SAS115358, a 6-month safety and benefit study of inhaled fluticasone propionate/ salmeterol combination versus inhaled fluticasone propionate in the treatment of 6,200 pediatric subjects 4-11 years old with persistent asthma.

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Ethical review	Approved WMO
Status	Will not start
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON37737

Source
ToetsingOnline

Brief title
VESTRI

Condition

- Respiratory disorders NEC

Synonym
asthma

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline Research & Development Limited
Source(s) of monetary or material Support: GSK

Intervention

Keyword: asthma, children, fluticasone propionate, salmetarol

Outcome measures

Primary outcome

The primary safety endpoint is the number of subjects experiencing an event in the composite endpoint of serious asthma-related outcomes (hospitalizations, endotracheal intubations, or deaths) over the 6-month study treatment period.

The primary efficacy endpoint is asthma exacerbations (defined as deterioration of asthma requiring the use of systemic corticosteroids for at least 3 days or a single depot corticosteroid injection).

Secondary outcome

Secondary safety endpoints are asthma-related hospitalizations, endotracheal intubations, and deaths, and withdrawals from study treatment due to asthma exacerbation.

Secondary efficacy endpoints are rescue-free days and asthma control days.

Study description

Background summary

Safety assessments from studies in adults with asthma using long-acting beta2-agonists (LABAs) in single inhaler presentations have been associated with an increased risk for rare respiratory-related events including asthma-related death and intubation [Nelson, 2006; Castle, 1993]. These studies in adults suggest that the increased risk was primarily associated with subjects who were not receiving inhaled corticosteroids (ICSs), or who received inadequate doses of ICS. The data, though, are inadequate to demonstrate that the addition of an ICS to a LABA mitigates the risk that has been observed in studies of LABAs. In a study with formoterol in children <12 years of age where concurrent ICS use was high but not compulsory, the use of LABA was associated with an increased risk for asthma-related hospitalization [Bensch, 2002]. Therefore, the US product label was changed to reflect safety concerns for patients treated with LABA medicines.
While the safety profile of salmeterol used in a fixed-dose combination with fluticasone propionate (FP) has not shown an association with these same risks in adults, adolescents or children, despite extensive study in clinical trials and use worldwide [GlaxoSmithKline Briefing Information, 2008], there remains a public health debate whether the safety profile of fixed combination medications are fully established in the absence of a large, well-designed randomized controlled trial (RCT) to evaluate the occurrence of these rare events.
In order to assess the safety of salmeterol in combination with FP, this randomized, double-blind study will compare inhaled FP/salmeterol combination (FSC) with inhaled FP via the composite endpoint of serious asthma-related outcomes (hospitalizations, endotracheal intubations, or deaths). In addition, efficacy data will be collected for both inhaled FSC and FP.

Study objective

The primary objective is to evaluate whether the addition of a LABA to an ICS (FSC) therapy is non-inferior in terms of risk of serious asthma-related events (asthma-related hospitalizations, endotracheal intubations, and deaths) compared with ICS alone (FP) in pediatric subjects (age 4-11 years) with persistent asthma. To declare non-inferiority, the relative risk of serious asthma-related events associated with LABA plus ICS compared with ICS alone must be less than 2.7 (a 2.7-fold increase), based on the upper bound of the 95% confidence interval (CI) on the estimate of relative risk.
Additional safety measures include withdrawals from study treatment due to asthma exacerbation, adverse events leading to withdrawal from the study treatment, growth velocity, and serious adverse events (SAEs).
A secondary objective of the study is to evaluate whether the addition of LABA to ICS therapy (FSC) is superior to ICS therapy alone (FP) in terms of measures of efficacy in pediatric subjects (age 4-11 years) with persistent asthma. The primary measure of efficacy is the occurrence of a severe asthma exacerbation.

To declare superiority, the relative risk of an asthma exacerbation associated with LABA plus ICS compared with ICS alone must be less than 1.0 (unity), based on the upper bound of the 95% CI on the estimate of relative risk.
Additional efficacy measures include rescue albuterol/salbutamol use, asthma symptoms, unscheduled asthma-related healthcare utilization, productivity, and the Childhood Asthma Control Test.

Study design

This study will be a multi-center, randomized, stratified, double-blind, parallel group, 6-month study in pediatric subjects with persistent asthma. The study will randomize approximately 6,200 subjects with adequate representation throughout the ages of 4 to 11 years.
Potential subjects will be screened at Visit 1 to assess eligibility. At Visit 2, subjects will be randomized to 6-month double-blind treatment of either FSC 100/50mcg or FP 100mcg or FSC 250/50mcg or FP 250mcg based on their asthma control status as determined by assessment of the Childhood Asthma Control Test, number of exacerbations in the prior year, and their prior asthma medication use. Subjects will return to the clinic in 2 weeks (Visit 3), 2 months (Visit 4), 4 months (Visit 5), and 6 months (Visit 6). All subjects will be provided with albuterol/salbutamol (short-acting beta2-agonist) for quick relief of asthma symptoms and instructed in how and when to administer it. During the double-blind treatment period, subjects/caregivers will call daily into an Interactive Voice Response System (IVRS) to record subjects* asthma symptom score, rescue albuterol/salbutamol use (other than pre-exercise treatment), nighttime awakenings due to asthma, and work (caregiver) or school/daycare (subject) missed due to asthma. Subjects will be contacted by the study site via telephone monthly at 1, 3, and 5 months post-randomization to monitor asthma status and query concerning the study outcomes of interest. Subjects will receive a follow-up telephone call to query SAEs approximately 1 week after the end-of-treatment/early withdrawal visit for both subjects who complete 6-month double-blind study treatment and subjects who end their study treatment prematurely prior to completing 6-month treatment period (withdrawn early from study treatment). All randomized subjects will be tracked for the duration of the intended study period (i.e., 6 consecutive months following randomization) for the primary outcome of interest for the study (i.e., serious asthma-related outcome [hospitalization, endotracheal intubation, or death]).

Intervention

Subjects administer inhalation twice daily of one of the doses (FP 100mcg, FP 250 mgc, FSC 100/50mcg or FSC 250/50).

Study burden and risks

The most common side effects when using Seretide or Flixotide are:

•Mouth and throat irritation
•Fungal infection in the mouth and throat
•Hoarseness and voice changes
•Headache
•Upper respiratory infections (colds).
Less likely side effects when using Seretide are:
•Muscle pains
•Upset stomach
•Tiredness
•Stuffy nose
•Fever.
Rarely, Seretide or Flixotide can cause potentially serious side effects which include:
•Serious allergic reactions
•Sudden breathing problems immediately after taking Seretide or Flixotide
•Reduced adrenal function
•Weakened immune system and a higher chance of infection
•Eye problems.
Additional potential serious side effects that rarely occur in patients using Seretide are:
•Fast and irregular heartbeat
•Chest pain
•Tremors or nervousness

If subject were taking Seretide before entering this study and are assigned to take Flixotide during the study, there may
be a risk of losing asthma control if they benefited from the additional medicine (i.e., salmeterol). Seretide and Flixotide
should not be used in people with severe milk protein allergies.

SALBUTAMOL
The most common side effects when using salbutamol, the medicine in the rescue inhaler, are:
•Fast heartbeat
•Feeling nervous.
Less likely side effects from salbutamol are:
•Dry mouth and dry or sore throat
•Cough
•Feeling dizzy
•Sleep problems
•Breathing problems
•Muscle pain or cramps
•Rash, itching or swelling
•Headache
•Feeling sick to the stomach.
Rarely, salbutamol can cause potentially serious side effects which include:
•Sudden breathing problems immediately after taking salbutamol

•Serious allergic reactions.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Informed consent
• Subject*s legal guardian must be able and willing to give written informed consent to take part in the study. If applicable, subject must be able and willing to give assent to take part in the study according to the local requirement.
• Subject and their legal guardian understand that the study requires them to be treated on an outpatient basis.
• Subject and their legal guardian understand that they must comply with study medication and study assessments including recording of symptom scores and rescue albuterol/salbutamol use, attending scheduled study visits, and being accessible by a telephone call.

2. Age: 4-11 years of age at Visit 1
3. Gender: Male or eligible female
Female subjects should not be enrolled if they are pregnant, lactating or plan to become pregnant during the time of study participation. All females of childbearing potential must have a negative urine pregnancy test result prior to randomization to continue in the study. Females who become pregnant during the course of the study will be discontinued and the pregnancy outcome followed (see Section 6.2.5)
Females of childbearing potential are
• Females, regardless of their age, with functioning ovaries and no documented impairment of oviductal or uterine function that would cause sterility
• This category includes young females who have begun to menstruate, females with oligomenorrhea, and females who are perimenopausal.
4. Asthma diagnosis: Asthma, defined by the regional asthma guidelines (i.e., NIH, GINA, etc.), for at least 6 months prior to Visit 1.
Asthma is defined as a chronic inflammatory disorder associated with airway hyperresponsiveness and reversible airways obstruction that leads to recurrent episodes of wheezing, breathlessness, chest tightness, and coughing.
If the subject is naïve to the study site, the subject/guardian must self-report a physician diagnosis of asthma and the investigator must confirm by review of medical history with the subject/guardian.
5. Ability to answer questions regarding asthma control (with assistance of his/her parents [guardians], if needed), and use a metered-dose inhaler (MDI) and DISKUS effectively.
6. In countries where the product label includes a warning regarding more serious chickenpox infections in patients using corticosteroids (refer to the local product labels for varicella vaccine, ADVAIR DISKUS, and FLOVENT DISKUS) and/or varicella immunization is recommended for the age group, the subject must have a history of clinical varicella infection or recipient of a varicella vaccine before receiving any study drug. In those countries, subjects without a history of clinical varicella disease must receive varicella vaccine prior to randomization, and should follow standard guidelines regarding timing of second dose, if indicated.
7. Subject must have history of at least one occurrence (self-report by subject/guardian) of treatment with systemic corticosteroid [3 or more days of oral corticosteroid (OCS) or an equivalent depot corticosteroid injection] for an asthma exacerbation within the prior 12 months, excluding the 4 weeks immediately preceding Visit 1 (see Section 4.3, Exclusion Criteria #7).
8. Currently being treated for asthma and no change in asthma therapy for the last 4 weeks from Visit 1 and Subjects must meet one of the following pre-study asthma medication, impairment domain (Childhood Asthma Control Test) and risk domain (asthma exacerbations) criteria to be eligible for enrolment (Table 1).
• Subjects on SABA alone, LTRA, theophylline, or cromolyn as monotherapy with Childhood Asthma Control Test score *19 at Visit 1 and have had 2 or more asthma exacerbations in the previous year, or
• Subjects on low-dose ICS monotherapy with Childhood Asthma Control Test score *20 at Visit 1 and have had 2 or more asthma exacerbations in the previous year, or
• Subjects on low-dose ICS monotherapy with Childhood Asthma Control Test score *19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
• Subjects on low-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline)

with Childhood Asthma Control Test score *20 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
• Subjects on low-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score *19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
• Subjects on medium-dose ICS monotherapy with Childhood Asthma Control Test score *20 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
• Subjects on medium-dose ICS monotherapy with Childhood Asthma Control Test score *19 at Visit 1 and have had at least 1 asthma exacerbation in the previous year, or
• Subjects on medium-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score *20 at Visit 1 and have had only 1 asthma exacerbation in the previous year.
Note:
• Subjects receiving SABA only, LTRA, theophylline or cromolyn as monotherapy with Childhood Asthma Control Test >=20 are not eligible.
• Subjects receiving medium-dose ICS and one or more adjunctive therapy (LABA, LTRA, or theophylline) with Childhood Asthma Control Test score <=19 at Visit 1 are not eligible.
• To be eligible, subjects should not present signs of unstable asthma as described in Section 4.30, Exclusion Criterion #2.
• Subjects who are currently on high-dose ICS or high-dose ICS/LABA are not eligible for the study (Section 4.3 Exclusion Criterion #3).
• Subjects who had an asthma exacerbation within 4 weeks of Visit 1 or more than 4 asthma exacerbations in the last 12 months from Visit 1 are not eligible (Section 4.3, Exclusion Criterion #7).

Exclusion criteria

1. History of life-threatening asthma: Defined for this protocol as an asthma episode that required intubation, hypercapnea requiring non-invasive ventilatory support, respiratory arrest, hypoxic seizures or asthma-related syncopal episode(s).
2. Unstable asthma at Visit 1. Signs of unstable asthma include:
• Daily use of > 4 puffs of albuterol/salbutamol (other than pre-exercise treatment), >=8 puffs of albuterol/salbutamol for 2 or more consecutive 24-hour periods in the 7 days preceding Visit 1,
• >=2 nighttime awakenings due to asthma symptoms in the 7 days preceding Visit 1, or
• Investigator*s discretion (reason should be recorded in source documents).
3. Subjects who are currently receiving high-dose ICS or ICS/LABA therapy to treat asthma symptoms.
4. Concurrent respiratory disease: Current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, allergic bronchopulmonary aspergillosis, cystic fibrosis, bronchopulmonary dysplasia, or other severe respiratory abnormalities other than asthma.
5. Respiratory infection: Bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear (either culture-documented or suspected) that is not resolved at Visit 1 and that in the opinion of the investigator is expected to affect the subject*s asthma status or

the subject*s ability to participate in the study.
6. Subjects with only exercise-induced asthma are excluded from participation in this study.
7. Asthma exacerbation: An asthma exacerbation requiring systemic (tablets, suspension or injection) corticosteroids within 4 weeks of Visit 1 or more than 4 separate exacerbations in the last 12 months from Visit 1.
These include asthma exacerbations resulting from poor compliance with asthma medications.
Each asthma exacerbation must be separated by >7 days from the discontinuation of OCS to be considered an individual event.
8. Asthma hospitalization: Hospitalization for asthma within 4 weeks of Visit 1 or more than 2 hospitalizations (defined as overnight admission) for asthma in the last 12 months from Visit 1. Each hospitalization must be separated by >7 days to be considered an individual event (ED visits < 24 hours in duration are not considered hospitalizations).
9. Other current evidence of clinically significant uncontrolled diseases/conditions of any body or organ system. Excluded diseases/conditions includes, but are not limited to the following:
Uncontrolled hypertension1 Uncontrolled hematologic, hepatic, neurologic, or renal disease
Uncontrolled gastroesophageal reflux disease Immunologic compromise
Cardiac arrhythmias Tuberculosis (current or untreated)2
Congestive heart failure Cushing*s disease
Coronary artery disease Addison*s disease
Current malignancy Uncontrolled eosinophilic esophagitis
Uncontrolled diabetes mellitus Uncontrolled thyroid disorder
1. Two or more measurements with systolic or diastolic BP above the 95% percentile reference value for the subjects height and weight
2. Subjects with a history of tuberculosis infection who have completed an appropriate course of anti-tuberculosis treatment may be suitable for study entry provided that there is no clinical suspicion of active or recurrent disease;Significant is defined as any disease/condition that, in the opinion of the investigator, would put the safety of the subject at risk through study participation, or which would confound the interpretation of the study results if the disease/condition exacerbated during the study.
10. Neurological or psychiatric disease or history of drug or alcohol abuse (of a subject or his/her guardian) which in the opinion of the investigator could interfere with the subject*s proper completion of the protocol requirements excludes study participation.
11. Investigational medications: A subject must not have participated in an interventional study or used any investigational drug for any disease state within 30 days prior to Visit 1.
12.Drug allergy: Any adverse reaction including immediate or delayed hypersensitivity to any beta2-agonist, sympathomimetic drug, or any intranasal, inhaled, or systemic corticosteroid therapy, or vehicle contained within these medications.
13. Severe hypersensitivity to cow*s milk proteins. Any immediate hypersensitivity reaction such as urticaria, angioedema, rash, or bronchospasm to milk proteins.
14. Concomitant medications: Administration of prescription or over the counter medications that would significantly affect the course of asthma, or interact with sympathomimetic amines such as: anti-IgE (omalizumab), anticonvulsants (barbiturates, hydantoins, carbamazepine); polycyclic antidepressants, beta-adrenergic blockers; phenothiazines, monoamine oxidase (MAO) inhibitors, or diuretics.
15. Potent cytochrome P450 3A4 (CYP3A4) inhibitors: A subject is not eligible if he/she is

receiving potent CYP34A inhibitor within 4 weeks of Visit 1 (e.g., ritonavir, ketoconazole, itraconzole).
16. Affiliation with investigator*s site: A subject will not be eligible for this study if he/she is an immediate family member of the participating investigator, sub-investigator, study coordinator, or employee of the participating investigator.
17. Children in Care: A Child in Care (CiC) is a child who has been placed under the control or protection of an agency, organisation, institution or entity by the courts, the government or a government body, acting in accordance with powers conferred on them by law or regulation. The definition of a CiC can include a child cared for by foster parents or living in a care home or institution, provided that the arrangement falls within the definition above. The determination of whether a child meets the definition of CiC should be made with the study centre staff in consultation with the responsible Institutional Review Board (IRB)/Independent Ethics Committee (IEC).

Study design

Design

Study phase:	4
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-06-2012
Enrollment:	20
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Diskus
Generic name:	Fluticasone Propionate (100/250 mcg)

Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Seretide
Generic name:	Salmetarol / Fluticasone Propionate (50/100 and 50/250mcg)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	14-03-2012
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	12-07-2012
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2011□001643□79-NL
ClinicalTrials.gov	NCT01462344
CCMO	NL40007.075.12