

# Comparative effectiveness of triple therapy with Bisoprolol, Perindopril, Amlodipine, versus dual therapy in hypertensive patients: an observational retrospective cohort study

**First published:** 22/11/2024

**Last updated:** 30/01/2025

Study

Planned

## Administrative details

### EU PAS number

EUPAS1000000374

---

### Study ID

1000000374

---

### DARWIN EU® study

No

---

### Study countries

 United Kingdom

---

## **Study description**

This study aims to determine the effectiveness on blood pressure reduction of the triple combination of Perindopril+ Amlodipine+ Bisoprolol (used concomitantly as combination), compared to the respective dual therapy components in real life conditions.

Adult hypertensive patients on two-drug combination therapy (two drugs among Perindopril, Amlodipine and Bisoprolol) and who are not controlled by the dual therapy (with systolic blood pressure (SBP)  $\geq 140$ mmHg) will be included. Patients who will initiate the third drug and be on the Bisoprolol + Perindopril+ Amlodipine triple therapy will be compared to those who will remain on dual therapy.

The primary outcome will be the difference in change in SBP from baseline to week 8 between the two treatment groups, estimated with a Mixed Model of Repeated Measures. Diastolic blood pressure change at 8 weeks, blood pressure control at 8 weeks and rates of adverse events will be compared between the two treatment groups. Treatment patterns including adherence to index therapy and healthcare resource use will be also described for the triple therapy users. The rates of cardiovascular events including myocardial infarction, stroke, heart failure and chronic kidney disease as well as cardiovascular death will be also investigated as an exploratory objective.

These data will be used to generate evidence for the fixed-dose combination (FDC) of perindopril, amlodipine and bisoprolol, currently under development by Servier that may reduce pill burden in hypertensive patients.

---

## **Study status**

Planned

## **Research institutions and networks**

## Institutions

### Institut de Recherches Internationales Servier

**First published:** 01/02/2024

**Last updated:** 01/02/2024

**Institution**

### OXON Epidemiology



Spain



United Kingdom

**First published:** 06/12/2010

**Last updated:** 15/03/2024

**Institution**

**Laboratory/Research/Testing facility**

**Non-Pharmaceutical company**

**ENCePP partner**

## Contact details

### Study institution contact

CELINE DARRICARRERE [Global.RWE.Dept@servier.com](mailto:Global.RWE.Dept@servier.com)

**Study contact**

[Global.RWE.Dept@servier.com](mailto:Global.RWE.Dept@servier.com)

### Primary lead investigator

CELINE DARRICARRERE

Primary lead investigator

## Study timelines

### **Date when funding contract was signed**

Planned: 02/01/2023

---

### **Study start date**

Planned: 25/11/2024

---

### **Data analysis start date**

Planned: 17/02/2025

---

### **Date of final study report**

Planned: 21/08/2025

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Institut de Recherches Internationales Servier

## Regulatory

**Was the study required by a regulatory body?**

No

---

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

Not applicable

## 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)

**Data collection methods:**

Secondary use of data

---

**Study design:**

Retrospective observational cohort study. Patients will be identified in CPRD between January 2005 and September 2019 and followed until March 2020.

**Main study objective:**

The overall objective of the study is to study the effectiveness on blood pressure reduction of Bisoprolol (Biso), Perindopril (Per), Amlodipine (Amlo) and used concomitantly as free combination, compared to respective dual combination(s) of these 3 drugs in real life conditions, in order to confirm the contribution of all the active substances to the desired therapeutic effect on BP.

Primary objective: To compare the systolic blood pressure (SBP) change at 8 weeks between patients who started the combination of Biso/Per/Amlo (triple therapy) to those treated with the free or fixed combination of two drugs out of the three molecules (dual therapy) in hypertensive uncontrolled patients.

Secondary objectives

- To compare the diastolic blood pressure (DBP) change at 8 weeks between the patients who started the triple therapy to patients treated with the dual therapy.
- To compare the blood pressure control rate at 8 weeks between the patients who started the triple therapy to patients treated with the dual therapy.
- To estimate and compare incidence of adverse events (AEs) during follow-up between patients who started the triple therapy to those treated with the dual therapy.
- To describe treatment patterns of the three drugs taken concomitantly during follow-up and the adherence to treatment.
- To describe healthcare resource use in patients who started the triple therapy

Exploratory objective

- To estimate and compare incidence of cardiovascular events including cardiovascular death during follow-up

## Study Design

### **Non-interventional study design**

Cohort

## Study drug and medical condition

### **Medicinal product name, other**

Perindopril, Amlodipine, Bisoprolol

---

### **Study drug International non-proprietary name (INN) or common name**

AMLODIPINE

PERINDOPRIL ARGININE

---

### **Medical condition to be studied**

Hypertension

## Population studied

### **Short description of the study population**

Adult hypertensive patients uncontrolled on two-drug combination therapy identified in CPRD :

- Aged 18 years or over
- With at least one diagnosis record of primary hypertension
- Who have been prescribed concomitantly with two drugs (in free or fixed combination) among Bisoprolol, Perindopril, and Amlodipine at a stable dose for at least 4 weeks
- With uncontrolled blood pressure defined as SBP  $\geq$ 140mmHg using the most recent BP record in the 2 weeks before or at index date
- With no other antihypertensive treatment received in the 4 weeks before index date
- Who have no prescription of the third drug (the component that is not part of

the dual therapy) within 365 days before index date

- Who have been registered for at least one year in CPRD
  - With Hospital Episode Statistics (HES) and ONS linkage available
- 

### **Age groups**

- **Adult and elderly population ( $\geq 18$  years)**

## Study design details

### **Setting**

The source population for this study will be all patients identified in CPRD who meet inclusion and exclusion criteria , during the study inclusion period - January 2005 to September 2019. The latest data available at the time of application will be used to maximize the sample size, taking into account the latest linked data.

---

### **Comparators**

This study will compare the uncontrolled hypertensive patients on triple therapy to those on dual therapy.

- The treatment group will be the triple therapy group i.e., patients on dual therapy who start the third mono-component among the three targeted drugs (Biso, Per and Amlo) during the inclusion period of the study. This group will include patients on either Per+Amlo who add Biso, or Per+Biso who add Amlo, or Amlo+Biso who add Per.
- The control group will be the dual therapy group and will include patients on either Per+Amlo or Per+Biso or Amlo+Biso

Comparison of triple therapy users to dual therapy users will be done by creating exposure sets based on index date and dual-therapy components and

then matching using propensity score (PS) method to minimize the effect of confounding factors.

---

## **Outcomes**

### Primary outcome

The primary outcome will be change in SBP between ID and 8 weeks. We will identify an index value defined as the most recent SBP recorded in the two weeks preceding or at the ID, used for patient eligibility.

Post index measurements will be all SBP records reported (on distinct dates) within the time window of interest, from 4 weeks to 24 weeks after the ID and the change from index to week 8 will be estimated with a Mixed Model of Repeated Measures (MMRM) and compared between treatment groups.

### Secondary effectiveness outcomes

#### Change in DBP between ID and 8 weeks:

The change in DBP between index and post-index DBP values will be calculated and compared between treatment groups. The same period assessment used for SBP will be applied for DBP.

### Secondary safety outcome

The AEs to be studied are relevant safety events retrieved from the summary of product characteristics of each drug of interest (Biso, Per, Amlo); and from post-marketing safety data reported in the safety database among patient cases where bisoprolol, perindopril and amlodipine were co-administered.

---

## **Data analysis plan**

Exposure sets will be created by index date and dual-therapy components and patients will be matched using propensity score to ensure comparability between treatment groups in these exposure sets. Missing outcomes due to

change in treatment during outcome assessment period will be handled using Baseline Mean Carried Forward imputation method.

The primary outcome will be estimated on the matched cohort and with a Mixed Model of Repeated Measures.

## Data management

### ENCePP Seal

The use of the ENCePP Seal has been discontinued since February 2025. The ENCePP Seal fields are retained in the display mode for transparency but are no longer maintained.

## Data sources

### **Data source(s), other**

Clinical Practice Research Datalink (CPRD) AURUM

## 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