

GLAXOSMITHKLINE PLC  
Form 6-K  
March 17, 2016

FORM 6-K

SECURITIES AND EXCHANGE COMMISSION  
Washington D.C. 20549

Report of Foreign Issuer

Pursuant to Rule 13a-16 or 15d-16 of  
the Securities Exchange Act of 1934

For period ending March 2016

GlaxoSmithKline plc  
(Name of registrant)

980 Great West Road, Brentford, Middlesex, TW8 9GS  
(Address of principal executive offices)

Indicate by check mark whether the registrant files or  
will file annual reports under cover Form 20-F or Form 40-F

Form 20-F  Form 40-F

--

Indicate by check mark whether the registrant by furnishing the  
information contained in this Form is also thereby furnishing the  
information to the Commission pursuant to Rule 12g3-2(b) under the  
Securities Exchange Act of 1934.

Yes No

--

Issued: 17th March 2016, London UK

GSK's Advair® Diskus® achieves primary endpoint in LABA safety study of children aged 4-11 years with asthma

GlaxoSmithKline plc (GSK) today announced results from the paediatric 'LABA' (long acting beta2-agonist) safety study. VESTRI (SAS115358) compared Advair® Diskus® (FSC), a combination of the LABA, salmeterol, and the inhaled corticosteroid (ICS), fluticasone propionate (FP), to FP monotherapy in children aged 4 - 11 years. The study assessed the composite endpoint of serious asthma-related events (deaths, intubations or hospitalisations).

The VESTRI study randomised 6,250 children aged 4 - 11 years into the six month study, across 31 countries. The primary safety endpoint of the study showed FSC twice-daily (100/50mcg, 250/50mcg) demonstrated non-inferiority compared to corresponding doses of FP twice-daily (100mcg, 250mcg), on the risk of serious asthma-related events, Hazard Ratio (HR) 1.285, (95% CI 0.726, 2.272) p=0.006. All serious asthma-related events were hospitalisations (n=48), and there were no asthma-related deaths or intubations seen in either arm of the study.

In the study a non-statistically significant reduction of 14% was observed in the risk of time-to-first asthma exacerbation for FSC compared to FP (HR 0.859; 95% CI 0.729, 1.012).

VESTRI is the second study undertaken by GSK as a post-marketing requirement of the US Food and Drug Administration (FDA). The first study, AUSTRI, carried out with adolescent and adult patients with asthma, demonstrated non-inferiority of FSC compared to FP and these data have been published in the New England Journal of Medicine<sup>1</sup>. GSK was one of four manufacturers of LABA-containing products indicated for the treatment of asthma, required to undertake equivalent studies designed to evaluate whether the addition of a LABA to an ICS increased the risk of an event in the composite endpoint of serious asthma-related events (deaths, intubations or hospitalisations) in adolescents and adults. GSK was the only manufacturer to conduct a study in children aged 4-11 years of age, as it is the only manufacturer with a licence to treat this age group in the US. The FSC 250/50mcg dose is not licensed for the treatment of paediatrics with asthma.

#### Study Design

##### VESTRI Study (SAS115358)

A global, multicentre, randomised stratified, double-blind, parallel-group active comparator, six-month study in paediatric patients (4 - 11 years of age) with asthma. Patients were required to have a history of persistent asthma and a history of an asthma exacerbation in the year prior to study randomisation. Eligibility for participation into the study was based on a review of pre-study asthma medications, assessment of asthma control, based on the Childhood-Asthma Control Test 2 and a history of an asthma exacerbation requiring a systemic corticosteroid in the previous year.

Patients were screened at visit one to assess eligibility and subsequently randomised 1:1 to either FSC (100/50 mcg, 250/50 mcg) or FP (100mcg, 250 mcg) at visit two. Patients returned to the clinic after two weeks (visit three) and then at two-monthly intervals up to the final end of treatment clinic visit at six months. Patients' status in the months where there was not a visit was assessed by telephone contact. A follow-up phone call to query serious adverse events was made approximately one-week after end of treatment for both patients completing 6-month study treatment and those who ended study treatment prematurely. Patients were permitted to use albuterol/salbutamol rescue medication throughout the study. FSC 250/50 mcg and FP 250 mcg are not currently indicated in children 4 - 11 years of age according to US-approved product information.

The primary analysis was to determine whether the addition of LABA to ICS therapy (FSC) is non-inferior to ICS therapy alone (FP) in terms of the risk of a composite of serious asthma-related events (asthma-related hospitalisation,

intubation and death). To demonstrate non-inferiority, a predefined margin of 2.675 was required, meaning the upper limit of the 95% confidence interval needed to be less than 2.675 to rule out an increase in the risk of a serious asthma related event on FSC compared with FP. All serious asthma related events were adjudicated by an independent committee.

The full results for this study will be posted on the GSK Clinical Study Register and published in a peer-reviewed forum.

#### References

1. Stempel, et al. Serious Asthma Events with Fluticasone plus Salmeterol versus Fluticasone Alone. N Engl J Med 2016; <http://www.nejm.org/doi/full/10.1056/NEJMoa1511049>
2. Liu AH et al. Development and cross-sectional validation of the Childhood Asthma Control Test. J Allergy Clin Immunol 2007; 119: 817-25

#### About Advair/Seretide

ADVAIR DISKUS is indicated for the treatment of asthma in patients aged 4 years and older.

Long-acting beta2-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, 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 ADVAIR DISKUS 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 ADVAIR DISKUS) 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 ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

ADVAIR DISKUS is NOT indicated for the relief of acute bronchospasm.

[https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing\\_Information/Advair\\_Diskus/pdf/ADVAIR\\_DISKUS\\_Prescribing\\_Information.pdf](https://www.gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Advair_Diskus/pdf/ADVAIR_DISKUS_Prescribing_Information.pdf)

Seretide Accuhaler is indicated in Europe in the regular treatment of patients aged 4 and over with asthma, where use of a combination product (long-acting  $\beta$ 2-agonist, LABA, and inhaled corticosteroid, ICS) is appropriate: Patients not adequately controlled on both ICS and 'as-needed' short-acting  $\beta$ 2-agonist (SABA); Patients already adequately controlled on both ICS and LABA.

For the UK Summary of Product Characteristics (SmPC), please visit:

<https://www.medicines.org.uk/emc/medicine/2317/SPC/Seretide+100,+250,+500+Accuhaler>

#### Important Safety Information for ADVAIR DISKUS

**WARNING: ASTHMA-RELATED DEATH**

Long-acting beta<sub>2</sub>-adrenergic agonists (LABA), such as salmeterol, one of the active ingredients in ADVAIR DISKUS, increase the risk of asthma-related death. Data from a large placebo-controlled US trial that compared the safety of salmeterol with placebo added to usual asthma therapy showed an increase in asthma-related deaths in subjects receiving salmeterol (13 deaths out of 13,176 subjects treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 subjects on placebo). Currently available data are inadequate to determine whether concurrent use of inhaled corticosteroids or other long-term asthma control drugs mitigates the increased risk of asthma-related death from LABA. 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 ADVAIR DISKUS 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 ADVAIR DISKUS) 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 ADVAIR DISKUS for patients whose asthma is adequately controlled on low- or medium-dose inhaled corticosteroids.

#### CONTRAINDICATIONS

- ADVAIR DISKUS is contraindicated for primary treatment of status asthmaticus or other acute episodes of asthma or chronic obstructive pulmonary disease (COPD) where intensive measures are required.
- ADVAIR DISKUS is contraindicated in patients with severe hypersensitivity to milk proteins.

#### WARNINGS AND PRECAUTIONS

ADVAIR DISKUS should not be initiated in patients during rapidly deteriorating or potentially life-threatening episodes of asthma or COPD.

ADVAIR DISKUS should not be used for the relief of acute symptoms, i.e., as rescue therapy for the treatment of acute episodes of bronchospasm. An inhaled, short-acting beta<sub>2</sub>-agonist, not ADVAIR DISKUS, should be used to relieve acute symptoms such as shortness of breath.

ADVAIR DISKUS should not be used more often than recommended, at higher doses than recommended, or in conjunction with other medicines containing LABA, as an overdose may result. Clinically significant cardiovascular effects and fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs. Patients using ADVAIR DISKUS should not use another medicine containing a LABA (e.g., salmeterol, formoterol fumarate, arformoterol tartrate, indacaterol, vilanterol) for any reason.

Oropharyngeal candidiasis has occurred in patients treated with ADVAIR DISKUS. Advise patients to rinse the mouth with water without swallowing following inhalation to help reduce the risk of oropharyngeal candidiasis.

Patients who use corticosteroids are at risk for potential worsening of existing tuberculosis; fungal, bacterial, viral, or parasitic infections; or ocular herpes simplex. A more serious or even fatal course of chickenpox or measles may occur in susceptible patients. Use caution in patients with the above because of the potential for worsening of these infections.

Particular care is needed for patients who have been transferred from systemically active corticosteroids to inhaled corticosteroids because deaths due to adrenal insufficiency have occurred in patients with asthma during and after transfer from systemic corticosteroids to less systemically available inhaled corticosteroids. Slowly taper the dose of systemic corticosteroids if transferring patients to ADVAIR DISKUS.

Hypercorticism and adrenal suppression may occur with high doses of inhaled corticosteroids, including fluticasone propionate, or at the recommended dose in susceptible individuals. If such effects occur, discontinue ADVAIR DISKUS slowly.

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

If paradoxical bronchospasm occurs, discontinue ADVAIR DISKUS immediately and institute alternative therapy.

Salmeterol, a component of ADVAIR DISKUS, can produce a clinically significant cardiovascular effect in some patients as measured by pulse rate, blood pressure, and/or symptoms. If such effects occur, ADVAIR DISKUS may need to be discontinued. ADVAIR DISKUS should be used with caution in patients with cardiovascular disorders, especially coronary insufficiency, cardiac arrhythmias, and hypertension.

Decreases in bone mineral density (BMD) have been observed with long-term administration of products containing inhaled corticosteroids. Patients with major risk factors for decreased bone mineral content, such as prolonged immobilization, family history of osteoporosis, postmenopausal status, tobacco use, advanced age, poor nutrition, or chronic use of drugs that can reduce bone mass (e.g., anticonvulsants, oral corticosteroids) should be monitored and treated with established standards of care.

Inhaled corticosteroids, as well as poorly controlled asthma, may cause a reduction in growth velocity, and the long-term effect on final adult height is unknown. Patients should be maintained on the lowest dose of inhaled corticosteroid that effectively controls their asthma. Monitor growth of pediatric patients.

Glaucoma, increased intraocular pressure, and cataracts have been reported in patients with asthma and COPD following the long term administration of inhaled corticosteroids, including fluticasone propionate, a component of ADVAIR DISKUS. Therefore, close monitoring is warranted in patients with a change in vision or with a history of increased intraocular pressure, glaucoma, and/or cataracts.

Be alert to hypokalemia, hyperglycemia, and systemic eosinophilic conditions, such as Churg-Strauss syndrome.

Use with caution in patients with convulsive disorders, thyrotoxicosis, diabetes mellitus, ketoacidosis, and in patients who are unusually responsive to sympathomimetic amines.

## ADVERSE REACTIONS

Most common adverse reactions (incidence  $\geq 3\%$ ) in subjects with asthma taking ADVAIR DISKUS 100/50, ADVAIR DISKUS 250/50, and placebo, respectively, were upper respiratory tract infection (27%, 21%, 14%), pharyngitis (13%, 10%, 6%), upper respiratory inflammation (7%, 6%, 5%), sinusitis (4%, 5%, 4%), hoarseness/dysphonia (5%, 2%, <1%), oral candidiasis (1%, 4%, 0%), viral respiratory infections (4%, 4%, 3%), bronchitis (2%, 8%, 2%), cough (3%, 6%, 2%), headaches (12%, 13%, 7%), nausea and vomiting (4%, 6%, 1%), gastrointestinal discomfort and pain (4%, 1%, 1%), diarrhea (4%, 2%, 1%), viral gastrointestinal infections (3%, 0%, 2%), candidiasis unspecified site (3%, 0%, 1%), and musculoskeletal pain (4%, 2%, 3%). The types of adverse reactions and events reported were similar in subjects treated with ADVAIR DISKUS 500/50.

## DRUG INTERACTIONS

The use of strong cytochrome P450 3A4 (CYP3A4) inhibitors (e.g., ritonavir, atazanavir, clarithromycin, indinavir, itraconazole, nefazodone, nelfinavir, saquinavir, ketoconazole, telithromycin) with ADVAIR DISKUS is not recommended because increased systemic corticosteroid and increased cardiovascular adverse effects may occur.

ADVAIR DISKUS should be administered with extreme caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, or within 2 weeks of discontinuation of such agents, because the action of salmeterol, a component of ADVAIR DISKUS, on the vascular system may be potentiated by these agents.

Use beta-blockers with caution as they not only block the pulmonary effect of beta-agonists, such as salmeterol, a component of ADVAIR DISKUS, but may also produce severe bronchospasm in patients with asthma or COPD.

Use ADVAIR DISKUS with caution in patients taking non-potassium-sparing diuretics (such as loop or thiazide diuretics), as electrocardiographic changes and/or hypokalemia associated with non-potassium-sparing diuretics may worsen with coadministration with beta-agonists, such as salmeterol.

## USE IN SPECIFIC POPULATIONS

Fluticasone propionate and salmeterol are predominantly cleared by hepatic metabolism. Impairment of liver function may lead to accumulation of fluticasone propionate and salmeterol in plasma. Therefore, patients with hepatic disease should be closely monitored.

GSK - one of the world's leading research-based pharmaceutical and healthcare companies - is committed to improving the quality of human life by enabling people to do more, feel better and live longer. For further information please visit [www.gsk.com](http://www.gsk.com).

### GSK enquiries:

|                             |                 |                         |                     |
|-----------------------------|-----------------|-------------------------|---------------------|
| UK Media enquiries:         | Simon Steel     | +44 (0) 20 8047<br>5502 | (London)            |
|                             | Claire Brough   | +44 (0) 20 8047<br>5502 | (London)            |
| US Media enquiries:         | Sarah Alspach   | +1 202 715 1048         | (Washington,<br>DC) |
|                             | Sarah Spencer   | +1 215 751 3335         | (Philadelphia)      |
|                             | Mary Anne Rhyne | +1 919 483 0492         | (North<br>Carolina) |
|                             | Jenni Ligday    | +1 202 715 1049         | (Washington,<br>DC) |
|                             | Karen Hagens    | +1 919 483 2863         | (North<br>Carolina) |
| Analyst/Investor enquiries: | Ziba Shamsi     | +44 (0) 20 8047<br>5543 | (London)            |
|                             | Tom Curry       | + 1 215 751 5419        | (Philadelphia)      |
|                             | Gary Davies     |                         | (London)            |

Edgar Filing: GLAXOSMITHKLINE PLC - Form 6-K

+44 (0) 20 8047  
5503  
James Dodwell +44 (0) 20 8047 (London)  
2406  
Jeff McLaughlin +1 215 751 7002 (Philadelphia)

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 'Risk factors' in the company's Annual Report on Form 20-F for 2014.

Registered in England & Wales:  
No. 3888792

Registered Office:  
980 Great West Road  
Brentford, Middlesex  
TW8 9GS

SIGNATURES

Pursuant to the requirements of the Securities Exchange Act of 1934, the registrant has duly caused this report to be signed on its behalf by the undersigned, thereunto duly authorised.

GlaxoSmithKline plc  
(Registrant)

Date: March 17, 2016

By: VICTORIA WHYTE  
-----

Victoria Whyte  
Authorised Signatory for and on  
behalf of GlaxoSmithKline plc