1. Title page

TITLE	Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD
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This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments) and the Guidelines for Good Pharmacoepidemiology Practices (ISPE).

2. Abstract

Full Study Title: Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD			
Phase:	Not applicable (N/A)	**Type:**	External Comparator Arm (ECA) study
Number of Patients: 163 patients were treated with inhaled treprostinil in the INCREASE randomised controlled trial (RCT), 391 patients received the off-label pulmonary arterial hypertension (PAH) therapy, and 105 patients were treatment naïve.		**Duration of Patient Participation**: N/A	
Number of Sites: The INCREASE and INCREASE open-label extension (OLE) clinical trials included patients from 92 centres in the United States of America. The real-world (RW) comparator group included patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD) from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)[4], the Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease (REHAR)[5], and The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)[6].		**Duration of study**: Study outcomes were assessed at 28 weeks, 52 weeks, or 64 weeks.[7]	
Background and Rationale: Pulmonary hypertension (PH) is a pathophysiological condition marked by elevated mean pulmonary arterial pressure (mPAP) which can result in cardiac dysfunction and failure. The World Health Organization (WHO)			

[4] COMPERA contained data on WHO Group 1-5 patients from 61 centres in Europe (Germany, Italy, United Kingdom, Belgium, Netherlands, Switzerland, Austria, Greece, Slovakia, Hungary, Latvia, and Lithuania).

[5] REHAR contained data on WHO Group 3 PH patients from 14 centres across Spain.

[6] UKRB contained data on WHO Group 3 PH patients treated at the Royal Brompton Hospital National Pulmonary Hypertension Service in London, United Kingdom.

[7] For the real-world external comparator groups (treatment naïve and off-label PAH therapy), the nearest outcome measure to the time points of interest (28 weeks, 52 weeks, or 64 weeks) was used with a maximum variation of ±30 days.

categorises PH into five groups, based on pathophysiology and clinical presentation. Group 3 PH patients, those with PH linked to lung disease and/or hypoxia, experience the most severe outcomes and highest mortality rates. Interstitial lung disease (ILD) is one factor that can contribute to the development of PH, with varying prevalence rates depending on the type and severity of ILD. Prevalence estimates based on the previous definition of mPAP ≥25 mmHg have ranged from 3% to 64% in ILD patients. The coexistence of PH and ILD presents a substantial clinical and economic burden, leading to increased healthcare resource utilisation and costs. Studies have shown higher utilisation of diagnostic procedures, prescriptions, and treatments among PH-ILD patients, resulting in elevated costs primarily driven by inpatient admissions, prescriptions, and outpatient care. This trend is increasing over time.

PH in patients with ILD is associated with increased need for supplemental oxygen, reduced mobility, and decreased survival. However, due to the significant overlap in symptoms between ILD patients with and without PH, diagnosis is challenging. Markedly decreased diffusing capacity, shorter distance in the 6-minute walk test, evident exertional desaturation, and delayed heart rate recovery after exercise are all indicators of PH-ILD progression. Many diagnostic clinical tests lack specificity and sensitivity; therefore, right heart catheterisation (RHC) remains the gold standard for confirming a PH-ILD diagnosis.

Currently, there are no approved medical treatments for PH-ILD in Europe. Although vasodilator therapies investigated in clinical trials have shown inconclusive outcomes, the recent INCREASE trial demonstrated significant improvement in exercise capacity with inhaled treprostinil, a prostacyclin analogue that reduces pulmonary pressure and improves cardiac function in these patients.

By emulating a target trial using data from the INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) clinical trials with an external comparator group of RW patients from PH registries in Europe (COMPERA, REHAR, and UKRB), this study aimed to provide evidence of long-term comparative effectiveness of inhaled treprostinil over significantly longer follow-up periods of 28 weeks, 52 weeks, or 64 weeks, compared to the placebo-controlled 16-Week follow-up of INCREASE.

Objectives:

Research Question: What was the comparative effectiveness of inhaled treprostinil in the treatment of PH-ILD, between adult patients enrolled in the INCREASE and INCREASE OLE clinical trials and RW patients from Europe treated with current standard of care (SOC) (2 comparator groups were considered as SOC: off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB, and treatment naïve patients from REHAR and UKRB)[8]?

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 inhaled treprostinil exposure in patients from the INCREASE and INCREASE OLE clinical trials versus SOC[9] in Europe, among adult patients with PH-ILD.

[8] Where not all data sources had available data to assess each outcome, the choice of RW registry was dictated by data availability. Choice of RW data source for each outcome is presented in Table 2.

[9] Two separate comparator groups derived from RW data were considered as SOC in Europe: (1) off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB; (2) treatment naïve patients from REHAR and UKRB.

Secondary objectives:

1. To estimate incidence rates (IRs) and comparative ratios and differences for **clinical worsening**[10] up to 28 weeks and 64 weeks associated with exposure to inhaled treprostinil in patients from the INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

2. To estimate IRs and differences up to 28 weeks and 52 weeks and cumulative survival probabilities for **all-cause mortality** and first **cardiopulmonary hospitalisation** associated with exposure to inhaled treprostinil in patients from the 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, and in **N-terminal pro-B-type natriuretic peptide (NT-proBNP)** from baseline to 64 weeks associated with exposure to inhaled treprostinil in patients from the INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

4. To describe **oxygenation**[11] at 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from the 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 the INCREASE and INCREASE OLE clinical trials versus SOC in Europe, among adult patients with PH-ILD

Study design: This is an ECA study using data from the INCREASE and INCREASE OLE clinical trials and 3 PH registries in Europe (COMPERA, REHAR, and UKRB) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus SOC.

Exposure to inhaled treprostinil (patients randomised to inhaled treprostinil in the INCREASE RCT who then had the option to continue on inhaled treprostinil in the INCREASE OLE trial) was compared to SOC. Two comparator groups derived from RW data were considered as SOC: (1) off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB; (2) treatment naïve patients from REHAR and UKRB.

Study population: The study included adult patients (aged ≥18 years at index date) diagnosed with PH associated with ILD of various aetiologies, documented by an RHC.

Inclusion criteria

The following criteria were considered for patients to be included in the study:

- Age ≥18 years at index date

[10] Clinical worsening was defined as experiencing any of the following: hospitalisation from cardiopulmonary causes, a decrease in 6MWD ≥15% from baseline, a decrease in FVC ≥10% from baseline, or death from all causes.

[11] Defined as presence of hypoxia/hypoxemia.

- Diagnosis of WHO Group 3 PH before or at the index date associated with any form of ILD or combined pulmonary fibrosis and emphysema (CPFE)
- RHC up to 1 year before the index date with the following parameters:
  - pulmonary vascular resistance (PVR)[12] >3 Wood Units (WU)
  - pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg
  - mPAP of ≥25 mmHg
- 6MWD ≥100 metres at the index date (the closest measurement to the index date was used, with a maximum look-back period of 6 months)
- Patients with connective tissue disease (CTD) having a forced vital capacity (FVC) of <70% at the index date (the closest measurement to the index date was used, with a maximum look-back period of 6 months)
- A record of any off-label PAH therapy (excluding prostanoids)[13] at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

Exclusion criteria

Patients meeting any of the following criteria were not eligible for participation:

- A record of off-label PAH therapy[13] before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date
- A record of participation in any investigational study with therapeutic intent at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

Data Collection and Assessments: The study utilised two types of data: clinical trial data from INCREASE and its OLE (exposure to inhaled treprostinil) and data from RW disease-specific PH registries in Europe. COMPERA, a PH registry that spans multiple European countries, REHAR, a PH associated with lung disease registry in Spain, and UKRB, a PH-ILD registry in London, United Kingdom were selected to contribute patients to the two external comparator groups.

Statistical Methods: Descriptive statistics for baseline demographic data and clinical characteristics were presented for the inhaled treprostinil group and SOC groups in Europe.

IRs, together with 95% confidence intervals (CIs), were calculated for each event of interest at specific follow-up timepoints. Kaplan-Meier curves were plotted for all-cause mortality and cardiopulmonary hospitalisation and presented for the entire period at risk.

[12] In cases where PVR was not captured, but cardiac output was available, cardiac output was used to calculate PVR.

[13] A list of drug classes and active substances used in the treatment of PH-ILD have been presented in Appendix Table 3

Inverse probability of treatment weighting (IPTW) based on propensity scores (PS) was implemented to account for observed differences in patient characteristics between the inhaled treprostinil and SOC comparator groups, estimating the average treatment effect in the untreated population (ATU) and the average treatment effect in the overlap population (ATO).

The confounders/risk factors for the PS model were chosen a priori. However, some of the selected/defined covariates may suffer from reduced data quality (measurement error) due to RW documentation practices. Therefore, a sensitivity analysis was performed using an alternative PS model for the primary endpoint analysis that included only prognostic risk factors ($p<0.2$), which was expected to provide more precise estimates of the treatment effect.

The estimand strategy for the main analysis was based on the treatment policy approach. For the treatment policy strategy, "the intercurrent event is considered irrelevant in defining the treatment effect of interest: the value for the variable of interest is used regardless of whether or not the intercurrent event occurs".

To handle intercurrent events, supplementary analyses of the primary outcome were performed using the Inverse Probability of censoring weighting (IPCW) to generate a hypothetical estimand and the composite endpoint estimand strategy, which assigned a 6MWD result of 0 metres for deceased patients.

For longitudinal outcomes of interest weighted mixed effects models were performed. For each time-to-event outcome of interest, Royston-Parmar survival models were applied, and estimates were presented including respective 95% CIs. Restricted Mean Survival Time (RMST) differences together with 95% CIs for inhaled treprostinil versus SOC were estimated by utilising the KM curves as supplementary analysis.

Exploratory analysis for the proportion of treatment success at 64 weeks was performed. Subgroup analyses checked the primary outcome distribution for different patient characteristic groups. Additionally, sensitivity analyses were conducted to assess the robustness of the results.

The only confirmatory test procedure was applied for the primary endpoint of comparing the 6MWD at 52 weeks between trial data and the off-label PAH treatment. Comparisons against treatment naïve patients were considered descriptive only due to the anticipated low sample size.

Sample size: The sample size was based on evaluating the primary endpoint of mean difference at 52 weeks from baseline in 6MWD. Patients treated with inhaled treprostinil (6 mcg/breath) in the INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) clinical trials were compared with external comparators treated with SOC derived from RW data in Europe.

In the INCREASE RCT, a total of 326 patients were enrolled, of which, 163 were randomly assigned to inhaled treprostinil and 163 to placebo. 130 patients assigned to inhaled treprostinil and 128 patients assigned to placebo completed Week 16 of the study assessment. In the INCREASE OLE (RIN-PH-202), a total of 243 patients from INCREASE RCT were enrolled, of which, 119 continued on inhaled treprostinil (received inhaled treprostinil in INCREASE RCT) and 121 started on inhaled treprostinil (received placebo in INCREASE RCT). Of the 119 patients who continued on inhaled treprostinil in INCREASE OLE, 68 patients completed 52 weeks of study assessments for 6MWD.

Sample size calculations were performed to mimic an estimated mean difference in 6MWD of 30 metres between exposed subjects and unexposed subjects with a standard deviation of 75 metres, as targeted in the INCREASE (RIN-PH-201) clinical trial. In the case of a sample size of 70 patients, a minimum of 187 patients in each SOC group were needed to achieve 80% power when comparing the inhaled treprostinil group versus SOC. In all cases, variance inflation factor (VIF) corrections were considered.

Results: The study included adult patients (≥18 years) with PH-ILD, comparing the inhaled treprostinil group (from the INCREASE and INCREASE OLE trials) with RW comparator groups from European PH registries

(COMPERA, REHAR, UKRB). Baseline characteristics indicated that the inhaled treprostinil group (N=163 patients) had a lower mean age (65.53 vs. 69.62 years), fewer males (47.9% vs. 69.4%) and a higher percentage of never smokers (94.5% vs. 23%) than the off-label PAH therapy group (N=379 patients). Comorbidities were similar between the groups, although obstructive sleep apnoea was more common in the inhaled treprostinil group (27% vs. 8%), and idiopathic interstitial pneumonia was more prevalent in the off-label PAH therapy group (57% vs. 39.9%).

The median 6MWD was slightly higher in the inhaled treprostinil group compared to the off-label group (median: 256.00 metres, Q1-Q3: 160.50 to 315.00 vs. median: 250.00 metres, Q1-Q3: 186.50 to 330.00, respectively). Additionally, the inhaled treprostinil group had lower mean PVR (6.37 WU vs. 8.11 WU). The proportion of patients with normal oxygenation levels was 74.8% vs. 41.8% in the inhaled treprostinil and off-label therapy groups respectively; severe hypoxia/hypoxemia was more prevalent in the off-label PAH therapy group (44.2% of patients in the off-label therapy group vs. 6.1% of patients in the inhaled treprostinil group).

After IPTW with ATU, a significant proportion of the covariates exhibited standardized mean differences above the threshold, thereby the ATO constituted the primary analysis as per the pre-specified statistical analysis plan (SAP) decision criteria.

The primary objective compared the mean difference in 6MWD from baseline to 28 and 52 weeks between patients treated with inhaled treprostinil and patients treated with off-label PAH therapy.

In the primary analysis using the PS model with a priori selected confounders/risk factors (initial PS), the overall treatment difference in 6MWD was 27.293 metres (95% CI: -10.41 to 65.00; P=0.1560), which was not statistically significant. Significant improvements were observed at 28 weeks (25.516 metres, 95% CI: 2.07 to 48.96; P=0.0329) in the inhaled treprostinil group, while the off-label PAH therapy group showed no significant change. At 52 weeks, the inhaled treprostinil group had a mean change of 18.894 metres (95% CI: -4.21 to 42.00; P=0.1090), and the off-label PAH therapy group had a mean change of -25.830 metres (95% CI: -72.28 to 20.62; P=0.2758), both not statistically significant.

Sensitivity analysis of the primary outcome using the revised PS model, including only prognostic factors, showed a significant overall treatment difference of 34.138 metres (95% CI: 1.99 to 66.28; P=0.0374), with improvements at 28 weeks (28.233 metres, 95% CI: 13.15 to 43.32; P=0.0002) and sustained at 52 weeks (25.480 metres, 95% CI: 8.95 to 42.00; P=0.0025).

The per-protocol treated set analysis also indicated a significant overall treatment difference of 43.403 metres (95% CI: 3.02 to 83.79; P=0.0352), with improvements at 28 weeks (32.011 metres, 95% CI: 6.82 to 57.20; P=0.0127), although being non-significant at 52 weeks (23.959 metres; 95% CI: -0.29 to 48.20; P=0.0528).

Subgroup analysis of the primary outcome revealed significant improvements for patients with PVR >5 WU in the inhaled treprostinil group at both 28 weeks (43.795 metres; 95% CI: 22.14 to 65.45; P=0.0001) and 52 weeks (33.666 metres; 95% CI: 5.30 to 62.03; P=0.0200). The off-label PAH therapy group showed no significant changes.

Handling the intercurrent events using a composite endpoint strategy revealed also a significant improvement favouring inhaled treprostinil (89.746 metres, 95% CI: 27.10 to 152.39; P=0.0050). The off-label PAH therapy group exhibited significant declines at both 28 weeks (-69.865 metres, 95% CI: -134.79 to -4.94; P=0.0349) and 52 weeks (-114.435 metres, 95% CI: -175.23 to -53.64; P=0.0002).

Secondary objectives showed no significant differences in clinical worsening, all-cause mortality, or cardiopulmonary hospitalisation between the groups at 28 and 64 weeks. Pulmonary function tests demonstrated significant improvements in FVC (% of predicted) at 28 weeks (3.164, 95% CI: 0.35 to 5.98; P=0.0275), which were sustained at 64 weeks (2.388, 95% CI: 0.31 to 4.47; P=0.0246). However, the normality assumption for

the residuals was not met, compromising the reliability of the results. Additionally, NT-proBNP levels at 64 weeks revealed no significant difference between the inhaled treprostinil and off-label PAH therapy groups.

Oxygen supplementation was required in 69.5% of patients in both groups, remaining relatively stable in the inhaled treprostinil group at 67.3% at Week 28 and 64.6% at Week 52, while increasing in the off-label PAH therapy group to 84.1% at Week 28 and 87.2% at Week 52.

Discussion and Conclusions: This ECA study provided valuable insights into the long-term comparative effectiveness of inhaled treprostinil versus off-label PAH therapy in patients with PH-ILD.

The primary analysis based on the initial PS model showed a non-significant overall treatment difference of 27.293 metres (95% CI: -10.41 to 65.00). Significant results were observed at 28 weeks (25.516 metres; 95% CI: 2.07 to 48.96), but not significant at 52 weeks (18.894 metres; 95% CI: -4.21 to 42.00) in the inhaled treprostinil group. The off-label PAH therapy group did not show significant changes at either time point.

The revised PS model revealed a significant overall treatment difference favouring treprostinil (34.138 metres, 95% CI: 1.99 to 66.28), significant at 28 weeks (28.233 metres, 95% CI: 13.15 to 43.32) and sustained at 52 weeks (25.480 metres, 95% CI: 8.95 to 42.00). The off-label PAH therapy group did not show significant changes at either time point.

The per-protocol analysis revealed a significant overall treatment difference favouring inhaled treprostinil (43.403 metres, 95% CI: 3.02 to 83.79), suggesting the effectiveness of the treatment under optimal conditions. This difference was significant at 28 weeks (32.011 metres, 95% CI: 6.82 to 57.20), although it was non-significant at Week 52 (23.959 metres, 95% CI: -0.29 to 48.20). The off-label PAH therapy group did not show significant changes at either time point.

Subgroup analyses indicated significant improvements in exercise capacity for patients with PVR >5 WU, with 6MWD improvements of 43.795 metres (95% CI: 22.14 to 65.45) at 28 weeks and 33.666 metres (95% CI: 5.30 to 62.03) at 52 weeks. However, the overall treatment difference of 29.962 metres (95% CI: -23.38 to 83.30) was not statistically significant.

The composite endpoint strategy also showed a significant overall treatment difference favouring treprostinil (89.746 metres; 95% CI: 27.10 to 152.39), while the off-label PAH therapy group experienced significant declines at 28 weeks (-69.865 metres; 95% CI: -134.79 to -4.94) and 52 weeks (-114.435 metres; 95% CI: -175.23 to -53.64).

Non-significant results were observed for clinical worsening, all-cause mortality, cardiopulmonary hospitalisation, treatment success, pulmonary function, and NT-proBNP.

The increase in supplementary oxygen therapy use observed in the off-label therapy group over time versus the stable use in the inhaled treprostinil group, suggests that oxygenation did not worsen in the inhaled treprostinil group. These findings align with the results of the INCREASE studies, where inhaled treprostinil maintained oxygenation levels without increasing the need for supplemental oxygen over a 16-Week period and extended up to 64 weeks in the OLE. Additionally, Agarwal and Waxman observed that over 6-month period, patients with WHO Group-3 PH treated with inhaled treprostinil showed stable oxygenation. Japanese patients with PH-ILD receiving inhaled treprostinil, showed stable arterial oxygen saturation and no significant increase in supplemental oxygen needs over a 12-Week treatment period. This stability further supports the potential effectiveness of inhaled treprostinil compared to off-label therapy. In contrast, comparative studies in patients with PH-ILD treated with off-label therapies such as bosentan, riociguat, or other prostacyclin analogue such as epoprostenol, highlight the challenges of managing oxygenation in these patients.

The significant benefits of inhaled treprostinil in improving exercise capacity, particularly in patients with higher PVR, sustained over the long-term, show promise in meeting the unmet needs of this patient population.

The revised PS model and the composite endpoint strategy are scientifically preferable analysis approaches, which support together with the per-protocol analysis the positive assessment of study results.

The initial PS model was developed based on a priori decisions to select confounders and risk factors. However, the inclusion of variables that are related to the exposure but not the outcome will decrease the precision of the effect estimate without removing bias, particularly in small studies. Additionally, some of the a priori selected covariates in the initial PS model may be suspected to suffer from reduced data quality (measurement error) due to RW documentation practices, which can introduce other sources of bias such as misclassification.

In contrast, the revised PS model suggested by Brookhart *et al.* only includes prognostic variables to reduce bias and improve precision.

The handling of intercurrent events using the composite endpoint strategy, according to the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9(R1) assigns a 6MWD result of 0 metres for deceased patients and provides a more holistic view of treatment effectiveness by ensuring that patients with missing outcome data due to death are assigned the worst outcome. This approach is scientifically preferred because it provides a more meaningful and interpretable estimand compared to the primary analysis conducted using the treatment policy approach, which does not take into account intercurrent events such as death.

Together, these scientifically preferred analysis approaches provide a robust framework for evaluating the results observed in the study.

Ethical and Regulatory Considerations: This non-interventional study was conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to International Society of Pharmacoepidemiology, and the ethical principles of the Declaration of Helsinki and applicable privacy laws. Data protection and privacy regulations were strictly observed in capturing, forwarding, processing, and storing patient data. Every effort was made to protect participant confidentiality in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the European Council (27 April 2016) on the protection of natural persons regarding the processing of personal data.

17. Ferrer Signature

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

I have read this Study Report and I confirm that it describes the procedure and the results of the study.

Ferrer Internacional S.A representatives

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