NON-INTERVENTIONAL STUDY PROTOCOL

TITLE	Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD
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This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organisation of the study and on condition that all such persons agree not to further disseminate it.

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Principal Investigator Signature Page

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

Study number: 2953067

Protocol version: 1.0 dated 16 January 2024

I herewith certify that I agree to content of the Study Protocol v1.0 and to all documents referenced in the Study Protocol version v1.0.

Investigator:

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List of Abbreviations

Abbreviation or special term	Explanation
6MWD	six-minute walk distance
AE	adverse event
ATO	average treatment effect on the overall population
ATU	average effect in the untreated population
CI	confidence interval
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
CPFE	combined pulmonary fibrosis and emphysema
CTD	connective tissue disease
DMP	Data Management Plan
ECA	external comparator arm
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FVC	forced vital capacity
GPP	Guideline for Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
ILD	interstitial lung disease
INCREASE	A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease
IPTW	inverse probability of treatment weighting
IPWs	inverse probability weights
IRs	incidence rates
LVEF	left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MI	multiple imputation
mPAP	mean pulmonary arterial pressure
N/A	not applicable
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
OLE	open-label extension
PAH	pulmonary arterial hypertension

PFT	pulmonary function test
PCWP	pulmonary capillary wedge pressure
PH	pulmonary hypertension
PH-ILD	pulmonary hypertension - interstitial lung disease
PS	propensity scores
PVR	pulmonary vascular resistance
QC	quality control
RCT	randomised controlled trial
REHAR	Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease
RHC	right heart catheterisation
RMST	restricted mean survival time
RV	right ventricle
RW	real-world
RWD	real-world data
RWE	real-world-evidence
SAP	statistical analysis plan
SAS	statistical analytical software
SGCs	soluble guanylate cyclase stimulators
SMD	standardised mean difference
SOC	standard of care
SOP	standard operating procedure
UT	United Therapeutics
UK	United Kingdom
UKRB	The Royal Brompton Hospital PH registry in the United Kingdom
VIF	variance inflation factor
WHO	World Health Organization
WU	Wood Units

Study Synopsis

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: The INCREASE randomised controlled trial (RCT) enrolled 326 patients who either received placebo (163 patients) or inhaled treprostinil (TYVASO) (163 patients) for 16 weeks. Of the 163 patients treated with inhaled treprostinil in the INCREASE RCT, 119 patients continued treatment in the INCREASE open-label extension (OLE) study: 101 of those patients completed 28 weeks of study assessment, 76 patients completed 52 weeks of study assessment, and 71 patients completed 64 weeks of study assessment as the maximum follow-up for the current study. In the standard of care (SOC) arm a minimum number of patients between 101 and 187 will be needed to ensure a minimum 80% of statistical power.		**Duration of Patient Participation**: N/A	
Number of Sites: INCREASE and INCREASE OLE clinical trials included patients from 93 centres in the United States of America. The real-world (RW) comparator group will include patients from Comparative, Prospective Registry of Newly Initiated		**Duration of study**: Study outcomes will be assessed at 28 weeks, 52 weeks, or 64 weeks.[4]	

[4] 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) will be used with a maximum variation of ±30 days.

Therapies for Pulmonary Hypertension (COMPERA)[1], Registry of Pulmonary Hypertension Associated with Respiratory Disease (REHAR)[2], and The Royal Brompton Hospital PH registry in the United Kingdom (UKRB)[3].	

Background:

Pulmonary hypertension (PH) is a pathophysiological disorder characterised by elevated mean pulmonary arterial pressure that can lead to cardiac dysfunction and failure. World Health Organization (WHO) classifies PH into 5 groups, depending on pathophysiology and clinical presentation. Group 3 PH patients – those with PH associated with lung disease and/or hypoxia – experience the most severe outcomes and mortality. 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 mean pulmonary arterial pressure (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 demonstrated 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 ILD patients is associated with increased need for supplemental oxygen, reduced mobility, and decreased survival, but given the significant overlap in symptoms in ILD patients with and without PH, diagnosis is difficult. Significantly decreased diffusing capacity, reduced distance in the 6-minute walk test, evident exertional desaturation, and delayed heart rate recovery after exercise are all signs of PH-ILD progression. Many diagnostic clinical tests lack specificity and sensitivity and therefore, right heart catheterisation (RHC) is the gold standard for verifying a PH-ILD diagnosis.

[1] 61 centers from Germany, Italy, United Kingdom, Belgium, Netherlands, Switzerland, Austria, Greece, Slovakia, Hungary, Latvia, and Lithuania contribute to COMPERA.

[2] 14 centers across Spain contribute to REHAR.

[3] Contains clinical data on WHO group 3 PH patients treated at the Royal Brompton Hospital National Pulmonary Hypertension Service in London, United Kingdom.

Currently, there are no approved medical treatments for PH-ILD in Europe, and while 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.
Rationale: 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 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[5] 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[5] 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

[5] Two separate comparator groups will be considered as the current standard of care in Europe: (1) treatment naive patients; (2) patients treated with off-label PAH therapy (excluding prostanoids).

inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[5] 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[5] 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[5] 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: This is an ECA study using data from the INCREASE and INCREASE OLE clinical trials and COMPERA, REHAR, and UKRB registries to generate evidence on the comparative effectiveness of inhaled treprostinil versus SOC in Europe.

Exposure to inhaled treprostinil (patients randomised to inhaled treprostinil in the INCREASE RCT who then continued on inhaled treprostinil in INCREASE OLE trial) will be compared to SOC in Europe. In Europe 2 different comparator groups derived from RW data will be considered as SOC: (1) an external comparator group of treatment naïve patients; (2) an external comparator group of patients treated with off-label pulmonary arterial hypertension (PAH) therapy (excluding prostanoids).

Study population: The study will include 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 must be met in order to be included in the study:

- Informed consent according to national and local standards, where applicable[6]
- Age ≥18 years at index date
- Diagnosis of WHO Group 3 PH before or at 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 parametres:
  - pulmonary vascular resistance (PVR) >3 Wood Units (WU)
  - pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg
  - mPAP of ≥25 mmHg
- 6MWD ≥100 meters before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- Patients with connective tissue disease (CTD) have a forced vital capacity (FVC) of <70% before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- A record of any approved therapy for PAH (excluding prostanoids)[7] during the study period (for the external comparator group treated with off-label PAH therapy only)

Exclusion criteria

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

- A record of any approved therapy for PAH[7] before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date, or during the study period (for the treatment naïve external comparator group only)

Data collection/ Data Sources:

The study utilises 2 types of data: clinical trial data from INCREASE and its OLE (exposure to inhaled treprostinil) and data from RW PH registries (treatment naïve patients and patients treated with off-label PAH therapy). 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 2 external comparator groups.

[6] Informed consent is specific to entry into the register and not study specific. In the United Kingdom secondary data can be used for other purposes (e.g., research) with a consent waiver. However, patients have the possibility to opt out.

[7] A list of drug classes and active substances used in the treatment of PH-ILD have been presented in Table 9.

Data Management and Quality Assurance:

The study protocol will adhere to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and the Guideline for Good Pharmacoepidemiology Practices (GPP) and will be conducted in accordance with IQVIA's Quality Management System, which includes a Quality Control plan covering all aspects of the study. Quality control procedures will ensure accuracy and reproducibility of the final report. Data cleaning, extraction and transformation processes will be verified and monitored. On-site monitoring will not be performed due to the type of study design (non-interventional study utilising secondary data). A data management plan will be created to guide data collection, cleaning, and validation. Manual data review and automated quality checks will be conducted to maintain high data quality standards. These procedures are aligned with the European Medicines Agency guidance.

Safety:

According to Good Pharmacovigilance Practices (GVP) module VI, VI.C.1.2.1.2, adverse event (AE) reporting will not be conducted as part of this study given the study objectives will be met utilising secondary data. AEs, occurring within INCREASE and INCREASE OLE clinical trials have been reported in accordance with their study protocol.

Statistical Considerations:

Descriptive statistics for baseline demographic data, clinical characteristics, and duration of exposure will be presented for inhaled treprostinil group and SOC group in Europe.

IRs together with 95% confidence intervals (CIs) will be calculated for each event of interest over the entire observation period and at different follow-up timepoints. Kaplan-Meier (K-M) curves will be plotted for all-cause mortality and all-cause hospitalisation.

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

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 SOC 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 outcome distribution

for different patients' characteristics groups. Additionally, sensitivity analyses will be conducted to assess the robustness of the results.

Sample size

The sample size will be based on evaluating the 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 will be compared with external comparators treated with SOC derived from RW data in Europe.

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. A total of 326 patients enrolled in the INCREASE RCT, with 163 randomly assigned to inhaled treprostinil and 163 to placebo. 130 of the patients assigned to inhaled treprostinil and 128 of the patients assigned to placebo completed week 16 of study assessment. A total of 243 patients enrolled in INCREASE OLE (RIN-PH-202). 119 of those patients 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, such that the expected number of patients who completed 52 weeks assessment for 6MWD will be between 68 and 119 patients. To investigate multiple relevant scenarios, the sample size calculations assumed 70, 90, and 110 completers.

In the case of 70 patients, a minimum of 187 patients in each SOC group will be needed to compare the inhaled treprostinil arm versus SOC group. In case of 90 patients, a minimum of 122 patients in each SOC group will be needed. In the case of 110 patients having the primary endpoint available after 52 weeks, a minimum of 101 patients in each SOC group will be needed. In all cases, variance inflation factor (VIF) corrections were considered.

Final Analyses: One final analysis will be performed. The final report will include all planned descriptive, comparative, sensitivity, and exploratory analyses including the assessment of the comparability of the INCREASE clinical trial internal comparator group to the European external RW treatment naïve group, and imputation techniques for missing data.

Ethical and Regulatory Considerations: This non-interventional study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to GPP, and the ethical principles of the Declaration of Helsinki and applicable privacy laws. Data protection and privacy regulations will be strictly observed in capturing, forwarding, processing, and storing patient data. Every effort will be made to protect participant confidentiality in compliance with the Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons regarding the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC (General Data Protection Regulation).

Documentation of Protocol Amendments

Not applicable.

Milestones

The planned dates for the study milestones are described in Table 1 below. The dates associated with these milestones are subject to amendment during study conduct.

Table 1: Provisional dates of study milestones

Milestone	Planned date
Finalisation of the quantitative feasibility report	Q1 2024
Finalisation of the protocol	Q1 2024
Update of the registration in the EU PAS Register	Q1 2024
Finalisation of the statistical analysis plan	Q2 2024
Delivery of the final analysis	Q3 2024
Delivery of the final study report	Q4 2024

Abbreviations: EU PAS Register, European Union electronic Register of Post-Authorisation Studies; Q, quarter.

1. BACKGROUND

1.1 Disease Burden of PH-ILD

Pulmonary hypertension (PH) is a pathophysiological disorder characterised by an increase in mean pulmonary arterial pressure that can lead to right ventricle (RV) hypertrophy, RV dilatation, RV dysfunction and, if left untreated, RV failure [1–3]. After a recent change in its definition PH is now defined by a mean pulmonary arterial pressure (mPAP) of >20 mmHg at rest [4] and is classified into the following 5 groups based on similar pathophysiology, clinical presentation, haemodynamic characteristics and therapeutic management: pulmonary arterial hypertension (PAH) (Group 1), PH associated with left heart disease (Group 2), PH associated with lung disease and/or hypoxia (Group 3), chronic thrombo-embolic PH (Group 4), and PH with unclear and/or multifactorial mechanisms (Group 5) [1,4,5].

PH can arise due to various factors, including interstitial lung disease (ILD). ILD is an umbrella term used for a group of diseases that cause fibrosis of the lungs [6] which can lead to the narrowing and obstruction of blood vessels, increasing resistance to blood flow through the pulmonary arteries. This pulmonary vascular resistance (PVR), along with the loss of pulmonary vascular beds, contributes to the development of PH in ILD patients. PH can exacerbate ILD by further impairing gas exchange and oxygenation, accelerating disease progression, and increasing the risk of complications [6]. PH associated with ILD (PH-ILD) is frequently observed and is captured in the World Health Organization (WHO) Group 3 category.

PH is estimated to affect approximately 20 to 70 million people worldwide [7]. The United Kingdom (UK) reported a 5-fold increase in the annual incidence of PH from 2004 to 2021 [8]. According to a population-based cohort study in Canada, which assessed the prevalence of PH among groups 1 to 4, the annual prevalence of PH has considerably increased from 1993 to 2012 (99.8 to 127.3 cases per 100,000 population), with the highest mortality observed in groups 2 and 3 [5]. The prevalence of PH among patients with ILD varies [9,10] and is influenced by factors such as the type and severity of ILD and the diagnostic criteria used [11]. Prevalence estimates based on the previous definition of mPAP of ≥25 mmHg, measured by right heart catheterisation (RHC), have ranged from 3% to 64% in ILD patients [11]. In 2021, EU4 regions (Germany, France, Italy, and Spain) and the UK reported 57,138 cases of PH-ILD, with projections indicating an increase by 2032. Among these regions, Germany had the highest prevalence of PH-ILD with 13,868 cases, followed by the UK with 13,166 cases [12].

The presence of PH alongside an underlying lung disease poses a considerable clinical and economic burden. In a retrospective observational cohort study, Group 3 PH patients underwent more diagnostic procedures, made higher claims for cardiovascular-related prescriptions and pharmacy claims for PAH-related drugs, and received more therapeutic treatment compared with the comparator group. Also, Group 3 patients bore higher all-cause utilisation costs ($44,732 versus $7,051) than the comparator group. The costs were related to inpatient

admissions (35.4%), prescriptions (33.0%), and outpatient care (26.5%) [13]. A retrospective cohort study evaluating healthcare resource utilisation (HCRU) among patients with PH-ILD, found that the percentage of patients with PH-ILD requiring hospitalisation doubled ($p<0.0001$) from 29.5% in the pre-index to 59.0% in the post-index period, with a significant increase ($p<0.0001$) in healthcare costs from $43,201 to $108,387, respectively [14].

1.2 Current Diagnosis and Treatment Paradigm

PH in ILD patients is associated with increased need for supplemental oxygen, reduced mobility, and decreased survival [11]. Given the significant overlap in symptoms with those of ILD without PH, a strong suspicion is necessary to make the diagnosis [15]. Significantly decreased diffusing capacity, reduced distance in the 6-minute walk test, evident exertional desaturation, and delayed heart rate recovery after exercise are all signs of PH-ILD progression. The most often used screening diagnostic for PH-ILD is traditional transthoracic echocardiography, although it brings sensitivity and specificity concerns [16]. Although newer echocardiographic methods that use multidimensional imaging methods may improve detection of patients with PH-ILD, RHC is still the gold standard for verifying a PH-ILD diagnosis [17].

In Europe, there is currently no approved medicinal treatment for PH-ILD. Given the absence of approved therapies for PH-ILD addressing the underlying lung illness and adopting medications that help manage PH-ILD while reducing healthcare usage and cost can be critical. Vasodilator therapy for PH, such as sildenafil, ambrisentan, riociguat, and endothelin receptor antagonists investigated in clinical trials have been controversial given their association with an increased risk of disease progression, respiratory hospitalisations, and adverse events (AEs) or negative results among patients [1].

The recently published INCREASE trial however, showed significant improvements with inhaled treprostinil among patients with PH-ILD. Treprostinil is a chemically stable prostacyclin analogue, and causes direct vasodilation, which reduces pulmonary and systemic arterial pressure, thereby reducing right and left ventricular afterload, leading to improved cardiac output. It also has an antiplatelet effect [18].

The INCREASE trial showed a significant difference in the change in peak 6-minute walk distance (6MWD) from baseline to week 16, between the inhaled treprostinil group (N=163) and the placebo group (N=163), with a least-squares mean difference between the groups of 31.12 m (95% confidence interval [CI]: 16.85 to 45.39; $p<0.001$). Clinical worsening reduced in the treprostinil group compared with placebo group (22.7% versus 33.1%), with a hazard ratio of 0.61 (95% CI: 0.40 to 0.92; $p=0.04$ by the log-rank test), and treprostinil decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels from baseline (15% versus 46%), with a treatment ratio of 0.58 (95% CI: 0.47 to 0.72; $p<0.001$) [19]. The INCREASE open-label extension (OLE) trial evaluated long-term effects of inhaled treprostinil in PH-ILD. The mean 6MWD at week 52 was 279.1 m and the median change from INCREASE trial baseline was 3.5 m. The median NT-proBNP decreased from 389 pg/mL at INCREASE trial baseline to 359

pg/mL at week 64. Patients who received inhaled treprostinil versus placebo in the INCREASE trial had a 31% lower relative risk of exacerbated underlying lung disease in the OLE (hazard ratio: 0.69; 95% CI: 0.49 to 0.97; p=0.03) [20].

Treprostinil is the first medication approved by United States Food and Drug Administration, by the National Administration of Drugs, Foods, and Medical Devices in Argentina, and by the Pharmaceutics Division of the Ministry of Health in Israel for PH-ILD [21]. However, it is yet to be approved in other geographies, including Europe. To address the dearth of data on treprostinil in real-world (RW) PH-ILD populations of Europe, this RW study evaluates comparative effectiveness of treprostinil between INCREASE and INCREASE OLE trials for PH-ILD population (treatment group) and European RW PH patients treated with standard of care (SOC) (external comparator).

2. RATIONALE

Evidence for the use of medication approved for PAH in the treatment of patients with WHO Group 3 PH is limited and conflicting [1] and it is an area of failed therapies. Several Phase II and Phase III clinical trials have investigated the use of endothelin receptor antagonists (ERAs) [22–24] and phosphodiesterase type-5 inhibitors (PDE5s) [25,26] in patients with PH-ILD with negative results. To the contrary, promising results were obtained with inhaled treprostinil in the United States of America (USA) based INCREASE and INCREASE OLE clinical trials [19,20].

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 Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), the Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease (REHAR), and The Royal Brompton Hospital PH registry in the United Kingdom (UKRB), this study will aim to generate evidence to gauge the applicability of the pivotal INCREASE study to the European setting. In the INCREASE OLE extension study, all patients were allocated to receive inhaled treprostinil, with no comparator group. 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.

3. OBJECTIVES

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 SOC (2 separate comparator groups, treatment naïve and treated with off-label PAH therapy, will be considered as SOC)

The **primary objective** of the study is:

1. To describe and compare the mean difference in **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[8] in Europe, among adult patients with PH-ILD

The **secondary objectives** of the study are:

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[8] 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 **all-cause hospitalisation** associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[8] 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[8] in Europe, among adult patients with PH-ILD

The **exploratory objectives** of the study are:

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[8] 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

[8] Two separate comparator groups will be considered as the current standard of care in Europe: (1) treatment naive patients; (2) patients treated with off-label PAH therapy.

4. STUDY DESIGN

4.1 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. Details relating to the data sources are provided in Section 4.7. Overview of the design is presented in Figure 1.

Exposure to inhaled treprostinil (patients randomised to inhaled treprostinil in the INCREASE RCT who then continued on inhaled treprostinil in INCREASE OLE trial) will be compared to SOC in Europe. In Europe 2 different comparator groups derived from RW data will be considered as SOC: (1) an external comparator group of treatment naïve patients; (2) an external comparator group of patients treated with off-label PAH therapy (excluding prostanoids).

This ECA will use data from historic and contemporary RW comparators who are either treatment naïve or on off-label PAH therapy constructed using observational patient-level data from disease specific registries [27].

The study design and analytical approaches are guided by the target trial emulation framework, which provides a formal methodology for estimating causal effects from real-world data (RWD) (see Appendix A for INCREASE/INCREASE OLE eligibility criteria) [28,29].

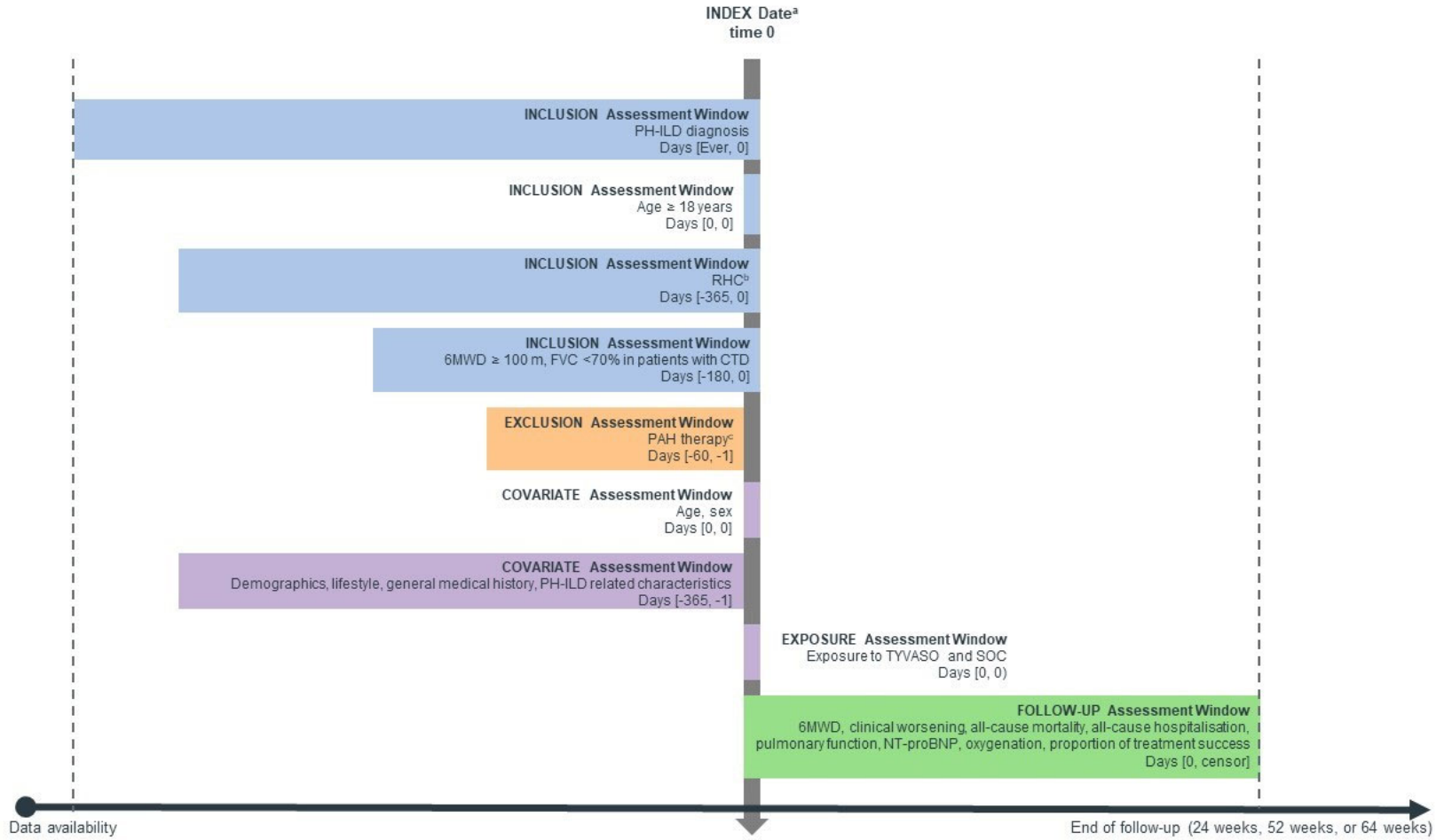


Figure 1: Overview of the study design

Abbreviations: 6MWD, six-minute walk distance; CTD, connective tissue disease; ILD, interstitial lung disease; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; PH, pulmonary hypertension; RHC, right heart catheterisation; SOC, standard of care.

[a] For the definition of index date see Section 4.2
[b] RHC with the following parameters:
- pulmonary vascular resistance >3 Wood Units (WU)
- pulmonary capillary wedge pressure of ≤15 mmHg
- mean pulmonary arterial pressure of ≥25 mmHg
[c] Exposure to PAH in the time period of 60 days before the index date.

4.1.1 Rational for the Study Design

Although randomised controlled trials (RCTs) are considered as the "gold standard" for generating evidence to assess the efficacy and safety of medicines, this design can be challenging to apply especially in severe or rare disease where there are few or no alternative treatments [27,30]. RCTs require large numbers of patients, and it is often not feasible or ethical to randomise patients to a placebo or SOC treatment known to have limited effectiveness [27,31]. This 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.

4.2 Study Period

Period start of INCREASE to the end of INCREASE OLE is February 2017 to June 2021. PH is an area of failed therapies. According to relevant treatment guidelines, management and treatment of PH has not significantly changed during the past 2 decades [1,32–34]. Thus, to increase patient counts, the period of data extraction from the PH registries will be extended to all available data at data extraction (for COMPERA, patients who entered the data source between 01 January 2006 to 31 December 2022; for REHAR, to be confirmed; for UKRB, patients diagnosed between 01 January 2000 to 06 December 2021).

The study will be designed such that the index date coincides with treatment initiation and the beginning of follow-up for all patients to avoid time-related biases such as immortal time bias. The **index date** for the inhaled treprostinil treatment and off-label PAH comparator group, will be at initiation of inhaled treprostinil and initiation of off-label PAH therapy, respectively. For the treatment naïve group, the index date for each patient will be obtained by drawing a random time from the observed distribution of time between initial PH-ILD diagnosis and treatment initiation in the inhaled treprostinil treated group and adding this to the treatment naive patient´s initial PH-ILD diagnosis date (Figure 2). Other strategies for selecting time-zero for untreated patients may be explored and defined in the SAP [35,36].

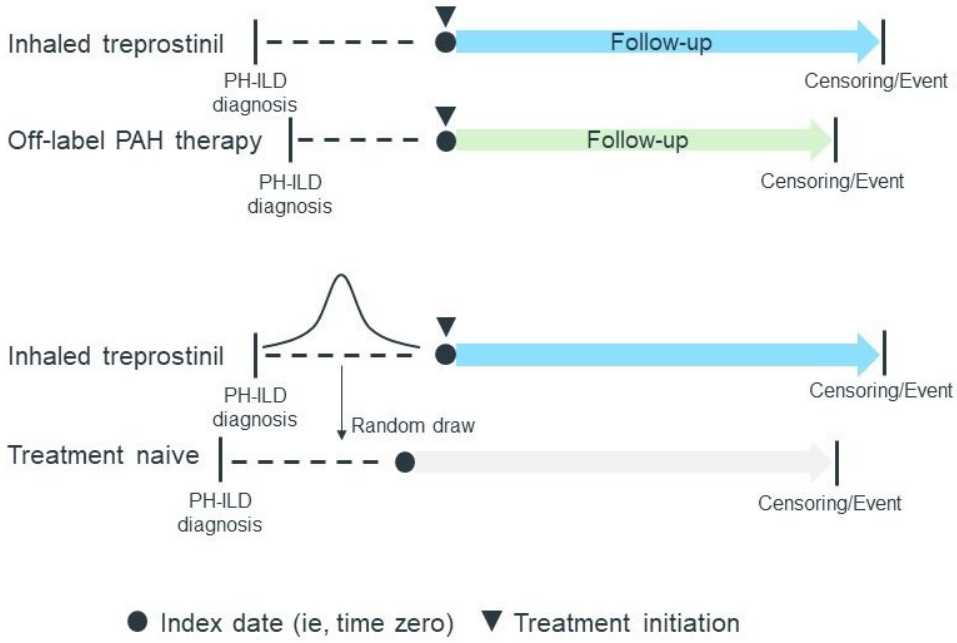


Figure 2: Overview of the index date

Abbreviations: PAH, pulmonary arterial hypertension; PH-ILD, pulmonary hypertension - interstitial lung disease.

4.3 Study Population

This study will include adult patients (aged ≥18 years at index date) diagnosed with PH associated with ILD of various aetiologies, documented by an RHC.

The intervention (inhaled treprostinil) group is captured in the INCREASE trial (RIN-PH-201), a multicentre, randomised, double-blind, placebo-controlled, 16-week Phase III trial, and INCREASE OLE trial (RIN-PH-202), an open-label extension study with a follow-up of up to 108 weeks. The RW comparator group will be derived from European disease specific data sources COMPERA, REHAR, and UKRB (see Section 4.7).

The intervention arm of the INCREASE and INCREASE OLE clinical trials will be compared with 2 different comparator groups derived from RWD in Europe: (1) an external comparator group of treatment naïve patients; (2) an external comparator group of patients treated with off-label PAH therapy (excluding prostanoids).

4.3.1 Inclusion Criteria

The following criteria must be met to be included in the study:

- Informed consent according to national and local standards, where applicable[9]
- Age ≥18 years at index date
- Diagnosis of WHO Group 3 PH before or at 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:
  - PVR >3 Wood Units (WU)
  - pulmonary capillary wedge pressure (PCWP) of ≤15 mmHg
  - mPAP of ≥25 mmHg
- 6MWD ≥100 meters before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- Patients with connective tissue disease (CTD) have a forced vital capacity (FVC) of <70% before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- A record of any approved therapy for PAH (excluding prostanoids)[10] during the study period (for the external comparator group treated with off-label PAH therapy only)

4.3.2 Exclusion Criteria

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

- A record of any approved therapy for PAH[10] before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date, or during the study period (for the treatment naïve external comparator group only)

[9] Informed consent is specific to entry into the register and not study specific. In the United Kingdom secondary data can be used for other purposes (e.g., research) with a consent waiver. However, patients have the possibility to opt out.

[10] A list of drug classes and active substances used in the treatment of PH-ILD have been presented in Table 9.

4.3.3 Follow-up

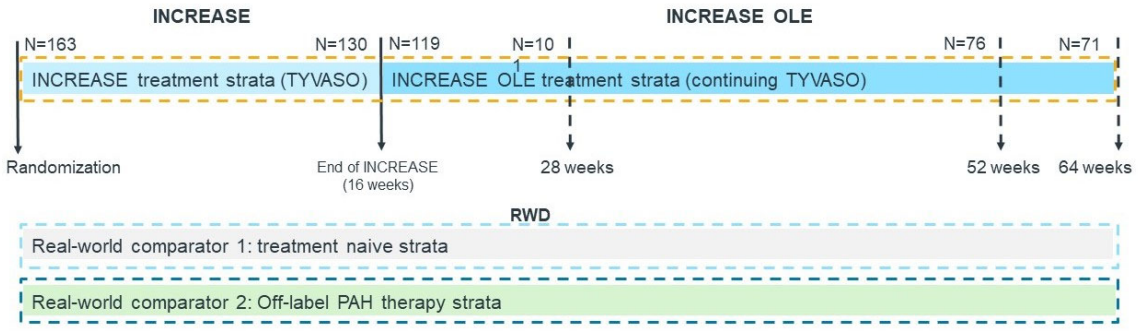
Study subjects will be followed-up from the index date until the date of any of the following events, whichever comes first:

- Exit from the clinical trial/data source
- Outcome of interest[11]
- Lung transplantation
- Death
- End of study[12]

4.4 Exposures of Interest

The primary exposure of interest is inhaled treprostinil (TYVASO). The exposed group will consist of patients who were randomised to inhaled treprostinil in the INCREASE RCT (163 patients) and then continued treatment with inhaled treprostinil in the INCREASE OLE trial (119 patients) (Figure 3).

Exposure to inhaled treprostinil will be compared to SOC in Europe (Figure 3). The comparator group will consist of patients from RW data sources (COMPERA, REHAR, and UKRB) who are treatment naïve or treated with off-label PAH therapy. PAH approved therapy for the off-label treatment of PH-ILD include ERAs, PDE5s, and soluble guanylate cyclase stimulators (SGCs) (see Table 9 in Appendix B).



[11] For time-to event outcomes.

[12] End of 52 weeks or 64 weeks of follow-up for the inhaled treprostinil treatment group or date of last available data on data extraction for the real-world SOC comparator groups.

Figure 3: Overview of the exposure and comparator groups

Abbreviations: INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; N, sample size; OLE, open-label label extension; PAH, pulmonary arterial hypertension; RWD, real-world data.

4.5 Outcomes of Interest

Study outcomes and respective definitions are summarised in Table 2.

Table 2: Outcomes of Interest

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	RW population	Assessment time point(s)[a]	Outcome type
1	6MWD	Peak 6MWD measured within 10 to 60 minutes after the most recent dose of TYVASO	A record of 6MWD measured during a routine healthcare visit	PH-ILD patients from COMPERA, REHAR, and UKRB[b]	28 weeks ±30 days 52 weeks ±30 days	Primary
2	Clinical worsening	a) Hospitalisation (all causes) b) Decrease in 6MWD ≥ 15% from baseline c) Decrease in FVC ≥ 10% from baseline d) Death (all causes)	a) Hospitalisation (all causes) b) Decrease in 6MWD ≥ 15% from baseline c) Decrease in FVC ≥ 10% from baseline d) Death (all causes)	Subsample of PH-ILD patients from COMPERA and REHAR[c]	Up to 28 weeks +30 days Up to 64 weeks +30 days	Secondary
3	All-cause mortality	Death from all causes occurring during the study period	Death from all causes as recorded in the data source	PH-ILD patients from COMPERA, REHAR, and UKRB[b]	Up to 28 weeks +30 days Up to 52 weeks +30 days	Secondary

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	RW population	Assessment time point(s)[a]	Outcome type
					Also analysed as time-to-event endpoint using all available follow-up data.	
4	Pulmonary function (FEV1, FVC, TLC, DLCO)	PFTs performed after recovering from 6MWTs and included the following evaluations: FEV1, FVC, TLC, and DLCO	PFTs performed during a routine healthcare visit	PH-ILD patients from COMPERA, REHAR, and UKRB[b]	28 weeks ±30 days 64 weeks ±30 days	Secondary
5	All-cause hospitalisation	Hospitalisation from all causes occurring during the study period	Hospitalisation from all causes as recorded in the data source	Subsample of PH-ILD patients from COMPERA and REHAR[c]	Up to 28 weeks +30 days Up to 52 weeks +30 days Also analysed as time-to-event endpoint using all available follow-up data.	Secondary
6	NT-proBNP	Blood for NT-proBNP assessment drawn prior to conducting the 6MWT	Blood for NT-proBNP assessment drawn during a routine healthcare visit.	PH-ILD patients from COMPERA, REHAR, and UKRB[b]	64 weeks ±30 days	Secondary

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	RW population	Assessment time point(s)[a]	Outcome type
7	Oxygenation	SpO2 assessed immediately prior to, throughout the conduct of, and immediately after each scheduled 6MWT assessment. Supplemental oxygen requirement assessed as the amount of supplemental oxygen required at rest.	As assessed in the specific data source	PH-ILD patients from COMPERA, REHAR, and UKRB[b]	28 weeks ±30 days 52 weeks ±30 days	Secondary
8	Proportion of treatment success	Assessed in a 3-step hierarchical order: 1) Survival 2) No clinical worsening 3) Treatment success (15% increase in 6MWD	Assessed in a 3-step hierarchical order: 1) Survival 2) No clinical worsening 3) Treatment success (15% increase in 6MWD and 30%	Subsample of PH-ILD patients from COMPERA and REHAR[c]	64 weeks +30 days	Exploratory

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	RW population	Assessment time point(s)[a]	Outcome type
		and 30% decrease in NT-proBNP)	decrease in NT-proBNP)			

Abbreviations: 6MWD, six-minute walk distance; 6MWT, six-minute walk test; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; OLE, open-label extension; PFTs, pulmonary function tests; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; RW, real-world; RWD, real-world data; SpO2, saturation of peripheral capillary oxygenation; TLC, total lung capacity; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom.

[a] The nearest outcome measure to the time points of interest (28 weeks, 52 weeks, and 64 weeks) will be used with a maximum variation of ±30 days.

[b] Datasets from COMPERA, REHAR and UKRB will be combined for analysis.

[c] Datasets from COMPERA and REHAR will be combined for analysis.

4.6 Other Variables (Covariates)

The variables presented in Table 3 will be considered as selection criteria, to describe the study cohort´s baseline characteristics, or as adjustment variables for confounding control. The final choice of baseline characteristics, potential risk factors, and confounders will depend on the availability and completeness of data across the data sources and clinical relevance (Appendix C). Specific definitions for all variables will be presented in detail in the SAP.

At baseline, the variables presented in Table 3, will be considered to create the PS, since they may influence the decision of prescribing TYVASO or other PH-ILD SOC drugs and are considered potential risk factors for each outcome. Confounding variables will be retrieved at index date or in the look-back period as presented in Figure 1.

Table 3: Patients´ characteristics and potential confounders/risk factors

	Baseline characteristics	**Candidate for PS**
Demographic characteristics		
Age	x	x
Sex	x	x
Lifestyle characteristics		
Height, weight, and/or body mass index	x	x
Smoking	x	x
General medical history		
Cardiovascular disease	x	x
LVEF	x	x
Diabetes	x	x
Obstructive sleep apnoea	x	x
PH-ILD disease history and clinical characteristics		
Time since PH-ILD diagnosis	x	x
Aetiology of lung disease	x	x

6MWD	x	x
PVR	x	x
PCWP	x	x
mPAP	x	x
Oxygenation	x	x
TLC	x	x
FVC	x	x
FEV1	x	x
DLCO	x	x
NT-proBNP or BNP	x	x

Abbreviations: 6MWD, six-minute walk distance; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; PCWP, pulmonary capillary wedge pressure; PH-ILD, pulmonary hypertension - interstitial lung disease; PS, propensity scores; PVR, pulmonary vascular resistance; TLC, total lung capacity.

For the analysis of functional capabilities, exercise capacity (assessed by 6MWD), and survival potential confounders include demographics (eg, older age) and lifestyle characteristics (eg, smoking) [37–39], PH-ILD disease history (eg, disease severity, 6MWD at diagnosis) [40,41], and other clinical characteristics (eg, FVC, PVR, diffusing capacity of the lungs for carbon monoxide, SpO2, NT-proBNP) [38,42,43]. Risk factors for AEs (eg, exacerbations) include vital capacity, FVC and total lung capacity [44]. Comorbidities recognised as risk factors for survival include left-sided heart disease (assessed by LVEF) and other cardiovascular disease (eg, coronary artery disease, atrial fibrillation) [43].

4.7 Data Sources and Collection

Appropriateness and data capture of 3 relevant PH data sources (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre [ASPIRE], COMPERA, and REHAR) were assessed during the qualitative feasibility led by Orpha Strategy and 2 of them, COMPERA and REHAR, were considered suitable for this study. A third data source (UKRB) was subsequently identified for inclusion as part of this study and a high-level qualitative assessment was conducted to better understand this data source. A quantitative feasibility assessment study of all 3 data sources is planned ahead of full study execution.

Two types of data sources will be used in this study: (1) data for the inhaled treprostinil group will be obtained from clinical trial data; (2) data for the SOC (treatment naïve and off-label PAH therapy) will be obtained from RW disease specific PH registries (Table 4).

A quantitative feasibility study will be conducted between March 2023 and January 2024 to assess the suitability of COMPERA, REHAR, and UKRB to address this study´s research question and objectives. The feasibility study will include a feasibility plan, quantitative assessment of the data, and feasibility report. The data assessed in the feasibility assessment will focus on the external comparator data sources COMPERA, REHAR, and UKRB, which will include patients from Germany, Italy, UK, Belgium, Netherlands, Switzerland, Austria, Greece, Slovakia, Hungary, Latvia, Lithuania, and Spain. The data sources have been selected based on the ability to capture 6MWD and other study outcomes in addition to the size of the PH-ILD WHO Group 3 patient population in the registries.

Table 4: Overview of data sources

Arm	Patient population	Data source	Study type
Treatment arm	TYVASO treatment	INCREASE + INCREASE OLE	RCT + Open-label extension
Comparator 1	Treatment naïve	REHAR + UKRB	RWD
Comparator 2	Off-label PAH treatment	REHAR + UKRB + COMPERA	RWD

Abbreviations: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; OLE, open-label extension; RCT, randomised controlled trial; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; RWD, real-world data; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom.

4.7.1 Data from INCREASE and INCREASE OLE Clinical Trials (treatment group)

Patients who were randomised to inhaled treprostinil in INCREASE RCT and then continued inhaled treprostinil in its INCREASE OLE will compose the inhaled treprostinil group.

INCREASE was a randomised, placebo-controlled, double-blinded clinical trial that assessed the safety and effectiveness of inhaled treprostinil in patients with PH-ILD. INCREASE enrolled 326 patients from 93 centres across the USA, with 163 patients randomised to the inhaled treprostinil group. The study period for INCREASE comprised of 4 weeks for screening, and 16 weeks for treatment, with an additional 30 days for AE follow-up after trial discontinuation. Subjects who completed the INCREASE study were offered the opportunity to continue in INCREASE OLE. 119 patients from the INCREASE treatment strata (see Figure 3) continued treatment with inhaled treprostinil in INCREASE OLE.

4.7.2 Data from Disease Specific Registries (comparator group)

RWD from disease specific registries will be used for the 2 comparators: (1) an external comparator group of treatment naïve patients; (2) an external comparator group of patients treated with off-label PAH therapy (excluding prostanoids).

4.7.2.1 REHAR

REHAR is a Spanish database that began data collection in 2017 from voluntary participants with PH, who also have associated respiratory conditions [45]. REHAR has both retrospective and prospective data capture across 14 centres, which is used for scientific purposes and maintained by relevant data and privacy protection laws.

The 3 goals of this database are to increase understanding of the clinical characteristics, care and management of this patient population, to determine prevalence more accurately, and to better comprehend the short- and long-term effects of the disease and available treatment options.

Only WHO Group 3 PH patients, as defined by the World Symposium of Pulmonary Hypertension, are included in the registry. This classification includes (i) a diagnosis of respiratory disease according to the clinical guidelines of the European Respiratory Society/American Thoracic Society and the regulations of the Spanish Society of Pulmonology and Thoracic Surgery; and (ii) a diagnosis of PH by RHC in an expert centre of PH.

4.7.2.2 COMPERA

COMPERA was established in 2007 and is one of the largest prospective PH registries globally, including approximately 11,000 patients across Europe [46] from 61 recruiting centres. This data source includes PH patients from WHO groups 1 to 5. While the data source originates in Germany, countries recruiting to this database also include Austria, Belgium, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Slovakia, Switzerland, and the UK. COMPERA collects detailed but pseudonymised data on PH patients' demographics, incidence, treatment-based and survival outcomes, and AEs. It is fully internet-based and complies with high standards using a number of techniques, including source data verification and automated checks for plausibility of data-entry.

The overall goals of this registry include providing RWD to support RCT in PH and serving as a quality control tool for treatment facilities to compare their outcomes to the averages of other centres.

This registry does not allow for self-registration; rather, patients must register through one of the participating centres. The registry was initiated by researchers, is fully independent of the pharmaceutical industry, and is being financed with educational funds from Acceleron, AOP Orphan, Bayer, Ferrer, Janssen and Open Monoclonal Technology, Inc. [46].

4.7.2.3 UKRB

The UKRB PH registry is a research ready dataset, collecting routine clinical information on PH-ILD patients treated at the Royal Brompton Hospital National Pulmonary Hypertension Service (London, UK). The Royal Brompton and Harefield hospitals are tertiary centres and together form the largest specialist centre for the treatment of heart and lung disease in the UK, and among the largest in Europe. Data has been collected on consecutive patients treated at this centre and meeting the dataset inclusion criteria since 1 January 2000 [47]. The registry is focused on WHO group 3 PH-ILD patients and was created to understand the causes of pulmonary hypertension and prognosis. Funding for this database was awarded by Ferrer pharmaceuticals.

5. STATISTICAL METHODS

5.1 Sample Size

The main objective of this external comparator study is to compare the mean difference at 52 weeks from baseline in 6MWD associated with exposure to inhaled treprostinil in patients from INCREASE (RIN-PH-201), and INCREASE OLE (RIN-PH-202) clinical trials versus SOC in Europe, among patients with PH-ILD.

The sample size will be based on evaluating the mean difference from baseline in 6MWD, as performed in the INCREASE (RIN-PH-201) clinical trial setting. Treated subjects with inhaled treprostinil (6 mcg/breath) in the INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) will be compared with external subjects derived from RWD in Europe, as described in Section 4.3.

In INCREASE (RIN-PH-201) trial, a total of 326 patients were enrolled at 93 centres from February 3, 2017, through August 30, 2019, and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients). Of the 163 treated subjects, 130 completed week 16 of study assessment. In INCREASE OLE (RIN-PH-202) setting a total of 243 patients enrolled in the trial and 119 patients continued receiving inhaled treprostinil after week 16. Of the 119 patients, 68 patients already completed 52 weeks of 6MWD assessments. Thus, the final number of patients completing 52 weeks is currently unknown, but the number will be between 68 and 119 patients. To investigate multiple relevant scenarios, the sample size calculations below will assume 70, 90, and 110 completers.

The necessary sample size for each SOC group is estimated based on sufficient test measurements across the data sources. For this purpose, 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.

5.1.1 Power Estimates

Sample size calculation was carried out in the R version 4.1.3 using the command *pwr.t2n.test* Estimates of sample size are presented for various scenarios under the following assumptions:

- Estimated mean difference at 52 weeks from baseline in 6MWD 30 metres with standard deviation of 75 metres. These targeted parameters lead to an effect size equal to 0.4.
- Level of significance: two-sided 0.05
- Power: From 80% to 90%
- Targeted number of patients in the treprostinil arm: 70, 90, and 110 patients
- VIF correction: 10%

Table 5: Needed sample sizes in the SOC group to estimate the targeted mean difference of 30 metres with standard deviation of 75 meters, by power and targeted treprostinil sample (treprostinil arm: exposed in INCREASE and INCREASE OLE, SOC group: derived from RWD in Europe)

Treprostinil arm	Power	SOC group	SOC group with VIF correction
70	80%	168	187
	85%	291	323
	90%	1091	1212
90	80%	110	122
	85%	153	170
	90%	248	276
110	80%	91	101
	85%	117	130
	90%	165	183

Abbreviations: SOC, Standard of care; VIF, variance inflation factor.

Table 5 shows the needed sample size for each SOC group that will ensure at least 80% of statistical power based on the available patients in the treprostinil arm.

In the case of 70 patients, a minimum of 187 patients in each SOC group will be needed to compare the treprostinil arm versus SOC group. In case of 90 patients, a minimum of 122 patients in each SOC group will be needed. In the case of 110 patients having the primary endpoint available after 52 weeks, a minimum of 101 patients in each SOC group will be needed. In both cases, variance inflation factor (VIF) corrections were performed by assuming 10% variance inflation due to weighting as described in Section 5.2.2.3 [48]. The applied correction factor is a multiplication by 1/(1-0.1).

5.2 Data Analyses

5.2.1 General Considerations

A statistical analysis plan (SAP) will be developed to describe with full detail variable definitions for exposures, outcomes, covariates, and sub-groups of interest. All analytic methods will be detailed, and a full set of table shells will be included. The SAP will be developed after final protocol approval.

Results will be summarised in tables and/or figures in Word format and analyses will be performed with R, version 4.1.3 or later (https://www.r-project.org/), or Statistical Analysis System (SAS), version 9.2 or later (SAS Institute Inc., Cary, NC, United States of America), or other statistical software as appropriate.

Continuous and categorical variables will be described using the relevant metrics, as described below in Section 5.2.2.1. 95% CI will be presented for means using a normal approximation and for proportions using a binomial approximation.

The total number of patients and missing data for each variable will be reported.

To yield reliable inferences in time-to-event analysis, it is generally recommended to have a minimum of 10–20% of the arm free of events and unfiltered by the end of the follow-up period [49]. To estimate the incidence and risk effect, this criterion will be used.

5.2.2 Planned Analyses

5.2.2.1 Descriptive statistics

5.2.2.1.1 Summary statistics

To gain an understanding of overall patterns, descriptive analyses will be performed utilising number and percent within each category for categorical variables, and mean (standard deviation), median (interquartile range), and other relevant summary statistics for continuous variables.

5.2.2.1.2 Incidence rate estimation

Incidence rates (and corresponding 95% CI) of the outcomes of interest will be estimated for each defined arm. The incidence rate per 1,000 person-years will be defined as the number of new cases with the outcome of interest in the defined time period divided by the number of person-years at risk and multiplied by 1,000:

$$incidence\ rate = \frac{number\ of\ new\ cases\ with\ outcome\ of\ interest\ during\ period\ of\ follow\text{-}up}{person\text{-}years\ at\ risk} \cdot 1000$$

A patient will only be considered at risk until end of follow-up, as defined in Section 4.3.3. Since the incidence rate of the outcome of interest during the entire follow-up is not expected to be constant, its estimation will be stratified based on follow-up periods (ie, 3 months, 6 months, and 1 year of follow-up).

5.2.2.1.3 Time-to-event analysis

The time from index date to time-to-event outcomes of interest or to censoring, as described in Section 4.3.3, is considered as the period at risk. Kaplan-Meier curves for the time-to-event will be presented for the entire period at risk.

5.2.2.2 Average treatment effect in the untreated population

To estimate the treatment effect the outcomes of the inhaled treprostinil group will be compared to those of the comparator group. For that, the average treatment effect in the untreated population (ATU) will be estimated. The ATU [50,51] is a marginal estimator which standardises the treatment effect according to the baseline covariate values as observed in the comparator group.

To estimate the ATU, a suitable external comparator group will be identified consisting of individuals who did not receive inhaled treprostinil. Propensity score (PS) weighting will be employed to balance the covariate distributions between the treprostinil arm and SOC comparator groups, as described below in Section 5.2.2.3.

5.2.2.3 Propensity score and Inverse Probability Weighting

The PS will reflect the probability of a subject being assigned to inhaled treprostinil or the comparator exposure arm, given a set of observed covariates.

The logistic regression model will be used to obtain PS. The list of covariates for the PS model can be found in Section 4.6. Including these variables will reduce bias and enhance the precision of the estimated treatment effect [52].

The PS will be used to calculate the inverse probability of treatment weights (IPTW) to balance baseline patient characteristics between inhaled treprostinil and SOC groups. To assess the balance of observed potential confounders between the exposure categories in the weighted sample using IPTWs, standardised differences in all covariates will be calculated and assessed. Balance diagnostics in covariates will be reported before any outcome description.

Application of the IPTW creates a pseudo-population in which the distribution of baseline covariates is independent of treatment assignment and permits estimation of the marginal effect of the treatment on the outcome, given that all confounders are appropriately accounted for in the PS model [53].

The weights are calculated separately for those in the inhaled treprostinil and SOC arm as: Untreated group (SOC)=1, Treated group (Treprostinil)=PS/(1-PS). This method results in estimation of the ATU [54–57].

Subjects with very low scores in the comparator group may result in extremely large weights. Such weights can increase the variability of the estimated treatment effect, such weights will be truncated at the 99th percentile [58].

Absolute standardised mean differences (SMDs) above 0.25 will be interpreted as inacceptable imbalance, while imbalances between 0.1 and 0.25 will be interpreted as moderate imbalance [59]. If ≥10% of the included covariates' SMDs are higher than 0.1, the average treatment effect on the overlap population (ATO) will be estimated in addition to the ATU, and will become the primary analysis approach. If <10% but >0% of the included covariates' SMDs are higher 0.1, the ATO will be estimated as a supplementary analysis.

Results from different PS adjustments (ie, PS matching, standardised mortality ratio weighting, etc.) may be explored.

5.2.2.4 Comparative analyses

To estimate the treatment effect on survival outcomes, Restricted Mean Survival Time (RMST) models (and Cox proportional hazard regression as a potential sensitivity analysis [60,61]) will be applied. For each time-to-event outcome of interest an RMST model will be developed to estimate RMSTs, RMST differences and 95% CIs of inhaled treprostinil versus SOC in PH patients.

To estimate the treatment effect on longitudinal outcomes weighted mixed effects models [62–64] will be used. The weights will be incorporated into the analysis to appropriately adjust for differences in baseline covariates. For each longitudinal outcome of interest, the difference in weighted means and 95% CIs will be reported.

The summary table (Table 6) for all planned analysis described in Section 5.2.2 for each different outcome described in Section 4.5 can be find below:

Table 6: Summary of planned analyses

Outcome	Outcome type	Planned analysis
6MWD	Primary outcome	Weighted summary statistics Weighted mixed-effects models
Clinical worsening*	Secondary outcome	Weighted summary statistics Weighted incidence rates
All-cause mortality	Secondary outcome	

Outcome	Outcome type	Planned analysis
All-cause hospitalisation	Secondary outcome	*Weighted mixed-effects models Weighted RMST models (and Cox Proportional Hazards regression as a potential sensitivity analysis)
Pulmonary function (FEV1, FVC, TLC, DLCO)	Secondary outcome	Weighted summary statistics Weighted mixed effects models
NT-proBNP	Secondary outcome	
Oxygenatiom	Secondary outcome	

Abbreviations: 6MWD, six-minute walk distance; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; RMST, restricted mean survival time; TLC, total lung capacity.

5.2.3 Exploratory Analyses

To assess the proportion of treatment success as defined in Section 4.5, statistical methods for PS weighting in Section 5.2.2.3 will be used and weighted summary statistics as described in Section 5.2.2.1 will be reported.

To demonstrate that the population of the pivotal INCREASE study is of relevance to the European setting, the comparability of INCREASE and INCREASE OLE internal trial comparator group to the European external RW group will be explored.

The SMD will be used as a balance measure of individual covariates before and after adjustment.

SMDs between the INCREASE and INCREASE OLE internal trial comparator group and external comparator naïve group will be calculated for all the included covariates (Section 4.6) before adjustment and after adjustment using a PS model.

For this exploratory analysis, the PS model will reflect the probability of a subject being assigned to placebo or the treatment naïve arm. The described statistical methods for PS weighting in Section 5.2.2.3 and treatment effect estimation in Section 5.2.2.4 will be used. If the measured covariates have sufficiently adjusted for confounding, the adjusted effect in the primary outcome 6MWD, should approximate the null effect.

5.2.4 Subgroup Analyses

Subgroup analyses for the primary outcome will be conducted according to:

PH-ILD aetiology categories:

- Idiopathic interstitial pneumonia
- CPFE
- CTD
- Other PH-ILD aetiologies.

PVR categories:
- PVR >5 WU
- PVR ≤5 WU

In the subgroup analyses of the primary outcome descriptive statistics will be reported, as described in Section 5.2.2.1. Comparative analyses will only be undertaken if sufficient outcome events are observed, as it will be defined in the SAP. For this comparison, statistical methods described in Section 5.2.2.4 will be used and further details will be provided in the SAP. The same weights as in the overall analysis will be applied, such that no new re-weighting in a subgroup analysis will be attempted.

5.2.5 Handling of Missing Data

It is optimal to prevent missing data to the extent possible through strategies set forth in the design and conduct of a study. For the current study, it is aimed to minimise missing information by checking for patterns of missingness and addressing any issues with targeted operational strategies.

The number of missing values for data elements will be reported and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed [65–71].

Multiple imputation (MI) [65–71] will be used as the primary approach to handle missing covariate data [70]. After that PS and IPW will be calculated as described in Section 5.2.2.3.

A sensitivity analysis will be carried out comparing the results from the MI with an alternative missing data handling approach (eg, only using covariates with sufficient completeness).

5.2.6 Sensitivity and Supplementary Analyses

5.2.6.1 Sensitivity analyses for unmeasured confounding

To assess how robust an association is to potential unmeasured confounding E-value will be calculated [72].

The E-value is defined as the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and the primary outcome to fully explain away a specific treatment-outcome association, conditional on the measured covariates [72].

A large E-value implies that considerable unmeasured confounding would be needed to explain away an effect estimate. A small E-value implies little unmeasured confounding would be needed to explain away an effect estimate [72].

5.2.6.2 Supplementary analyses: Handling intercurrent events

Intercurrent events, such as death to all causes, would affect the existence of the primary measurements. To handle these terminal events in the primary analysis, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 (R1) addendum specifies several possible analysis approaches, including the treatment policy strategy, the composite endpoint strategy and the hypothetical strategy [50,73]. The strategy for the main analysis will be based on the treatment policy approach.

To provide an additional perspective to the treatment effect, a composite strategy or a hypothetical approach will be applied. For the composite endpoint strategy, intercurrent events will be incorporated into the endpoint's definition. For the hypothetical approach, intercurrent events will be statistically adjusted by modelling missing endpoint data (eg, by Inverse Probability of Censoring Weights) [74].

5.3 Data Reporting

A final analysis will be performed.

5.3.1 Final Analyses and Reporting

The final report will encompass all planned analyses, including a description of the complete study population as described above in Section 5.2 and fully detailed in the SAP.

6. LIMITATIONS OF RESEARCH METHODS

Although efforts will be made to ensure robustness of the study, several limitations inherent to the study design, data collection, and analysis should be acknowledged.

The characteristics of patients who were eligible for INCREASE/INCREASE OLE trial may differ from those in the external comparator group (ie, the exposed group and comparator group may not be exchangeable). This may lead to differences in potential outcomes [75]. To mitigate this, the study design and analytical approaches will be guided by the target trial emulation framework [28,29]. Key eligibility criteria from INCREASE/INCREASE OLE trials will be emulated and measured adjustment variables will be used for confounding control. However, residual differences may still exist due to unknown or unmeasured covariates. Thus, to assess the robustness of the association to potential unmeasured confounding, the E-value will be calculated (see Section 5.2.6).

Trial patients (ie patients from INCREASE/INCREASE OLE trial) are more likely to be adherent to treatment. However, in RW practice patient decisions to use a particular medication

can frequently change. Misclassification of exposure in the external comparator group, may result in bias of effect measures. Defining exposure on an as-treated basis can decrease the probability of misclassifying nonexposed patients as exposed [75].

The validity of any secondary data analysis depends on the accuracy and completeness of available information in the RW data sources. Missing information may further vary between individual RW data sources. To minimise the risk of including inaccurate information, all retrieved data will be reviewed for possible inconsistences or implausible information. Missing information will be handled as described in Section 5.2.5. Percentage of missing information will be reported.

This ECA study seeks to compare TYVASO treated patients from USA based INCREASE/INCREASE OLE trials with RW patients on SOC in Europe. Period start of INCREASE to the end of INCREASE OLE was February 2017 to June 2021. The period of data extraction from the PH registries will be extended to all available data at data extraction (see Section 4.2). There may be differences in patient characteristics or the quality of care (eg, whether the SOC landscape can be considered sufficiently stable in the study period and the quality of care can be regarded comparable across sites) which may act as unmeasured confounders.

Patients in routine clinical practice are not followed-up as closely and frequently as patients in clinical trials. Information on some outcome variables may not be collected, are only collected in some of the individual RW data sources (eg, hospitalisation is only available in COMPERA and REHAR), or outcome definition differs from trial patients (eg, in COMPERA only hospitalisations related to PAH or PH are captured). Interval of six-minute walk tests, PFTs, and laboratory measurements are expected to be less frequent in RWD. Further, loss to follow-up (eg, in REHAR when a patient transfers from one region to another) may be a concern in RWD. A feasibility assessment of presence and frequency of assessments for outcomes will be conducted to understand whether differential capture of outcomes between the study groups can be expected [75].

In INCREASE/INCREASE OLE outcome assessment occurred every 4-12 weeks with a variation of ±14 days. In the RW comparator group, the nearest outcome measure to the time points of interest (28 weeks, 52 weeks, or 64 weeks) will be used with a maximum variation of ±30 days. Bias may occur if the RWD comparators' outcome assessments differs markedly from INCREAS/INCREAS OLE trial patients in terms of measurement frequency, method of ascertainment, or definition [75].

Immortal time refers to a span of time in the observation period during which the outcome under study could not have occurred. It usually occurs with the passing of time before a subject initiates a given exposure. An incorrect consideration of this unexposed time period in the study design may lead to immortal time bias [76]. Alignment of eligibility, beginning of treatment,

and index date across trial and external comparator group is planned to avoid immortal time bias.

7. STUDY MANAGEMENT

This study will be performed by IQVIA with guidance, input, review, and approval of Ferrer.

7.1 Quality Control

The study will be conducted according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [77], the ENCePP Checklist for Study Protocols (see Appendix D), the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practice Guidelines (GPP) [78] and IQVIA standard operating procedures (SOPs). At the study level, all aspects of the study from protocol development to the reporting of the results will be conducted within the framework of the IQVIA Quality Management System.

According to the policies and procedures above, a quality control (QC) plan for the study will be developed and executed, which will include QC on the protocol in general, study methodology, SAP, programming, data management and analysis, and study report including study results and conclusions.

- The study QC plan will establish ownership for the execution of the individual QC steps. The principle of the independence of QC applies.
- IQVIA project management will ensure that individuals responsible for the execution of specific QC steps will have the knowledge, capability and experience that are adequate for the task.
- The result of the individual steps of the QC plan will be documented, and corrective actions required, if any, will be included.
- Datasets and analytic programmes will be stored according to IQVIA and data holder procedures, with access restricted to authorised study personnel at the respective entities.

The Project Manager will verify training compliance of IQVIA employees contributing to the study, in accordance with Ferrer´s SOPs.

The executed QC plan will be subjected to a final review and approval for sufficiency and completeness by the IQVIA project management team.

7.2 Data Management

A Data Management Plan (DMP) has been created for the feasibility assessment; amendments will be made to the DMP for the full study. The DMP will describe data extraction, transfer, and storage, as well as QC and cleaning of the data.

To use the PH databases' data for the purposes of this study, all required ethics approvals and access to the study data will be applied for by IQVIA. A contract will be signed between the sponsor and each database for the purposes of this study. After ethics approval is obtained, IQVIA will provide specifications for data extraction for the purposes of this study to the PH databases. Data from the INCREASE trial will be provided by United Therapeutics (UT) Corporation, the current owners of the trial data, after a mutual agreement to use this data for the purposes of addressing the research question stated in this protocol. UT have granted authorisation to Ferrer for its data use in Marketing Authorisation Applications worldwide.

For the data transfer process, IQVIA will utilise a Secure File Transfer Protocol, which is supported by a system called MOVEIT Transfer. MOVEIT Transfer utilises enterprise level advanced security features, and proven encryption to ensure complete security of transferred data, including Level 3 sensitive data.

IQVIA will maintain appropriate data storage, including periodic backup of files and archiving procedures. The de-identified patient-level data will be stored in IQVIA's secure, restricted server environment, known as the IQVIA Level 3 Enclave, based in Woking, UK. This Enclave ensures that all data processing remains within its protected confines, supported by International Organization for Standardization 27001 certified security measures and comprehensive information security policies. Access to the study data is restricted to IQVIA team members assigned to work on data management and statistical programming tasks. Access to the patient-level study data cannot be given to any third parties; only aggregated results will be presented to the Sponsor or otherwise published.

Within the Level 3 Enclave, another 2 security levels will be implemented to prevent the scientific team from being influenced by outcome data. Once the data can be accessed, a non-scientific IQVIA team-member will access the full dataset and segregate the outcome data to a folder which cannot be accessed by the scientific team (epidemiologists, biostatisticians, and statistical programmers). Data segregation will be performed for the data received from COMPERA, REHAR, and UKRB, as well as the INCREASE and OLE data.

R language v4.1.3 or later [79] (https://www.r-project.org), or SAS version 9.2 or later (SAS Institute Inc., Cary, NC, United States of America), or other statistical software as appropriate will be used for managing data and creating the analysis database. Additionally, they will be used for statistical analysis to generate tabulations and graphics, as well as for statistical modelling.

High data quality standards will be maintained, and processes and procedures utilised to repeatedly ensure that the data are as clean and accurate as possible when presented for analysis. Data quality will be enhanced through a series of programmed data quality checks that automatically detect out of range or anomalous data.

In COMPERA, the patients are pseudonymised during data-entry by creating a new and unique study identification number. IQVIA will not have access to the key which links the individual

identifiers to the study identification number, thus individuals cannot be directly identified. In REHAR and UKRB, all patient-level data accessible to IQVIA will have original personal identifies replaced with a study identification number. Thus, IQVIA will not have access to data that allow individuals to be directly identified. Ferrer will not have access to the registries' patient-level data at any time of the study.

IQVIA oversees archiving and destructing the data. Study data and supporting documents will be kept for 5 years after the completion of the final study report. Prior to this period, IQVIA shall not destroy any study material without approval from the Marketing Authorisation Holder (MAH). Secure archives will be maintained for the orderly storage and retrieval of all study related material. An index shall be prepared to identify the archived contents and their location. Access to the archives will be controlled and limited to authorised personnel only.

The study data cannot be used for other purposes than described in this protocol. All requests to use the study data for other purposes must be subjected to appropriate ethics approval and contracting processes.

7.3 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments.

7.4 Publication Policy

Study findings will be communicated at appropriate scientific meetings and/or published in relevant peer-reviewed journals.

7.5 Disclosures

Ferrer Internacional S.A. provides funding for all of the data sources, COMPERA, REHAR, and UKRB, participating in this study.

8. SAFETY REPORTING

8.1 Procedure for Reporting Adverse Events

Pursuant to the requirements for reporting of AEs for secondary data, according to Good Pharmacovigilance Practices (GVP) module VI, VI.C.1.2.1.2, AE reporting will not be conducted as part of this study given the study objectives will be met using secondary data [80].

AEs, occurring within the clinical INCREASE + INCREASE OLE trial have been reported in accordance with their study protocol.

9. ETHICAL AND REGULATORY CONSIDERATIONS

9.1 Guiding Principles

The study will be designed and conducted in accordance with the ENCePP Code of Conduct [81], the Guidelines for Good Pharmacovigilance Practices [82], the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations. IQVIA (who will perform the study on behalf of Ferrer) will take responsibility for obtaining necessary approvals (ethical or otherwise), and access to the study data.

To ensure the full data protection of patients, all the research data in each country is pseudonymised. The implications of the General Data Protection Regulation (EU) 2016/679 on the national legislations, during the course of the study, will be considered.

Before commencement of the study, an application including the study protocol and other necessary study documentation will be submitted to relevant independent Ethical/Research Review Boards in each country. Permit processes by other agencies, data holders, or regulatory entities may also be required. Country-specific details of the requirements of the local Ethical Research Review Boards, any outcome of an ethical review procedure, and data protection requirements will be described and addressed in country-specific sections of the SAP.

9.2 Independent Ethics Committee / Institutional Review Board

This study does not require formal ethical approval by an Institutional Review Board but will seek favourable opinion from ethical committees for the conduct of the study and access to data from clinical registries. By being included in these registries, patients consented to the use of data for research purposes. The anonymised data used in the analysis is securely transmitted to a server in the UK and is only used for the purpose of conducting that analysis.

For access to the COMPERA dataset, a favourable opinion from the ethics committee of the Hannover Medical School was sought. For REHAR, the scientific committee approved the study. For the UKRB, this study sought approval from the Health Research Authority (including Research Ethics Committee review) via central Integrated Research Approval System application ID 335576.

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11. APPENDICES

Appendix A. Complete list of eligibility criteria applied in the INCREASE and INCREASE OLE trials, and respective availability in RWD

Table 7: INCREASE clinical trial eligibility criteria

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
INCLUSION CRITERIA					
1	Subject voluntarily gives informed consent to participate in the study	Available	Available	Not available[a]	Informed consent according to national and local standards, where applicable[b]
2	Males and females aged 18 years or older at the time of informed consent	Available	Available	Available	Age ≥18 years at index date, year of birth
2a	Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and nonlactating, and will: Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), or Use 2 medically acceptable, highly effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug	Partially available	Not available	Not available	A record of pregnancy during the study

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
2b	Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug	N/A	N/A	N/A	N/A
3	The subject has a confirmed diagnosis of WHO Group 3 PH based on CT imaging, which demonstrates evidence of diffuse parenchymal lung disease performed within 6 months prior to randomisation. Subjects may have any form of ILD or CPFE	Available	Available	Available	Diagnosis of WHO Group 3 PH before or at index date associated with any form of ILD or CPFE
4	Subjects are required to have a RHC within 1 year prior to randomisation with the following documented parametres: PVR >3 WU PCWP of ≤15 mmHg mPAP of ≥25 mmHg	Available	Available	Available	RHC up to 1 year before the index date with the following parameters: PVR >3 WU PCWP of ≤15 mmHg mPAP of ≥25 mmHg
5	Baseline 6MWD ≥100 meters	Available	Available	Available	6MWD ≥100 meters before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
6	Subjects on a chronic medication for underlying lung disease (ie, pirfenidone, nintedanib, etc.) must be on a stable and optimised dose for ≥30 days prior to randomisation	Not available	Partially available	Partially available	Patients on medication(s) for underlying lung disease (eg, pirfenidone, nintedanib) with no dose modification in the last 30 days, before the index date
7	In the opinion of the Investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits	N/A	N/A	N/A	N/A
8	Subjects with CTD must have a Baseline FVC of <70%	Available	Available	Available	Patients with CTD have a FVC of <70% before or at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
EXCLUSION CRITERIA					
1	The subject has a diagnosis of PAH or PH for reasons other than WHO Group 3 PH-ILD as outlined in inclusion criterion 3	Available	Available	Available	Diagnosis PAH or PH for reason other than WHO Group 3 PH-ILD before or at index date

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
2	The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy	Not available	Not available	Not available	A record of treatment with prostacyclin or prostacyclin analogue that was discontinued
3	The subject has received any PAH approved therapy including prostacyclin therapy (ie, epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), ERA, PDE5, SGC stimulator within 60 days of randomisation	Not available	Not available	Not available	A record of any approved therapy for PAH before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date
4	The subject has evidence of clinically significant left-sided heart disease as defined by PCWP >15 mmHg LVEF <40%	Available	Available	Available	Record of a left-sided heart disease before or at index date with: PCWP >15 mmHg LVEF <40%
5	The subject is receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline	Not available	Available	Available	Oxygen supplementation of >10 L/min at rest by any mode of delivery before or at index date (closest measurement to index date will be used,

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
					with a maximum look-back period of 6 months)
6	Current use of any inhaled tobacco/marijuana products or a significant history of drug abuse at baseline timepoint designation	Smoking status is available	Smoking status is available	Smoking status is available	A record of smoking or drug abuse
7	Exacerbation of underlying lung disease or active pulmonary or upper respiratory infection within 30 days of randomisation	Not available	Exacerbation of underlying lung disease are available	Not available	A record of hospitalisation or emergency visit for underlying lung disease exacerbation or pulmonary or respiratory infection before index date, with a look-back period of 30 days
8	Initiation of pulmonary rehabilitation within 12 weeks prior to randomisation	Not available	Not available	Not available	Participation in pulmonary rehabilitation before index date, with a look-back period of 12 weeks
9	In the opinion of the Investigator, the subject has any condition that would interfere with the interpretation of study assessments or has any disease or condition (ie, peripheral vascular disease, musculoskeletal disorder, morbid obesity)	N/A	N/A	N/A	N/A

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
	that would likely be the primary limit to ambulation (as opposed to PH)				
10	Use of any investigational drug/device, or participation in any investigational study with therapeutic intent within 30 days prior to randomisation	Not available	Not available	Not available	N/A
11	Severe concomitant illness limiting life expectancy (<6 months)	Not available	Not available	Not available	A record of active malignancy up to 5 years before index date, except for fully excised or treated basal cell carcinoma, cervical carcinoma in-situ, or ≤2 squamous cell carcinomas of the skin
12	Acute pulmonary embolism within 90 days of randomisation	Not available	Not available	Not available	A record of acute pulmonary embolism before the index date, with a look-back period of 90 days

Abbreviations: 6MWD, six-minute walk distance; NO, number of order; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FVC, forced vital capacity; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; N/A, not available; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PDE5, phosphodiesterase type 5 inhibitor; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; PH, pulmonary hypertension; PH-ILD, pulmonary

hypertension - interstitial lung disease; PI, prostaglandin I2; RHC, right heart catheterisation; PVR, pulmonary vascular resistance; SGC, soluble guanylate cyclase; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom; WHO, World Health Organization; WU, Wood units.

[a] In the United Kingdom secondary data can be used for other purposes (eg, research) with a consent waiver. However, patients have the possibility to opt out.

[b] Informed consent is specific to entry into the register and not study specific.

Table 8: INCREASE OLE clinical trial eligibility criteria

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
INCLUSION CRITERIA					
1	Subject voluntarily gives informed consent to participate in the study	Available	Available	Not available[a]	Informed consent to be included in the registry
2	The subject participated in study RIN-PH-201 AND:	N/A	N/A	N/A	N/A
2a	remained on study drug and completed all scheduled study visits OR	N/A	N/A	N/A	N/A
2b	permanently discontinued study drug during the RIN-PH-201 study due to clinical worsening and completed all remaining required scheduled study visits OR	N/A	N/A	N/A	N/A
2c	was enrolled in study RIN-PH-201 at the time that the study/study subject was discontinued by the sponsor	N/A	N/A	N/A	N/A

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
3	Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and nonlactating, and will:	Partially available	Not available	Not available	A record of pregnancy during the study
3a	Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), OR	N/A	N/A	N/A	N/A
3b	Use 2 medically acceptable, highly effective forms of contraception for the duration of study, and at least 30 days after discontinuing study drug	N/A	N/A	N/A	N/A
4	Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug	N/A	N/A	N/A	N/A
EXCLUSION CRITERIA					
1	The subject is pregnant or lactating	Partially available	Not available	Not available	A record of pregnancy during the study
2	The subject was prematurely discontinued from study RIN-PH-201 due to treatment related AEs	N/A	N/A	N/A	N/A

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
3	The subject was prematurely discontinued from study RIN-PH-201 due to clinical worsening and did not undergo premature termination assessments prior to discontinuing study drug and/or did not complete all remaining study visits through the final scheduled visit.	N/A	N/A	N/A	N/A
4	The subject developed a concurrent illness or condition during the conduct of RIN-PH-201 which, in the opinion of the Investigator, would represent a risk to overall health if they enrolled in this study.	N/A	N/A	N/A	N/A

Abbreviations: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; N/A, not available; NO, number of order; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom.

[a] In the United Kingdom secondary data can be used for other purposes with a consent waiver. However, patients have the possibility to opt out.

Appendix B. EXEMPLARY list of drug classes and active substances used in the treatment of PH-ILD

Table 9: Overview of drug classes and active substances used in the treatment of PH-ILD

Drug class and active substance	ATC code(s)
Endothelin receptor antagonists (ERAs)	
ambrisentan	C02KX02, C02KX52
bosentan	C02KX01
macintentan	C02KX04
Phosphodiesterase type-5 inhibitors (PDE5)	
sildenafil	G04BE03
tadalafil	C02KX52, G04CB51, C02KX54, G04BE08, G04CA54
Prostanoids	
epoprostenol	B01AC09
iloprost	B01AC11
selexipag	B01AC27
treprostinil (study drug)	B01AC21
Soluble guanylate cyclase stimulators (SGCs)	
riociguat	C02KX05

Abbreviations: ATC, Anatomical Therapeutic Chemical, ERA, Endothelin receptor antagonists; PDE5, Phosphodiesterase type-5 inhibitors; PH-ILD, pulmonary hypertension - interstitial lung disease; SGCs, Soluble guanylate cyclase stimulators.

Appendix C. Key confounding variables for the primary outcome of 6MWD

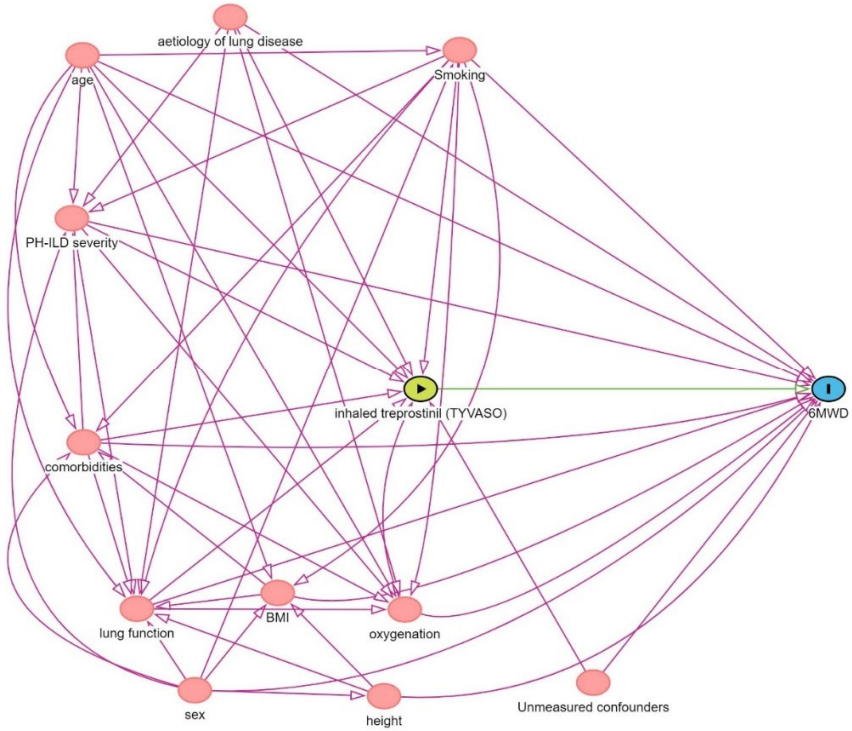

Figure 4: Directed Acyclic Graph for 6MWD

Abbreviations: 6MWD, six-minute walk distance; PH-ILD, pulmonary hypertension - interstitial lung disease.

Appendix D. ENCePP checklist for study protocols

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

EU PAS Register® number: not applicable
Study reference number (if applicable): 2953067

Section 1: Milestones	Yes	No	N/A	Section number
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[a]	☒	☐	☐	Milestones
1.1.2 End of data collection[b]	☒	☐	☐	Milestones
1.1.3 Progress report(s)	☐	☐	☒	-
1.1.4 Interim report(s)	☐	☐	☒	-
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	Milestones
1.1.6 Final report of study results	☒	☐	☐	Milestones

Comments:

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Section 2: Research question	Yes	No	N/A	Section number
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	3. Objectives
2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	3. Objectives
2.1.2 The objective(s) of the study?	☒	☐	☐	3. Objectives
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	3. Objectives
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	-
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	-

Comments:

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Section 3: Study design		Yes	No	N/A	Section number
3.1	Is the study design described? (eg, cohort, case-control, cross-sectional, other design)	☒	☐	☐	4.1 Study Design
3.2	Does the protocol specify whether the study is based on primary, secondary, or combined data collection?	☒	☐	☐	4.1 Study Design
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	3. Objectives 5.2.2.1 Descriptive statistics
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm)	☒	☐	☐	3. Objectives 5.2.2.4 Comparative analysis
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, adverse events that will not be collected in case of primary data collection)	☒	☐	☐	8. Safety Reporting

Comments:

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Section 4: Source and study populations		Yes	No	N/A	Section number
4.1	Is the source population described?	☒	☐	☐	4.1 Study Population
4.2	Is the planned study population defined in terms of:				
	4.2.1 Study time period	☒	☐	☐	4.2 Study Period
	4.2.2 Age and sex	☒	☐	☐	4.3 Study Population
	4.2.3 Country of origin	☒	☐	☐	4.3 Study Population
	4.2.4 Disease/indication	☒	☐	☐	4.3 Study Population
	4.2.5 Duration of follow-up	☒	☐	☐	4.4 Follow-up
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	4.3 Study Population

Comments:

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Section 5: Exposure definition and measurement		Yes	No	N/A	Section number
5.1	Does the protocol describe how the study exposure is defined and measured? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4.5 Exposure of interest
5.2	Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	4.5 Exposure of interest
5.3	Is exposure categorised according to time windows?	☐	☒	☐	-
5.4	Is intensity of exposure addressed? (eg, dose, duration)	☐	☒	☐	-
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	4.5 Exposure of interest
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	4.5 Exposure of interest

Comments:

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Section 6: Outcome definition and measurement		Yes	No	N/A	Section number
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	4.6 Outcomes of interest
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4.6 Outcomes of interest
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	-
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, health-related quality of life, quality-adjusted life years, disability-adjusted life year, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

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Section 7: Bias	Yes	No	N/A	Section number
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☒	☐	☐	5.2.6 Sensitivity analysis
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	4.3 Study population
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	4.2 Study period

Comments:

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Section 8: Effect measure modification	Yes	No	N/A	Section number
8.1 Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	5.2.4 Subgroup analyses

Comments:

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Section 9: Data sources	Yes	No	N/A	Section number
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4.8 Data sources
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4.8 Data sources
9.1.3 Covariates and other characteristics?	☒	☐	☐	4.8 Data sources
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	Will be added after finalization of the feasibility report

Section 9: Data sources	Yes	No	N/A	Section number
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	Will be added after finalization of the feasibility report
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	Will be added after finalization of the feasibility report
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical Classification System)	☐	☒	☐	-
9.3.2 Outcomes? (eg, International Classification of Diseases, Medical Dictionary for Regulatory Activities)	☐	☒	☐	-
9.3.3 Covariates and other characteristics?	☐	☒	☐	
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☐	☐	☒	-

Comments:

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Section 10: Analysis plan	Yes	No	N/A	Section number
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	5.2 Data Analysis
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	5.2 Data Analysis
10.3 Are descriptive analyses included?	☒	☐	☐	5.2 Data Analysis
10.4 Are stratified analyses included?	☐	☐	☒	
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	5.2 Data Analysis
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	5.2 Data Analysis
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	5.2 Data Analysis
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	5.2 Data Analysis

Comments:

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Section 11: Data management and quality control	Yes	No	N/A	Section number
11.1 Does the protocol provide information on data storage? (eg, software and information technology environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7. Study Management
11.2 Are methods of quality assurance described?	☒	☐	☐	7. Study Management
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7. Study Management

Comments:

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Section 12: Limitations	Yes	No	N/A	Section number
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	6. Limitations of research methods
12.1.2 Information bias?	☒	☐	☐	6. Limitations of research methods
12.1.3 Residual/unmeasured confounding? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	6. Limitations of research methods
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	5.1 Sample size

Comments:

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Section 13: Ethical/data protection issues	Yes	No	N/A	Section number
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9. Ethical and regulatory
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9. Ethical and regulatory
13.3 Have data protection requirements been described?	☒	☐	☐	9. Ethical and regulatory

Comments:

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Section 14: Amendments and deviations	Yes	No	N/A	Section number
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	Documentation of protocol amendments

Comments:

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Section 15: Plans for communication of study results	Yes	No	N/A	Section number
15.1 Are plans described for communicating study results (eg, to regulatory authorities)?	☒	☐	☐	7. Publication Policy
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	7. Publication Policy

Comments:

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[a] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[b] Date from which the analytical dataset is completely available.

Name of the main author of the protocol: [redacted]

Date: 16 January 2024

Signature: _____