A Phase IV, 12-week, randomised, double-blind, triple dummy study to compare single inhaler triple therapy, fluticasone furoate/umeclidinium/vilanterol (FF/UMEC/VI) with multiple inhaler therapy (budesonide/formoterol plus tiotropium) based on lung function and symptoms in participants with chronic obstructive pulmonary disease

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Primary:To evaluate the effects of singleinhaler triple therapy (FF/UMEC/VI)compared to multiple inhaler triplecombination therapy withbudesonide/formoterol plus tiotropiumafter 12 weeks of treatment on lungfunctionOther:To evaluate the effects of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Bronchial disorders (excl neoplasms)
Study type	Interventional

Summary

ID

NL-OMON46566

Source
ToetsingOnline

Brief title
TRELEGY

Condition

- Bronchial disorders (excl neoplasms)

Synonym
Chronic Obstructive Pulmonary Disease, COPD

Research involving
Human

Sponsors and support

Primary sponsor: GlaxoSmithKline
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: COPD, Inhaler, Phase IV, Triple therapy

Outcome measures

Primary outcome

Primary

Weighted mean change from baseline in

FEV1over 0-24 hours at Week 12

Secondary

*Change from baseline in trough FEV1

on Day 2, Day 28, Day 84 and Day 85

*Weighted mean change from baseline

in FEV1over 0-24 hours on Day 1

Secondary outcome

Proportion of responders based on the St George*s Respiratory Questionnaire

(SGRQ) Total Score at Week 4 and Week 12

Change from baseline in SGRQ Total Score at Week 4 and Week 12

Proportion of responders based on the COPD Assessment Test (CAT) Total Score at

Week 4 and Week 12

Change from baseline in CAT Total Score at Week 4 and Week 12

Moderate or severe exacerbation event

Peak Inspiratory Flow Rate (PIFR) at Screening (Week -4)

Safety:

*Incidence of adverse events

*Vital signs

Please refer to For a clear overview of the objectives and their corresponding

endpoints

Study description

Background summary

Chronic obstructive pulmonary disease (COPD) guidelines advocate the use of long-acting muscarinic receptor antagonists (LAMA) added to the combination

of
inhaled corticosteroids plus a long-acting *2-adrenergic receptor agonist (LABA) as
second line therapy for the most advanced patients with significant symptoms and a high
risk of exacerbations. Regular treatment with ICS containing regimens has been reported
to improve respiratory symptoms, lung function, health related quality of life (HRQoL)
and reduce the frequency of COPD exacerbation in patients with a forced expiratory flow
in 1 second (FEV1) <60% predicted.
Population based studies of COPD treatment patterns demonstrate that *open* triple
therapy (use of ICS/LAMA/LABA delivered via multiple inhalers) is already widely used
in the real-life management of COPD. In 2011, 26% of patients in the United States (US)
who were taking controller medicines for the treatment of COPD were taking an *open*
triple therapy, typically by adding fluticasone propionate/salmeterol (ICS/LABA) to
tiotropium (LAMA) or vice versa. A study in the United Kingdom (UK) Clinical Practice
Research Database (CPRD) revealed that over a two-year period of time, 35% of COPD
patients initially prescribed a LAMA and 39% initially prescribed an ICS/LABA stepped
up to an *open* triple therapy regimen. In the four-year long term safety study conducted
with tiotropium, 46% of patients were receiving a concurrent fixed combination of
ICS/LABA in addition to tiotropium.
A number of studies have assessed the use of an *open* triple therapy of fluticasone
propionate/salmeterol or budesonide/formoterol (ICS/LABA) with LAMA in moderatesevere
COPD patients. These studies have reported greater improvements in lung
function, HRQoL, hospitalization rates and rescue medication use, compared to dual
(ICS/LABA) or LAMA alone, thus supporting the use of triple therapy in COPD. These
studies have also shown that the number and type of reported adverse events (AE) were
generally similar with administration of dual or monotherapy doses for periods of up to
one year, and were mostly related to their pharmacological mode of action.

GlaxoSmithKline (GSK) is currently developing a once-daily *closed* triple therapy of a ICS/LAMA/LABA combination [fluticasone furoate (FF)/umeclidinium (UMEC)/vilanterol (VI) (100/62.5/25 mcg)] in a single inhaler, with the aim of providing a new treatment option for the management of symptomatic COPD patients at risk of exacerbations which will reduce the exacerbation frequency, allow for a reduced burden of polypharmacy, convenience, and increase the potential for improvement in lung function, HRQoL and symptom control over established dual/monotherapies.
GSK conducted a Phase III study comparing once-daily FF/UMEC/VI to twice-daily Symbicort MDI (budesonide/formoterol) 400/12 mcg in COPD participants that were symptomatic and at risk of an exacerbation despite receiving maintenance therapy (CTT116853). FF/UMEC/VI demonstrated statistically significant improvements in trough FEV1, a statistically significant reduction in the annual rate of moderate or severe COPD exacerbations, and a statistically significant reduction of COPD symptoms (using Exacerbations and Chronic Pulmonary Disease * Respiratory Symptoms [E-RS]) when compared to budesonide/formoterol. Additionally, clinically meaningful improvements from baseline in St. George*s Respiratory Questionnaire (SGRQ) total score were observed, with a statistically significant improvement compared to budesonide/formoterol. This Phase III study provided compelling efficacy data compared with an established ICS/LABA and demonstrated the clinical value of single inhaler triple-therapy compared to ICS/LABA therapy in patients with COPD.
The primary purpose of this study is to evaluate lung function and HRQoL after 84 days of treatment with a single inhaler triple therapy combination of FF/UMEC/VI (100/62.5/25 mcg) once daily via the ELLIPTA* compared with a multiple inhaler combination therapy of Symbicort Metered Dose Inhaler (MDI) (budesonide/formoterol 320/9 mcg) twice daily plus Spiriva HandiHaler (tiotropium 18 mcg) once daily. The study will inform healthcare providers that patients can be effectively and safely switched to FF/UMEC/VI single inhaler therapy from a multiple inhaler triple therapy regimen of Symbicort MDI and Spiriva Handihaler.

Study objective

Primary:
To evaluate the effects of single

inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on lung function

Other:
To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status

To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on Health Status

To evaluate the effects of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium after 12 weeks of treatment on COPD exacerbations

Assess how inspiratory airflow limitation affects ability to use the ELLIPTA

Safety:
To evaluate the safety profile of single inhaler triple therapy (FF/UMEC/VI) compared to multiple inhaler triple combination therapy with budesonide/formoterol plus tiotropium over 12 weeks of treatment

Study design

This is a Phase IV, 12-week, randomised, double-blind, triple-dummy, parallel group,
multicentre study evaluating single inhaler triple therapy (FF/UMEC/VI) once daily via
the ELLIPTA, compared to multiple inhaler triple combination therapy budesonide/formoterol MDI (320/9 mcg) twice daily plus once daily tiotropium (18 mcg), in participants with COPD.

Eligible participants at Screening (V1) will be current or former smokers, with an
established clinical history of COPD, receiving daily maintenance COPD therapy for at
least 3 months, with a post-bronchodilator FEV1 of <50% predicted (or <80% predicted
with a documented history of at least 2 moderate or 1 severe [hospitalised] exacerbation
in the last 12 months) and a CAT score of *10 at Visit 1 and at Visit 2. Participants will
be requested to participate in the study for approximately 17 weeks, consisting of a 4-
week run-in period, 12-week treatment period and a 1-week follow-up period.
*Pre-screening: Details about the study and procedures will be explained through the informed consent process. The Pre-screening Visit (Visit 0), including the informed consent process, must be completed prior to any protocol-required changes to a participant*s usual COPD treatment and the initiation of any Visit 1 procedures. Participants will continue treatment with their regular (i.e. pre-study) COPD medication(s) during the pre-screening period, except for medications that are prohibited within a specified time interval prior to Visit 1.
*Screening/run-in: Eligible participants will be allowed to continue their usual COPD medications until the day before Screening, Visit 1. On the morning of the Screening Visit participants will refrain from taking their morning dose of their usual COPD medications. Participants who meet all of the eligibility criteria at Visit 1, will enter the 4-week run-in period during which they will discontinue all existing COPD medications and receive their run-in treatment: budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus placebo via the ELLIPTA. Participants will not use any other COPD medications (except for those allowed per protocol). Participants will be provided with short-acting albuterol/salbutamol to be used on an as-needed basis (rescue medication) throughout the study. At Screening, each participant will be instructed on the proper use of the ELLIPTA, MDI and HandiHaler and will self-administer their first doses of their run-in treatment during the Screening Visit. On the morning of the other study visits (Visit 2 onwards), participants will refrain from taking their morning dose of study treatment until instructed to
do so by clinic personnel.
*Randomisation/treatment: On the day before the Randomisation Visit (Visit

2), participants will take their last dose of run-in treatment and will not use any
other COPD medications (except for those allowed per protocol) until the end of the study. Rescue albuterol/salbutamol can be used throughout the study asneeded but must be withheld for at least 4 hours prior to conducting spirometry.
At Visit 2 (the Randomisation Visit), participants who meet all of the randomisation criteria will discontinue their run-in treatments and will be randomised in 1:1 ratio to receive one the following double-blind study treatments for 84 days:
Either:
FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
+ placebo to match budesonide/formoterol via MDI, two inhalations twice daily
+ placebo to match tiotropium via HandiHaler once daily in the morning
or,
Budesonide/formoterol 320/9 mcg via MDI, twice daily*
+ tiotropium 18mcg via HandiHaler once daily in the morning
+ placebo via the ELLIPTA once daily in the morning
*
Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg, via the MDI in the morning and two inhalations in the evening. The total dose is therefore 320/9 mcg twice daily.
At Visit 2 participants will refrain from taking their morning doses of run-in study medication and will self-administer study treatment at the clinic, when instructed to do so. Participants will remain at the clinic for at least 24 hours, for
serial spirometry assessments.
On the morning of Visits 3 and 4, participants will refrain from taking their morning dose of study treatment until instructed to do so by clinic personnel. At
Visits 3, and 4 participants will self-administer study treatment whilst at the clinic. Participants will take their last doses of study treatment in the clinic on
Day 84 (Visit 4, when instructed to do so by clinic personnel), and continue to remain at the clinic until at least 24 hours after their last morning dose, for their
clinical assessments, which include serial spirometry assessments.On non-clinic visit days participants are expected to take their study treatment at home each day in the morning and in the evening at approximately the same time, as directed by the clinic.
*Safety/follow-up: A safety follow-up telephone contact or clinic visit (Visit 5)
will be conducted approximately 7 days after the participant completes all of the
protocol-defined procedures for Visit 4/End of Study (EOS) or, if applicable, the
Study Treatment Discontinuation Visit.
Participants that permanently discontinue study treatment are not required to

withdraw
from the study. If for any reason a participant must permanently discontinue study
treatment, every effort should be made by the Investigator/staff to keep the participant in
the study and complete all remaining protocol specified clinic visits. However, a
participant may voluntarily withdraw from participation in this study at any time. The
Investigator may also, at his or her discretion, withdraw a participant from further study
participation. Participants who are withdrawn from the study will not be replaced.
A participant will be considered to have completed the study when they have completed
all phases of the study including screening, run-in, the randomised treatment phase, and
safety follow-up.

Intervention

Participants who meet all the eligibility criteria and who have successfully completed all
protocol procedures at Screening will enter the 4-week run-in period and will take
budesonide/formoterol (320/9 mcg) twice daily plus tiotropium (18 mcg) once daily plus
placebo via the ELLIPTA. Following the run-in period, eligible participants will be
randomised (1:1) to one of the following double-blind, triple-dummy treatment groups
for 84 days:
Either:
*FF/UMEC/VI 100/62.5/25 mcg via the ELLIPTA once daily in the morning
+ placebo to match budesonide/formoterol via MDI, two inhalations twice daily
+ placebo to match tiotropium via HandiHaler once daily in the morning
or,
Budesonide/formoterol 160/4.5 mcg via MDI, two inhalations twice daily
+ tiotropium 18mcg via HandiHaler once daily in the morning
+ placebo via the ELLIPTA once daily in the morning
*
Participants are required to take two inhalations of budesonide/formoterol 160/4.5 mcg,
via the MDI in the morning and two inhalations in the evening. The total dose is therefore
320/9 mcg twice daily.

Study burden and risks

Side effects from study procedures
Stopping or changing your usual COPD medications
There may be certain medicines that you are currently taking that you must stop using in order to be in the study. If this applies to you, the study doctor will discuss stopping the medicine with you.
Blood draw
When giving samples of blood this might cause you to feel faint, or experience mild pain, bruising, irritation or redness at the site. In rare cases, you may get an infection.
X-ray
A chest x-ray test exposes you to a small dose of radiation.
ECG
When the ECG is done the sticky pads that are placed on your chest to monitor your heart may irritate your skin and cause itching and redness.
Spirometry (breathing test)
The breathing tests can be quite tiring and repetitive. During the tests you might experience shortness of breath, coughing, light-headedness or fainting, and/or chest tightness. If any of these happen to you, you may receive medical treatment. There are no likely long-term side effects and no serious risks are expected

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Informed consent: capable of giving signed informed consent prior to study start which includes compliance with the requirements and restrictions listed in the informed consent form (ICF) and in this protocol.;2. Type of participant: Outpatient.;3. Age: Participants 40 years of age or older at Screening (Visit 1).;4. Gender: Male or female participants.;Female participants:;A female participant is eligible to participate if she is not pregnant, not breastfeeding, and at least one of the following conditions applies:;Not a woman of childbearing potential (WOCBP);OR;A WOCBP who agrees to follow the contraceptive guidance in Appendix 3 of the protocol during the treatment period and until the safety follow-up contact after the last dose of study treatment.;5. COPD Diagnosis: An established clinical history of COPD in accordance with the definition by the American Thoracic Society/European Respiratory Society [Celli, 2004].;6. Smoking History: Current or former cigarette smokers with a history of cigarette smoking of *10 pack-years at Screening (Visit 1) [number of pack years <= (number of cigarettes per day / 20) x number of years smoked (e.g., 20 cigarettes per day for 10 years, or 10 cigarettes per day for 20 years)]. Previous smokers are defined as those who have stopped smoking for at least 6 months prior to Visit 1. ;Note: Pipe and/or cigar use cannot be used to calculate pack-year history.;7. Severity of COPD symptoms: A score of *10 on the COPD Assessment Test (CAT) at Screening (Visit 1).;8. Severity of Disease: ;Participants must demonstrate at Screening: a post-bronchodilator FEV1<50 % predicted normal;OR a post-bronchodilator FEV1<80 % predicted normal and a documented history of *2 moderate exacerbations or one severe (hospitalized) exacerbation in the previous 12 months.;Participants must also have a measured post albuterol/salbutamol FEV1/forced vital capacity (FVC) ratio of <0.70 at screening.;Note: Percent predicted will be calculated using the European Respiratory Society Global Lung Function Initiative reference equations [Quanjer, 2012].;Note: A documented history of a COPD exacerbation (e.g., medical record verification) is a medical record of worsening COPD symptoms that required systemic/oral corticosteroids and/or antibiotics (for a moderate exacerbation) or;hospitalization (for a severe exacerbation). Prior use of antibiotics alone does not qualify as an exacerbation history unless the use was associated with treatment of worsening symptoms of COPD, such as increased dyspnoea, sputum volume, or sputum purulence (colour). Participant verbal reports are not acceptable.;9. Existing COPD maintenance treatment: participant must have been receiving daily maintenance treatment for their COPD for at least 3 months prior to Screening.;Note: Participants taking only as-needed COPD

medications are not eligible.

Exclusion criteria

1. Pregnancy: Women who are pregnant or lactating or are planning on becoming pregnant during the study.;2. Asthma: Participants with a current diagnosis of asthma. (Participants with a prior history of asthma are eligible if they have a current diagnosis of COPD).;3. *1-antitrypsin deficiency: Participants with *1-antitrypsin deficiency as the underlying cause of COPD.;4. Other respiratory disorders: Participants with active tuberculosis, lung cancer, and clinically significant: bronchiectasis, sarcoidosis, lung fibrosis, pulmonary hypertension, interstitial lung disease or other active pulmonary diseases.;5. Lung resection: Participants who have undergone lung volume reduction surgery within the 12 months prior to Screening.;6. Risk Factors for Pneumonia: immune suppression (e.g. advanced human immunodeficiency virus [HIV] with high viral load and low CD4 count, lupus on immunosuppressants) that in the opinion of the investigator would increase risk of pneumonia or other risk factors for pneumonia (e.g. neurological disorders affecting control of the upper airway, such as Parkinson*s Disease, Myasthenia Gravis).;Participants at potentially high risk for pneumonia (e.g. very low body mass index [BMI], severely malnourished, or very low FEV1) will only be included at the discretion of the Investigator.;7. Pneumonia and/or moderate or severe COPD exacerbation that has not resolved at least 14 days prior to Screening and at least 30 days following the last dose of oral/systemic corticosteroids (if applicable).;8. Respiratory tract infection that has not resolved at least 7 days prior to Screening.;9. Abnormal Chest x-ray: Chest x-ray (posteroanterior and lateral) reveals evidence of pneumonia or a clinically significant abnormality not believed to be due to the presence of COPD, or another condition that would hinder the ability to detect an infiltrate on chest X-ray (e.g. significant cardiomegaly, pleural effusion or scarring).;All participants will have a chest X-ray at Screening Visit 1 (or historical radiograph or computerized tomography [CT] scan obtained within 3 months prior to screening).;Note: Participants who have experienced pneumonia and/or moderate or severe COPD exacerbations within 3 months of screening must provide a post pneumonia/exacerbation chest X-ray or have a chest X-ray conducted at Screening.;For sites in Germany: If a chest x-ray (or CT scan) within 3 months prior to Screening (Visit 1) is not available, approval to conduct a diagnostic chest x-ray will need to be obtained from the Federal Office for Radiation Protection (BfS).;10. Other diseases/abnormalities: Participants with historical or current evidence of clinically significant cardiovascular, neurological, psychiatric, renal, hepatic, immunological, gastrointestinal, urogenital, nervous system, musculoskeletal, skin, sensory, endocrine (including uncontrolled diabetes or thyroid disease) or haematological abnormalities that are uncontrolled. Significant is defined as any disease that, in the opinion of the Investigator, would put the safety of the participant at risk through participation, or which would affect the efficacy or safety analysis if the disease/condition exacerbated during the study.;11. Unstable liver disease: ALT >2x Upper Limit of Normal (ULN); and bilirubin >1.5x ULN (isolated bilirubin >1.5x ULN is acceptable if bilirubin is fractionated and direct bilirubin <35 %);Current active liver or biliary disease (with the exception of Gilbert*s syndrome or asymptomatic gallstones or otherwise stable chronic liver disease per investigator assessment).;NOTES:;Stable chronic liver disease should generally be defined by

the absence of ascites, encephalopathy, coagulopathy, hypoalbuminaemia, oesophageal or gastric varices, or persistent jaundice, or cirrhosis.;Chronic stable hepatitis B and C (e.g., presence of hepatitis B surface antigen (HBsAg) or positive hepatitis C antibody test result at screening or within 3 months prior to first dose of study treatment) are acceptable if participant otherwise meets entry criteria.;12. Unstable or life threatening cardiac disease: Participants with any of the following at Screening (Visit 1) would be excluded:;- Myocardial infarction or unstable angina in the last 6 months;- Unstable or life threatening cardiac arrhythmia requiring intervention in the last 3 months;- New York Heart Association (NYHA) Class IV Heart failure

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:	Recruitment stopped
Start date (anticipated):	03-09-2018
Enrollment:	77
Type:	Actual

Medical products/devices used

Generic name:	Ellipta
Registration:	No
Product type:	Medicine
Brand name:	Spiriva
Generic name:	tiotropium bromide
Registration:	Yes - NL intended use

Product type:	Medicine
Brand name:	Symbicort
Generic name:	budesonide/formoterol fumarate dihydrate
Registration:	Yes - NL intended use
Product type:	Medicine
Brand name:	Trelegy Ellipta
Generic name:	Fluticasone Furoate(FF)/umeclidinium bromide(UMEC)/vilanterol(VI)
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	30-04-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-08-2018
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	07-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	26-11-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	21-12-2018
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO Date:	02-01-2019
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	EUCTR2017-001149-28-NL
ClinicalTrials.gov	NCT03478683
CCMO	NL64743.100.18

Study results

Date completed:	13-02-2019
Actual enrolment:	24

Summary results
Trial is onging in other countries