup>®</sup>. In addition, Innoviva retains a 15 percent economic interest in future payments made by GSK for earlier-stage programs partnered with Theravance Biopharma, Inc., including the closed triple combination therapy for COPD. For more information, please visit Innoviva's website at [www.inva.com](http://www.inva.com).

### **Cautionary statement regarding forward-looking statements**

GSK cautions investors that any forward-looking statements or projections made by GSK, including those made in this announcement, are subject to risks and uncertainties that may cause actual results to differ materially from those projected. Such factors include, but are not limited to, those described under Item 3.D Principal risks and uncertainties in the company's Annual Report on Form 20-F for 2016.

### **Innoviva forward-looking statements**

This press release contains certain "forward-looking" statements as that term is defined in the Private Securities Litigation Reform Act of 1995 regarding, among other things, statements relating to goals, plans, objectives and future events, including the expected use of the data from the Salford Lung Study and the potential benefits thereof. Innoviva intends such forward-looking statements to be covered by the safe harbor provisions for forward-looking statements contained in Section 21E of the Securities Exchange Act of 1934 and the Private Securities Litigation Reform Act of 1995. Such forward-looking statements involve substantial risks, uncertainties and assumptions. These statements are based on the current estimates and assumptions of the management of Innoviva as of the date of this press release and are subject to risks, uncertainties, changes in circumstances, assumptions and other factors that may cause the actual results of Innoviva to be materially different from those reflected in the forward-looking statements. Important factors that could cause actual results to differ materially from those indicated by such forward-looking statements are described under the headings "Risk Factors" and "Management's Discussion and Analysis of Financial Condition and Results of Operations" contained in Innoviva's Annual Report on Form 10-K for the year ended December 31, 2016 and Quarterly Report on Form 10-Q for the quarter ended June 30, 2017, which are on file with the U.S. Securities and Exchange Commission (SEC) and available on the SEC's website at [www.sec.gov](http://www.sec.gov). In addition to the risks described above and in Innoviva's other filings with the SEC, other unknown or unpredictable factors also could affect Innoviva's results. No forward-looking statements can be guaranteed and actual results may differ materially from such statements. Given these uncertainties, you should not place undue reliance on these forward-looking statements. The information in this press release is provided only as of the date hereof, and Innoviva assumes no obligation to update its forward-looking statements on account of new information, future events or otherwise, except as required by law. (INVA-G).

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