Effect of roflumilast on exacerbation rate in patients with COPD treated with fixed combinations of LABA and ICS. A 52-week, randomised double-blind trial with roflumilast 500 µg versus placebo.

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* To investigate the effect of roflumilast 500 µg tablets once daily versus placebo on exacerbation rate, and pulmonary function and major adverse cardiovascular events (MACE) in COPD patients who are concomitantly treated with a fixed combination...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Respiratory disorders NEC
Study type	Interventional

Summary

ID

NL-OMON38122

Source
ToetsingOnline

Brief title
REACT_RO-2455-404-RD

Condition

- Respiratory disorders NEC

Synonym
Chronic obstructive pulmonary disease (COPD)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: COPD, Fixed combination LABA and ICS, Roflumilast

Outcome measures

Primary outcome

Primary endpoint:

Rate of moderate or severe COPD exacerbations per patient per year. Moderate exacerbations are defined as requiring oral or parental glucocorticosteroids, severe as requiring hospitalisation and/or leading to death.

Secondary outcome

Key-secondary endpoints:

- Change from randomisation (V2) over 52 weeks of treatment in post-bronchodilator FEV1.

- Rate of severe COPD exacerbations per patient per year.

Other secondary endpoints are described in protocol section 11.

Study description

Background summary

Roflumilast (DAXAS®) was approved in the European Union for the maintenance treatment of sever COPD associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add on to bronchodilator treatment. The use of fixed combinations of LABAs and ICS is recommended by international COPD treatment guidelines. Roflumilast was shown to be effective and safe when combined with either LABA or ICS. However, no trials have been performed so far to demonstrate benefits of roflumilast when added on to fixed combinations of

LABA and ICS, which will be investigated in this trial.

Study objective

* To investigate the effect of roflumilast 500 µg tablets once daily versus placebo on exacerbation rate, and pulmonary function and major adverse cardiovascular events (MACE) in COPD patients who are concomitantly treated with a fixed combination of long-acting β2-agonists (LABA) and inhaled glucocorticosteroids (ICS)
* To obtain data on safety and tolerability of roflumilast in COPD patients concomitantly treated with a fixed combination of LABA and ICS.
* To further characterise the population pharmacokinetic profile of roflumilast and roflumilast N-oxide.
* To further characterise the pharmacokinetics/pharmacoynamics (PK/PD) relationship of roflumilast, roflumilast N-oxide and 'total phosphodiesterase 4 inhibitory' activity (tPDE4i) in terms of efficacy and relevant safety aspects.

Study design

Phase III / IV, randomised, double-blind, placebo controlled study.

Intervention

Roflumilast 500 µg tablets, once daily or placebo tablets, once daily.

Study burden and risks

Roflumilast can have the following side-effects:
Common (less than 10%): Weigh decrease, decreased appetite, sleeplessness, headache, diarrhoea, nausea, stomach ache.

Uncommon (less than 1%) : Hypersensitivity, feeling anxious, trembling, sensation of spinning head (vertigo), dizziness, sensation of rapid or irregular heartbeat (palpitations), gastritis, vomiting, reflux of stomach acid to the gullet (acid regurgitations), indigestion, rash, muscle pain or cramps, back pain, feeling of weakness or tiredness, feeling unwell.

Rare (less than 0.1%): Male breast enlargement, feeling nervous or depressed, decreased sense of taste, respiratory tract infections (excluding pneumonia), bloody stools, constipation, elevation of liver or muscle enzymes in blood tests, wheals (urticaria).

Procedures when completing the entire research:
2 x Chest X-ray or CT-scan, if not performed within the last 3 months
1 x MRC dyspnoe scale

1 x HADS questionnaire
9 x questionnaire COPD assessment
2 x physical exam
2 x lenght
9 x weight
10 x pulmonary function test
2 x ECG

Contacts

Public
Takeda

Langebjerg 1
Roskilde 4000
DK
Scientific
Takeda

Langebjerg 1
Roskilde 4000
DK

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

2. History of COPD (according to GOLD 2009) for at least 12 months prior to baseline Visit V0 associated with chronic productive cough for 3 months in each of the 2 years prior to baseline Visit V0 (with other causes of productive cough excluded).

3. Age >= 40 years
4. Forced expiratory volume after one second (FEV1) / forced vital capacity (FVC) ratio (post-bronchodilator) < 70%
5. FEV1 (post-bronchodilator) <= 50% of predicted
6. At least two documented moderate or severe COPD exacerbations, separated by at least 10 days, within one year prior to baseline visit V0.
7. Patients must be pre-treated with LABA and ICS for at least 12 months before baseline Visit V0. Up to 3 months before baseline Visit V0 free or fixed combinations of LABA and ICS are allowed, including changes in dose, active substances, and brands. In the last 3 months before baseline Visit V0 patients must be pre-treated with fixed combinations of LABA and ICS at a constant dose (maximum approved dosage strength of the combination)
8. Former smoker (defined as smoking cessation at least one year ago) or current smoker both with a smoking history of at least 20 pack years.

Exclusion criteria

1. Moderate or severe COPD exacerbations and/or COPD exacerbations treated with antibiotics ongoing at the baseline visit V0
2. Lower respiratory tract infection not resolved 4 weeks prior to the baseline visit V0
3. Diagnosis of asthma and/or other relevant lung disease
4. Current participation in a pulmonary rehabilitation program or completion of a pulmonary rehabilitation program within 3 months preceding the baseline visit V0. However, physical exercise maintenance following the completion of the initial pulmonary rehabilitation program and which is continuously performed within 3 months preceding baseline Visit V0 and during the complete trial is allowed.
5.Known alpha-1-antitrypsin deficiency.;Exclusion criteria within ethical considerations in terms of general health are listed in the protocol, section 6.2.2.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-11-2011
Enrollment:	50
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Daxas
Generic name:	Roflumilast
Registration:	Yes - NL intended use

Ethics review

Approved WMO Date:	24-03-2011
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	05-07-2011
Application type:	First submission
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	18-01-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	26-01-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	21-06-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

Approved WMO Date:	31-07-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	20-12-2012
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)
Approved WMO Date:	05-03-2013
Application type:	Amendment
Review commission:	METC Noord-Holland (Alkmaar)

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	EUCTR2010-019685-87-NL
ClinicalTrials.gov	NCT01329029
CCMO	NL35334.094.11