NON-INTERVENTIONAL STUDY PROTOCOL

TITLE	Effectiveness of inhaled treprostinil versus standard of care for the treatment of pulmonary hypertension associated with interstitial lung disease: A propensity score-weighted study of the INCREASE trial and registry data from Europe
PROTOCOL/ STUDY NO.	3049399
VERSION	V1.0 Draft: 30 April 2024
SPONSOR	Ferrer Internacional S.A. Avenida Diagonal 549, 08029 Barcelona, Spain +34 936 003 700
CONDUCTED BY	IQVIA Global Database Studies Metsänneidonkuja 6, 02130 Espoo, Finland +358 (0)9 4241 3800

This protocol contains confidential information that should only be disclosed to those persons responsible for execution and organization of the study and on condition that all such persons agree not to further disseminate it.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

Principal Investigator Signature Page

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

Study number: 3049399

Protocol version 1.0 dated 30 April 2024

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

Investigator:

[redacted]

Print Name

Signature

Date

IQVIA,
Global Database Studies,
Metsänneidonkuja 6,
02130 Espoo, Finland

Print Name of Institution or Practice and Location

RETURN ORIGINAL TO FERRER OR IQVIA

RETAIN COPY

Sponsor Signature Page

Reviewed and Approved by:

Gabriela Bacchini Jeanneret		Corporate Medical Affairs Head, Pulmonary Vascular & Interstitial lung Diseases Therapeutic Area	
Ferrer	**Signature**	**Title**	**Date**
Míriam Fernández Delgado		Corporate Market Access & Pricing Senior Manager	
Ferrer	**Signature**	**Title**	**Date**
Martí Hopmans Galofré		Corporate Market Access & Pricing Senior Manager	
Ferrer	**Signature**	**Title**	**Date**
[redacted]		Lead Epidemiologist	
IQVIA	**Signature**	**Title**	**Date**
[redacted]		Principal Investigator	
IQVIA	**Signature**	**Title**	**Date**

Informational Contacts

Sponsor

The Marketing Authorisation Holder (MAH) will serve as the sponsor of this study. It is the responsibility of the MAH to ensure proper monitoring of the study and compliance with all applicable regulatory guidelines and laws.

Name: Diego Funes

Role/Title: Corporate Medical Lead, Pulmonary Vascular & Interstitial Lung Diseases Franchise, Ferrer

Address: Avinguda Diagonal 549, Barcelona, Spain

Phone: +34 936 003 700

Fax or Email: dfunes@ferrer.com

Clinical research organisation responsible for the management of the study

IQVIA

Global Database Studies

Metsänneidonkuja 6,

02130 Espoo, Finland

+358 (0)9 4241 3800

List of Abbreviations

Abbreviation or special term	Explanation
6MWD	six-minute walk distance
AE	adverse event
ASPIRE	Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre
ATO	average treatment effect on the overlap population
ATT	average effect of treatment on treated
BMI	body mass index
BNP	brain natriuretic peptide
CI	confidence interval
COMPERA	Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension
COVID-19	coronavirus disease of 2019
CPFE	combined pulmonary fibrosis and emphysema
CTD	connective tissue disease
DataSAT	Data Suitability Assessment Tool
DLCO	diffusing capacity of the lungs for carbon monoxide
DMP	Data Management Plan
ECA	external comparator arm
eCRF	electronic Case Report Form
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FEV1	forced expiratory volume in 1 second
FVC	forced vital capacity
GORD	gastro-oesophageal reflux disease
GPP	Good Pharmacoepidemiology Practices
HCRU	health care resources utilisation
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
INCREASE OLE	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 – open-label extension

Abbreviation or special term	Explanation
IR	incidence rate
LVEF	left ventricular ejection fraction
MAH	Marketing Authorisation Holder
MI	multiple imputation
mPAP	mean pulmonary arterial pressure
NHS	National Health Service
NO	number of order
NT-proBNP	N-Terminal pro-B-type Natriuretic Peptide
OLE	open-label extension
PAH	pulmonary arterial hypertension
PCWP	pulmonary capillary wedge pressure
PDE5i	phosphodiesterase type-5 inhibitors
PH	pulmonary hypertension
PH-ILD	pulmonary hypertension associated with interstitial lung disease
PS	propensity scores
PVR	pulmonary vascular resistance
QC	quality control
QoL	quality of life
RCT	randomised controlled trial
RHC	right heart catheterisation
RMST	restricted mean survival time
RV	right ventricle
RW	real-world
RWD	real-world data
SAP	statistical analysis plan
SAS	Statistical Analysis System
SGRQ	St Georges Respiratory Questionnaire
SMD	standardised mean difference
SOC	standard of care
SOP	standard operating procedure

Abbreviation or special term	Explanation
TLC	total lung capacity
UK	United Kingdom
UKRB	The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom
USA	United States of America
WHO	World Health Organization

Study Synopsis

Full Study Title: Effectiveness of inhaled treprostinil versus standard of care for the treatment of pulmonary hypertension associated with interstitial lung disease: A propensity score-weighted study of the INCREASE trial and registry data from Europe			
Phase:	Not applicable (N/A)	**Type:**	External Comparator Arm (ECA) study
Number of Patients: 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 (INCREASE) enrolled 326 patients who either received placebo (163 patients) or inhaled treprostinil (163 patients) for 16 weeks. Of the 163 patients treated with inhaled treprostinil in the INCREASE randomised controlled trial (RCT), 119 patients continued treatment with inhaled treprostinil in the INCREASE open-label extension (OLE) and 37 patients completed the maximum follow-up of 124 weeks (16 weeks in INCREASE and additional 108 weeks in OLE). The expected number of patients in the standard of care (SOC) group is up to 322.[1]		**Duration of Patient Participation**: N/A	
Number of Sites: INCREASE and INCREASE OLE clinical trials included patients from 92 centres in the United States of America. The real-world (RW) comparator group will include patients with pulmonary hypertension associated with interstitial lung disease (PH-ILD) from The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB) which contains clinical data on World Health Organization (WHO) Group 3 pulmonary hypertension (PH) patients treated at the Royal		**Duration of study**: Study outcomes will be assessed at 28 weeks, 52 weeks or 64 weeks, and 124 weeks.[2]	

[1] 311 off-label PDE5i treated patients from COMPERA, 11 off-label phosphodiesterase type-5 inhibitors (PDE5i) treated patients from UKRB, 4 endothelin receptor antagonist (ERA) treated patients from UKRB, and 11 treatment naïve patients from UKRB (after applying the study eligibility criteria).

[2] For the real-world external comparator group (off-label PDE5i treated patients from UKRB and COMPERA, treatment naïve patients from UKRB, and blended RW patients [off-label PAH treated and treatment naive] from UKRB), the nearest outcome measure to the time points of interest (28 weeks, 52 weeks or 64 weeks, 124 weeks) will be used with a maximum variation of ±30 days.

Brompton Hospital National Pulmonary Hypertension Service in London and the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA), a PH registry which contains data on WHO Group 1-5 patients and spans multiple countries in Europe.	

Background: PH is a pathophysiological disorder characterised by elevated mean pulmonary arterial pressure (mPAP) that can lead to cardiac dysfunction and failure. The 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 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 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.

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

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

Primary objective:

1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[3] on **all-cause mortality** up to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD

Secondary objectives:

1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[3] on **cardiopulmonary hospitalisation**[4] up to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD
2. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[3] on **six-minute walk distance** (**6MWD**) from baseline to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD
3. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[3] on **forced vital capacity (FVC)** from baseline to 28 weeks, 64 weeks, and 124 weeks, among adult patients with PH-ILD

Study design: This is an ECA study using data from the INCREASE and INCREASE OLE clinical trials and 2 PH registries in Europe (UKRB and COMPERA) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus SOC.

Exposure to inhaled treprostinil (patients randomised to inhaled treprostinil in the INCREASE RCT who then continued on inhaled treprostinil in the INCREASE OLE trial) will be compared to SOC. Three comparator groups derived from RW data will be considered as SOC: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

[3] Three comparator groups derived from RW data will be considered as SOC: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

[4] As hospitalisations are not captured in UKRB a subsample of PH-ILD patients from COMPERA will be used for this analysis.

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:

- 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:
  - pulmonary vascular resistance >3 Wood Units
  - pulmonary capillary wedge pressure of ≤15 mmHg
  - mPAP of ≥25 mmHg
- 6MWD ≥100 metres 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 must have a FVC of <70% at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- A record of off-label PDE5i or PAH treatment at the time of patient eligibility (for the external comparator groups treated with off-label PDE5i or PAH therapy only)

Exclusion criteria

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

- A record of off-label PAH treatment before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date

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 disease-specific PH registries in Europe.

Data Management and Quality Assurance: The study will be guided by the National Institute for Health and Care Excellence NICE real-world evidence framework (1) and Canada´s Drug and Health Technology Agency Guidance for Reporting Real-World Evidence (2). The study protocol will adhere to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct (3) and to International Society of Pharmacoepidemiology Good Pharmacoepidemiology Practices (GPP) (4) guidelines and will be conducted in accordance with IQVIA's Quality Management System, which includes a quality control (QC) plan covering all aspects of the study. QC 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 European Medicines Agency Good Pharmacovigilance Practices 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.

Sample size:

The study applies a two-group design to compare the survival of patients exposed to inhaled treprostinil with those receiving the SOC, among adult patients with PH-ILD. The study's participants will be evaluated regarding their survival curves and at 28, 52 and 124 weeks.

A previous study (5,6) compared 119 patients who had received inhaled treprostinil with 121 patients who had received placebo during INCREASE RCT. The study observed a hazard ratio of 0.67 when assessing the risk of death during OLE. Specifically, the median time to death was 62.0 weeks for the patients who had received inhaled treprostinil during INCREASE RCT, compared to 31.3 for the patients who had received placebo during INCREASE RCT.

Taking this information into account, along with the expected number of patients for this study (322 patients in the control group and 163 in the treatment group) the power of the two-sided log-rank test to compare survival of these 2 groups is assessed in the following:

A two-sided log-rank test with an overall sample size of 485 subjects (322 in the control group and 163 in the treatment group) achieves 77% power at a 0.05 significance level to detect a hazard ratio of 0.6 when the control group median survival time is 31 weeks, assuming that the study will last for 124 weeks.

Data analysis:

Incidence rates (IRs), comparative ratios, differences and their corresponding 95% confidence interval (CI) for the outcomes of interest will be estimated. Weighted Kaplan-Meier curves for the time-to-event will be presented.

To retain all sample, propensity score weighting will be implemented to account for observed differences in patient characteristics between the inhaled treprostinil and SOC comparator group, estimating the average treatment effect in the treated population.

To estimate the treatment effect for longitudinal outcomes, weighted mixed effects models will be used. To estimate the treatment effect for survival outcomes, weighted Restricted Mean Survival Time (RMST) models will be applied to estimate RMSTs, RMST differences and 95% CIs of inhaled treprostinil versus SOC in PH-ILD patients.

Results reporting: Study report will include all planned descriptive, comparative, and sensitivity analyses.

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 International Society of Pharmacoepidemiology 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 2016/679 of the European Parliament and of the European Council (27 April 2016) on the protection of natural persons regarding the processing of personal data.

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 qualitative feasibility report	Q2 2024
Finalisation of the protocol	Q2 2024
Registration of the study in the EU PAS Register	Q2 2024
Finalisation of the statistical analysis plan	Q3 2024
Delivery of the final analysis	Q3 2024
Delivery of the final study report	Q4 2024/Q1 2025

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 (mPAP) that can lead to right ventricle (RV) hypertrophy, RV dilatation, RV dysfunction, and RV failure (7–9). After a recent change in its definition PH is now defined by a mPAP of >20 mmHg at rest (10) and is classified into the following 5 World Health Organization (WHO) 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) (7,10,11).

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 (12) 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 (12). Pulmonary hypertension associated with interstitial lung disease (PH-ILD) is frequently observed and is captured in the WHO Group 3 category.

PH is estimated to affect approximately 20 to 70 million people worldwide (13). The United Kingdom (UK) reported a 5-fold increase in the annual incidence of PH from 2004 to 2021 (14). 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) (11), with the highest mortality observed in Group 3 (15). The prevalence of PH among patients with ILD varies (16,17) and is influenced by factors such as the type and severity of ILD and the diagnostic criteria used (18). 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 (18). In 2021 the UK reported 57,138 cases of PH-ILD, with projections indicating an increase by 2032 (19).

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 lung disease patients without PH. 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%) (20). A retrospective cohort study evaluating healthcare resource utilisation among patients with PH-ILD, found that

the percentage of patients with PH-ILD experiencing hospitalisation doubled (p<0.0001) from 29.5% before PH diagnosis to 59.0% after PH diagnosis, with a significant increase (p<0.0001) in healthcare costs from $43,201 to $108,387, respectively (21).

1.2 Current Treatment Paradigm

In Europe, there is currently no approved medicinal treatment for PH-ILD. Given the absence of approved therapies for PH-ILD the use of medications that address the underlying lung disease and help manage PH-ILD symptoms while reducing healthcare usage and cost can be critical. Vasodilator therapy for PH, such as sildenafil, riociguat, and endothelin receptor antagonists investigated in clinical trials have been controversial given their association with negative results eg, increased risk of clinical worsening events (7).

However, promising results have been demonstrated with inhaled treprostinil. Results from the recently published 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 (INCREASE) and its open-label extension (OLE), showed significant clinical improvements eg, enhanced exercise capacity, extended time to clinical worsening, and lower relative risk of exacerbation with inhaled treprostinil among patients with PH-ILD (5,6). Inhaled treprostinil is a synthetic analogue of prostacyclin which is delivered through ultrasonic pulsed delivery nebulisation in up to 12 breaths per session for a total of 72 µg, 4 times per day. It 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 (22). It is currently approved for the treatment of WHO Group 1 PAH and WHO Group 3 PH-ILD by the United States of America (USA) Food and Drug Administration, by the National Administration of Drugs, Foods, and Medical Devices in Argentina, by the Institute of Public Health of the Ministry of Health of Chile, by the Ministry of Public Health and Social Assistance in the Dominican Republic, and by the Pharmaceutics Division of the Ministry of Health in Israel. Outside of the USA, Argentina, Chile, Dominican Republic, and Israel, patients are either treatment naïve or, in some cases, may have received off-label treatment with Group 1 PAH therapies, such as phosphodiesterase type-5 inhibitors (PDE5i).

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 (7) and it is an area of failed therapies. Several Phase II and Phase III clinical trials have investigated the use of endothelin receptor antagonists (23–25) and PDE5i (26,27) in patients with PH-ILD with negative results. To the contrary, promising results were obtained with inhaled treprostinil in the USA based INCREASE and INCREASE open-label extension (OLE) clinical trials (5,6).

By emulating a target trial utilising data from INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) clinical trials with an external comparator group of real-world (RW) patients from PH registries in Europe (28), this study aims to generate evidence of long-term comparative effectiveness of inhaled treprostinil in adult patients with PH-ILD. In the INCREASE OLE extension study all patients were allocated to receive inhaled treprostinil for 108 weeks. However, the measurement of effectiveness against a placebo group was limited to the initial 16 weeks, with no comparator group included for the subsequent period. Consequently, this external comparator arm (ECA) study seeks to assess the long-term comparative effectiveness of inhaled treprostinil in the treatment of PH associated with ILD, between adult patients enrolled in the INCREASE and INCREASE OLE clinical trials and European RW patients treated with the current standard of care (SOC). Furthermore, the current analysis will extend beyond comparisons with placebo, or treatment naïve patients, to include those treated with off-label PAH treatments, specifically PDE5i. This comparison is pertinent to the UK and wider European context as off-label PDE5i are the preferred choice of off-label PAH therapy in PH-ILD patients (29) and therefore represents an appropriate SOC.

3. OBJECTIVES

Research Question: What is the comparative effectiveness of inhaled treprostinil in the treatment of PH-ILD, between adult patients enrolled in the INCREASE and INCREASE OLE clinical trials and RW patients from Europe treated with current SOC (3 comparator groups will be considered as SOC: off-label PDE5i treated patients from The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom [UKRB] and Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension [COMPERA], treatment naïve patients from UKRB, and blended RW patients [off-label PAH treated and treatment naive] from UKRB)?

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

1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[5] on **all-cause mortality** up to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD

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

1. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[5] on **cardiopulmonary hospitalisation** up to 28 weeks, 52 weeks, and 124 weeks, among adult patients with PH-ILD

[5] Three comparator groups derived from RW data will be considered as SOC: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

2. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[5] on **six-minute walk distance** (**6MWD**) from baseline to 28 weeks, 52 weeks, and 124 weeks, in adult patients with PH-ILD
3. To estimate the effect associated with exposure to inhaled treprostinil versus SOC[5] on **forced vital capacity** (**FVC**) from baseline to 28 weeks, 64 weeks, and 124 weeks, in adult patients with PH-ILD

4. STUDY DESIGN

4.1 Study Design

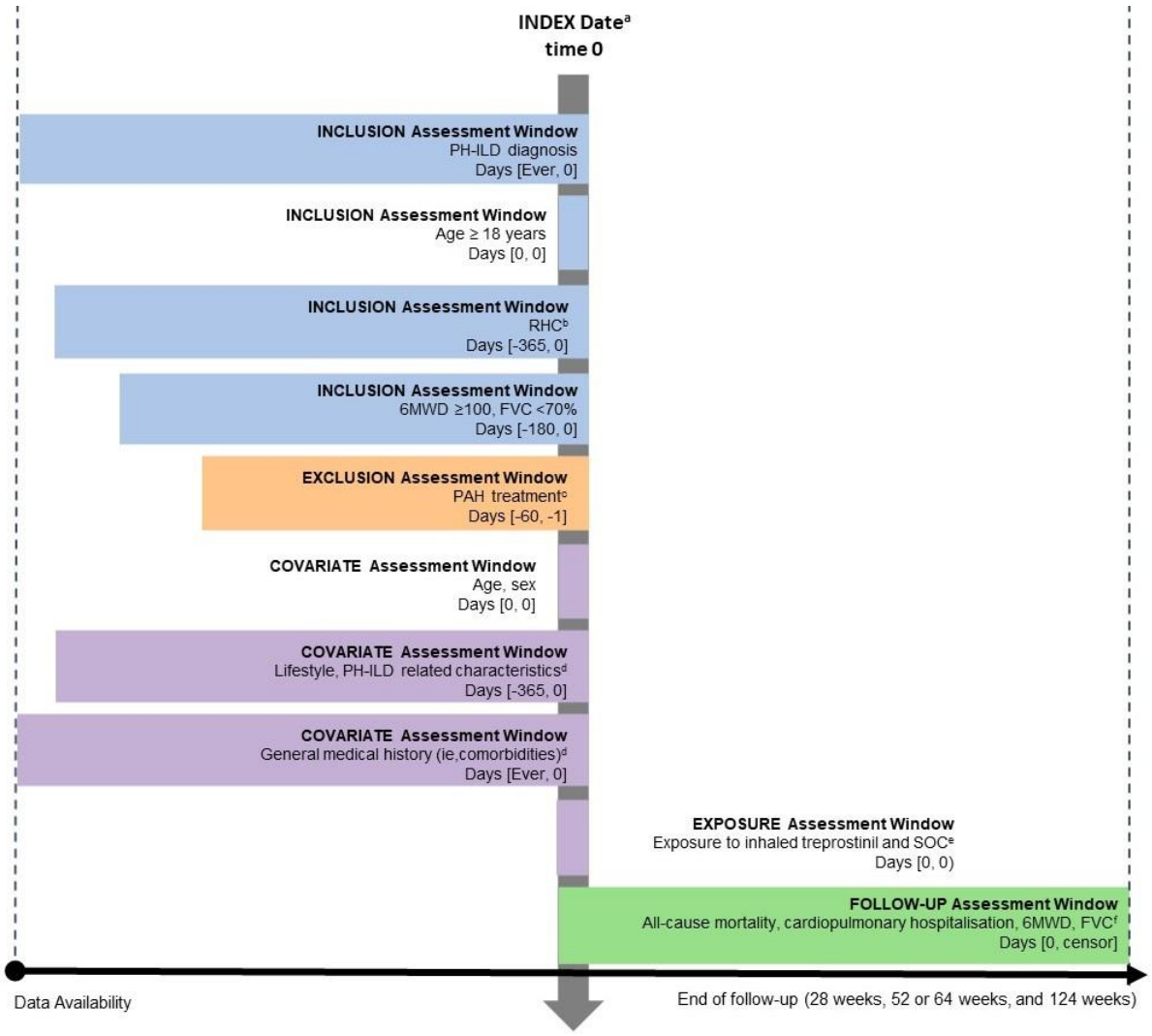
This is an ECA study using data from the INCREASE and INCREASE OLE clinical trials (treatment group) and PH registries UKRB and COMPERA (external comparator) to generate evidence on the long-term efficacy of inhaled treprostinil versus SOC in Europe. Details relating to the data sources are provided in Section 4.8. Overview of the design is presented in Figure 1.

Exposure to inhaled treprostinil (exposed patients from the INCREASE and INCREASE OLE clinical trials) will be compared to SOC in Europe. SOC comprises of 3 comparator groups derived from RW data: off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

This ECA will use data from historic and contemporary RW comparators who are either treatment naïve or on off-label PAH treatment, constructed using observational patient-level data from PH registries in Europe (see Section 4.8.1).

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) (30,31).

Figure 1: Overview of the Study Design.



Abbreviations: 6MWD, six-minute walk distance; FVC, forced vital capacity; ILD, interstitial lung disease; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; RHC, right heart catheterisation; SOC, standard of care.

[a] For the definition of index date see Section 4.2.
[b] For relevant right heart catheterisation parameters see Section 4.3.1.
[c] For the exclusion criteria see Section 4.3.2.
[d] For the covariates see Section 4.7.
[e] For the exposure of interest see Section 4.5
[f] For the outcomes of interest see Section 4.6

4.1.1 Rational for the Study Design

Although randomised controlled trials (RCTs) are considered 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 (32,33). 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 (33,34). This RW evidence study will provide evidence on comparative effectiveness for a substantially longer follow-up window of 28 weeks, 52 weeks or 64 weeks, and 124 weeks as compared to the placebo-controlled 16-week follow-up of INCREASE.

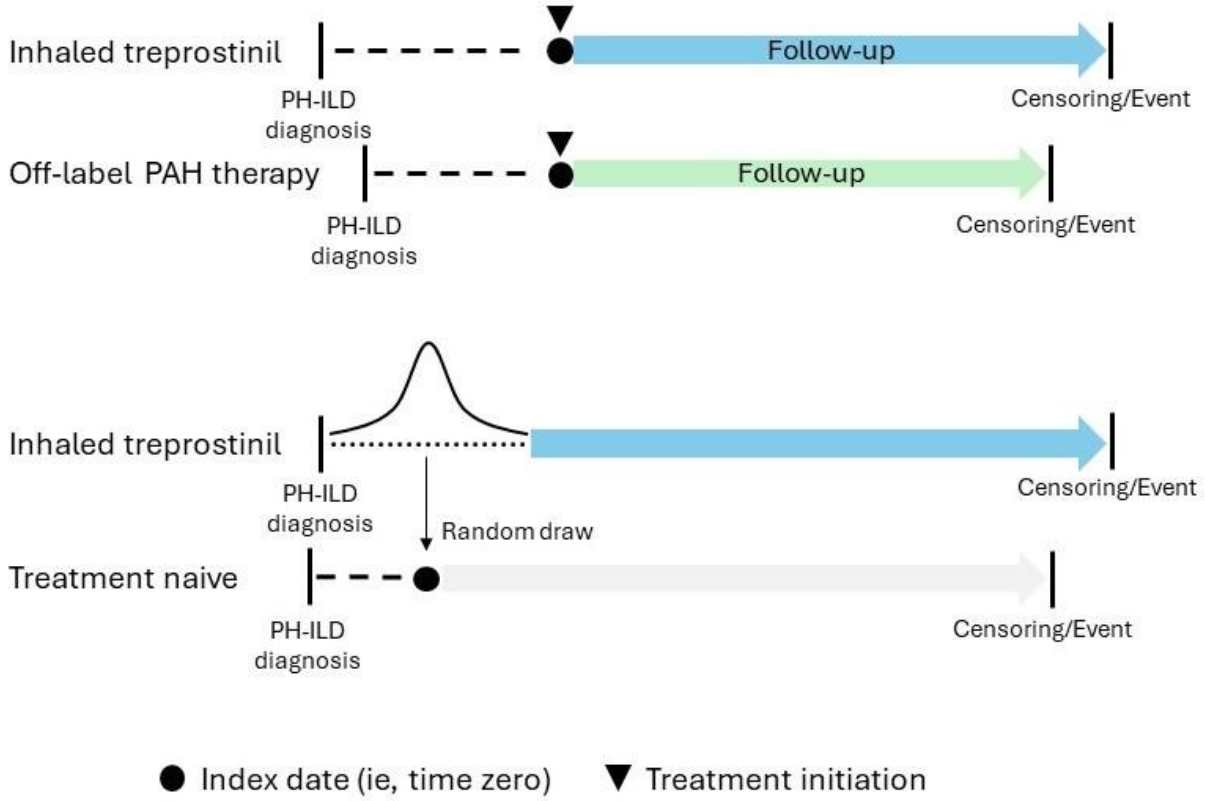
4.2 Study Period

Period start of INCREASE to the end of INCREASE OLE is February 2017 to June 2021. PH is an area of failed therapies. Although there have been universal advancements in medical care, according to relevant treatment guidelines, management and treatment of PH has not significantly changed during the past 2 decades (7,35–37). 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 UKRB, patients diagnosed between 01 January 2000 to 06 December 2021; for COMPERA, patients who entered the data source between 01 January 2006 and 31 December 2022).

The **index date** for the inhaled treprostinil treatment and off-label PDE5i or PAH comparator groups, will be at initiation of inhaled treprostinil and initiation of off-label PDE5i or PAH therapy, respectively. For treatment naïve patients, 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 initial PH-ILD diagnosis date (

Figure 2). Other strategies for selecting time zero for treatment naïve patients may be explored and defined in the statistical analysis plan (SAP) (38,39).

Figure 2: Overview of Index Date.



Abbreviations: PAH, pulmonary arterial hypertension; PH-ILD, pulmonary hypertension associated with 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 OLE study with a follow-up of 108 weeks (total follow-up of 124 weeks). The RW-comparator groups will be derived from European PH registries UKRB and COMPERA (see Section 4.8.1.2).

The intervention group of the INCREASE and INCREASE OLE clinical trials will be compared with 3 comparator groups derived from RWD in Europe: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

4.3.1 Inclusion Criteria

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

- 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
  - pulmonary capillary wedge pressure of ≤15 mmHg
  - mPAP of ≥25 mmHg
- 6MWD ≥100 metres 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 must have a FVC of <70% at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
- A record of off label PDE5i or PAH treatment at the time of patient eligibility (for the external comparator groups treated with off-label PDE5i or PAH therapy only)

4.3.2 Exclusion Criteria

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

- A record of off-label PAH treatment before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date

4.4 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[6], including death
- Lung transplantation
- End of study[7]

[6] For time-to-event outcomes.

[7] Defined as the date of last available data.

4.5 Exposures of Interest

The primary exposure of interest is inhaled treprostinil. The exposed groups will consist of patients who were randomised to inhaled treprostinil for 16 weeks in the INCREASE RCT (163 patients) and then had the option to continue treatment with inhaled treprostinil for additional 108 weeks in the INCREASE OLE trial (119 patients) (Figure 3). Two different exposed groups will be considered:

- Inhaled treprostinil treated – patients randomised to inhaled treprostinil[8].
- Inhaled treprostinil treated who reach the target dose – patients randomised to inhaled treprostinil, reach and sustain the target dose of 9-12 inhalations (total 72 µg), 4 times daily(5)[9].

Exposure to inhaled treprostinil will be compared to SOC in Europe (Figure 3). The comparator group will consist of patients from UKRB and COMPERA, who are treatment naïve or treated with off-label PDE5i or PAH therapy.

Six different comparator groups will be considered:

- Off-label PDE5i treated – patients who initiate off-label PDE5i therapy[8].
- Off-label PDE5i treated with target dose – patients who initiate off-label PDE5i therapy, reach and sustain respective target dose (see Table 2)[10].
- Treatment naïve – patients who are treatment naïve[11, 12].
- Blended RW patients (off-label PAH treated and treatment naive) – patients who initiate off-label PAH therapy or are treatment naïve[8].
- Blended RW patients (off-label PAH treated and treatment naive) treated with target dose – patients who initiate off-label PAH therapy, reach and sustain respective target dose (see Table 2) or are treatment naive[12, 13].

[8] Non-compliance with the treatment strategy after index date will be ignored.

[9] Patients who deviate from the target dose or discontinue inhaled treprostinil will be considered non-compliant to the inhaled treprostinil treated strategy and censored at the date of deviation or discontinuation.

[10] Patients who deviate from the target dose or discontinue off-label PDE5i will be considered non-compliant to the PDE5i treated strategy and censored at the date of deviation or discontinuation.

[11] When using the intention-to-treat population, non-compliance with the treatment naïve strategy after the index date will be ignored.

[12] When using the safety population, patients who initiate off-label PAH therapy after index date will be considered non-compliant with the treatment naïve strategy and censored at the date of treatment initiation.

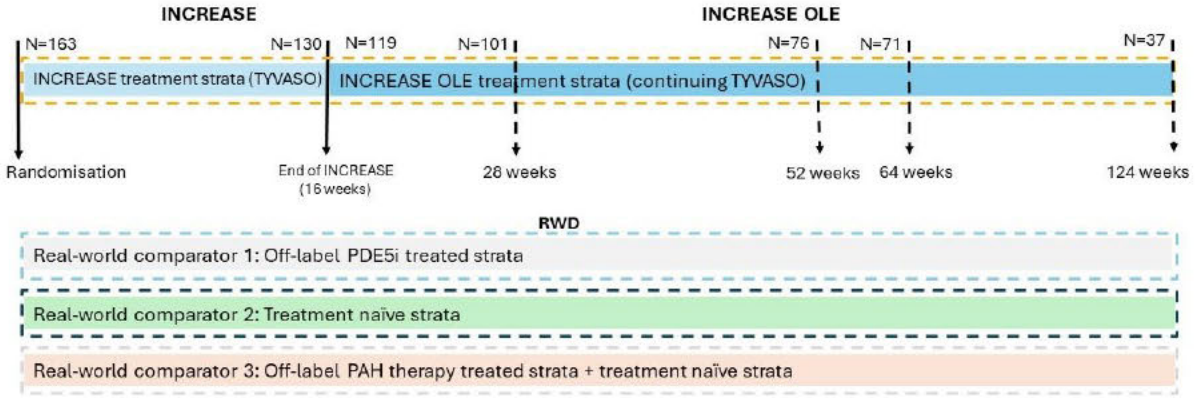
[13] Patients who deviate from the target dose or discontinue off-label PAH therapy will be considered non-compliant to the PAH treated strategy and censored at the date of deviation or discontinuation.

Table 2: Off-label PDE5i treatment dose.

Active substance	Target dose
Sildenafil	20-80 mg TID
Tadalafil	20-40 mg QD
Bosentan	62,5-250mg BID

Abbreviations: BID, twice a day; QD, once a day; TID, three times a day.

Figure 3: Overview of the Exposure and Comparator Groups.



Abbreviations: INCREASE, A Multicentre, 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; PDE5i, phosphodiesterase type-5 inhibitors; RWD, real-world data.

4.6 Outcomes of Interest

Study outcomes and respective definitions are summarised in Table 3.

Table 3: Outcomes of Interest.

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	Assessment time point(s)	Outcome type
1	All-cause mortality	Death from all causes occurring during the study period	Death from all causes as recorded in the data source[a]	Up to 28 weeks, Up to 52 weeks, Up to 124 weeks	Primary

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RWD	Assessment time point(s)	Outcome type
2	First cardiopulmonary hospitalisation	A record of cardiopulmonary related hospitalisation occurring during the study period	A record of cardiopulmonary related hospitalisation as recorded in the data source[b]	Up to 24 weeks, Up to 52 weeks, Up to 124 weeks	Secondary
3	6MWD	Peak 6MWD measured within 10 to 60 minutes after the most recent dose of inhaled treprostinil	A record of 6MWD measured during a routine healthcare visit[a]	24 weeks ±30 days, 52 weeks ±30 days 124 weeks ± 30 days	Secondary
4	FVC	The volume of air in litres that can be forcibly exhaled after a full inhalation	The volume of air in litres that can be forcibly exhaled after a full inhalation[a]	24 weeks ±30 days, 64 weeks ±30 days 124 weeks ± 30 days	Secondary

Abbreviations: 6MWD, six-minute walk distance; FVC, forced vital capacity; INCREASE, A Multicentre, 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; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease, RWD, real-world data.

[a] PH-ILD patients from UKRB and COMPERA.
[b] Subsample of PH-ILD patients from COMPERA.

4.7 Other Variables (Covariates)

The variables presented in Table 4 will be used to determine eligibility, describe baseline characteristics, and adjust for confounding. The final choice of baseline characteristics and potential confounders will depend on the availability and completeness of data across the data sources and their clinical relevance. Specific definitions for all variables will be presented in detail in the SAP.

At baseline, the variables presented in Table 4, will be considered to estimate propensity scores (PS), since they may influence the decision of prescribing inhaled treprostinil or other PH-ILD SOC drugs and are considered potential risk factors for each outcome (Appendix B, Figure 4). Confounding variables will be retrieved at index date or within the look-back period as presented in Figure 1.

Table 4: Patient Characteristics and Potential Confounders.

	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		
Coronary heart disease/coronary artery disease	x	x
Hypertension	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

	Baseline characteristics	Candidate for PS
FEV1	x	x
DLCO	x	x
NT-proBNP or BNP	x	x

Abbreviations: 6MWD, six-minute walk distance; BNP, Brain natriuretic peptide; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; PCWP, pulmonary capillary wedge pressure; PH-ILD, pulmonary hypertension associated with interstitial lung disease; PS, propensity scores; PVR, pulmonary vascular resistance; SpO_2, oxygen saturation; TLC, total lung capacity.

For the analysis of functional capabilities, ie, exercise capacity (assessed by 6MWD), and survival, potential confounders include demographics (eg, older age) and lifestyle characteristics (eg, smoking) (40–42), PH-ILD disease history (eg, disease severity, 6MWD at diagnosis) (43,44), and other clinical characteristics (eg, FVC, PVR, diffusing capacity of the lungs for carbon monoxide, oxygen saturation (SpO_2), N-Terminal pro-B-type Natriuretic Peptide) (41,45,46). Risk factors for adverse events (AEs) (eg, exacerbations) include vital capacity, FVC, and total lung capacity (47). Comorbidities that are recognised as risk factors for survival include left-sided heart disease (assessed by left ventricular ejection fraction) and other cardiovascular disease (eg, coronary artery disease, atrial fibrillation) (46).

4.8 Data Sources

4.8.1 Overall Description of the Data Sources

Two types of data sources will be used in this study: (1) data for the inhaled treprostinil group will be obtained from the INCREASE and INCREASE OLE clinical trial data; (2) data for SOC (treatment naïve and off-label PDE5i) will be obtained from PH registries UKRB and COMPERA.

4.8.1.1 Data from INCREASE and INCREASE OLE Clinical Trials (Treatment Group)

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

INCREASE was a randomised, placebo-controlled, double-blinded clinical trial that assessed the safety and efficacy of inhaled treprostinil in patients with PH-ILD. INCREASE enrolled 326 patients from 92 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. A total of 119 patients from the INCREASE treatment strata continued treatment with inhaled treprostinil in INCREASE OLE.

4.8.1.2 Data from Disease-Specific Registries (Comparator Group)

RWD from 2 PH registries (UKRB and COMPERA) will be used to construct 3 comparator groups: (1) off-label PDE5i treated patients from UKRB and COMPERA; (2) treatment naïve patients from UKRB; (3) blended RW patients (off-label PAH treated and treatment naive) from UKRB.

4.8.1.2.1 UKRB

The UKRB PH registry is a research-ready dataset, that collects routine clinical information on PH 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. Data has been collected on consecutive PH patients treated at this centre since 01 January 2000 (29). The registry is focused on WHO Group 3 PH patients and was created to understand the causes and prognosis of PH. The registry is funded by the NHS and additional funding was awarded in 2023 by Ferrer pharmaceuticals to support a research fellow to coordinate the inception of the registry.

4.8.1.2.2 COMPERA

COMPERA was established in 2007 and is one of the largest prospective PH registries globally, including approximately 11,000 patients across Europe (28) 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.

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. (28).

4.8.2 Feasibility Assessment

Appropriateness and data capture of one PH data source in the UK (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre [ASPIRE]) was assessed during a qualitative feasibility led by Orpha Strategy. ASPIRE was deemed unsuitable for this study

given that it does not capture one of the key eligibility criteria and outcome of interest, the 6MWD. Additional data sources, such as the UKRB and COMPERA were subsequently identified for inclusion and a qualitative feasibility assessment of UKRB is planned ahead of full study execution.

A qualitative feasibility study was conducted between January and April 2024 to assess the suitability of the data sources to address this study's research question and objectives. The feasibility study included a feasibility plan, qualitative assessment of the data, and a feasibility report. The feasibility assessment focused on the UKRB external comparator data as well as the INCREASE and INCREASE OLE trial data and recommended the inclusion of an additional data source in order to improve statistical power. The COMPERA registry was therefore considered. COMPERA has undergone a quantitative feasibility assessment previously and previous knowledge was utilised in the sections below. The data sources have been selected based on their ability to capture mortality, 6MWD, and other study outcomes in addition to the size of the PH-ILD WHO Group 3 patient population.

The feasibility assessment evaluated the fitness of data for addressing the study's research question and objectives. This assessment is structured into 4 sections, encompassing the evaluation of data suitability, including data provenance, quality, and relevance, utilising the recommended Data Suitability Assessment Tool (DataSAT) by the National Institute for Health and Care Excellence (48), as well as the assessment of study variables and their availability (ie, data availability).

4.8.2.1 Data Provenance

The table below (Table 5) is derived from the DataSAT tool, and presents items related to data provenance for both the UKRB, COMPERA, and INCREASE and INCREASE OLE datasets and includes items related to data collection, setting, and governance.

Table 5: Description of Data Provenance for INCREASE/INCREASE OLE, UKRB and COMPERA.

Item	INCREASE/INCREASE OLE	UKRB	COMPERA
Data sources	INCREASE and INCREASE OLE clinical trials. https://clinicaltrials.gov/study/NCT02630316	The Royal Brompton Pulmonary Hypertension Registry in the United Kingdom. https://www.rbht.nhs.uk/our-services/heart/pulmonary-hypertension-service	COMPERA https://www.compera.org/
Data linkage and data pooling	Data from INCREASE and INCREASE OLE clinical trials will be used, where INCREASE OLE is the continuation of INCREASE, and as such no data pooling is required. Linkage of INCREASE data is not planned or possible.	Linkage is not planned for this study. Data pooling between UKRB and other data sources may be possible using a common data model, provided that the data is found to be compatible across datasets.	Linkage is not planned for this study. Data pooling between UKRB and COMPERA may be possible using a common data model, provided that the data is found to be compatible across datasets.
Type of data source	Clinical trial data.	Disease-specific patient registry.	Disease-specific patient registry across multiple European countries and hospital sites.
Purpose of data collection	Data was collected during a multicentre, randomised controlled trial which aimed to evaluate the safety and efficacy of inhaled treprostinil in patients with PH-ILD.	Registry was created to understand the pathophysiology of PH related to chronic lung disease (WHO Group 3 PH patients). It collects anonymised patient data from the records of Royal Brompton and Harefield hospitals.	The 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.
Data collection	Data collection was performed by the trial sponsor (United Therapeutics) according to a prespecified protocol. Data were recorded prospectively via eCRF at each study visit, and medical examinations and clinical assessments were conducted by qualified, trained personnel. No change in data collection practices were recorded. Data include demographics (eg, age, gender,	UKRB data are collected from consecutive incident patients referred to the Royal Brompton Hospital National Pulmonary Hypertension Service (London, UK) (29). Data include demographics (eg, age, gender, ethnicity), lifestyle characteristics (eg, smoking status), general medical history (eg, comorbidities, comedication), PH-ILD disease history and clinical characteristics	COMPERA data are collected via eCRF from consecutive patients with newly initiated treatment of PH/PAH who attend any of the participating centres. The dataset includes comprehensive data on demographics (eg, age, gender, ethnicity), general medical history (eg, comorbidities), PH-ILD disease history and clinical characteristics of incident and prevalent cases

Item	INCREASE/INCREASE OLE	UKRB	COMPERA
	ethnicity), lifestyle characteristics (eg, smoking status), general medical history (eg, comorbidities, comedication), PH-ILD disease history and clinical characteristics (eg, 6MWD, aetiology of lung disease, exercise capacity), disease outcomes (eg, lung transplantation, mortality). No changes were made in the collection of data during the study.	(eg, 6MWD, aetiology of lung disease, exercise capacity), disease outcomes (eg, lung transplantation, mortality). Data is manually transcribed from electronic health records by a treating clinician or other healthcare professional. There have been no major changes in the data collection	(eg, 6MWD, aetiology of lung disease, exercise capacity), disease outcomes (eg, lung transplantation, mortality). The eCRF has experienced a number of changes in recent years. As well as improvements in the structure and metadata collection of the form, some of the more relevant changes include, in February 2014, the modification of inclusion criteria to only incident cases, in 2016 the eCRF was streamlined, including the deletion of free text fields, and in 2019 new fields for echocardiography. In October 2021, the QoL questionnaire EQ-5D was dropped due to low completion.
Care setting	Trial procedures were carried out in specialist clinics.	Specialist care centre.	Specialist care centre.
Geographical setting	Multiple states in USA.	London, UK	Multi-national. Includes centres in Germany, Austria, Belgium, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Slovakia, Switzerland, and the UK.
Population coverage	The INCREASE RCT enrolled 326 patients with PH-ILD who either received placebo (163 patients) or inhaled treprostinil (163 patients). Sociodemographic characteristics (gender and age) of these patients were comparable to previous PH-ILD studies (20,49).	The data source includes approximately 900 patients referred to the Royal Brompton Pulmonary Hypertension Service. Of these, we expect to receive a dataset with 128 patients who have had their PH-ILD diagnosis confirmed by a multi-disciplinary team.	The dataset contains 1,781 patients, 763 of which are over the age of 18 and have a diagnosis of WHO Group 3 PH associated with ILD.
Time period of data	Period start of INCREASE to the end of INCREASE OLE is February 2017 to June 2021.	The dataset includes patients diagnosed with PH-ILD between 01 January 2000 to 06 December 2021. Follow-up data is available until February 2024.	The dataset includes patients from 01 January 2006 until 31 December 2022.

Item	INCREASE/INCREASE OLE	UKRB	COMPERA
Data preparation	Data will be de-identified before transfer of the patient-level data to IQVIA. No other details are available.	Data will be de-identified before transfer of the patient-level data to IQVIA. No other details are available.	Anonymised raw data can be accessed for analysis.
Data governance	Data from the INCREASE/INCREASE OLE clinical trials will be provided by United Therapeutics Corporation, the current owners of the trial data. United Therapeutics Corporation and Ferrer have a data sharing agreement in place which allows Ferrer to use this data to prepare for regulatory and reimbursement applications.	Royal Brompton Hospital research governance department is the controller of the UKRB registry data. The registry is supported by the NHS and Ferrer have previously licenced data from this registry to support a RW research study. Additional funding was awarded in 2023 by Ferrer pharmaceuticals to support a research fellow for a prospective PH-ILD registry. To access the data, the current study will seek approval from the Health Research Authority (including Research Ethics Committee review) via central Integrated Research Approval System application identification number 340955.	The data is controlled by the COMPERA Study Group, and it is investigator-initiated, so the investigators own the data. The principal investigator is Dr Marius M Hoeper, Department of Pulmonology, Medical School Hannover, Germany. The registry is fully independent of the pharmaceutical industry and is being financed with unrestricted educational funds from Acceleron, AOP Orphan, Bayer, Ferrer, Janssen and OMT. Ethics approval is required for access to the data and scientific registry management & Steering Committee are responsible for scientific publications.
Data specification	No data specification model was used. Data were collected via specifically designed eCRF.	Fields in the UKRB dataset are derived from hospital records. Variable list was shared by the UKRB.	Data specification is provided, alongside a registry eCRF.
Data management plan and quality assurance methods	A data management and quality assurance plan were set out as referred to in the published protocol (see https://www.nejm.org/doi/suppl/10.1056/NEJMoa2008470/suppl_file/nejmoa2008470_protocol.pdf). For quality assurance a representative from the sponsor verified eCRF data fields against source documentation and reviewed by the investigator for completeness and accuracy.	A management plan has not been established. However, a data dictionary is accessible through the data source. Quality is assessed through medical review of the data. Highly skilled professionals (eg, clinical research fellows) are trained to enter the data under close supervision from the PI. Ad-hoc data verification may occur via discussion between the data-entry professional and PI.	Data management and quality assurance plans were shared by the data source.

Item	INCREASE/INCREASE OLE	UKRB	COMPERA
Other documents	Links to publications: Waxman et al., 2021 Nathan et al., 2021 Waxman et al., 2023	Link to publication: Dawes et al., 2023 https://www.rbht.nhs.uk/our-services/heart/pulmonary-hypertension-service	Link to COMPERA website, which includes a description and key publications. https://www.compera.org/

Abbreviations: 6MWD, six-minute walk distance; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; eCRF, electronic Case Report Form; ILD, interstitial lung disease; INCREASE, A Multicentre, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; NHS, National Health Service; OLE-open-label extension; PAH, pulmonary arterial hypertension; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; QoL, quality of life; RCT, randomised controlled trial; RWD, real-world data; UK, United Kingdom; UKRB, The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom; USA, United States of America; WHO, World Health Organization.

4.8.2.2 Data Availability

This section presents an overview of the data availability for exposure, outcome variables, and covariates included in the study. Variables are classified as available, partially available, not available, or unknown. Data availability refers to the collection status of variables, while the volume of data and, consequently, its quality or completeness are evaluated in Section 4.8.2.3.

Exposure:

The table below (Table 6Table 6) shows the availability of treatment related variables. All the key study variables relating to administration and dosage of inhaled treprostinil are available in the INCREASE/INCREASE OLE dataset, whereas all key study variables relating to off-label PDE5i therapy are available in UKRB and COMPERA.

Table 6: Variable Availability for Exposure Variables for INCREASE/INCREASE OLE, UKRB and COMPERA.

Variable Captured	INCREASE/ INCREASE OLE	UKRB	COMPERA
Date of off-label PDE5i therapy initiation	Not available	Available	Available
Date of off-label PDE5i cessation	Not available	Available	Available
Dose of off-label PDE5i therapy	Not available	Available	Available
Date of inhaled treprostinil therapy initiation	Available	Not available	Not available
Date of inhaled treprostinil therapy cessation	Available	Not available	Not available
Dose of inhaled treprostinil therapy	Available	Not available	Not available

Abbreviations: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; INCREASE, A Multicentre, Randomised, 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; PDE5i, Phosphodiesterase type-5 inhibitors; UKRB, The Royal Brompton Pulmonary Hypertension Registry in the United Kingdom

Key:		Available		Not available

Outcomes:

The table below (Table 7) shows the availability of outcome variables. It should be noted that quality of life instruments differ between INCREASE/INCREASE OLE, UKRB, and COMPERA, with each dataset recording St. George's Respiratory Questionnaire and the emPHasis-10, and the EQ-5D questionnaire, respectively. As these scoring systems are different, direct comparisons may not be feasible.

Table 7: Variable Availability for Outcome Variables for INCREASE/INCREASE OLE, UKRB and COMPERA.

Variable Captured	INCREASE/ INCREASE OLE	UKRB	COMPERA
Date of death	Available	Available	Available
Date of lung disease/ILD exacerbation	Available	Not available	Not available
Date of lung transplantation	Partially available[a]	Partially available[b]	Available
Concomitant medication	Available	Partially available[c]	Partially available[c]
Wheelchair use	Not available	Not available[d]	Not available
HCRU[4]	Not available	Partially available[e]	Partially available[e]
Date of 6MWT	Available	Available	Available
6MWD	Available	Available	Available
Quality of life assessment	Available	Available	Available
Date of quality-of-life assessment	Available	Available	Available
FVC	Available	Available	Available
Date of loss to follow-up	Available	Available	Available
Dyspnoea	Not available	Not available	Partially available[f]
All-cause hospitalisation	Partially available[g]	Not available	Partially available[g]

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; ; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; FVC, forced vital capacity; HCRU, health care resources utilisation; ILD, interstitial lung disease; ; INCREASE, A Multicentre, Randomised, 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; UKRB, The Royal Brompton Pulmonary Hypertension Registry in the United Kingdom
Footnotes: [a] Only available in INCREASE, not in INCREASE OLE. [b] Only transplantation status available. [c] Only some concomitant medications available. [d] HRCU includes the following variables: Primary care encounters, Outpatient healthcare encounters, Emergency visits, and cardiopulmonary rehabilitation. [e] Only outpatient PH specialist encounters are available. [f] Borg dyspnoea index captured but incomplete. [g] Only date of encounter and primary diagnosis available for hospitalisations related to cardiopulmonary diagnosis in INCREASE/INCREASE OLE, or if captured as an adverse event, and PH/PAH diagnosis in COMPERA.

Key:		Available		Partially available		Not available

Covariates:

The table below (Table 8) shows the availability of covariates in the data sources. These will be used to determine eligibility, describe baseline characteristics, and adjust for confounding.

Table 8: Variable Availability for Covariates for INCREASE/INCREASE OLE, UKRB and COMPERA.

Variable Captured	INCREASE/ INCREASE OLE	UKRB	COMPERA
Sex	Available	Available	Available
Race or ethnic group	Partially available[a]	Not available	Not available
Weight	Available	Available	Available
Height	Available	Available	Available
BMI	Available	Available	Available
Cardiovascular disease	Available	Partially available[b]	Partially available[c]
LVEF	Not available	Available	Available
Diabetes	Available	Available	Available
Thyroid disease	Available	Not available	Available
GORD	Available	Available	Not available
Lung cancer	Available	Partially available[d]	Not available
Depression	Available	Not available	Not available
Obstructive sleep apnoea	Available	Available	Available
Dyspnoea	Not available	Not available	Partially available[e]
Number of medications for ILD	Available	Available	Not available
Number of concomitant medications	Available	Partially available[f]	Partially available[f]
NT-proBNP or BNP	Available[d]	Partially available[g]	Available[h]

Abbreviations: BMI, body mass index; GORD, gastro-oesophageal reflux disease; ILD, interstitial lung disease; ; INCREASE, A Multicentre, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLE, Open-label extension; UKRB, The Royal Brompton Pulmonary Hypertension Registry in the United Kingdom

Footnotes: [a] Ethnicity categories available Hispanic/Latino or not Hispanic/Latino and race categories available: American Indian/Alaska native, Asian, Black or African American, Native Hawaiian or White. [b] Coronary artery disease, hypertension, arrhythmia, stroke captured. [c] Only coronary heart disease and arterial hypertension available. [d] Only general cancer diagnosis captured. [e] Borg dyspnoea index captured but incomplete. [f] Only specified concomitant medications available. [g] Only BNP captured. [h] NT-proBNP available.

Key:		Available		Partially available		Not available

4.8.2.3 Data Quality

The table below (Table 9) is derived from the DataSAT tool, and presents items related to data quality for key study variables in the INCREASE and INCREASE + OLE data source, including population eligibility criteria, outcomes, interventions or exposures, and covariates.

Given that the COMPERA data underwent a separate feasibility study, the assessment methodology differed to that followed with INCREASE/INCREASE OLE data and UKRB data. For COMPERA, a quantitative completeness assessment was conducted, and the assessment result is based on those findings, rather than a qualitative discussion with the principal investigator. This may result in inconsistencies of feasibility reporting between the other data sources and COMPERA.

In this data quality assessment, accuracy was also considered, even though it could not be evaluated on a variable-by-variable basis. For all data sources, there is an absence of specific validation studies published on the preciseness and correctness of the data. However, for all 3 data sources, it is expected that the data from these sources are accurate due to systematic data collection procedures and robust quality assurance processes. The data from INCREASE/INCREASE OLE were systematically collected by trained and qualified professionals using electronic Case Report Forms (eCRFs). Additionally, a sponsor representative cross-verified the eCRF data fields against the source documentation, and the PI reviewed them for completeness and accuracy. As for the UKRB, data are collected under the supervision of the PI by highly skilled professionals, such as clinical research fellows, with quality assessments conducted ad-hoc through a medical review process. Moreover, for key variables like mortality, a high-level of accuracy is expected as the data are accessed through clinical information systems linked to the NHS Spine, which integrates national databases to securely hold details of all people registered to use the NHS in England. Data in COMPERA are collected by experienced professionals and adhere to detailed data management and quality assurance plans.

Table 9: Data Quality Assessment Results for Key Study Variables Available in INCREASE/INCREASE OLE, UKRB, and COMPERA.

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
Population	Diagnosis of WHO Group 3 PH-ILD	Diagnosis of PH-ILD with a confirmation by RHC with the following parameters: PVR >3 WU. PCWP of ≤15 mmHg. mPAP of ≥25 mmHg.	Completeness	Completeness was assessed using a qualitative scale[a] for the following variables PVR, PCWP, and mPAP.	High	High[c]	High
Population/covariates	Age	Date of birth.	Completeness	Completeness was assessed using the qualitative scale for date of birth.	High	High	High
Population	Exercise capacity	INCREASE: 6MWD ≥ 100 metres assessed during clinical trial screening for eligibility. UKRB: 6MWD ≥ 100 metres assessed during a routine clinical visit (45).	Completeness	Completeness was assessed using a qualitative scale[a] for 6MWD.	High	High	Moderate[e]
Population	Comedication	Patients on medication(s) for underlying lung disease (eg, pirfenidone, nintedanib) are on stable dose without any dose	Completeness	Completeness was assessed using a qualitative scale[a] for name (active substance)	High	High[c]	Variables not available.

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
		modification in the last 30 days, before the index date.		and date of treatment initiation for treatments for underlying ILD.			
Population	Baseline FVC (CTD patients only)	FVC of <70% at index date.	Completeness	Completeness was assessed using a qualitative scale[a] for FVC.	High	High	Moderate[e]
Population	Left-sided heart disease	Record of a left-sided heart disease before or at index date with: PCWP >15 mmHg, LVEF <40%.	Completeness	Completeness was assessed using a qualitative scale[a] for PCWP and LVEF.	High for PCWP. Variable not available for LVEF.	High[c]	High for PCWP. Low for LVEF.
Population	Oxygen supplementation	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, with a maximum look-back period of 6 months).	Completeness	Completeness was assessed using a qualitative scale[a] for oxygen supplementation.	High	Moderate	Moderate[e]
Intervention	Inhaled Treprostinil treatment	A record of inhaled treprostinil treatment start date, end date and dosage.	Completeness	Completeness was assessed using a qualitative scale[a] for date of inhaled	High	Not applicable	Not applicable

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
				treprostinil initiation, date of inhaled treprostinil cessation and dose of inhaled treprostinil therapy.			
Comparison	Treatment naïve	No prescription or record of any PDE5i usage.	Completeness	Completeness was assessed using a qualitative scale[a] for date of off-label PDE5i therapy initiation, date of off-label PDE5i therapy cessation, and dose of off-label PDE5i therapy.	Not applicable	High[c]	High
Comparison/ population	Off-label PDE5i treatment	A prescription or record of PDE5i usage.	Completeness	Completeness was assessed using a qualitative scale[a] for date of off-label PDE5i therapy initiation, date of off-label PDE5i therapy cessation, and dose of off-label PDE5i therapy.	Not applicable	High[c]	High

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
Outcome	All-cause mortality	A record of death by any cause.	Completeness	Completeness was assessed using a qualitative scale[a] for date of death.	High	High	High
Outcome	Disease progression	Composite of decline in 6MWD ≥15%, exacerbation of underlying lung disease, decline in FVC ≥10%, cardiopulmonary hospitalisation, lung transplantation, all-cause mortality.	Completeness	Completeness was assessed using a qualitative scale[a] for 6MWD, exacerbation of underlying lung disease, FVC, cardiopulmonary hospitalisation, lung transplantation, all-cause mortality.	High for 6MWD, exacerbation of underlying lung disease, FVC, cardiopulmonary hospitalisation, and all-cause mortality. Moderate for lung transplantation.[b]	High for 6MWD, FVC, all-cause mortality, and lung transplantation. Variables not available for cardiopulmonary hospitalisation and exacerbation of underlying	High for cardiopulmonary hospitalisation, lung transplantation, and all-cause mortality. Moderate for 6MWD[b], and FVC[b]. Variables not available for exacerbation of underlying lung disease.

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
						lung disease.	
Outcome	Quality of Life	INCREASE: SGRQ questionnaire UKRB: emPHasis-10 questionnaire (46).	Completeness	Completeness was assessed using a qualitative scale[a] for quality of life assessment.	High	Moderate[d]	Low[f]
Outcome	HCRU	Number of inpatient and outpatient healthcare encounters (both general practitioner and specialist care) and number or emergency care visits occurring during the study period.	Completeness	Completeness was assessed using a qualitative scale[a] for date of hospitalisation, primary care encounters, outpatient healthcare encounters, and emergency care visits.	High for date of hospitalisation (only available for cardiopulmonary diagnosis). Variables not available for primary care encounters, outpatient healthcare encounters, and	High for outpatient healthcare encounters (only specialist PH-ILD). Variable not available for date of hospitalisation, primary care encounters, emergenc	High for date of hospitalisation, inpatient outpatient healthcare encounters relevant to PH or PAH. Variable not available for primary care encounters and emergency care visits.

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
					emergency care visits.	y care visits.	
Outcome	6MWD	Total distance walked during the completion of the 6MWT.	Completeness	Completeness was assessed using a qualitative scale[a] for 6MWD.	High	High	Moderate[e]
Outcome	FVC	The volume of air exhaled with maximal forced effort from a maximal inspiration.	Completeness	Completeness was assessed using a qualitative scale[a] for FVC.	High	High	Moderate[e]
Outcome/population	All-cause hospitalisation	Hospitalisation due to any cause.	Completeness	Completeness was assessed using a qualitative scale[a] for date of hospitalisation and primary diagnosis.	High	Variables not available.	High for PH related hospitalisation.
Outcome	Exacerbation of underlying lung disease	Record of exacerbation of underlying lung disease.	Completeness	Completeness was assessed using a qualitative scale[a] for date of underlying lung/ILD exacerbation.	High	Variable not available.	Variable not available.
Covariates	Sex	Biological sex at birth.	Completeness	Completeness was assessed using a qualitative scale[a] for sex.	High	High	High

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
Covariates	BMI	Body mass in kilograms divided by the square of body height in metres (kg/m²).	Completeness	Completeness was assessed using a qualitative scale[a] for body mass index.	High	High	High
Covariates/population	Smoking	Smoking status including current, ex-smoker and non-smoker.	Completeness	Completeness was assessed using a qualitative scale[a] for smoking status.	High	High	To be confirmed with COMPERA
Covariates	Comorbidities	The presence of coexisting or co-occurring conditions.	Completeness	Completeness was assessed using a qualitative scale[a] for cardiovascular disease, diabetes, thyroid disease, GORD, lung cancer, depression, obstructive sleep apnoea.	High	High for cardiovascular disease, diabetes, GORD, and obstructive sleep apnoea. Variables not available for thyroid disease and	High for cardiovascular disease, diabetes, thyroid disease, and GORD. Variables not available for lung cancer, depression, and obstructive sleep apnoea.

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
						depression .	
Covariates	Number of medications for ILD	The total number of medications prescribed for the treatment of ILD.	Completeness	Completeness was assessed using a qualitative scale[a] for number of medications for underlying ILD.	High	High[c]	Variable not available.
Covariates	Number of comedication	The total number of concomitant medications prescribed.	Completeness	Completeness was assessed using a qualitative scale[a] for number of concomitant medications.	High	High[c]	Variable not available.
Covariates	Time since PH-ILD diagnosis	Time from PH-ILD diagnosis until study inclusion.	Completeness	Completeness was assessed using a qualitative scale[a] for date of entry into the data source and date of PH-ILD diagnosis.	High	High	High
Covariates	Aetiology of lung disease	Aetiology of lung disease.	Completeness	Completeness was assessed using a qualitative scale[a] for aetiology of lung disease.	High	High	High

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
Covariates	PVR	The resistance that blood must overcome to pass through the pulmonary vasculature (mmHg·min/l).	Completeness	Completeness was assessed using a qualitative scale[a] for date of RHC with recorded results of PVR.	High	High	High
Covariates	PCWP	Pressure measured by wedging a pulmonary artery catheter with an inflated balloon into a small pulmonary arterial branch (mmHg).	Completeness	Completeness was assessed using a qualitative scale[a] for date of right heart catheterisation with recorded results of PCWP.	High	High	High
Covariates	mPAP	Mean pulmonary artery pressure calculated from systolic and diastolic pulmonary artery pressures (mmHg).	Completeness	Completeness was assessed using a qualitative scale[a] for date of RHC with recorded results of mPAP.	High	High	High
Covariates	Total lung capacity	The volume of air in the lungs upon the maximum effort of inspiration (litres).	Completeness	Completeness was assessed using a qualitative scale[a] for total lung capacity.	High	High	Moderate[e]

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA
Covariates	FVC	The volume of air that can be exhaled from the lungs after taking the deepest breath possible (litres).	Completeness	Completeness was assessed using a qualitative scale[a] for FVC.	High	High	Moderate[e]
Covariates	FEV1	The proportion of a person's vital capacity that they are able to expire in the first second of forced expiration to the full, FVC (litres).	Completeness	Completeness was assessed using a qualitative scale[a] for FEV1.	High	High	Moderate[e]
Covariates	DLCO	Partial pressure difference between inspired and expired carbon monoxide (ml/min/kPa).	Completeness	Completeness was assessed using a qualitative scale[a] for DLCO.	High	High	Moderate[e]
Covariates	NT-proBNP or BNP	Levels of NT-proBNP or BNP in the bloodstream (pmol/l or pg/mL).	Completeness	Completeness was assessed using a qualitative scale[a] for NT-proBNP or BNP.	High	High	Moderate

Abbreviations: 6MWD, 6-minute walk distance; 6MWT, 6-minute walk test; BMI, body mass index; BNP, brain natriuretic peptide; CTD, connective tissue disease; DLCO, Diffusing capacity for carbon monoxide; FEV1, Forced Expiratory Volume in 1 second; FVC, Forced Vital Capacity; GORD, gastro-oesophageal reflux disease; HCRU, health care resources utilisation; ILD, interstitial lung disease; INCREASE, A Multicentre, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; OLE, open-label extension; PCWP, pulmonary capillary wedge pressure; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung

Study Variable	Target Concept	Operational Definition	Quality Dimension	Assessment Method	Assessment Result		
					INCREASE/ INCREASE OLE	UKRB	COMPERA

disease; PVR, pulmonary vascular resistance; RHC, right heart catheterisation; RW, real-world; SGRQ, St Georges Respiratory Questionnaire; SOC, standard of care; UKRB, Royal Brompton Pulmonary Hypertension Registry in the United Kingdom; WHO, World Health Organisation; WU, Wood units.

Footnotes: [a] The qualitative scale for completeness is as follows: High, variable records expected to exist for the majority of the cases when the variable should be captured in the dataset; Moderate, variable records expected to exist for a few of the cases when the variable should be captured in the dataset.; Low, Variable records expected to exist for the minority of the cases when the variable should be captured in the dataset; Unknown, more investigation is required, the data holder does not know the answer. [b] Only available in INCREASE, not in INCREASE OLE. [c] For these variables, high completeness is expected at baseline and may not be captured repeated at each follow-up. Completeness is assessed as high as this variable is only required for study analysis at baseline; [d] Only completed in patients diagnosed more recently; [e] Completeness was high at baseline and moderate at follow-up. [f] Due to low completeness this variable was removed from the eCRF in October 2020.

Key:		Target concept can be addressed		Target concept could be addressed, with amendment		Target concept cannot be addressed

4.8.2.4 Data Relevance

Data relevance was evaluated for all data sources and is presented in Table 10. These results summarise whether the data from the assessed data sources are robust enough to address the study's research question and objectives, as well as whether they accurately represent the population of interest. The items assessed for data relevance include population, care setting, treatment pathway, availability of key study elements, study period, timing of measurements, follow-up, and sample size.

Table 10: Data Relevance.

Item	Response	Response	Response
Data sources	INCREASE/INCREASE OLE	UKRB	COMPERA
Population	INCREASE and INCREASE OLE clinical trials included patients from 92 centres in the USA. The extent to which the sample reflects the target population may be limited given that RCTs typically have more restrictive eligibility criteria. In this study, patients were excluded based on severity measures such as minimum 6MWD.	There are 7 specialist PH centres in the UK which offer care for patients with PH. Royal Brompton Hospital is the largest specialist heart and lung medical centre in the UK. Data from the UKRB patient registry is expected to be representative of WHO Group 3 patients in the UK.	COMPERA captures data on patients from centres in numerous European countries, including the UK. It is one of the largest registries of its indication worldwide. Nevertheless, majority of patients in the study sample are from Germany (97.4%). The study sample also includes a small number of patients from Italy (0.3%), Latvia (0.3%), Netherlands (0.3%), Switzerland (0.60%), and the UK (1.1%). Data from COMPERA is expected to be representative of PH-ILD patients in Germany.
Care setting	INCREASE and INCREASE OLE clinical trials included patients from 92 specialist clinics in the USA, patients were under PH specialist supervision.	Royal Brompton and Harefield hospitals is a tertiary care centre designated to provide pulmonary hypertension services for adults. The centres offer treatment for PH and are responsible for prescribing complex therapies and managing patient care.	COMPERA encompasses specialist PH centres across Europe, which serve as primary hubs where patients receive treatment and undergo continuous monitoring throughout their disease.
Treatment pathway	The treatment employed in this study (inhaled treprostinil) for PH is not yet available in the UK, meaning that treatment pathways in this study will not represent routine NHS care. Even though clinical trials follow specific treatment pathways and diagnostic tests tailored to the trial's objectives, clinical assessments used in this study are comparable to those used in the UK. Concomitant	Data from the UKRB is expected to represent routine clinical practice in the management of PH-ILD in specialist centres in the UK.	Data from COMPERA reflects clinical practice in Europe and includes centres in the UK. It is therefore expected to represent typical treatment pathways in this region.

Item	Response	Response	Response
Data sources	INCREASE/INCREASE OLE	UKRB	COMPERA
	medications were permitted for patients upon study entry, ensuring that the treatment pathways observed in the data mirror the typical treatment pathways.		
Availability of key study elements	All key study elements are available in this dataset.	Data to inform eligibility criteria, exposure, outcome variables, and covariates is sufficient. However, data is not available on the following outcomes of interest: exacerbations, disease progression, hospitalisations.	The dataset meets the requirements for the research question as it includes variables on key eligibility criteria, the main outcome of mortality, treatment information, and key covariates. It does not, however, record information on exacerbations and a number of most common comorbidities in ILD (52) (eg, gastro-oesophageal reflux disease, lung cancer, depression).
Study period	Period start of INCREASE to the end of INCREASE OLE is February 2017 to June 2021. The database underwent an early data lock in 2020 due to the COVID-19 pandemic. According to relevant treatment guidelines, management and treatment of PH has not significantly changed during the past 2 decades (7,35–37).	All patients diagnosed between 01 January 2000 and October 2021 with PH-ILD are included in the data set. According to relevant treatment guidelines, management and treatment of PH has not significantly changed during the past 2 decades (7,35–37).	The study period began in 2007 and is ongoing. According to relevant treatment guidelines, management and treatment of PH has not significantly changed during the past 2 decades (7,35–37).
Timing of measurements	Assessments were carried out at every 4 weeks from the beginning of the trial until week 16, when the INCREASE trial ended. In this stage of the trial patients were also contacted at least weekly to assess patient tolerance to study drug, AEs, and changes in concomitant medications. The first	Frequency of visits is decided by the treating physician and is expected to reflect routine clinical practice. Standard follow-up period is between 6-12 months.	Frequency of visits is decided by the treating physician and is expected to reflect routine clinical practice. Standard follow-up period is between 6-12 months.

Item	Response	Response	Response
Data sources	INCREASE/INCREASE OLE	UKRB	COMPERA
	assessment for patients participating in INCREASE OLE was designated by the patient's final assessment as part of INCREASE at week 16. Patients were then assessed at total week 20, at week 28, and then every 12 weeks up to the end of the study.		
Follow-up	In the INCREASE study, patients were followed up at weeks 4, 8, 12, and 16, while those who continued in the OLE were further assessed at weeks 20,28, and every 12 weeks thereafter until week 124. This is sufficient for PH-ILD given that the survival rates at 1, 3, and 5 years have been reported as 72–79%, 47–52%, and 37–38%, respectively (53).	Patients are followed up until death or transplantation, on average for up to 5 to 10 years.	Patients are followed up on average for up to 10 years.
Sample size	The INCREASE study enrolled 326 patients who either received placebo (163 patients) or inhaled treprostinil (163 patients).	The UKRB dataset includes 128 patients with PH-ILD documented with RHC.	The dataset contains 1,781 patients, 763 of which are over the age of 18 and have a diagnosis of WHO Group 3 PH-ILD.

Abbreviations: 6MWD, six-minute walk distance; AEs, adverse events; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; COVID-19, coronavirus disease of 2019; ILD, interstitial lung disease; INCREASE, A Multicentre, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; NHS, National Health Service; OLE-open-label extension; RCTs, randomised controlled trials; RHC, right heart catheterisation; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; UK, United Kingdom; UKRB, The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom; USA, United States of America, WHO, World Health Organization.

5. STATISTICAL METHODS

5.1 Sample Size

The study applies a two-group design to compare the survival of patients exposed to inhaled treprostinil with those receiving SOC, among adult patients with PH-ILD. The study's participants will be evaluated regarding their survival curves at 28, 52 and 124 weeks.

A previous study (5,6) compared 119 patients who had received inhaled treprostinil with 121 patients who had received placebo during INCREASE RCT. The study observed a hazard ratio of 0.67 when assessing the risk of death during OLE. Specifically, the median time to death was 62.0 weeks for the patients who had received inhaled treprostinil during INCREASE RCT, compared to 31.3 for the patients who received placebo during INCREASE RCT.

By using the rank-preserving structural failure time model to evaluate the overall survival for the event of death comparing 163 patients treated with inhaled treprostinil vs. placebo (54), a hazard ratio of 0.26 was estimated.

Taking this information into account, along with the expected number of patients for this study (163 subjects in the treatment group, and up to 322 subjects in the control group) the statistical power to compare survival of these 2 groups is assessed in the following:

A two-sided log-rank test with an overall sample size of 485 subjects (322 in the control group and 163 in the treatment group) achieves 77% power at a 0.05 significance level to detect a hazard ratio of 0.6 when the control group median survival time is 31 weeks, assuming that the study will last for 124 weeks. This power estimation constitutes an approximation, since the use of causal inference methods like propensity score weighting (instead of the simplistic log-rank test application) will reduce power due to variance inflation.

This sample size calculation has been carried out by using log-rank's procedure from "PASS 2021" (Power Analysis and Sample Size Software [2021]). Number Cruncher Statistical Systems, Limited Liability Company. Kaysville, Utah, USA.

5.2 Data Analyses

5.2.1 General Considerations

The analysis plan will be developed in a written SAP. The SAP will describe with full detail variable definitions for exposures, outcomes, covariates, and subgroups of interest. All analytic methods will be detailed and a full set of table shells will be included.

Results will be summarised in tables and/or figures in Excel or Word format and analyses will be performed with R, version 4.1.3 or higher, or Statistical Analysis System (SAS), version 9.4 or higher (SAS Institute Inc., Cary, NC, USA), or other statistical software as appropriate.

5.2.1.1 Summary statistics

Descriptive analyses will be performed to gain an understanding of the qualitative and quantitative nature of the data collected and the characteristics of the sample studied. Continuous variables will be reported as mean, standard deviation, median, interquartile range, and minimum/maximum values. Categorical variables will be summarised as number and percent within each category.

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

5.2.1.2 Incidence Rates, Comparative Ratios and Differences

The incidence rates (IRs), comparative ratios, differences and their corresponding 95% confidence interval (CI) for the outcomes of interest will be estimated.

The IR 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 multiplied by 1,000.

A patient will only be considered at risk until end of follow-up, as defined in Section 4.4. Since the IR of the outcome of interest during 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).

The comparative ratio will be defined as the IR for the outcome of interest in the intervention group divided by the IR in the RW-comparator groups.

Differences will be defined as the subtraction of the IRs between the defined groups.

5.2.1.3 Time-to-event analysis

The time from index date to time-to-event outcomes of interest or to censoring, as described in Section 4.4, is considered as the period at risk. Weighted Kaplan-Meier curves for the time-to-event will be presented for the entire period at risk.

The weighted cumulative time-to-event probabilities (and corresponding 95% CI) will be estimated for the outcomes of interest. The cumulative probability at a given time point will be defined as the proportion of patients who have not experienced the outcome of interest by that time.

5.2.1.4 Average treatment effect in the treated population

To estimate the treatment effect, the outcomes of the inhaled treprostinil group will be compared with those of the comparator group. For that, the average treatment effect in the treated population (ATT) will be estimated. The ATT (55,56) is a marginal estimator that standardises the treatment effect according to the baseline covariate values as observed in the treated group. The average treatment effect in the comparator population will also be estimated (average treatment effect in the untreated population), but only for the primary endpoint.

PS weighting will be employed to balance the covariate distributions between the treprostinil group and SOC comparator groups, as described in the next Section 5.2.1.5.

5.2.1.5 5.2.1.5Propensity Score Weighting

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

Logistic regression will be used to estimate the PS. The list of potential covariates for the PS model can be found in Section 4.7. Including these variables will reduce bias and enhance the precision of the estimated treatment effect (57).

The PS will be used to apply PS weighting to balance baseline patient characteristics between inhaled treprostinil and SOC groups. This application creates a pseudo-population in which the distribution of observed baseline covariates is independent of treatment assignment and permits estimation of the marginal treatment effect given that all confounders are appropriately accounted for in the PS model (58). The weights are calculated separately for those in the inhaled treprostinil and SOC group as: Treated group (Treprostinil)=1, Comparator group=PS/(1-PS). This method results in the estimation of the ATT (59–62).

To assess the balance of observed potential confounders between the exposure categories in the weighted sample, standardised mean differences (SMDs) for all covariates will be calculated and assessed. Balance diagnostics in covariates will be investigated before any outcome analyses are carried out.

Absolute SMDs above 0.25 will be interpreted as unacceptable imbalance, while imbalances between 0.1 and 0.25 will be interpreted as moderate imbalance (63). If at least 1 covariate's SMD is higher than 0.25 or 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 ATT and will become the primary analysis approach. If <10% but >0% of the included covariates' SMDs are higher 0.1, the ATO will be provided as a supplementary analysis for the primary endpoint.

Subjects with very low PS in the comparator group may result in extreme weights. Such weights can increase the variability of the estimated treatment effect, such weights will be truncated at the 99th percentile (64).

5.2.1.6 Comparative analyses

To estimate the treatment effect for survival outcomes, weighted Restricted Mean Survival Time (RMST) models (and weighted Cox proportional hazard regression as a potential sensitivity analysis (63,65,66)) will be applied to estimate RMSTs, RMST differences (and 95% CIs) of inhaled treprostinil versus SOC in PH patients. Weighted RMSTs may be estimated by utilising weighted Kaplan-Meier curves.

To estimate the treatment effect for longitudinal outcomes, weighted mixed effects models (67–69) 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.

To estimate the treatment effect on binary outcomes, weighted logistic regression models will be applied.

5.2.2 Analysis Populations

The analysis populations will be defined according to the groups presented in Section 4.5 by treatment exposition:

- The primary exposure groups:
  - Inhaled treprostinil treated
  - Inhaled treprostinil treated who reach and sustain the target dose
- The comparator groups of SOC in Europe:
  - Off-label PDE5i treated
  - Off-label PDE5i treated with target dose
  - Treatment naïve patients
  - Blended (off-label PAH treated and treatment naïve)
  - Blended (off-label PAH treated and treatment naïve) treated with target dose

5.2.3 Planned Analyses

5.2.3.1 Primary Objective - All-cause mortality

The differences in the survival distributions associated with treatment exposure will be estimated and a comparative analysis will be assessed as defined in Section 5.2.1.6.

The cumulative survival probabilities and corresponding 95% CIs will be estimated for all-cause mortality as defined in Section 5.2.1.3.

The IRs and their corresponding 95% CIs for all-cause mortality will be estimated for each group: the intervention group (patients exposed to inhaled treprostinil) and the RW-comparator groups (SOC in among adult patients with PH-ILD) at 28, 52 and 124 weeks of follow-up as described in Section 5.2.1.2. Also, comparative ratios and differences with 95% CIs will be estimated.

5.2.3.2 Secondary Objectives

5.2.3.2.1 First cardiopulmonary hospitalisation

The IR, and their corresponding 95% CI for the first cardiopulmonary hospitalisation will be estimated separately for each group at 28, 52 and 124 weeks of follow-up as described in Section 5.2.1.2. Also, comparative ratios and differences with 95% CIs will be estimated.

The cumulative survival probabilities and corresponding 95% CI will be estimated for the first PH related hospitalisation as defined in Section 5.2.1.3.

5.2.3.2.2 6MWD

To describe and compare the mean difference in 6MWD associated with treatment exposure, summary statistics as described in Section 5.2.1.1 and weighted mixed effects models as described in Section 5.2.1.6 will be applied. The timepoints considered will be from baseline to 28 weeks, 52 weeks, and 124 weeks of follow-up.

5.2.3.2.3 FVC

To describe and compare the mean difference in FVC associated with treatment exposure, summary statistics as described in Section 5.2.1.1 and weighted mixed effects models as described in Section 5.2.1.6 will be applied. The timepoints considered will be from baseline to 28 weeks, 64 weeks, and 124 weeks of follow-up.

5.2.4 Subgroup Analyses

Data will be examined by specific subgroups, where relevant, according to the SAP. The potential subgroups selected may include but are not limited to the following:

- Subgroups by aetiology and/or severity categories:
  - Excluding all patients with CPFE.
  - Including only patients with PH associated idiopathic interstitial pneumonias and connective tissue disease-related ILD.
  - Including only patients with severe or non-severe PH-ILD at baseline with a PVR score greater than 5, indicating severe PH-ILD.

The subgroup analyses for the primary outcome will report descriptive statistics as described in Section 5.2.1.1. Comparative analyses will only be undertaken if sufficient outcome events are observed, as defined in the SAP. For this comparison, statistical methods described in Section 5.2.1.6 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

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 (70–76).

Multiple imputation (MI) (70–76) will be used as the primary approach to handle missing covariate data (75). After that, PS weighting will be applied as described in Section 5.2.1.5.

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

5.2.6 Sensitivity and Supplementary Analysis

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 (77). 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 (77). 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 (77).

5.2.6.2 Supplementary analyses: Handling intercurrent events

Intercurrent events, such as death from all causes, would affect the existence of some endpoints. 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 (56,78). The strategy for the main analysis will be based on the treatment policy approach. Supplementary estimands based on a composite endpoint estimand or hypothetical strategy may be performed in addition.

5.3 Data Reporting

A final analysis will be performed, and its results will be reported.

5.3.1 Final Analyses and Reporting

The final report will encompass all planned analyses, irrespectively of the interim findings, including a description of the complete study population as described above in Section 5.2and in fully detailed 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 (79). To mitigate this, the study design and analytical approaches will be guided by the target trial emulation framework (30,31). Key eligibility criteria from INCREASE/INCREASE OLE trials will be emulated and measured adjustment variables (Appendix B, Figure 4) 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 5.2.6.1).

Trial patients (ie, patients from INCREASE/INCREASE OLE trial) are more likely to be adherent to randomised treatment. However, in RW practice, both prescribing decisions and 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. To mitigate this, routine care for the target patient population in the proposed external control group will be evaluated during the feasibility assessment (79).

Furthermore, selection bias may arise if the sample obtained from the RW is not representative of the population intended to be analysed. To mitigate this, all data sources used in this study (INCREASE/INCREASE OLE clinical trial data, data from UKRB registry, and data from COMPERA) will be assessed in terms of data relevance.

The validity of any secondary data analysis depends on the accuracy and completeness of available information in the RW data source (ie, UKRB and COMPERA). To minimise the risk of including inaccurate information, all retrieved data will be reviewed for possible inconsistences or implausible information. UKRB data source will be assessed in terms of its suitability to address the study research question using the DataSAT. 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 patients treated with inhaled treprostinil 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 desired outcome variables may not be collected (eg, hospitalisation is not available in UKRB), or outcome definition differs from trial patients. Interval of six-minute walk tests, pulmonary function tests, and laboratory measurements are expected to be less frequent in RWD. Further, loss to follow-up may be a concern in RWD. A qualitative 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 (79).

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 INCREASE/INCREASE OLE trial patients in terms of measurement frequency, method of ascertainment, or definition (79).

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 (80). Alignment of eligibility, beginning of treatment, and index date across trial and external comparator group is planned to reduce the risk for 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 guided by the National Institute for Health and Care Excellence NICE real-world evidence framework (1) and Canada´s Drug and Health Technology Agency Guidance for Reporting Real-World Evidence (2). The study will be conducted according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology (81), the ENCePP Checklist for Study Protocols (see Appendix C), the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practice (GPP) guidelines (4) 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 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 and UKRB, as well as the INCREASE and OLE data.

R language v4.1.3 or later (82) (https://www.r-project.org), or SAS version 9.2 or later (SAS Institute Inc., Cary, NC, USA), 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 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 the data sources, COMPERA and UKRB, participating in this study.

8. SAFETY REPORTING

8.1 Procedures for Reporting Adverse Events

Pursuant to the requirements for reporting of AEs for secondary data, according to European Medicines Agency Good Pharmacovigilance Practices 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 (83).

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 (3), the International Society of Pharmacoepidemiology GPP (4), 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 European Parliament and of the European Council General Data Protection Regulation 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 the UKRB, this study sought approval from the

Health Research Authority (including Research Ethics Committee review) via central Integrated Research Approval System application identification number 340955.

10. REFERENCES

1. NICE. NICE real-world evidence framework, corporate document [ECD9] [Internet]. National Institute for Health and Care Excellence; 2022. Available from: https://www.nice.org.uk/corporate/ecd9/resources/nice-realworld-evidence-framework-pdf-1124020816837

2. CADTH. Guidance for Reporting Real-World Evidence [Internet]. Canada´s Drug and Health Technology Agency; 2023. Available from: https://www.cadth.ca/sites/default/files/RWE/MG0020/MG0020-RWE-Guidance-Report-Secured.pdf

3. European Medicines Agency. The ENcePP Code Of Conduct For Scientific Independence And Transparency In The Conduct Of Pharmacoepidemiological And Pharmacovigilance Studies. European Medicines Agency; 2018.

4. Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). Pharmacoepidemiol Drug Saf. 2016 Jan;25(1):2–10.

5. Waxman A, Restrepo-Jaramillo R, Thenappan T, Ravichandran A, Engel P, Bajwa A, et al. Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. N Engl J Med. 2021 Jan 28;384(4):325–34.

6. Waxman A, Restrepo-Jaramillo R, Thenappan T, Engel P, Bajwa A, Ravichandran A, et al. Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study. Eur Respir J. 2023 Apr 20;2202414.

7. Humbert M, Kovacs G, Hoeper MM, Badagliacca R, Berger RMF, Brida M, et al. 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Heart J. 2022 Oct 11;43(38):3618–731.

8. Dhont S, Zwaenepoel B, Vandecasteele E, Brusselle G, De Pauw M. Pulmonary hypertension in interstitial lung disease: an area of unmet clinical need. ERJ Open Res. 2022 Oct;8(4):00272–2022.

9. Mandras SA, Mehta HS, Vaidya A. Pulmonary Hypertension: A Brief Guide for Clinicians. Mayo Clin Proc. 2020 Sep;95(9):1978–88.

10. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019 Jan;53(1):1801913.

11. Wijeratne DT, Lajkosz K, Brogly SB, Lougheed MD, Jiang L, Housin A, et al. Increasing Incidence and Prevalence of World Health Organization Groups 1 to 4 Pulmonary Hypertension: A Population-Based Cohort Study in Ontario, Canada. Circ Cardiovasc Qual Outcomes. 2018 Feb;11(2):e003973.

12. Piccari L, Allwood B, Antoniou K, Chung JH, Hassoun PM, Nikkho SM, et al. Pathogenesis, clinical features, and phenotypes of pulmonary hypertension associated with interstitial lung disease: A consensus statement from the Pulmonary Vascular Research Institute's Innovative Drug Development Initiative - Group 3 Pulmonary Hypertension. Pulm Circ. 2023 Apr;13(2):e12213.

13. Rich S, Haworth SG, Hassoun PM, Yacoub MH. Pulmonary hypertension: the unaddressed global health burden. Lancet Respir Med. 2018 Aug;6(8):577–9.

14. Statista. Annual number of patients with pulmonary hypertension in the united kingdom (uk) from 2004 to 2021 [Internet]. 2022 [cited 2023 Aug 6]. Available from: https://www.statista.com/statistics/571912/patients-with-pulmonary-hypertension-in-the-united-kingdom-uk/

15. NHS Digital. National Audit of Pulmonary Hypertension Great Britain, 2021-22. 13th Annual Report [Internet]. 2023. Available from: https://files.digital.nhs.uk/36/B8B717/NAPH%2013AR%20-%20Main%20Report%20v1.0.pdf

16. Handa T, Nagai S, Miki S, Ueda S, Yukawa N, Fushimi Y, et al. Incidence of pulmonary hypertension and its clinical relevance in patients with interstitial pneumonias: comparison between idiopathic and collagen vascular disease associated interstitial pneumonias. Intern Med. 2007;46(12):831–7.

17. Todd NW, Lavania S, Park MH, Iacono AT, Franks TJ, Galvin JR, et al. Variable prevalence of pulmonary hypertension in patients with advanced interstitial pneumonia. J Heart Lung Transplant. 2010 Feb;29(2):188–94.

18. Nikkho SM, Richter MJ, Shen E, Abman SH, Antoniou K, Chung J, et al. Clinical significance of pulmonary hypertension in interstitial lung disease: A consensus statement from the Pulmonary Vascular Research Institute's innovative drug development initiative-Group 3 pulmonary hypertension. Pulm Circ. 2022 Jul;12(3):e12127.

19. DelveInsight. Pulmonary Hypertension associated with Interstitial Lung Disease (PH-ILD) - Market Insight, Epidemiology And Market Forecast - 2032. 2022.

20. Heresi GA, Platt DM, Wang W, Divers CH, Joish VN, Teal SA, et al. Healthcare burden of pulmonary hypertension owing to lung disease and/or hypoxia. BMC Pulm Med. 2017 Apr 11;17(1):58.

21. Heresi G, Castillo H, Lee H, Classi P, Stafkey-Mailey D, Morland K, et al. Burden of illness in patients with pulmonary hypertensiondue to interstitial lung disease: a real-world analysisusing US claims data. CHEST. 2021 Oct 1;160(4):A2322–3.

22. Zare P, Heller D. Treprostinil. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 [cited 2023 Jun 12]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK545152/

23. Raghu G, Behr J, Brown KK, Egan JJ, Kawut SM, Flaherty KR, et al. Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. Ann Intern Med. 2013 May 7;158(9):641–9.

24. King TE, Behr J, Brown KK, du Bois RM, Lancaster L, de Andrade JA, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2008 Jan 1;177(1):75–81.

25. King TE, Brown KK, Raghu G, du Bois RM, Lynch DA, Martinez F, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. Am J Respir Crit Care Med. 2011 Jul 1;184(1):92–9.

26. Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, Anstrom KJ, Collard HR, Flaherty KR, et al. A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. N Engl J Med. 2010 Aug 12;363(7):620–8.

27. Kolb M, Raghu G, Wells AU, Behr J, Richeldi L, Schinzel B, et al. Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis. N Engl J Med. 2018 Nov 1;379(18):1722–31.

28. COMPERA [Internet]. [cited 2023 Jun 6]. Available from: https://www.compera.org/

29. Dawes TJW, McCabe C, Dimopoulos K, Stewart I, Bax S, Harries C, et al. Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: A Bayesian retrospective observational cohort study. Respirology. 2023 Mar;28(3):262–72.

30. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. American Journal of Epidemiology. 2016 Apr 15;183(8):758–64.

31. U.S. Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products [Internet]. U.S. Food and Drug Administration; 2023 [cited 2023 Jun 28]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/considerations-design-and-conduct-externally-controlled-trials-drug-and-biological-products

32. Gray CM, Grimson F, Layton D, Pocock S, Kim J. A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data. Drug Saf. 2020 Jul;43(7):623–33.

33. Mack C, Christian J, Brinkley E, Warren EJ, Hall M, Dreyer N. When Context Is Hard to Come By: External Comparators and How to Use Them. Ther Innov Regul Sci. 2020 Jul;54(4):932–8.

34. Yap TA, Jacobs I, Baumfeld Andre E, Lee LJ, Beaupre D, Azoulay L. Application of Real-World Data to External Control Groups in Oncology Clinical Trial Drug Development. Front Oncol. 2021;11:695936.

35. Galiè N, Torbicki A, Barst R, Dartevelle P, Haworth S, Higenbottam T, et al. Guidelines on diagnosis and treatment of pulmonary arterial hypertension. The Task Force on Diagnosis and Treatment of Pulmonary Arterial Hypertension of the European Society of Cardiology. Eur Heart J. 2004 Dec;25(24):2243–78.

36. Task Force for Diagnosis and Treatment of Pulmonary Hypertension of European Society of Cardiology (ESC), European Respiratory Society (ERS), International Society of Heart and Lung Transplantation (ISHLT), Galiè N, Hoeper MM, Humbert M, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. Eur Respir J. 2009 Dec;34(6):1219–63.

37. Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). European Heart Journal. 2016 Jan 1;37(1):67–119.

38. Wakabayashi R, Hirano T, Laurent T, Kuwatsuru Y, Kuwatsuru R. Impact of “time zero” of Follow-Up Settings in a Comparative Effectiveness Study Using Real-World Data with a Non-user Comparator: Comparison of Six Different Settings. Drugs Real World Outcomes. 2023 Mar;10(1):107–17.

39. Hatswell AJ, Deighton K, Snider JT, Brookhart MA, Faghmous I, Patel AR. Approaches to Selecting "Time Zero" in External Control Arms with Multiple Potential Entry Points: A Simulation Study of 8 Approaches. Med Decis Making. 2022 Oct;42(7):893–905.

40. Gall H, Felix JF, Schneck FK, Milger K, Sommer N, Voswinckel R, et al. The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. J Heart Lung Transplant. 2017 Sep;36(9):957–67.

41. Jang HJ, Woo A, Kim SY, Yong SH, Park Y, Chung K, et al. Characteristics and risk factors of mortality in patients with systemic sclerosis-associated interstitial lung disease. Ann Med. 2023 Dec;55(1):663–71.

42. Zubairi ABS, Ahmad H, Hassan M, Sarwar S, Abbas A, Shahzad T, et al. Clinical characteristics and factors associated with mortality in idiopathic pulmonary fibrosis: An experience from a tertiary care center in Pakistan. Clin Respir J. 2018 Mar;12(3):1191–6.

43. Sangani RA, Lui JK, Gillmeyer KR, Trojanowski MA, Bujor AM, LaValley MP, et al. Clinical characteristics and outcomes in pulmonary manifestations of systemic sclerosis: Contribution from pulmonary hypertension and interstitial lung disease severity. Pulm Circ. 2022 Oct;12(4):e12117.

44. Shlobin OA, Kouranos V, Barnett SD, Alhamad EH, Culver DA, Barney J, et al. Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: results from an international registry. Eur Respir J. 2020 May;55(5):1901747.

45. Alhamad EH, Cal JG, Alrajhi NN, Alharbi WM. Predictors of Mortality in Patients with Interstitial Lung Disease-Associated Pulmonary Hypertension. J Clin Med. 2020 Nov 26;9(12):3828.

46. Rose L, Prins KW, Archer SL, Pritzker M, Weir EK, Misialek JR, et al. Survival in pulmonary hypertension due to chronic lung disease: Influence of low diffusion capacity of the lungs for carbon monoxide. J Heart Lung Transplant. 2019 Feb;38(2):145–55.

47. Qiu M, Chen Y, Ye Q. Risk factors for acute exacerbation of idiopathic pulmonary fibrosis: A systematic review and meta-analysis. Clin Respir J. 2018 Mar;12(3):1084–92.

48. NICE. NICE real-world evidence framework, corporate document [ECD9]. DataSAT assessment template. [Internet]. 2022. Available from: https://www.nice.org.uk/corporate/ecd9/chapter/appendix-1-data-suitability-assessment-tool-datasat#datasat-assessment-template

49. Parikh R, Konstantinidis I, O'Sullivan DM, Farber HW. Pulmonary hypertension in patients with interstitial lung disease: a tool for early detection. Pulm Circ. 2022 Oct;12(4):e12141.

50. Yorke J, Corris P, Gaine S, Gibbs JSR, Kiely DG, Harries C, et al. emPHasis-10: development of a health-related quality of life measure in pulmonary hypertension. European Respiratory Journal. 2014 Apr 1;43(4):1106–13.

51. ATS Statement. Am J Respir Crit Care Med. 2002 Jul;166(1):111–7.

52. Margaritopoulos GA, Antoniou KM, Wells AU. Comorbidities in interstitial lung diseases. Eur Respir Rev. 2017 Jan;26(143):160027.

53. Kacprzak A, Tomkowski W, Szturmowicz M. Pulmonary Hypertension in the Course of Interstitial Lung Diseases—A Personalised Approach Is Needed to Identify a Dominant Cause and Provide an Effective Therapy. Diagnostics (Basel). 2023 Jul 13;13(14):2354.

54. Nathan SD, Johri S, Joly JM, King CS, Raina A, McEvoy CA, et al. Survival analysis from the INCREASE study in PH-ILD: evaluating the impact of treatment crossover on overall mortality. Thorax. 2023 Nov 18;thorax-2023-220821.

55. The International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use. Addendum on estimands and sensitivity analysis in clinical trials to the guideline on statistical principles for clinical trials E9(R1) [Internet]. 2019. Available from: https://database.ich.org/sites/default/files/E9-R1_Step4_Guideline_2019_1203.pdf

56. Wang A, Nianogo RA, Arah OA. G-computation of average treatment effects on the treated and the untreated. BMC Medical Research Methodology. 2017 Jan 9;17(1):3.

57. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015 Dec;34(28):3661–79.

58. Vaughan AS, Kelley CF, Luisi N, del Rio C, Sullivan PS, Rosenberg ES. An application of propensity score weighting to quantify the causal effect of rectal sexually transmitted infections on incident HIV among men who have sex with men. BMC Medical Research Methodology. 2015 Mar 21;15(1):25.

59. Brookhart MA, Wyss R, Layton JB, Stürmer T. Propensity score methods for confounding control in nonexperimental research. Circ Cardiovasc Qual Outcomes. 2013 Sep 1;6(5):604–11.

60. Gökbuget N, Kelsh M, Chia V, Advani A, Bassan R, Dombret H, et al. Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. Blood Cancer J. 2016 Sep 23;6(9):e473.

61. Davies J, Martinec M, Delmar P, Coudert M, Bordogna W, Golding S, et al. Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib. J Comp Eff Res. 2018 Sep;7(9):855–65.

62. Thompson C, Lamm M, Yung YF. Causal Effect Estimands: Interpretation, Identification, and Computation. In 2020 [cited 2023 Jul 4]. Available from: https://support.sas.com/resources/papers/proceedings20/4322-2020.pdf

63. Zhang Z, Kim HJ, Lonjon G, Zhu Y. Balance diagnostics after propensity score matching. Ann Transl Med. 2019 Jan;7(1):16.

64. Lee BK, Lessler J, Stuart EA. Weight Trimming and Propensity Score Weighting. PLOS ONE. 2011 Mar 31;6(3):e18174.

65. Kleinbaum D, Klein M. Survival Analysis. A Self-Learning Text. 3rd ed. Springer New York; 2012.

66. Lee-Jen We DHK. Restricted Mean Survival Time as a Measure to Interpret Clinical Trial Results. JAMA Cardiol. 2017 Nov 1;2(11):1179–80.

67. Gałecki A, Burzykowski T. Linear Mixed-Effects Models Using R. A Step-by-Step Approach. Springer New York; 2013.

68. Raudenbush S, Bryk A. Hierarchical Linear Models: Applications and Data Analysis Methods (Advanced Quantitative Techniques in the Social Sciences). 2nd ed. Sage Publications; 2001.

69. Hox J, Moerbeek M, de Schoot R. Multilevel Analysis: Techniques and Applications, Second Edition (Quantitative Methodology Series). 2nd ed. Routledge; 2010.

70. Horton NJ, Lipsitz SR, Parzen M. A Potential for Bias When Rounding in Multiple Imputation. The American Statistician. 2003 Nov 1;57(4):229–32.

71. Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. Stat Med. 1995 Sep 15;14(17):1913–25.

72. Little R, Schenker N. Handbook of statistical methodology – Missing data. New York: Plenum Press; 1995.

73. Rubin D. Multiple imputations in sample surveys – A phenomenological Bayesian approach to nonresponse. Imputations and editing of faulty or missing survey data. U.S. Department of Commerce; 1978.

74. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991 Apr;10(4):585–98.

75. Rubin DB, editor. Multiple Imputation for Nonresponse in Surveys [Internet]. Hoboken, NJ, USA: John Wiley & Sons, Inc.; 1987 [cited 2023 Jan 11]. (Wiley Series in Probability and Statistics). Available from: http://doi.wiley.com/10.1002/9780470316696

76. Schafer J. Analysis of Incomplete Multivariate Data. Chapman and Hall; 1997.

77. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017 Aug 15;167(4):268.

78. European Medicines Agency. E 9 Statistical Principles for Clinical Trials [Internet]. European Medicines Agency; 2006. Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/ich-e-9-statistical-principles-clinical-trials-step-5_en.pdf

79. Seeger JD, Davis KJ, Iannacone MR, Zhou W, Dreyer N, Winterstein AG, et al. Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. Pharmacoepidemiol Drug Saf. 2020 Nov;29(11):1382–92.

80. Suissa S. Immortal Time Bias in Pharmacoepidemiology. American Journal of Epidemiology. 2008 Feb 15;167(4):492–9.

81. ENCePP. ENCePP Checklist for Study Protocols (Revision 4). 2018 Oct 15 [cited 2023 Aug 16]; Available from: https://www.encepp.eu/standards_and_guidances/methodologicalGuide.shtml

82. R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. [Internet]. Available from: URL http://www.R-project.org/

83. European Medicines Agency. Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2). 2017;1–144.

11. APPENDICES

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

Table 11: INCREASE Clinical Trial Eligibility Criteria.

NO.		UKRB	COMPERA	Potential proxy
Inclusion criteria				
1	Subject voluntarily gives informed consent to participate in the study	Not available[a]	Available	N/A
2	Males and females aged 18 years or older at the time of informed consent	Available	Available	Age ≥18 years at index date
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	Not available	Partially available	Record of pregnancy or breastfeeding during the study period
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
3	The subject has a confirmed diagnosis of WHO Group 3 PH based on CT imaging, which demonstrates evidence of diffuse Parenchymal Lung	Available	Available	Diagnosis (eg, direct record of diagnosis or result & date of CT) of WHO Group 3 PH before or at index

NO.		UKRB	COMPERA	Potential proxy
	Disease performed within 6 months prior to randomisation. Subjects may have any form of ILD or CPFE			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 parameters: PVR >3 WU PCWP of ≤15 mmHg mPAP of ≥25 mmHg	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 metres	Available	Available	6MWD ≥100 metres at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)
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	Available	Not Available	Patients on medication(s) for underlying lung disease (eg, pirfenidone, nintedanib) are on stable dose without any 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

NO.		UKRB	COMPERA	Potential proxy
8	Subjects with CTD must have a baseline FVC of <70%	Available	Available	Patients with CTD must have a FVC of <70% 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	Record of PAH during the study period
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	N/A
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, PDE5i, or SGC stimulator within 60 days of randomisation	Available	Partially available	A record of off-label PAH treatment 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	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	Available	Available	Oxygen supplementation of >10 L/min at rest by

NO.		UKRB	COMPERA	Potential proxy
	supplementation by any mode of delivery at rest at baseline			any mode of delivery before or at index date (closest measurement to index date will be used, 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	Partially available	Partially 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	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	Participation in pulmonary rehabilitation before index date, with a look-back period of 3 months
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) that would likely be the primary limit to ambulation (as opposed to PH)	N/A	N/A	N/A

NO.		UKRB	COMPERA	Potential proxy
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	N/A
11	Severe concomitant illness limiting life expectancy (<6 months)	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	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; INCREASE, A Multicentre, Randomised, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; N/A, not available; OLE-open-label extension; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PDE5i, phosphodiesterase type 5 inhibitor; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; PI, prostaglandin I2; RHC, right heart catheterisation; PVR, pulmonary vascular resistance; SGC, soluble guanylate cyclase; UKRB, The Royal Brompton Hospital Pulmonary Hypertension 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.

Table 12: INCREASE OLE Clinical Trial Eligibility Criteria.

NO.		UKRB	COMPERA	Potential proxy
Inclusion criteria				
1	Subject voluntarily gives informed consent to participate in the study	Not available[a]	Available	N/A
2	The subject participated in study RIN-PH-201 AND:	N/A	N/A	N/A
2a	remained on study drug and completed all scheduled study visits OR	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
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
3	Females of reproductive potential must be non-pregnant (as confirmed by a urine pregnancy test at screening) and nonlactating, and will:	Not available	Partially available	Record of pregnancy or breastfeeding during the study period
3a	Either abstain from intercourse (when it is in line with their preferred and usual lifestyle), OR	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

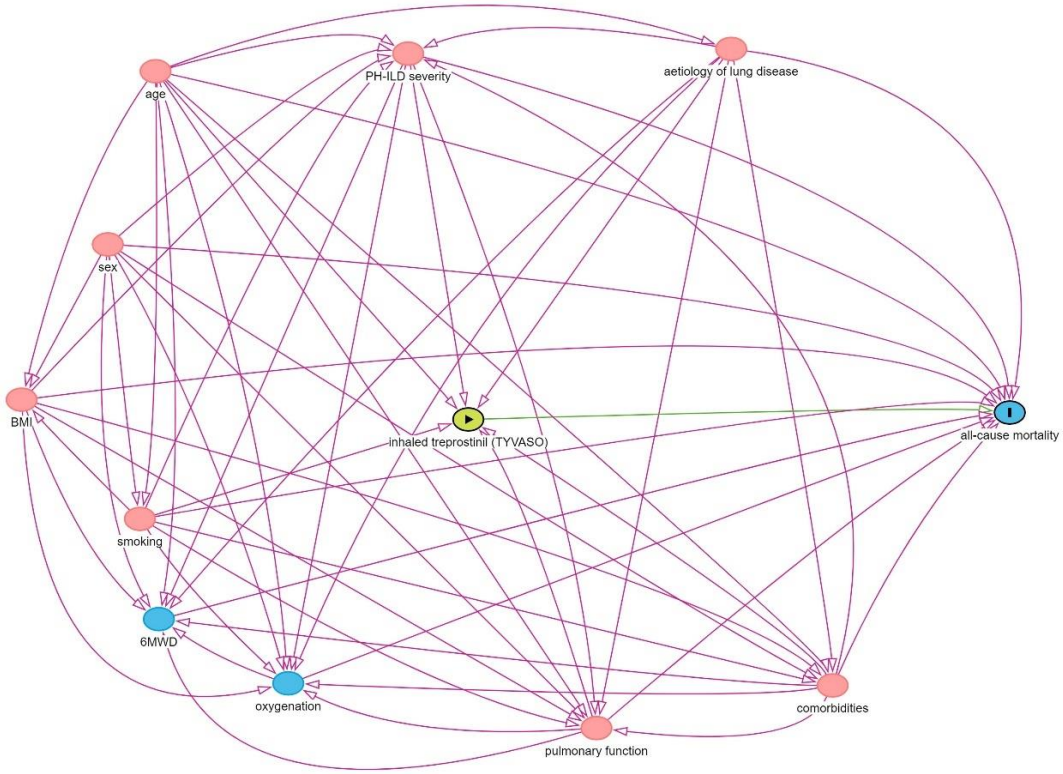
NO.		UKRB	COMPERA	Potential proxy
4	Males with a partner of childbearing potential must use a condom for the duration of treatment and for at least 48 hours after discontinuing study drug	N/A	N/A	N/A
Exclusion criteria				
1	The subject is pregnant or lactating	Not available	Partially available	Record of pregnancy or breastfeeding during the study period
2	The subject was prematurely discontinued from study RIN-PH-201 due to treatment related AEs	N/A	N/A	N/A
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
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

Abbreviations: COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; INCREASE, A Multicentre, Randomised, 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/A, not available; NO, number of order; OLE-open-label extension; UKRB, The Royal Brompton Hospital Pulmonary Hypertension 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. Key confounding variables for the primary outcome of all-cause mortality

Figure 4: Directed Acyclic Graph for All-cause Mortality.



Abbreviations: 6MWD, six-minute walk distance; BMI, body mass index; PH-ILD, pulmonary hypertension associated with interstitial lung disease.

[a] PH-ILD severity will be defined using PVR.

Appendix C. ENCePP checklist for study protocols

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

EU PAS Register® number: not applicable
Study reference number (if applicable): 3049399

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:

-

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:

-

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:

-

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section number**
4.1	Is the source population described?	☒	☐	☐	4.3 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:

-

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:

-

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)	☒	☐	☐	4.8.3 Data suitability assessment
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)	☒	☐	☐	4.6 Outcomes of interest

Comments:

-

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:

-

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)	☐	☒	☐	-

Comments:

-

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 finalisation 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 finalisation 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 finalisation 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:

-

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:

-

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:

-

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:

-

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:

-

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:

-

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:

-

[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.

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

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

Date: 30 April 2024

Signature: _____