SAS115359, a Safety and Efficacy Study of Inhaled Fluticasone Propionate/Salmeterol Combination versus Inhaled Fluticasone Propionate in the Treatment of Adolescent and Adult Subjects with 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-OMON37915

Source
ToetsingOnline

Brief title
AUSTRI

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, fluticasone propionate, salmetarol, treatment

Outcome measures

Primary outcome

The primary safety endpoint is the number of subjects experiencing an event in the composite endpoint of serious asthma outcomes (i.e., asthma-related hospitalization, asthma-related endotracheal intubation, or asthma-related death) over the 26-week study period.

Secondary outcome

Secondary safety endpoints include the individual component endpoints of asthma-related hospitalization, endotracheal intubation, and death, and withdrawals from the study treatment due to asthma exacerbation.

Study description

Background summary

A systematic review of GSK randomized controlled trials was conducted in 2008 [GlaxoSmithKline Briefing Information, 2008] to summarize the efficacy and risks of asthma control provided by salmeterol administered with ICS in adults and children. The results from this review demonstrated that treatment with salmeterol plus ICS resulted in greater benefit in lung function compared with ICS or ICS plus other treatment (e.g. montelukast). Similar results were seen for symptom-free days, rescue-free days, and quality of life in adults and children. Concurrent use of salmeterol and ICS was also shown to significantly reduce exacerbations requiring treatment with systemic corticosteroids and did

not show an association with the risk for asthma-related death in adults, adolescents or children in clinical trials and observational studies [GlaxoSmithKline Briefing Information, 2008].

However, the FDA conducted a meta-analysis using data provided by AstraZeneca, GlaxoSmithKline and Novartis which suggested a potential risk of serious asthma outcomes (a composite endpoint defined as asthma-related hospitalizations, intubations, and death). There remains a public health debate whether the use of a LABA with an ICS increases the risk of serious asthma outcomes [FDA, 2010; Chowdhury, 2010;
Lemanske, 2010].

In order to further assess the safety of salmeterol in combination with FP, this global, randomized, stratified, double-blind study will compare inhaled fluticasone propionate/salmeterol combination (FSC) with inhaled FP by a composite endpoint of serious asthma outcomes (i.e., asthma-related hospitalization, asthma-related endotracheal intubation, and asthma-related death). Similar brand specific studies will be performed by the other manufacturers (Sponsors) of LABAs that have an indication for asthma.

Study objective

The primary objective of the study is to evaluate whether the addition of LABA to ICS therapy (FSC) is non-inferior to ICS therapy alone (FP) in terms of the risk of serious asthma related events (asthma-related hospitalization, endotracheal intubation, and death). To declare non-inferiority the relative risk of serious events associated with LABA plus ICS compared with ICS alone must be less than 2.0 (a 2-fold increase), based on the upper bound of the 95% confidence interval on the estimate of relative risk. Similar brand specific studies will be performed by the other manufacturers (Sponsors) of LABAs that have an indication for asthma. Thus, a further objective is to study asthmarelated mortality jointly across the brand specific studies in order to evaluate rare events such as asthma-related deaths and intubations.
Each sponsor specific study is statistically powered on the same primary objective.

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. 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% confidence interval on the estimate of relative risk. A secondary measure of efficacy is albuterol/salbutamol use.
Additional variables include rescue-free days, productivity (i.e., days of missed work/school), nighttime awakenings, ACQ-6 score, and unscheduled healthcare utilization for asthma (i.e., telephone contacts, emergency room

visits, unplanned office visits, urgent care visits, and hospitalizations, etc.).

Study design

This study will be a global, multicenter, randomized, stratified, double-blind, parallel group, active comparator, 26-week study in 11,664 adolescent (12 * 17 years of age) and adult (18 years of age and older) subjects whose asthma warrants treatment with a controller asthma therapy (see study design schematic in Appendix 2). This study will be conducted at approximately 1100 centers in approximately 50
countries. Each site will recruit an estimated 10-12 subjects. Subjects who provide informed consent, and assent if appropriate, and meet all of the inclusion criteria and none of the exclusion criteria will be randomized to the treatment phase of the study. Subjects will participate in the study for a maximum of 29 weeks, comprised of a randomization visit (Visit 2) followed by a treatment period of 26 weeks and a follow-up phone call to assess for serious adverse events that occur within the 7 days after cessation of double-blind study treatment. Subjects may be screened for eligibility up to 15 days prior to Visit 2. A subject who fails screening may be rescreened after at least 4-weeks since screen failure have passed but is only permitted to be re-screened once per calendar year (approximately every 52-weeks).

Intervention

Subjects administer inhalation twice daily of one of the doses (FP 100mcg, FP 250 mgc, FSC 100/50mcg, FSC 250/50 mcg of FSC 500/50 mgc)

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
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Informed Consent:;* The subject and/or the subject*s legal guardian (if applicable) must provide;written informed assent/consent to take part in the study.;* Subjects and/or their legal guardians (if applicable) understand that they must;comply with study treatment and study assessments including recording of daily;information regarding their asthma status and attend scheduled study visits, and;be accessible by telephone.;2. Subject: 12 years of age and older.;3. Gender: Male or female.;4. Asthma Diagnosis: Persistent asthma, defined by national and international asthma;guidelines [GINA, 2009; NIH, 2007; etc.] for at least 1 year prior to study enrolment.;If the subject is naïve to the study site, the diagnosis of asthma must be confirmed by subject history.;5. PEF: A clinic PEF*50% of predicted normal value. Percent predicted PEF values;must be calculated using NHANES III with relevant equations that adjust for race;and national origin. [Hankinson, 1999; Hankinson, 2010].;6. Current Asthma Therapy: Subjects must be appropriately using one of the;following for the treatment of asthma and meet the criteria outlined below:;* ICS or ICS with one or more adjunctive therapies (LABA, LTRA or;theophylline) for at least 4 weeks prior to randomization (see Table 1: for ICS;dose equivalents). Any subject maintained on a stable high dose ICS or stable;high dose ICS with one or more adjunctive therapies (LABA, LTRA or;theophylline) must have an ACQ-6 < 1.5 (i.e., controlled) at Visit 1.;* Leukotriene receptor antagonist (i.e. LTRAs such as montelukast, zafirlukast, or;pranlukast) OR theophylline as monotherapy at a stable dose for at least 4 weeks;prior to randomization. Subjects on LTRAs or theophylline are eligible only if;they record an ACQ-6 score of * 1.5 (i.e. not well controlled) and in the;Investigator*s clinical judgement, the subject*s asthma severity could justify;treatment with ICS or ICS + LABA.;* Daily rescue medication (e.g., albuterol/salbutamol or other inhaled short-

acting;beta-agonist used to treat acute asthma) in the 4 weeks prior to randomization;Subjects on daily rescue medication are eligible only if they record an ACQ-6;score of * 1.5 and in the investigator*s clinical judgement, the subject*s asthma;severity could justify treatment with ICS or ICS + LABA.;7. Exacerbation History: Subject must have a history of one of the following:;* at least one asthma exacerbation requiring treatment with a systemic;corticosteroid (tablets, suspension, or injection) between 30 days and 12 months;prior to randomization OR;* an asthma-related hospitalization (defined as an inpatient stay or a 24-hour stay;in an observation area in an emergency room or other equivalent facility);between 30 days and 12 months prior to randomization;8. Questionnaire: Ability to answer questions regarding asthma status and quality of;life and ability to use a daily electronic data capture system.;9. Inhaler Usage: Ability to demonstrate proper use of a metered-dose inhaler and dry powder inhaler (DPI) device.

Exclusion criteria

1. History of Life-Threatening Asthma: Defined for this protocol as an asthma episode that required intubation and/or was associated with hypercapnea requiring non-invasive ventilatory support.;2. Concurrent Respiratory Disease: Subjects with current evidence of pneumonia, pneumothorax, atelectasis, pulmonary fibrotic disease, allergic bronchopulmonary aspergillosis, cystic fibrosis, bronchopulmonary dysplasia, or other respiratory abnormalities other than asthma.;3. Chronic Obstructive Pulmonary Disease: chronic bronchitis, emphysema, or chronic obstructive pulmonary disease.;4. Tobacco Use.;5. Exercise-induced Asthma: Subjects with exercise induced asthma (as the only asthma-related diagnosis) not requiring daily asthma control medicine.;6. Respiratory Infection: Culture-documented or suspected bacterial or viral infection of the upper or lower respiratory tract, sinus or middle ear that is not resolved at randomization.;7. Unstable Asthma Status: Subjects must not meet the following unstable asthma severity criteria within 7-days prior to randomization:;* Asthma symptoms that persisted throughout the day on 2 consecutive days;* Nighttime awakening due to asthma *3 times;* Albuterol/salbutamol (or equivalent) use for the acute worsening of asthma;symptoms >8 puffs a day over 2 consecutive days or *25 puffs in one day;* Asthma symptoms so severe that the subject was limited in their ability to perform normal daily activity on any 1 day;8. Asthma Exacerbation: An asthma exacerbation requiring systemic (tablets, suspension or injection) corticosteroids within 4 weeks of randomization or more than 4 separate exacerbations in the 12 months preceding randomization. For exacerbations to be considered separate events there must be at least 7 days from the resolution of one exacerbation to the start of the second exacerbation.;9. Asthma Hospitalizations: More than 2 hospitalizations for greater than 24 hours duration for treatment of asthma in the 12 months preceding randomization. Each hospitalization must be separated by >7 days to be considered;an individual event.;10. Pregnancy and Lactation: 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.;11. Concurrent Diseases/Abnormalities: A subject with any known, pre-existing,;clinically significant condition, disorder or disease of any body or organ system that is uncontrolled with standard treatment and that, in the opinion of the investigator, would put

the safety of the subject at risk through study participation or would confound the interpretation of the results if the condition, disorder or disease exacerbated during the study.;12. Investigational Medications: A subject who has participated in an interventional study, or used any investigational drug for any disease state, within 30 days prior to randomization.;13. Participation in a Concurrent LABA Safety Study: A subject who has taken at least one dose of study medication in one of the other sponsored studies, being conducted concurrently, to investigate the safety of the addition of LABA to ICS.;14. 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 any component of these combination medications including severe milk protein hypersensitivity.;15. Monoclonal Antibody Use: Anti-IgE, or any other monoclonal antibody, for any reason in the 6-months prior to randomization.;16. Concomitant Medications: Use of *-blockers within 1 day prior to first dose of study medication. Use of ICS, LABA, ICS+LABA, LTRAs, leukotriene modifiers, anticholinergics, or theophylline must be discontinued prior to the first dose of study;medication. Use of prescription or non-prescription drugs, including vitamins, herbal and dietary supplements (including St John*s Wort) within 7 days (or 14 days if the drug is a potential enzyme inducer) or 5 half-lives (whichever is longer) prior to the first dose of study medication, unless in the opinion of the Investigator and study Medical Monitor the medication will not interfere with the study procedures or compromise subject safety.;17. Potent Cytochrome P450 3A4 (CYP3A4) inhibitors: A subject who has received potent CYP34A inhibitor within 4 weeks of randomization.;18. Risk of Non-Compliance: Subjects who are unable to follow study instructions such;as dosing directions or use of the DISKUS/ACCUHALER or metered dose inhaler.;A subject who has any neurological or psychiatric disease or history of drug or alcohol use which in the opinion of the Investigator could interfere with the subject*s proper completion of the protocol requirements.;19. Child in Care.;20. Affiliation with Investigator*s Site.

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
Enrollment:	50
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	Diskus
Generic name:	Fluticasone Propionate (100/250/500 mcg)
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Seretide
Generic name:	Salmetarol / Fluticasone Propionate (50mcg)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	27-02-2012
Application type:	First submission
Review commission:	METC Isala Klinieken (Zwolle)
Approved WMO Date:	27-08-2012
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	EUCTR2011-001644-29-NL
ClinicalTrials.gov	NCT01475721
CCMO	NL39428.075.12