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

First published: 12/04/2024

Last updated: 23/07/2024

Study Ongoing

Administrative details

EU PAS number

EUPAS1000000109

Study ID

1000000109

DARWIN EU® study

No

Study countries

- [ ] Germany
- [ ] Spain
- [ ] 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, 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.

Study status

Ongoing

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

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Study timelines

Date when funding contract was signed

Planned: 09/03/2023

Actual: 09/03/2023

Study start date

Planned: 01/06/2023

Actual: 17/07/2023

Data analysis start date
Planned: 01/07/2024

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)

Ferrer_PH-ILD_TYVASO_ECA_protocol_v2.0_09072024_signed.pdf(2.06 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

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, 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

Non-interventional study design, other

External comparator arm study

Study drug and medical condition

Name of medicine, other

TYVASO

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

AMBRISENTAN

BOSENTAN MONOHYDRATE

EPOPROSTENOL

MACITENTAN

RIOCIGUAT

SILDENAFIL

TADALAFIL

TREPROSTINIL SODIUM

Anatomical Therapeutic Chemical (ATC) code

(B01AC) Platelet aggregation inhibitors excl. heparin

Platelet aggregation inhibitors excl. heparin

(B01AC21) treprostinil

treprostinil

Medical condition to be studied

Pulmonary hypertension

Interstitial lung disease

Additional medical condition(s)

PH WHO Group 3.2

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).

Age groups

Adult and elderly population (≥18 years)

Adults (18 to < 65 years)

Adults (18 to < 46 years)

Adults (46 to < 65 years)

Elderly (≥ 65 years)

Adults (65 to < 75 years)

Adults (75 to < 85 years)

Adults (85 years and over)

Estimated number of subjects

187

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.

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)

Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension

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Data source(s), other

- 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 CPFE (RIN-PH-202, NCT02633293)

Data sources (types)

Clinical trial

Disease registry

Use of a Common Data Model (CDM)

CDM mapping

Yes

CDM Mappings

CDM name (other)

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CDM version

In Progress

Data quality specifications

Check conformance

Yes

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