A Randomized, Double-Blind, Double Dummy, Parallel Group, Multicenter 24 to 52 Week Variable Length Study to Assess the Efficacy and Safety of Budesonide, Glycopyrronium, and Formoterol Fumarate Metered Dose Inhaler (MDI) Relative to Budesonide and Formoterol Fumarate MDI and Symbicort® Pressurized MDI in Adult and Adolescent Participants with Inadequately Controlled Asthma (KALOS)

Published: 03-12-2020
Last updated: 08-04-2024

To evaluate the effect of triple-therapy wih Budesonide, Glycopyrronium and Formoterol Fumarate (PT010) versus dual therapy with Budesonide and Formoterol Fumarate on asthma exacerbations in adult and adolescent subjects with inadequately controlled...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON51184

Source
ToetsingOnline

Brief title
KALOS

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Asthma, Respiratory Disease

Research involving
Human

Sponsors and support

Primary sponsor: Astra Zeneca
Source(s) of monetary or material Support: opdrachtgever/sponsor AstraZeneca

Intervention

Keyword: BGF MDI, Inadequately Controlled Asthma, Triple-combination

Outcome measures

Primary outcome

Primary objective is to assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma, using the primary endpoint of change from baseline in morning pre-dose trough FEV1 over 24 Weeks

Secondary outcome

Secondary objectives are (1.) to assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function in participants with inadequately controlled asthma and (2.) to assess the effect of BGF MDI relative to BFF MDI or Symbicort pMDI on lung function, PROs, and symptoms in participants with inadequately controlled asthma.

Secondary endpoints are (1.) Change from baseline in FEV1 AUC0-3 over 24 Weeks, (2.) Percentage of responders in ACQ-7 (*0.5 decrease equals response) at Week

24, over 24 Weeks or over 12 to 24 Weeks, (3.) Percentage of responders in ACQ-5 (*0.5 decrease equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks, (4.) Percentage of responders in the Asthma Quality of Life Questionnaire for 12 years and older (AQLQ +12) (*0.5 increase equals response) at Week 24, over 24 Weeks or over 12 to 24 Weeks, (5.) Percentage of responders in the St. George*s Respiratory Questionnaire (SGRQ) (*4.0 unit decrease equals response) at Week 24, (6.) Onset of action on Day 1: Absolute change in FEV1 at 5 minutes on Day 1 and (7.) Rate of severe asthma exacerbations over the Treatment Period

Study description

Background summary

Asthma is a heterogeneous disease that is characterized by chronic airway inflammation and bronchial hyperreactivity. Worsening asthma symptoms/airway obstruction can be severe, resulting in an asthma exacerbation that may be life-threatening. Such events pose a significant burden to patients and result in significant direct and indirect economic costs. Asthma affects approximately 339 million people in all regions of the world. Globally, there are roughly 1000 asthma-related deaths per day, and this condition is among the leading causes of disability. There are adult and adolescent patients with asthma who remain inadequately controlled despite treatment with a medium or high dose of ICS/LABA, and the Global Initiative for Asthma (GINA) guidelines recommend a step-up in therapy. The addition of LAMA to ICS/LABA is an appropriate treatment option in this population. This addition could provide an important step up in care before escalation to systemic or invasive therapies such as bronchial thermoplasty, thus having a significant role in the management of asthma when used in combination with other controller medications. The aim of this study is to demonstrate benefit of the fixed-dose triple combination of ICS/LAMA/LABA in reducing severe asthma exacerbations and improving lung function and health-related quality of life measures.

Study objective

To evaluate the effect of triple-therapy wih Budesonide, Glycopyrronium and

Formoterol Fumarate (PT010) versus dual therapy with Budesonide and Formoterol Fumarate on asthma exacerbations in adult and adolescent subjects with inadequately controlled asthma.

Study design

This is a Phase III randomized, double-blind, double dummy, parallel group, multicenter variable length efficacy and safety study comparing two doses of Budesonide, Glycopyrronium, and Formoterol Fumarate (BGF) Metered-Dose Inhaler (MDI) (320/28.8/9.6 *g and 320/14.4/9.6 *g) to Budesonide and Formoterol Fumarate (BFF) MDI 320/9.6 *g (an ICS/LABA currently under development) and Symbicort pMDI 320/9 *g in adult and adolescent participants who have asthma which remains inadequately controlled (ACQ-7 total score *1.5) despite treatment with a medium or high dose of ICS/LABA. Adult participants (but not adolescents) must also have a documented history of at least one asthma exacerbation in the 12 months prior to Visit 1. All doses represent the sum of two actuations. All study interventions will be administered twice daily (BID) for a minimum of 24 weeks and a maximum of 52 weeks. The study will end when the last randomized participant completes 24 weeks on randomized study intervention and a 2-week safety follow up, phone call. This study will be conducted at approximately 560 sites worldwide and will randomize approximately 2800 adult and adolescent participants. The number of participants per treatment arm may be increased based on a blinded sample size re-estimation (BSSR).

Intervention

Subjects will be randomized in a 1:1:1:1 ratio to either BGF MDI (320/57.6/9.6*g / day), BGF MDI (640/28.8/19.2*g / day), BFF MDI (640/19.2*g / day) or Symbicort pMDI (320/18*g / day).

Study burden and risks

The subject is asked to visit the site maximal 15 times. The visit time will last maximal 4 hours (although subjects that take part in the sub-studies will have visit times up to 13 hours). The subject will be contacted by telephone at least 1 time at the end of the study (2 weeks after the last dose). Blood and urine samples will be collected for safety laboratory assessment or exploratory biomarker sampling up to 4 times in this study. The total volume of blood that will be collected is approximately 50 ml. The subject will undergo physical examinations during 4 visits. The subject will undergo a spirometry test during every visit and 4 times a serial spirometry up to 4 hours. The subject will undergo a FeNO test twice during the study. Reversibility to albuterol will be evaluated once during the study, with a potential repeated measurement in the subsequent visit if reversibility criteria are not met the first time. An ECG will be performed at 5 visits during the study. Woman of child bearing

potential have to provide a urine sample to test for pregnancy at all site visits (15 times). The subject will be asked to fill out questionnaires at all hospital visits with a maximum of 15 times. The subject must fill out questionnaires every day (in the morning and evening) in an e-Diary.
The subject (only in the 12-hour spirometry sub-study) will undergo serial spirometry 12 hours post-dose at 2 visits during the study. The subject (only in the 12-hour pharmacokinetics sub-study) will undergo plasma sample collection 11 times during 1 of the site visits (total of 110 mL blood). The subject (only in the Holter sub-study) will undergo Holter monitoring for 24 hours initiated on 3 site visits during the study and the subject will be instructed to return to the clinic the following day for removal of the Holter Monitor.
The subject (only in the optional genetic analysis) will undergo blood sample collection (6 mL) once.

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.) Female or male subjects between 12-80 years inclusive, at the time of signing the ICF. (2.) Participants who have a documented history of physician-diagnosed asthma *1 year prior to Visit 1, according to GINA guidelines [GINA 2020]. Healthcare records for 1 year prior to Visit 1 must be provided for adolescent participants (12 to <18 years of age) to ensure consistent evaluation and follow-up of treatment in those participants. (3.) Participants who have been regularly using a stable daily ICS/LABA regimen (including a stable ICS dose), for at least 4 weeks prior to Visit 1. (4.) Have a documented history of at least one asthma exacerbation requiring use of systemic corticosteroids (oral or IV) for at least 3 days AND an associated physician visit, hospitalization, or ER visit due to asthma (within 3 days of the corticosteroid use) in the 12 months prior to Visit 1. (5.) ACQ-7 total score *1.5 at Visits 1, 3, and 5 (pre-randomization). (6.) A pre-bronchodilator FEV1 <80% predicted normal value at Visits 1, 2, 3, 4, and 5 (pre-randomization) for participants *18 years of age OR a pre-bronchodilator FEV1 <90% predicted normal value at Visits 1, 2, 3, 4, and 5 (pre-randomization) for participants 12 to <18 years of age. (7.) Documented reversibility to albuterol, which is defined as a post-albuterol increase in FEV1 of *12% and *200 mL for participants *18 years of age OR a post-albuterol increase of FEV1 of *12% for participants 12 to <18 years of age at Visit 2, or at Visit 3 if repeat testing necessary. (8.) Willing and, in the opinion of the Investigator, able to adjust current asthma therapy, as required by the protocol. (9.) Received no asthma medication other than run-in BFF MDI BID and albuterol as needed during screening, except for allowed medications defined in Table 8 and systemic corticosteroid or ICS for the treatment of an asthma exacerbation (see Section 5.5.2 regarding Screening extension). (10.) No respiratory infection within 4 weeks of randomization, or asthma exacerbation treated with systemic corticosteroid and/or additional ICS treatment within 4 weeks of randomization.

Exclusion criteria

(1.) Life-threatening asthma defined as a history of significant asthma episode(s) requiring intubation associated with hypercapnia, respiratory arrest, hypoxic seizures, or asthma-related syncopal episode(s). (2.) Completed treatment for respiratory infection or asthma exacerbation with systemic corticosteroids within 4 weeks of Visit 1. (3.) Hospitalization for asthma within 2 months of Visit 1. (4.) Historical or current evidence of a clinically significant disease including, but not limited to: cardiovascular, hepatic,

renal, hematological, neurological, endocrine, gastrointestinal, or pulmonary. (5.) Narrow angle glaucoma not adequately treated and/or change in vision that may be relevant, in the opinion of the Investigator, within 3 months of Visit 1. (6.) Symptomatic prostatic hypertrophy or bladder neck obstruction/urinary retention that, in the opinion of the Investigator, is clinically significant. (7.) Unresectable cancer that has not been in complete remission for at least 5 years prior to Visit 1. (8.) Oral and IV corticosteroid use (any dose) within 4 weeks of Visit 1. (9.) Depot corticosteroid use for any reason within 12 months of Visit 1. (10.) Use of LAMA as maintenance treatment, either alone or as part of an inhaled combination therapy, within 12 months prior to Visit 1. (11.) Use of oral beta2-agonist within 3 months of Visit 1. (12.) Any marketed (e.g., omalizumab, mepolizumab, benralizumab, reslizumab) or investigational biologic within 3 months or 5 half-lives of Visit 1 (13.) Regular use of a nebulizer or a home nebulizer for receiving asthma medications. (14.) Use of any immunomodulators or immunosuppressive medication within 3 months or 5 half-lives. (15.) Participants with a known hypersensitivity to beta2-agonists, corticosteroids, anticholinergics, or any component of the MDI or pMDI. (16.) Current smokers, former smokers with >10 pack-years history, or former smokers who stopped smoking <6 months prior to Visit 1. (17.) Planned hospitalization during the study. (18.) Previous or current randomization in any budesonide and formoterol fumarate studies (PT009), budesonide, glycopyrronium, and formoterol fumarate studies (PT010), or glycopyrronium studies (PT001). (19.) For women only * currently pregnant (confirmed with positive pregnancy test), breastfeeding, or planned pregnancy during the study or not using acceptable contraception measures, as judged by the Investigator.

Study design

Design

Study phase:	3
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:	28
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Generic name:	BFF MDI (budesonide and formoterol fumarate) Metered dose inhaler
Product type:	Medicine
Generic name:	BGF MDI (budesonide, glycopyrronium and formoterol fumarate) Metered dose inhaler
Product type:	Medicine
Brand name:	Symbicort
Generic name:	budesonide and formoterol fumarate pressurized Metered dose inhaler
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	03-12-2020
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-02-2021
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	29-04-2021
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	01-05-2021

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2020-001520-34-NL
ClinicalTrials.gov	NCT04609878
CCMO	NL75439.100.20