

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

**First published:** 12/04/2024

**Last updated:** 12/04/2024

Study

Ongoing

## Administrative details

### PURI

<https://redirect.ema.europa.eu/resource/1000000109>

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### EU PAS number

EUPAS1000000109

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### Study ID

1000000109

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### DARWIN EU® study

No

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### Study countries

Germany

Spain

United Kingdom

United States

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### 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, REHAR, and UK Royal Brompton registries (external comparator) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus standard of care in Europe.

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## Study status

Ongoing

## Research institution and networks

### Institutions

#### Ferrer Internacional

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

Last updated 01/02/2024

Institution

#### Global Database Studies (GloDaSt), IQVIA

Czechia

Finland

Germany

Slovakia

Spain

**First published:** 17/01/2011

Last updated 16/02/2024

Institution

ENCePP partner

Other

## Contact details

### Study institution contact

Diego Funes

Study contact

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### Primary lead investigator

Fabian Hoti

Primary lead investigator

### ORCID number:

0000-0002-7464-3549

## Study timelines

**Date when funding contract was signed**

Planned:

09/03/2023

Actual:

09/03/2023

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**Study start date**

Planned:

01/06/2023

Actual:

17/07/2023

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**Data analysis start date**

Planned:

01/07/2024

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**Date of final study report**

Planned:

31/01/2025

## Sources of funding

- Pharmaceutical company and other private sector

## More details on funding

Ferrer Internacional

## Study protocol

[Ferrer\\_PH-ILD\\_TYVASO\\_Protocol\\_V1.0\\_Signed\\_19JAN2024.pdf\(1.05 MB\)](#)

## Regulatory

**Was the study required by a regulatory body?**No

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

Not applicable

## Other study registration identification numbers and links

## Methodological aspects

### Study type

#### Study type list

**Study topic:**

Human medicinal product

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**Study type:**

Non-interventional study

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**Scope of the study:**

Effectiveness study (incl. comparative)

**Data collection methods:**

Combined primary and secondary data collection

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**Study design:**

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

**Main study objective:**

By emulating the INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) clinical trials with a European external comparator group of PH-ILD patients from disease specific PH registries (COMPERA, REHAR, and UKRB), this study will aim to generate evidence to gauge the applicability of the pivotal INCREASE study to the European setting. Further, this real-world-evidence (RWE) study will provide evidence on comparative effectiveness for a substantially longer follow-up window of 28 weeks, 52 weeks, or 64 weeks, as compared to the placebo-controlled 16-week follow-up of INCREASE.

Research Question: What is the comparative effectiveness of inhaled treprostinil (TYVASO) in the treatment of PH associated with ILD, between adult patients enrolled in the INCREASE and INCREASE OLE clinical trials and European RW patients treated with the current Standard Of Care (SOC), (2 separate comparator groups, treatment naïve and treated with off-label PAH therapy, will be considered as SOC).

Primary objective:

1. To describe and compare the mean difference in 6-minute walk distance (6MWD) from baseline to 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD.

Secondary objectives:

1. To estimate incidence rates (IRs) and comparative ratios and differences for clinical worsening up to 28 weeks and 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

2. To estimate IRs and comparative ratios and differences up to 28 weeks and 52 weeks and cumulative survival probabilities for all-cause mortality and first all-cause hospitalisation associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

3. To describe and compare the mean difference in pulmonary function from baseline to 28 weeks and 64 weeks, N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP) from baseline to 64 weeks, and oxygenation from baseline to 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD.

Exploratory objectives:

1. To describe proportion of treatment success at 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

2. Assess the comparability of INCREASE internal clinical trial comparator group to the European external RW treatment naïve group before and after adjustment for baseline confounding for the primary outcome of 6MWD.

## Study Design

### Non-interventional study design

Other

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### 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

EPOPROSTENOL  
MACITENTAN  
RIOCIQUAT  
SILDENAFIL  
TADALAFIL  
TREPROSTINIL SODIUM

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**Anatomical Therapeutic Chemical (ATC) code**  
(B01AC) Platelet aggregation inhibitors excl. heparin

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**Medical condition to be studied**  
Pulmonary hypertension  
Interstitial lung disease

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**Additional medical condition(s)**  
PH WHO Group 3.2

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## 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), Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease (REHAR), 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) external comparator group of treatment naïve patients; (2) an external comparator group of patients treated with off-label pulmonary arterial hypertension therapy (excluding prostanoids).

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**Age groups**  
Adult and elderly population (>18 years)

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**Estimated number of subjects**  
187

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## Study design details

## Comparators

Standard of Care: 2 separate comparator groups, treatment naïve and treated with off-label pulmonary arterial hypertension therapy (excluding prostanoids), will be considered as standard of care.

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## 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 untreated population.

For longitudinal outcomes of interest, weighted mixed effects models will be performed. For each time-to-event outcome of interest, restricted mean survival time models will be applied. RMSTs, RMST difference together with 95% CIs for inhaled treprostinil versus standard of care will be reported.

Exploratory analyses for the proportion of treatment success at 64 weeks and comparability of the internal comparator and external comparator will be performed. Subgroup analyses will check the primary outcome distribution for different patients' characteristics groups. Additionally, sensitivity analyses will be conducted to assess the robustness of the results.

## Data management

### Data sources

#### Data source(s), other

- Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA Registry)
- Registro Español de Hipertensión pulmonar Asociada a enfermedad Respiratoria (REHAR)
- Royal Brompton Hospital National Pulmonary Hypertension Service Pulmonary Hypertension Registry

Clinical trial data from:

- Safety and Efficacy of Inhaled Treprostinil in Adult PH With ILD Including CPFE (RIN-PH-201, NCT02630316)

- An Open Label Extension Study to Evaluate Inhaled Treprostinil in Adult PH With ILD Including CPE (RIN-PH-202, NCT02633293)

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### **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

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### **CDM version**

In Progress

## Data quality specifications

### **Check conformance**

Yes

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### **Check completeness**

Yes

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### **Check stability**

No

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### **Check logical consistency**

Yes

## Data characterisation

### **Data characterisation conducted**

Yes

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### **Data characterisation moment**

after extract-transform-load to a common data model