Effectiveness of inhaled treprostinil versus standard of care for the treatment of pulmonary hypertension associated with interstitial lung disease: A propensity score-weighted study of the INCREASE trial and registry data from Europe

First published: 05/07/2024

Last updated: 10/09/2024

Study Planned

Administrative details

EU PAS number

EUPAS1000000238

Study ID

1000000238

DARWIN EU® study

No

Study countries

Austria
Belgium
Germany
Greece
Hungary
Italy
Latvia
Lithuania
Netherlands
Slovakia
Switzerland
United Kingdom
United States

Study description

This is an external comparator arm study using data from the INCREASE randomised controlled trial (RCT) and its open-label extension (treatment group) and COMPERA, and UK Royal Brompton registries (external comparator) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus standard of care in adult patients with PH-ILD in Europe.

Study status

Planned

Research institutions and networks

Institutions

Ferrer Internacional

First published: 01/02/2024

Last updated: 01/02/2024

Institution

Global Database Studies, IQVIA

Czechia

Finland

Germany

Slovakia

Spain

First published: 17/01/2011

Last updated: 31/07/2024

Institution | Other | ENCePP partner

Contact details

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Study timelines

Date when funding contract was signed
Planned: 04/12/2023

Actual: 04/12/2023

Study start date
Planned: 07/12/2023

Data analysis start date
Planned: 26/07/2024

Date of final study report
Planned: 23/01/2025

Sources of funding

- Pharmaceutical company and other private sector

More details on funding

Ferrer internacional

Study protocol

Ferrer_TYVASO_HTA_ECA_protocol_v1.0.pdf (11.24 MB)

Ferrer_TYVASO_HTA_ECA_Protocol v2.0_FULLY SIGNED 31Aug2024 HMA.pdf
(2.13 MB)

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

FITREP-NIS-2402

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:

Combined primary data collection and secondary use of data

Study design:

This is an external comparator arm (ECA) study using data from the INCREASE and INCREASE OLE clinical trials (treatment group) and COMPERA and UKRB registries (external comparator) to generate evidence on the comparative effectiveness of inhaled treprostinil versus SOC in Europe.

Main study objective:

By emulating a target trial utilising data from INCREASE (RIN-PH-201) and INCREASE OLE (RINPH-202) clinical trials with an external comparator group of RW patients from PH registries in Europe, this study aims to generate evidence of long-term comparative effectiveness of inhaled treprostinil in adult patients with PH-ILD.

Research Question: What is the comparative effectiveness of inhaled treprostinil in the treatment of PH-ILD, between adult patients enrolled in INCREASE and INCREASE OLE clinical trials and RW patients from Europe treated with current SOC (3 comparator groups will be considered as SOC: off-label phosphodiesterase type-5 inhibitor (PDE5i) treated patients from UKRB and COMPERA, treatment naïve patients from UKRB, and RW patients [off-label PAH treated and treatment naive] from UKRB)?

Primary objective:

1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC3 on all-cause mortality up to 28 weeks, 52 weeks, and 124 weeks, among

adult patients with PH-ILD.

Secondary objectives:
1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC3 on cardiopulmonary hospitalisation up to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD.
2. To estimate the effect associated with exposure to inhaled treprostinil versus SOC3 on six-minute walk distance (6MWD) from baseline to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PHILD.
3. To estimate the effect associated with exposure to inhaled treprostinil versus SOC3 on forced vital capacity (FVC) from baseline to 28 weeks, 64 weeks, and 124 weeks, among adult patients with PHILD.

Study Design

Non-interventional study design

Other

Non-interventional study design, other

External comparator arm study

Study drug and medical condition

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

AMBRISENTAN

BOSENTAN MONOHYDRATE

MACITENTAN

RIOCIGUAT

SILDENAFIL

TADALAFIL

TREPROSTINIL SODIUM

Anatomical Therapeutic Chemical (ATC) code

(B01AC) Platelet aggregation inhibitors excl. heparin

Platelet aggregation inhibitors excl. heparin

Medical condition to be studied

Pulmonary hypertension

Interstitial lung disease

Combined pulmonary fibrosis and emphysema

Additional medical condition(s)

PH WHO Group 3.2 and 3.3

Population studied

Short description of the study population

This study will include adult patients (aged more or equal to 18 years at index date) diagnosed with pulmonary hypertension associated with interstitial lung disease of various aetiologies, documented by right heart catheterisation.
The exposure (inhaled treprostinil) is captured in the INCREASE trial (RIN-PH-201), a multicentre, randomised, doubleblind, placebo-controlled, 16-week Phase III trial, and its open-label extension (RIN-PH-202), with an additional follow-up of up to 108 weeks. The real-world comparator group will be derived from European disease specific data sources: Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) and Royal Brompton Hospital National Pulmonary Hypertension Service research ready

dataset (UKRB). Exposure to inhaled treprostinil will be compared to 2 different comparator groups derived from real-world data in Europe: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) RW patients (off-label PAH treated and treatment naive) from UKRB.

Age groups

- **Adult and elderly population (≥18 years)**

Estimated number of subjects

500

Study design details

Comparators

Standard of Care: 3 separate comparator groups, treatment naïve and treated with off-label pulmonary arterial hypertension therapy (excluding prostanoids), will be considered as standard of care

Data analysis plan

A statistical analysis plan will be developed prior to the statistical analysis and will describe all planned analysis. In short, descriptive statistics for baseline demographic data, clinical characteristics, and duration of exposure will be presented for inhaled treprostinil group and standard of care group in Europe. IRs together with 95% CIs will be calculated for each event of interest over the entire observation period and at different follow-up timepoints. Kaplan Meier curves will be plotted for all-cause mortality and all-cause hospitalisation and presented for the entire period at risk.

IPTW based on propensity scores will be implemented to account for observed differences in patient characteristics between the treprostinil and standard of care comparator group, estimating the average treatment effect in the treated

population.

To estimate the treatment effect for survival outcomes, Royston-Parmar models with zero (Weibull distribution) or more knots will be applied as a primary analysis and estimates with the respective 95% CIs and p-values will be presented. Additionally, Restricted Mean Survival Time (RMST) will be estimated as a supplementary analysis, by utilising the Kaplan-Meier curve to estimate RMSTs, RMST differences and 95% CIs of inhaled treprostinil versus SOC in PH patients. Weighted RMSTs may be estimated by utilising weighted Kaplan-Meier curves.

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)

Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension

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Data source(s), other

Royal Brompton Hospital National Pulmonary Hypertension Service Pulmonary Hypertension Registry (UKRB PH)

Clinical trial data from:

- Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (RIN-PH201, NCT02630316)

Data sources (types)

Clinical trial

Disease registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name (other)

Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD

Data quality specifications

Check conformance

Unknown

Check completeness

Yes

Check stability

No

Check logical consistency

Yes

Data characterisation

Data characterisation conducted

Yes

Data characterisation moment

after extract-transform-load to a common data model