Comparative effectiveness of triple therapy in COPD: A new-user cohort study

First published: 19/10/2018

Last updated: 15/10/2026

Study Finalised

Administrative details

EU PAS number

EUPAS26211

Study ID

28740

DARWIN EU® study

No

Study countries

United Kingdom

Study description

The treatment of COPD involves multiple therapies, including long-acting bronchodilators (LAMAs and LABAs) and inhaled corticosteroids (ICS), with dual combinations of these drugs now formulated into single inhalers. Recently,

several single-inhaler triple therapies involving an LABA-LAMA-ICS combination are being developed and being tested for effectiveness in randomized trials. The TRILOGY and TRINITY trials compared a single-inhaler triple therapy with an LABA-ICS and a LAMA respectively and found greater benefit with triple therapy. The TRIBUTE trial and ongoing IMPACT trial also compare triple therapy with a dual long-acting bronchodilator regimen (LABA-LAMA). These trials, however, have methodological issues related to the deleterious effect of withdrawal of maintenance treatment at randomization, the use of run-in periods and the truncated follow-up at treatment discontinuation. Moreover, they represent a limited view of the patients who could potentially use these treatments, so that a real-world study of patients who are representative of clinical practice is of interest.As many of these drugs have been in use in separate inhalers for many years, an observational study of the comparative effectiveness of triple therapy is feasible and would provide useful data on the relative benefits of different combinations in the treatment of COPD. The intended audience is payers and prescribers. The results from the study will be published in the scientific literature.

Study status

Finalised

Research institutions and networks

Institutions

McGill University

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Institution

Center for Clinical Epidemiology

Contact details

Study institution contact

Samy Suissa samy.suissa@mcgill.ca

Study contact

samy.suissa@mcgill.ca

Primary lead investigator

Samy Suissa

Primary lead investigator

Study timelines

Date when funding contract was signed

Planned: 23/01/2017

Actual: 23/01/2017

Study start date

Planned: 10/11/2018

Actual: 10/11/2018

Data analysis start date
Planned: 12/11/2018

Actual: 12/11/2018

Date of final study report
Planned: 31/05/2019

Actual: 24/04/2019

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Boehringer Ingelheim International GmbH

Study protocol

Suissa_double_triple study.pdf (874.08 KB)

Regulatory

Was the study required by a regulatory body?

No

Is the study required by a Risk Management Plan (RMP)?

Not applicable

Other study registration identification numbers and links

1237-0078

NCT03724877

Methodological aspects

Study type

Study type list

Study topic:

Human medicinal product

Study type:

Non-interventional study

Scope of the study:

Effectiveness study (incl. comparative)

Safety study (incl. comparative)

Data collection methods:

Secondary use of data

Study design:

Population-based incident new-user cohort design with high-dimensional time-conditional propensity score matching.

Main study objective:

To assess the effectiveness of maintenance treatment of COPD with the LABA-LAMA-ICS combination with a LABA-LAMA combination on the risk of COPD

exacerbation and the safety on the incidence of community acquired pneumonia.

Study Design

Non-interventional study design

Cohort

Study drug and medical condition

Anatomical Therapeutic Chemical (ATC) code

(R03AC19) olodaterol

olodaterol

(R03AL06) olodaterol and tiotropium bromide

olodaterol and tiotropium bromide

(R03BB04) tiotropium bromide

tiotropium bromide

(R03AL) Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids

Adrenergics in combination with anticholinergics incl. triple combinations with corticosteroids

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Medical condition to be studied

Chronic obstructive pulmonary disease

Population studied

Short description of the study population

The base cohort will consist of all patients in the CPRD with a diagnosis of COPD who received at least one prescription for a LABA, LAMA, or an ICS from 1 January 2002 until 31 December 2016. To increase the likelihood of a diagnosis of COPD and decrease the likelihood of including misdiagnosed asthma patients, we will only
include patients 55 years of age or older on the date of this initial prescription and exclude all patients with a diagnosis of asthma at any time prior to the study cohort entry date.

Age groups

- Adults (46 to < 65 years)
- Adults (65 to < 75 years)
- Adults (75 to < 85 years)
- Adults (85 years and over)

Estimated number of subjects

6.000

Study design details

Setting

The study will be conducted in a general practice setting, within the United Kingdom’s Clinical Practice Research Datalink (CPRD; details in Section 7.5). It will be restricted to the practices which can be linked to the Hospital Episodes Statistics (HES) database. The maximal observation period will be from January 1995 until December 2017.

Outcomes

The primary outcome event is the first COPD exacerbation to occur after cohort entry. The event is defined as a hospitalization for COPD (severe exacerbation) or the prescription of an oral corticosteroid, namely prednisolone (moderate exacerbation). The first secondary outcome is the rate of COPD exacerbations over the one-year follow-up. This outcome will be based on the number of hospitalizations and on the number of courses of treatment with an oral corticosteroid. A gap of at least 30 days between treatment courseswill be required to consider the exacerbations as separate

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Data analysis plan

For the analysis of the primary objective, the Kaplan-Meier approach will be used with the matched cohort to estimate the crude 1-year cumulative incidence of severe and moderate COPD exacerbations for the two combination treatment groups. The primary comparative analysis will also be based on the matched cohort and a time-dependent Cox proportional hazard regression model to perform an as-treated analysis that assesses the effect of current use of LABA-LAMA-ICS combination versus the LABA-LAMA combination on the risk of a first COPD exacerbation. It will provide an estimate of the hazard ratio (HR) of a COPD exacerbation associated with LABA-LAMA-ICS use relative to LABA-LAMA use, along with 95% confidence intervals (CI). Current use will be defined as prescriptions dispensed within the 60-day period of the date defined by the risk set of the Cox model.

Summary results

The source data included 669,626 patients with a prescription for LABA, LAMA or ICS between January 1, 2002 and December 31, 2015, from CPRD practices linked to the HES database. After exclusions related to age, COPD diagnosis, and asthma, the base cohort included 56,460 eligible subjects of initiators of these treatments. After

matching, the study cohort included 6,921 initiators of LAMA-LABA ICS matched to 1,932 initiators of LAMA-LABA.

The adjusted hazard ratio (HR) of a moderate or severe COPD exacerbation associated with LAMA-LABA-ICS initiation compared with LAMA-LABA initiation was 0.97 (95% CI: 0.87-1.09). However, for patients with blood eosinophils >6% (as a percent of the white blood cell count), the HR was 0.66 (95% CI: 0.46-0.94) and for patients with two or more prior exacerbations it was 0.83 (95% CI: 0.70-0.98). The incidence of severe pneumonia requiring hospitalization was increased with LAMA-LABA-ICS initiation (HR 1.46; 95% CI: 1.03-2.07).

Documents

Abstract of study report

1237-0078_Synopsis.pdf (227.46 KB)

Data management

Data sources

Data source(s)

Clinical Practice Research Datalink

Data sources (types)

Electronic healthcare records (EHR)

Use of a Common Data Model (CDM)

CDM mapping

No

Data quality specifications

Check conformance

Unknown

Check completeness

Unknown

Check stability

Unknown

Check logical consistency

Unknown

Data characterisation

Data characterisation conducted

No