NON-INTERVENTIONAL STUDY PROTOCOL

TITLE	Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD
PROTOCOL NO.	2953067
VERSION	V2.0 Dated 09 July 2024
SPONSOR	Ferrer Internacional S.A. Avenida Diagonal 549, 08029 Barcelona, Spain +34 936 003 700
CONDUCTED BY	IQVIA 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 organisation 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

LIST OF APPENDICES

Principal Investigator Signature Page

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

Study number: 2953067

Protocol version: 2.0 dated 09 July 2024

I herewith certify that I agree to content of the Study Protocol v2.0 and to all documents referenced in the Study Protocol version v2.0.

Investigator:

[redacted]

Print Name

DocuSigned by Fabian Hoti
Fabian Hoti
I approve this document
09-Jul-2024 | 4:13:49 PM EEDT
B63C1BB408A04080B6F32045ABC28A90

09-Jul-2024

Date

IQVIA,
Metsänneidonkuja 6,
02130 Espoo, Finland
+358 (0)9 4241 3800

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	Firmado por Gabriela Silvina Bacchini Jeanneret Gabriela Silvina Bacchini Jeanneret 51AF2AA497CF470B93BDFFAE2C8A4223 Apruebo este documento 10-jul.-2024 | 12:46:12 PM EEDT	Corporate Medical Affairs Head, Pulmonary Vascular & Interstitial lung Diseases Therapeutic Area, Ferrer	10-jul.-2024
Ferrer	Signature	Title	Date
Tania Nadal Boeufvé	DocuSigned by Tania Nadal Boeufvé Tania Nadal Boeufvé B3B2F9CA280343D697DCBD3F6C211BE1 Apruebo este documento 09-jul.-2024 | 3:23:13 PM EEDT	Clinical Development Director, Ferrer	09-jul.-2024
Ferrer	Signature	Title	Date
Miriam Fernández Delgado	DocuSigned by Miriam Fernández Delgado Miriam Fernández Delgado E2C4F05C0DA24AC2B31DE20595400A73 Apruebo este documento 09-jul.-2024 | 3:20:22 PM EEDT	Head of Corporate Market Access, Ferrer	09-jul.-2024
Ferrer	Signature	Title	Date
[redacted]	[redacted]	, IQVIA	22-Jul-2024
IQVIA			Date
[redacted]	DocuSigned by Fabian Hoti Fabian Hoti B63C1BB408A04080B6F32045ABC28A90 I approve this document 09-Jul-2024 | 4:14:12 PM EEDT	Principal Investigator, IQVIA	09-Jul-2024
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 Therapeutic Area, Ferrer

Address: Avenida Diagonal 549, 08029, Barcelona, Spain

Mobile: +34 936 003 700

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

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

Study Synopsis

Full Study Title: Real-World Comparative Effectiveness Study of TYVASO (Inhaled Treprostinil) in the Treatment of PH-ILD			
Phase:	Not applicable (N/A)	**Type:**	External Comparator Arm (ECA) study
Number of Patients: The 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): 101 of those patients completed 28 weeks of study assessment, 76 patients completed 52 weeks of study assessment, and 71 patients completed 64 weeks of study assessment as the maximum follow-up for the current study. The expected number of patients in the standard of care (SOC) group is up to 391[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 Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA)[2], Registry of Pulmonary Hypertension Associated with Respiratory Disease		**Duration of study**: Study outcomes will be assessed at 28 weeks, 52 weeks, or 64 weeks.[5]	

[1] 346 PAH therapy treated patients from COMPERA, 30 from REHAR, and 15 from UKRB.

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

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

(REHAR)[3], and The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB)[4].	

Background:

Pulmonary hypertension (PH) is a pathophysiological disorder characterised by elevated mean pulmonary arterial pressure (mPAP) that can lead to cardiac dysfunction and failure. World Health Organization (WHO) classifies PH into 5 groups, depending on pathophysiology and clinical presentation. Group 3 PH patients – those with PH associated with lung disease and/or hypoxia – experience the most severe outcomes and mortality. Interstitial lung disease (ILD) is one factor that can contribute to the development of PH, with varying prevalence rates depending on the type and severity of ILD. Prevalence estimates based on the previous definition of mPAP ≥25 mmHg have ranged from 3% to 64% in ILD patients. The coexistence of PH and ILD presents a substantial clinical and economic burden, leading to increased healthcare resource utilisation and costs. Studies have demonstrated higher utilisation of diagnostic procedures, prescriptions, and treatments among PH-ILD patients, resulting in elevated costs primarily driven by inpatient admissions, prescriptions, and outpatient care. This trend is increasing over time.

PH in ILD patients is associated with increased need for supplemental oxygen, reduced mobility, and decreased survival, but given the significant overlap in symptoms in ILD patients with and without PH, diagnosis is difficult. Significantly decreased diffusing capacity, reduced distance in the 6-minute walk test, evident exertional desaturation, and delayed heart rate recovery after exercise are all signs of PH-ILD progression. Many diagnostic clinical tests lack specificity and sensitivity and therefore, right heart catheterisation (RHC) is the gold standard for verifying a PH-ILD diagnosis.

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 (COMPERA, REHAR, and UKRB), this study aims to generate evidence of long-term comparative effectiveness of inhaled treprostinil for a substantially longer follow-up window of 28 weeks, 52 weeks, or 64 weeks, as compared to the placebo-controlled 16-week follow-up of INCREASE.

Research Question: What is the comparative effectiveness of inhaled treprostinil 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 (2 comparator groups will be considered as SOC: off-label pulmonary arterial

[3] REHAR contains data on WHO Group 3 PH patients from 14 centers across Spain.

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

hypertension (PAH) therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB, and treatment naïve patients from REHAR and UKRB)[6]?
Primary objective: 1. To describe and compare the mean difference in **6-minute walk distance (6MWD)** from baseline to 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[7] in Europe, among adult patients with PH-ILD **Secondary objectives:** 1. To estimate incidence rates (IRs) and comparative ratios and differences for **clinical worsening**[8] up to 28 weeks and 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[6] in Europe, among adult patients with PH-ILD 2. To estimate IRs and differences up to 28 weeks and 52 weeks and cumulative survival probabilities for **all-cause mortality** and first **cardiopulmonary hospitalisation** associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[6] in Europe, among adult patients with PH-ILD 3. To describe and compare the mean difference in **pulmonary function** from baseline to 28 weeks and 64 weeks, and in **N-Terminal pro-B-type Natriuretic Peptide (NT-proBNP)** from baseline to 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[6] in Europe, among adult patients with PH-ILD 4. To describe **oxygenation**[9] at 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[6] in Europe, among adult patients with PH-ILD **Exploratory objectives:** 1. To describe **proportion of treatment success** at 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[6] in Europe, among adult patients with PH-ILD
Study design: This is an ECA study using data from the INCREASE and INCREASE OLE clinical trials and 3 PH registries in Europe (COMPERA, REHAR, and UKRB) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus SOC.

[6] Where not all data sources have available data to assess each outcome, the choice of RW registry will be dictated by data availability. Choice of RW data source for each outcome is presented in Table 4.

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

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

[9] Defined as presence of hypoxia/hypoxemia.

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

Study population: The study 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 (PVR)[10] >3 Wood Units (WU)
  - pulmonary capillary wedge pressure (PCWP) 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 (CTD) must have a forced vital capacity (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 any off-label PAH therapy (excluding prostanoids)[11] at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

Exclusion criteria

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

- A record of off-label PAH therapy[10] before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date
- A record of participation in any investigational study with therapeutic intent at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

Data collection/ Data Sources:

[10] In cases where PVR is not captured, but cardiac output is available, cardiac output will be used to calculate PVR.

[11] A list of drug classes and active substances used in the treatment of PH-ILD have been presented in **Error! Reference source not found.**.

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. COMPERA, a PH registry that spans multiple European countries, REHAR, a PH associated with lung disease registry in Spain, and UKRB, a PH-ILD registry in London, United Kingdom were selected to contribute patients to the 2 external comparator groups.

Data Management and Quality Assurance:

The study protocol will adhere to European Network of Centres for Pharmacoepidemiology and Pharmacovigilance Code of Conduct [1] and to International Society of Pharmacoepidemiology Good Pharmacoepidemiology Practices (GPP) [2] guideline 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.

Statistical Considerations:

Descriptive statistics for baseline demographic data and clinical characteristics will be presented for inhaled treprostinil group and SOC groups in Europe.

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

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

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

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

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

Sample size

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

Sample size calculations were performed to mimic an estimated mean difference in 6MWD of 30 metres between exposed subjects and unexposed subjects with a standard deviation of 75 metres, as targeted in the INCREASE (RIN-PH-201) clinical trial. A total of 326 patients enrolled in the INCREASE RCT, with 163 randomly assigned to inhaled treprostinil and 163 to placebo. 130 of the patients assigned to inhaled treprostinil and 128 of the patients assigned to placebo completed week 16 of study assessment. A total of 243 patients enrolled in INCREASE OLE (RIN-PH-202). 119 of those patients continued on inhaled treprostinil (received inhaled treprostinil in INCREASE RCT) and 121 started on inhaled treprostinil (received placebo in INCREASE RCT). Of the 119 patients who continued on inhaled treprostinil in INCREASE OLE, 68 patients completed 52 weeks of study assessments for 6MWD.

In the case of 70 patients, a minimum of 187 patients in each SOC group will be needed to achieve 80% power when comparing the inhaled treprostinil group versus SOC. In all cases, variance inflation factor (VIF) corrections were considered.

Final Analyses: One final analysis will be performed. The final report will include all planned descriptive, comparative, sensitivity, and exploratory analyses, and imputation techniques for missing data.

Ethical and Regulatory Considerations: This non-interventional study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to 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 (EU) 2016/679 of the European Parliament and of the European Council (27 April 2016) on the protection of natural persons regarding the processing of personal data.

Documentation of Protocol Amendments

Table 1: Amendments and updates

Number	Date	Section of study protocol	Amendment or update	Reason
1	09.07.2024	Milestones	Milestones have been updated and the delivery of the final study report is now planned in Q1 2025	Delays in the results of the Feasibility Study
2	09.07.2024	Study Synopsis	Addition of expected sample size in the SOC group	Availability of Feasibility Study results
3	09.07.2024	Study Synopsis 3. OBJECTIVES 4.5 Outcomes of Interest	Addition of a secondary outcome for oxygenation and changes to its definition	Definition of oxygenation was confirmed after the availability of the Feasibility Study results
4	09.07.2024	Study Synopsis 4.3.1 Inclusion Criteria	Deletion of the following inclusion criteria: “Informed consent according to national and local standards, where applicable”	Not applicable in RW data
5	09.07.2024	Study Synopsis 3. OBJECTIVES 5.2.3 Exploratory Analysis	The following exploratory objective was removed: “Assess the comparability of INCREASE internal clinical trial comparator group to the European external RW treatment naïve group before and after	Results of the Feasibility Study demonstrated that it is not feasible due to lack of data

			adjustment for baseline confounding for the primary outcome of 6MWD"	
6	09.07.2024	Study Synopsis 4.3.1 Inclusion Criteria	Addition of the following exclusion criteria: "A record of participation in any investigational study with therapeutic intent at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)"	To exclude patients in the SOC group coming from a clinical trial as the aim is to compare with RW patients receiving SOC during standard clinical practice
7	09.07.2024	Study Synopsis 4.4 Exposures of interest	Addition of the description for the different exposed and comparator groups	To ensure a more precise and effective analysis of the study results
8	09.07.2024	Study Synopsis 4.4 Exposures of interest	Change from 'all-cause hospitalisation' to 'cardiopulmonary hospitalisation'	Availability of Feasibility Study results
9	09.07.2024	4.5 Outcomes of Interest	Cardiopulmonary hospitalisation, clinical worsening, and proportion of treatment success will only be analysed in a subsample of COMPERA patients	Availability of Feasibility Study results

10	09.07.2024	4.6 Other Variables (Covariates)	The list of patients´ characteristics and potential confounders/risk factors was updated	Availability of Feasibility Study results
11	09.07.2024	4.7.2 Data from Disease-Specific Registries (comparator group)	Addition of Tables 7-9 to give a general overview of the included data source and availability of exposure, outcome and other (covariates) variables	Availability of Feasibility Study results
12	09.07.2024	Study Synopsis 5.2.2.3 Comparative analyses	Royston-Parmar models will be applied as a primary analysis instead of the RMST models. RMST will be estimated as a supplementary analysis	To align data analysis with the following Ferrer study protocol and SAP: "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"
13	09.07.2024	6. LIMITATIONS OF RESEARCH METHODS	Addition of further study limitations	Availability of Feasibility Study results
14	09.07.2024	Appendix A	Availability of eligibility criteria in RW data sources and the potential	Availability of Feasibility Study results

			proxies were updated	
15	09.07.2024	Throughout the protocol	Editorial changes, minor text correction, or changes to improve readability	To correct spelling mistakes and harmonise terms throughout the protocol

Abbreviations: 6MWD, six-minute walk distance, 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; PAH, pulmonary arterial hypertension; Q, quarter; RMST, restricted mean survival time; RW, real-world; SAP, statistical analysis plan; SOC, standard of care.

Milestones

The planned dates for the study milestones are described in Table 2 below. The dates associated with these milestones are subject to amendment during study conduct.

Table 2: Provisional dates of study milestones

Milestone	Planned date
Finalisation of the quantitative feasibility report	Q3 2024
Finalisation of the protocol version 1.0	Q1 2024
Protocol amendment	Q2 2024
Update of the registration in the HMA-EMA Catalogue of real-world data sources and studies	Q3 2024
Finalisation of the statistical analysis plan version 1.0	Q2 2024
Statistical analysis plan amendment	Q3 2024
Delivery of the final analysis	Q4 2024
Delivery of the final study report	Q1 2025

Abbreviations: EMA, European Medicines Agency; HMA, Heads of Medicines Agencies; 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 [3–5]. After a recent change in its definition PH is now defined by an mPAP of >20 mmHg at rest and is further categorised as pre-capillary PH (pulmonary capillary wedge pressure [PCWP] ≤15 mmHg, pulmonary vascular resistance [PVR] >2 WU) and post-capillary PH (PCWP >15 mmHg, PVR ≤2 WU) based on hemodynamic assessment [3,6]. PH 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) [3,6,7].

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 [8] which can lead to the narrowing and obstruction of blood vessels, increasing resistance to blood flow through the pulmonary arteries. 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 [8]. PH associated with ILD (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 [9]. The United Kingdom (UK) reported a 5-fold increase in the annual incidence of PH from 2004 to 2021 [10]. 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) [7], with the highest mortality observed in Group 3 [11]. The prevalence of PH among patients with ILD varies [12,13] and is influenced by factors such as the type and severity of ILD and the diagnostic criteria used [14]. 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 [14]. In 2021, EU4 regions (Germany, France, Italy, and Spain) and the UK reported 57,138 cases of PH-ILD, with projections indicating an increase by 2032. Among these regions, Germany had the highest prevalence of PH-ILD with 13,868 cases, followed by the UK with 13,166 cases [15].

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 $7,051) than the comparator group. The costs were related to inpatient admissions (35.4%), prescriptions (33.0%), and outpatient care (26.5%) [16]. A retrospective cohort study evaluating healthcare resource utilisation among patients with PH-ILD, found that the percentage of patients with PH-ILD requiring hospitalisation doubled ($p<0.0001$) from 29.5% in the pre-index to 59.0% in the post-index period, with a significant increase ($p<0.0001$) in healthcare costs from $43,201 to $108,387, respectively [17].

1.2 Current Diagnosis and Treatment Paradigm

PH in ILD patients is associated with increased need for supplemental oxygen, reduced mobility, and decreased survival [14]. Given the significant overlap in symptoms with those of ILD without PH, a strong suspicion is necessary to make the diagnosis [18]. Significantly decreased diffusing capacity, reduced distance in the 6-minute walk test, evident exertional desaturation, and delayed heart rate recovery after exercise are all signs of PH-ILD progression. The most often used screening diagnostic for PH-ILD is traditional transthoracic echocardiography, although it brings sensitivity and specificity concerns [19]. Although newer echocardiographic methods that use multidimensional imaging methods may improve detection of patients with PH-ILD, RHC is still the gold standard for verifying a PH-ILD diagnosis [20].

In Europe, there is currently no approved medicinal treatment for PH-ILD. Given the absence of approved therapies for PH-ILD, addressing the underlying lung disease and managing PH-ILD symptoms with available medications, while reducing healthcare usage and cost can be critical. Vasodilator therapy for PH, such as sildenafil, riociguat, and endothelin receptor antagonists (ERAs) investigated in clinical trials have been controversial given their association with negative results among patients e.g., increased risk of clinical worsening events [3]. A recent survey conducted among 55 clinicians across France, Germany, Italy, Spain, and the UK further underscored this issue. The majority of surveyed clinicians (69%) perceived a lack of efficacy or evidence supporting the use of current therapies, pointing to a significant gap in the management of PH-ILD [21].

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 e.g., enhanced exercise capacity, extended time to clinical worsening, and lower relative risk of exacerbation with inhaled treprostinil among patients with PH-ILD. 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].

The INCREASE trial showed a significant difference in the change in peak 6-minute walk distance (6MWD) from baseline to week 16, between the inhaled treprostinil group (N=163) and the placebo group (N=163), with a least-squares mean difference between the groups of 31.12 m (95% confidence interval [CI]: 16.85 to 45.39; p<0.001). Clinical worsening reduced in the treprostinil group compared with placebo group (22.7% versus 33.1%), with a hazard ratio of 0.61 (95% CI: 0.40 to 0.92; p=0.04 by the log-rank test), and treprostinil decreased N-terminal pro–B-type natriuretic peptide (NT-proBNP) levels from baseline (15% versus 46%), with a treatment ratio of 0.58 (95% CI: 0.47 to 0.72; p<0.001) [23]. The INCREASE open-label extension (OLE) trial evaluated long-term effects of inhaled treprostinil in PH-ILD. The mean 6MWD at week 52 was 279.1 m and the median change from INCREASE trial baseline was 3.5 m. The median NT-proBNP decreased from 389 pg/mL at INCREASE trial baseline to 359 pg/mL at week 64. Patients who received inhaled treprostinil versus placebo in the INCREASE trial had a 31% lower relative risk of exacerbated underlying lung disease in the OLE (hazard ratio: 0.69; 95% CI: 0.49 to 0.97; p=0.03) [24].

Inhaled treprostinil 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 for PH-ILD. 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.

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 [3] and it is an area of failed therapies. Several Phase II and Phase III clinical trials have investigated the use of ERAs [25–27] and phosphodiesterase type-5 inhibitors (PDE5i) [28,29] 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 OLE clinical trials [23,24].

By emulating a target trial utilising data from INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) clinical trials with a European external comparator group of real-world (RW) patients from PH registries Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) [30], the Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease (REHAR) [31], and The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom (UKRB) [32], this study aims to generate evidence of long-term comparative effectiveness of inhaled treprostinil for a substantially longer follow-up window of 28 weeks, 52 weeks, or 64 weeks, as compared to the placebo-controlled 16-week follow-up of INCREASE. Furthermore, the current analysis will

extend beyond comparisons with placebo, or treatment naïve patients, to include comparisons with those treated with off-label PAH treatments.

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 standard of care (SOC) (2 comparator groups will be considered as SOC: off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB, and treatment naïve patients from REHAR and UKRB)[12]?

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

1. To describe and compare the mean difference in **6MWD** from baseline to 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[13] in Europe, among adult patients with PH-ILD

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

1. To estimate incidence rates (IRs) and comparative ratios and differences for **clinical worsening**[14] up to 28 weeks and 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[13] in Europe, among adult patients with PH-ILD
2. To estimate IRs and differences up to 28 weeks and 52 weeks and cumulative survival probabilities for **all-cause mortality** and **cardiopulmonary hospitalisation** associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[13] in Europe, among adult patients with PH-ILD
3. To describe and compare the mean difference in **pulmonary function** from baseline to 28 weeks and 64 weeks, and in **NT-proBNP** from baseline to 64 weeks, associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[13] in Europe, among adult patients with PH-ILD

[12] Where not all data sources have available data to assess each outcome, the choice of RW registry will be dictated by data availability. Choice of RW data source for each outcome is presented in Table 4.

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

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

4. To describe **oxygenation**[15] at 28 weeks and 52 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[16] in Europe, among adult patients with PH-ILD

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

1. To describe **proportion of treatment success** at 64 weeks associated with exposure to inhaled treprostinil in patients from INCREASE and INCREASE OLE clinical trials versus SOC[16] in Europe, among adult patients with PH-ILD

4. STUDY DESIGN

4.1 Study Design

This is an external comparator arm (ECA) study using data from the INCREASE and INCREASE OLE clinical trials (treatment group) and COMPERA, REHAR, and UKRB registries (external comparator) to generate evidence on the long-term comparative effectiveness of inhaled treprostinil versus SOC in Europe. Details relating to the data sources are provided in Section 4.7. Overview of the design is presented in Figure 1.

Exposure to inhaled treprostinil (exposed patients from the INCREASE and INCREASE OLE clinical trials) will be compared to SOC in Europe. SOC comprises of 2 comparator groups derived from RW data: (1) off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB; (2) treatment naïve patients from REHAR and UKRB.

This ECA will use data from historic and contemporary RW comparators [33] who are either treatment naïve or on off-label PAH therapy constructed using observational patient-level data from PH registries in Europe (see Section 4.7).

The study design and analytical approaches are guided by the target trial emulation framework, which provides a formal methodology for estimating causal effects from RW data (see Appendix A for INCREASE/INCREASE OLE eligibility criteria) [34,35].

[15] Defined as presence of hypoxia/hypoxemia.

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

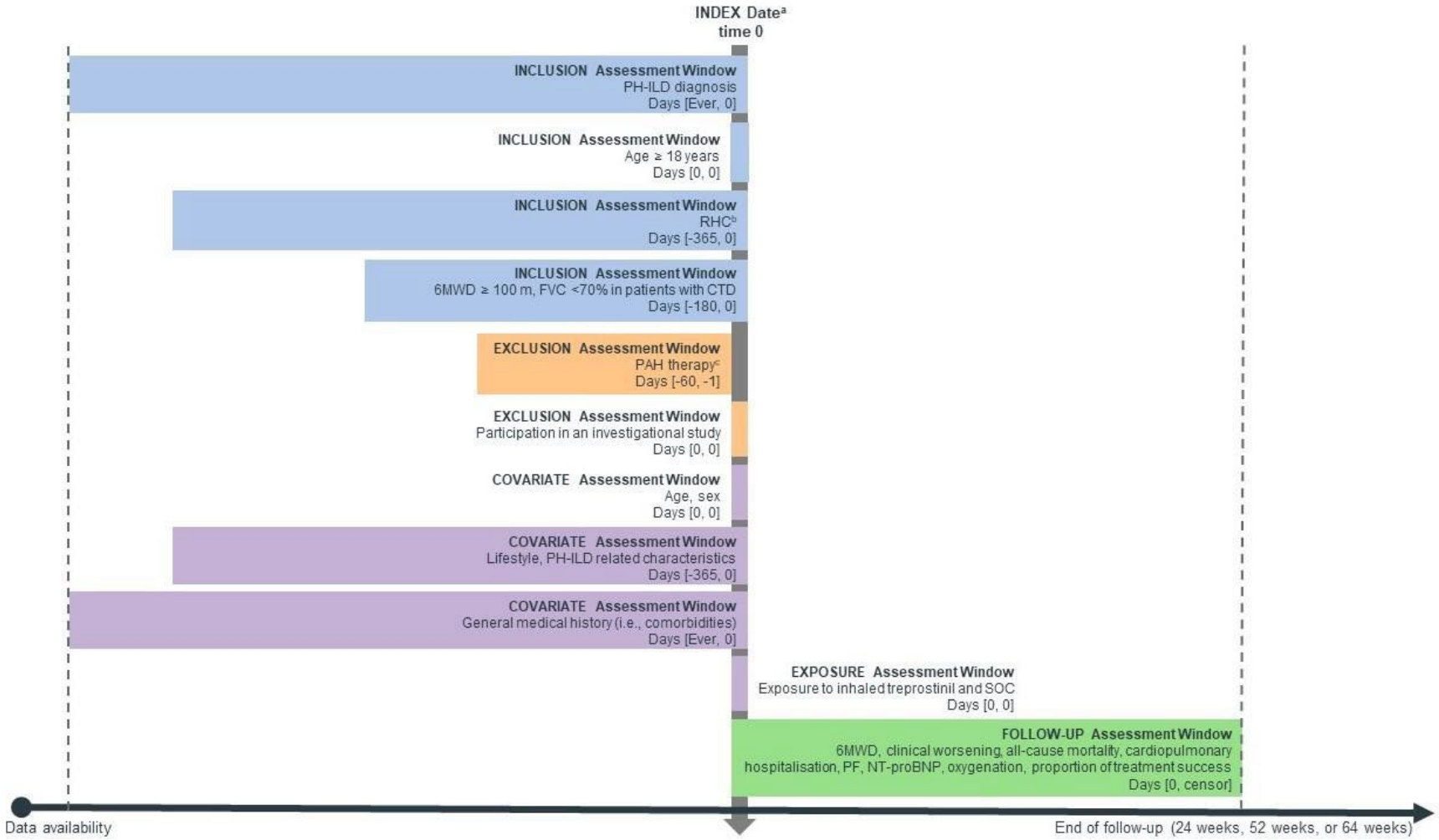

Figure 1: Overview of the study design

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

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

4.1.1 Rational for the Study Design

Although randomised controlled trials (RCTs) are considered as the "gold standard" for generating evidence to assess the efficacy and safety of medicines, this design can be challenging to apply especially in severe or rare disease where there are few or no alternative treatments [33,36]. RCTs require large number of patients, and it is often not feasible or ethical to randomise patients to placebo or SOC treatment known to have limited effectiveness [33,37]. 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, 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 [3,38–40]. Thus, to increase patient counts, the period of data extraction from the PH registries will be extended to all available data at data extraction (for COMPERA, June 2006-May 2023; for REHAR, May 2002-August 2023; for UKRB, May 2007-January 2024).

The **index date** for the inhaled treprostinil treated and off-label PAH comparator group will be at initiation of inhaled treprostinil and initiation of off-label PAH therapy, respectively[17]. For treatment naïve patients, the index date for each patient will be obtained by randomly drawing a time from the observed distribution of time between initial PH-ILD diagnosis[18] and treatment initiation in the inhaled treprostinil treated group and adding this to the initial PH-ILD diagnosis date (Figure 2). The feasibility of applying alternative methods for assigning index dates for untreated individuals will be explored and defined in the statistical analysis plan (SAP) [41,42].

[17] Index date will be at treatment initiation for both the treated and treated with target dose exposure groups.

[18] As date of PH-ILD is not captured in REHAR, date of RHC will be used as a proxy.

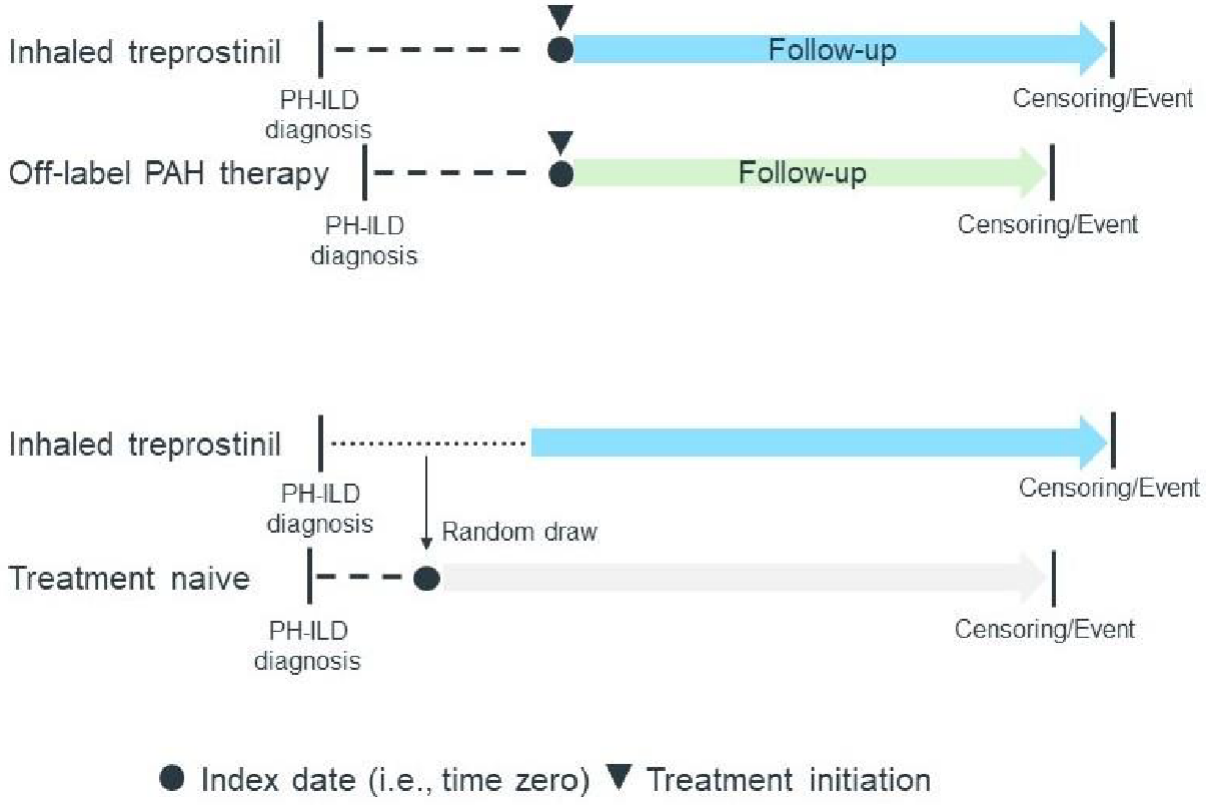

Figure 2: Overview of the index date

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-ILD of various aetiologies, documented by an RHC.

The intervention (inhaled treprostinil) group is captured in the INCREASE trial (RIN-PH-201), a multicentre, randomised, double-blind, placebo-controlled, 16-week Phase III trial, and INCREASE OLE trial (RIN-PH-202), an open-label extension study with a follow-up of up to 108 weeks (total follow-up of 124 weeks). The RW comparator groups will be derived from European PH registries COMPERA, REHAR, and UKRB (see Section 4.7).

The intervention group of the INCREASE and INCREASE OLE clinical trials will be compared with 2 comparator groups derived from RW data in Europe: (1) off-label PAH therapy

(excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB; (2) treatment naïve patients from REHAR and UKRB.

4.3.1 Inclusion Criteria

The following criteria must be met 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 (WU)[19]
  - PCWP 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 (CTD) must have a forced vital capacity (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 any off-label PAH therapy (excluding prostanoids)[20] at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

4.3.2 Exclusion Criteria

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

- A record of off-label PAH therapy[17] before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date
- A record of participation in any investigational study with therapeutic intent at the time of patient eligibility (for the external comparator group treated with off-label PAH therapy only)

[19] In cases where PVR is not captured, but cardiac output is available, cardiac output will be used to calculate PVR.

[20] A list of drug classes and active substances used in the treatment of PH-ILD have been presented in **Error! Reference source not found.**.

4.3.3 Follow-up

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

- Exit from the clinical trial/data source
- Outcome of interest[21]
- Lung transplantation
- Death
- End of study[22]

4.4 Exposures of Interest

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

Two different exposed groups will be considered:

- Inhaled treprostinil treated – patients randomised to inhaled treprostinil[23].
- Inhaled treprostinil treated who reach the target dose – patients randomised to inhaled treprostinil who reach the target dose of 9-12 inhalations (total 72 µg), 4 times daily at least once any time during the study [23][24].

Exposure to inhaled treprostinil will be compared to SOC in Europe (Figure 3). The comparator group will consist of patients from RW data sources (COMPERA, REHAR, and UKRB) who are treated with off-label PAH therapy (excluding prostanoids) or are treatment naïve. PAH approved therapy for the off-label treatment of PH-ILD include ERAs, PDE5s, and soluble guanylate cyclase stimulators (see Table 14 in Appendix B).

The following comparator groups will be considered:

- Off-label PAH treated – patients who initiate off-label PAH therapy[20]

[21] For time-to event outcomes.

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

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

[24] Patients who discontinue inhaled treprostinil will be considered non-compliant with the inhaled treprostinil treated strategy and censored at the date of discontinuation.

- Treatment naïve – patients who are treatment naïve[20]
- Off-label PAH treated with target dose – patients who initiate off-label PAH therapy and reach respective target dose (see Table 3)[25].

Table 3. Off-label PAH therapy dose

Active substance	Target dose
Ambrisentan	5-10 mg QD
Bosentan	62.5-250 mg BID
Macitentan	10 mg QD
Riociguat	1-2.5 mg TID
Sildenafil	20-80 mg TID
Tadalafil	20-40 mg QD

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

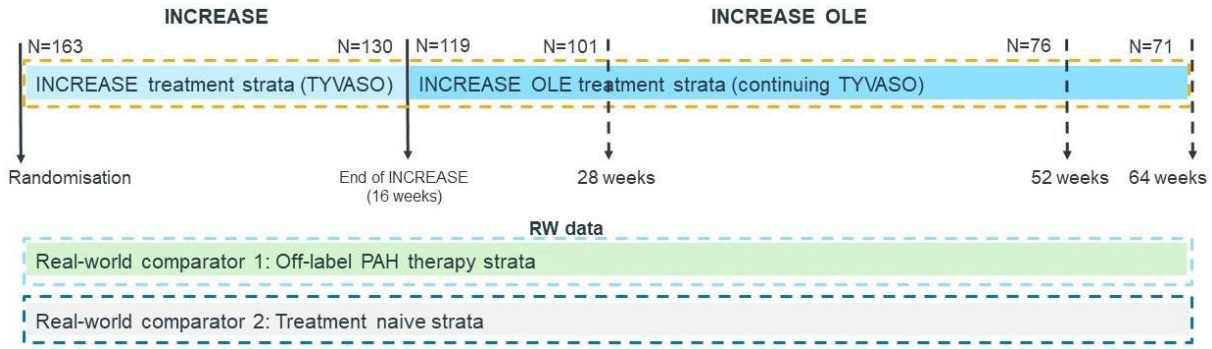

Figure 3: Overview of the exposure and comparator groups

[25] Patients who discontinue off-label PAH therapy will be considered non-compliant with the off-label PAH treated strategy and censored at the date of discontinuation.

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

4.5 Outcomes of Interest

Study outcomes and respective definitions are summarised in Table 4.

Table 4: Outcomes of Interest

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

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

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RW data	RW population[a]	Assessment time point(s)[b]	Outcome type
7	Oxygenation (presence of hypoxia/hypoxemia)	Moderate hypoxia: SpO2 at rest 89-93% Severe hypoxia: SpO2 at rest <89%	Moderate hypoxia: SpO2 or SaO2 at rest 89-93% Severe hypoxia: SpO2 or SaO2 at rest <89% OR Moderate hypoxemia: PaO2 at rest 56–59 mmHg Severe hypoxemia: PaO2 at rest <56 mmHg [43–46] as available in the specific data source	PH-ILD patients from COMPERA, REHAR, and UKRB[c]	28 weeks ±30 days 52 weeks ±30 days	Secondary
8	Proportion of treatment success	Assessed in a 3-step hierarchical order: 1) Survival 2) No clinical worsening 3) Treatment success (15%	Assessed in a 3-step hierarchical order: 1) Survival 2) No clinical worsening 3) Treatment success (15% increase in 6MWD and 30%	Subsample of PH-ILD patients from COMPERA	64 weeks +30 days	Exploratory

No.	Outcome of interest	Definition in INCREASE and INCREASE OLE	Definition in RW data	RW population[a]	Assessment time point(s)[b]	Outcome type
		increase in 6MWD and 30% decrease in NT-proBNP)	decrease in NT-proBNP)			

Abbreviations: 6MWD, six-minute walk distance; 6MWT, six-minute walk test; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; OLE, open-label extension; PaO2, partial pressure exerted by oxygen on the arterial wall; PFTs, pulmonary function tests; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; RW, real-world; SaO2, saturation of oxygen in arterial blood; SpO2, saturation of peripheral capillary oxygenation; TLC, total lung capacity; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom.

[a] Where RW population includes PH-ILD patients from COMPERA only, treatment-naïve patients are not included in comparisons due to the absence of such patients in this data source.

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

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

[d] As TLC is not captured in UKRB a subsample of patients from COMPERA and REHAR will be used for analysis.

4.6 Other Variables (Covariates)

The variables presented in Table 5 will be considered as selection criteria, to describe the study cohort´s baseline characteristics, or as adjustment variables for confounding control. The final choice of baseline characteristics, potential risk factors, and confounders will depend on the availability and completeness of data across the data sources and clinical relevance (Appendix C). Specific definitions for all variables will be presented in detail in the SAP.

At baseline, the variables presented in Table 5 will be considered to create the 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. Confounding variables will be retrieved at index date or in the look-back period as presented in Figure 1.

Table 5: Patients´ characteristics and potential confounders/risk factors

	Baseline characteristics	**Candidate for PS**
Demographic characteristics		
Age	x	x
Sex	x	x
Lifestyle characteristics		
BMI	x	x
Smoking	x	x
General medical history		
Coronary heart disease/coronary artery disease/ischemic heart 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

	Baseline characteristics	Candidate for PS
6MWD	x	x
PVR	x	x
PCWP	x	x
mPAP	x	x
Hypoxia/hypoxemia	x	x
Supplemental oxygen therapy	x	x
TLC	x	x
FVC	x	x
FEV1	x	x
DLCO	x	x
NT-proBNP	x	x

Abbreviations: 6MWD, six-minute walk distance; BMI, body mass index; 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 score; PVR, pulmonary vascular resistance; TLC, total lung capacity.

For the analysis of functional capabilities, exercise capacity (assessed by 6MWD), and survival potential confounders include demographics (e.g., older age) and lifestyle characteristics (e.g., smoking) [47–49], PH-ILD disease history (e.g., disease severity, 6MWD at diagnosis) [50,51], and other clinical characteristics (e.g., FVC, PVR, diffusing capacity of the lungs for carbon monoxide, SpO2, NT-proBNP) [48,52,53]. Risk factors for adverse events (AEs) (e.g., exacerbations) include vital capacity, FVC and total lung capacity [54]. Comorbidities recognised as risk factors for survival include left-sided heart disease (assessed by left ventricular ejection fraction) and other cardiovascular disease (e.g., coronary artery disease, atrial fibrillation) [53].

4.7 Data Sources and Collection

Appropriateness and data capture of 3 relevant PH data sources (Assessing the Spectrum of Pulmonary Hypertension Identified at a Referral Centre [ASPIRE], COMPERA, and REHAR)

were assessed during the qualitative feasibility led by Orpha Strategy and 2 of them, COMPERA and REHAR, were considered suitable for this study. A third data source (UKRB) was subsequently identified for inclusion as part of this study and a high-level qualitative assessment was conducted to better understand this data source. A quantitative feasibility assessment study of all 3 data sources is planned ahead of full study execution.

Two types of data sources will be used in this study: (1) data for the inhaled treprostinil group will be obtained from clinical trial data; (2) data for the SOC (off-label PAH therapy and treatment naïve) will be obtained from RW disease-specific PH registries (Table 6).

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

Table 6: Overview of data sources

Group	Patient population	Data source	Study type
Treatment group	Inhaled treprostinil treatment	INCREASE + INCREASE OLE	RCT + Open-label extension
Comparator 1	Treatment naïve	REHAR + UKRB	RW data
Comparator 2	Off-label PAH treatment	REHAR + UKRB + COMPERA	RW data

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

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

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

INCREASE was a randomised, placebo-controlled, double-blinded clinical trial that assessed the safety and effectiveness of inhaled treprostinil in patients with PH-ILD. INCREASE enrolled 326 patients from 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. 119 patients from the INCREASE treatment strata (see Figure 3) continued treatment with inhaled treprostinil in INCREASE OLE.

4.7.2 Data from Disease-Specific Registries (comparator group)

RW data from disease-specific registries will be used for the 2 comparators: (1) off-label PAH therapy (excluding prostanoids) treated patients from COMPERA, REHAR, and UKRB; (2) treatment naïve patients from REHAR and UKRB (see Table 7).

4.7.2.1 REHAR

REHAR is a Spanish database that began data collection in 2017 from voluntary participants with PH, who also have associated respiratory conditions [31]. REHAR has both retrospective and prospective data capture across 14 centres, which is used for scientific purposes and maintained by relevant data and privacy protection laws.

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

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

4.7.2.2 COMPERA

COMPERA was established in 2007 and is one of the largest prospective PH registries globally, including approximately 11,000 patients across Europe [30] from 61 recruiting centres. This data source includes PH patients from WHO groups 1 to 5. While the data source originates in Germany, countries recruiting to this database also include Austria, Belgium, Greece, Hungary, Italy, Latvia, Lithuania, the Netherlands, Slovakia, Switzerland, and the UK. COMPERA collects detailed but pseudonymised data on PH patients' demographics, incidence, treatment-based and survival outcomes, and AEs. It is fully internet-based and complies with high standards using a number of techniques, including source data verification and automated checks for plausibility of data-entry.

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

This registry does not allow for self-registration; rather, patients must register through one of the participating centres. The registry was initiated by researchers, is fully independent of the pharmaceutical industry, and is being financed with educational funds from Acceleron, AOP Orphan, Bayer, Ferrer, Janssen and Open Monoclonal Technology, Inc. [30].

4.7.2.3 UKRB

The UKRB PH registry is a research ready dataset, collecting routine clinical information on PH-ILD patients treated at the Royal Brompton Hospital National Pulmonary Hypertension Service (London, UK). The Royal Brompton and Harefield hospitals are tertiary centres and together form the largest specialist centre for the treatment of heart and lung disease in the UK, and among the largest in Europe. Data has been collected on consecutive patients treated at this centre and meeting the dataset inclusion criteria since 1 January 2000 [32]. The registry is focused on WHO group 3 PH-ILD patients and was created to understand the causes of pulmonary hypertension and prognosis. Funding for this database was awarded by Ferrer pharmaceuticals.

Table 7: Data source overview

	INCREASE/ INCREASE OLE	COMPERA	REHAR	UKRB
Country	USA	Germany, Italy, UK, Belgium, Netherlands, Switzerland, Austria, Greece, Slovakia, Hungary, Latvia, Lithuania	Spain	UK
Patients included in the data source	PH-ILD patients	WHO Group 1-5 patients	WHO Group 3 PH patients	WHO Group 3 PH patients
Data availability[a]	February 2017-June 2021	June 2006-May 2023	May 2002-August 2023	May 2007-January 2024
Coding system(s)	MedDRA, ATC	No standardised coding system[b]	No standardised coding system[b]	No standardised coding system[b]

Abbreviations: ATC, Anatomical Therapeutic Chemical code; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; MedDRA, Medical Dictionary for Regulatory Activities; OLE, open-label extension; PH-ILD, pulmonary hypertension associated with interstitial lung disease; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; UK, United

Kingdom; UKRB, The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom; WHO, World Health Organization.

[a] In the RW PH registries, this is defined as the date when the first patient entered the registry until date of last available data.

[b] Where possible, pre-specified options were provided, and could be supplemented with free text. Each registry had own quality checking systems to ensure data capture was aligned.

Table 8: Availability of exposure and outcomes

Data source	Exposure		Outcome							
	Inhaled treprostinil	SOC	6MWD	Clinical worsening	All-cause mortality	Pulmonary function	Cardio-pulmonary hospitalisation	NT-proBNP	Oxygenation[a]	Proportion of treatment success
INCREASE/ INCREASE OLE	Available	N/A	Available	Available	Available	Available	Available	Available	Available	Available
COMPERA	N/A	Available	Available	Available	Available	Available	Available	Available	Available	Available
REHAR	N/A	Available	Available	Not available	Available	Available	Not available	Available	Available	Not available
UKRB	N/A	Available	Available	Not available	Available	Partially available[b]	Not available	Not available	Available	Not available

Abbreviations: 6MWD, six-minute walk distance; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; N/A, not applicable; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; OLE, open-label extension; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; SOC, standard of care; UKRB, The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom.

[a] Defined by presence of hypoxia/hypoxemia and assessed by SpO2, SaO2, or PaO2 as available.

[b] Total lung capacity is not captured in UKRB.

Table 9: Availability of baseline characteristics and potential confounders/risk factors

Variable	INCREASE/ INCREASE OLE	COMPERA	REHAR	UKRB
Age	Available	Available	Available	Available
Sex	Available	Available	Available	Available
BMI	Available	Available	Available	Available
Smoking	Available	Available	Available	Available
Coronary heart disease/coronary artery disease	Available	Available	Available	Not available
Ischemic heart disease	Not available	Not available	Not available	Available
Hypertension	Available	Available	Available	Available
Diabetes	Available	Available	Available	Available
Obstructive sleep apnoea	Available	Available	Available	Available
Date of PH-ILD diagnosis	Available	Available	Not available	Available
Aetiology of lung disease	Available	Available	Available	Available
6MWD	Available	Available	Partially available[a]	Available
PVR[b]	Available	Available	Available	Available
PCWP	Available	Available	Available	Available
mPAP	Available	Available	Available	Available
SpO2	Available	Not available	Not available	Not available
SaO2	Not available	Not available	Available	Available
PaO2	Not available	Available	Available	Not available

Variable	INCREASE/ INCREASE OLE	COMPERA	REHAR	UKRB
Supplemental oxygen therapy	Available	Available	Available	Available
TLC	Available	Available	Available	Not available
FVC	Available	Available	Available	Available
FEV1	Available	Available	Available	Available
DLCO	Available	Available	Available	Available
NT-proBNP	Available	Available	Available	Not available
BNP	Not available	Available	Available	Available

Abbreviations: 6MWD, six-minute walk distance; BMI, body mass index; BNP, brain natriuretic peptide; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; INCREASE, A Multicenter, Randomized, Double-Blinded, Placebo-Controlled Trial to Evaluate the Safety and Efficacy of Inhaled Treprostinil in Subjects with Pulmonary Hypertension due to Parenchymal Lung Disease; mPAP, mean pulmonary arterial pressure; NT-proBNP, N-Terminal pro-B-type Natriuretic Peptide; OLE, open-label extension; PaO2, partial pressure exerted by oxygen on the arterial wall; PCWP, pulmonary capillary wedge pressure; PH-ILD, pulmonary hypertension associated with interstitial lung disease; PVR, pulmonary vascular resistance; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; SaO2, saturation of oxygen in arterial blood; SpO2, saturation of peripheral capillary oxygenation; TLC, total lung capacity; UKRB, The Royal Brompton Hospital Pulmonary Hypertension Registry in the United Kingdom.

[a] In REHAR, date of the 6MWT is not recorded, instead, the clinicians are instructed to record the result of the nearest 6MWT to the RHC procedure. However, based on the instructions to the clinicians provided by the data source, it can be assumed that the 6MWT is performed in the relevant time window.

[b] In cases where PVR is not captured, but cardiac output is available, cardiac output will be used to calculate PVR.

5. STATISTICAL METHODS

5.1 Sample Size

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

The sample size will be based on evaluating the mean difference from baseline in 6MWD, as performed in the INCREASE (RIN-PH-201) clinical trial setting. Treated subjects with inhaled

treprostinil (6 mcg/breath) in the INCREASE (RIN-PH-201) and INCREASE OLE (RIN-PH-202) will be compared with external subjects derived from RW data in Europe, as described in Section 4.3.

In INCREASE (RIN-PH-201) trial, a total of 326 patients were enrolled at 92 centres from February 3, 2017, through August 30, 2019, and were randomly assigned to receive placebo (163 patients) or inhaled treprostinil (163 patients). Of the 163 treated subjects, 130 completed week 16 of study assessment. In INCREASE OLE (RIN-PH-202) setting a total of 243 patients enrolled in the trial and 119 patients continued receiving inhaled treprostinil after week 16. Of the 119 patients, 68 patients completed 52 weeks of 6MWD assessments.

The necessary sample size for each SOC group is estimated based on sufficient test measurements across the data sources. For this purpose, sample size calculations were performed to mimic an estimated mean difference in 6MWD of 30 metres between exposed subjects and unexposed subjects with a standard deviation of 75 metres, as targeted in the INCREASE (RIN-PH-201) clinical trial.

5.1.1 Power Estimates

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

- Estimated mean difference at 52 weeks from baseline in 6MWD 30 metres with standard deviation of 75 metres. These targeted parameters lead to an effect size equal to 0.4.
- Level of significance: two-sided 0.05
- Power: From 80% to 90%
- Number of patients in the inhaled treprostinil group: 70
- Variance inflation factor (VIF) correction: 10%

Table 10: Needed sample sizes for the main comparator group to estimate the targeted mean difference of 30 metres with standard deviation of 75 meters, by power and inhaled treprostinil sample (inhaled treprostinil group: exposed in INCREASE and INCREASE OLE, main comparator group: off-label PAH treated patients)

Inhaled treprostinil group	Power	Main comparator group	Main comparator group with VIF correction
70	80%	168	187
	85%	291	323
	90%	1091	1212

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

Table 10 shows the needed sample size for the main comparator group that will ensure at least 80% of statistical power based on the available patients in the inhaled treprostinil group.

In the case of 70 patients having 6MWD assessed at 52 weeks, a minimum of 187 patients in the off-label PAH treated group will be needed to compare inhaled treprostinil group versus the comparator group. VIF corrections were performed by assuming 10% variance inflation due to weighting as described in Section 5.2.2.3 [55]. The applied correction factor is a multiplication by 1/(1-0.1).

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

5.2 Data Analyses

5.2.1 General Considerations

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

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

Continuous and categorical variables will be described using the relevant metrics, as described below in Section 5.2.2.1.1.

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

To yield reliable inferences in time-to-event analysis, it is generally recommended to have a minimum of 10–20% of the group free of events and unfiltered by the end of the follow-up period [56]. To estimate the incidence and risk effect, this criterion will be used.

5.2.2 Planned Analyses

A summary of the planned analyses, each corresponding to a different outcome as detailed in Section 4.5, is presented in the table below (Table 11). A more detailed description of each analysis is described in the subsequent sections.

Table 11: Summary of planned analyses

Outcome	Outcome type	Planned analysis
6MWD	Primary outcome	Weighted summary statistics Weighted mixed-effects models

Outcome	Outcome type	Planned analysis
Clinical worsening	Secondary outcome	Weighted incidence rates
All-cause mortality	Secondary outcome	Weighted incidence rates Weighted Royston-Parmar models (and RMSTs as a supplementary analysis)
Cardiopulmonary hospitalisation	Secondary outcome	
Pulmonary function (FEV1, FVC, TLC, DLCO)	Secondary outcome	Weighted summary statistics Weighted mixed-effects models
NT-proBNP	Secondary outcome	
Oxygenation	Secondary outcome	Weighted summary statistics
Treatment success	Exploratory outcome	Weighted incidence rates

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

5.2.2.1 Descriptive statistics

5.2.2.1.1 Summary statistics

To gain an understanding of overall patterns, descriptive analyses will be performed utilising number and percent within each category for categorical variables, and mean (standard deviation), median (first and third quartiles [Q1, Q3]), and other relevant summary statistics for continuous variables.

5.2.2.1.2 Incidence rate estimation

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

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

A patient will only be considered at risk until end of follow-up, as defined in Section 4.3.3. Since the incidence rate of the outcome of interest during the entire follow-up is not expected

to be constant, its estimation will be stratified based on follow-up periods. Person-years will be calculated only up to the timepoint of censoring. More details will be provided in the SAP.

5.2.2.1.3 Time-to-event analysis

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

5.2.2.2 Average treatment effect in the untreated population

To estimate the treatment effect the outcomes of the inhaled treprostinil group will be compared to those of the comparator group. For that, the average treatment effect in the untreated population (ATU) will be estimated. The ATU [57,58] is a marginal estimator which standardises the treatment effect according to the baseline covariate values as observed in the comparator group.

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

5.2.2.3 Propensity score and Inverse Probability Weighting

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

The logistic regression model will be used to obtain PS. The list of covariates for the PS model can be found in Section 4.6. Including these variables will reduce bias and enhance the precision of the estimated treatment effect [59].

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

Application of the IPTW creates a pseudo-population in which the distribution of baseline covariates is independent of treatment assignment and permits estimation of the marginal effect of the treatment on the outcome, given that all confounders are appropriately accounted for in the PS model [60].

The weights are calculated separately for those in the inhaled treprostinil and SOC arm as: Untreated group (SOC)=1, Treated group (Treprostinil)=PS/(1-PS). This method results in estimation of the ATU [61–64].

Subjects with very low propensity scores in the comparator group may result in extremely large weights. Such weights can increase the variability of the estimated treatment effect, thus weights will be truncated at the 99th percentile [65].

Absolute standardised mean differences (SMDs) above 0.25 will be interpreted as unacceptable imbalance, while imbalances between 0.1 and 0.25 will be interpreted as moderate imbalance [66]. 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 ATU and will become the primary analysis approach. If <10% but >0% of the included covariates' SMDs are higher 0.1, the ATO will be estimated as a supplementary analysis for the primary endpoint.

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

5.2.2.4 Comparative analyses

To estimate the treatment effect on survival outcomes, Royston-Parmar models will be applied as a primary analysis and estimates with the respective 95% CIs and p-values will be presented. Additionally, Restricted Mean Survival Time (RMST) will be estimated as a supplementary analysis, by utilising the KM curve to estimate RMSTs, RMST differences and 95% CIs of inhaled treprostinil versus SOC in PH patients.

To estimate the treatment effect on longitudinal outcomes weighted mixed-effects models [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.

Comparative analyses will only be undertaken if sufficient sample size is achieved.

5.2.3 Exploratory Analysis

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

5.2.4 Subgroup Analyses

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

PH-ILD aetiology categories:

- Idiopathic interstitial pneumonia
- CPFE

- CTD
- Other PH-ILD aetiologies.

PVR categories:

- PVR >5 WU
- PVR ≤5 WU

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

Subgroup analyses will only be undertaken if sufficient sample size is achieved, according to sample size calculations described in Section 5.1.

5.2.5 Handling of Missing Data

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

The number of missing values for data elements will be reported and the likely impact of missing data on the analysis and the pattern of the missing information will be assessed [70–76].

Multiple imputation (MI) [70–76] will be used as the primary approach to handle missing baseline covariate data [75]. After that PS and inverse probability weights will be calculated as described in Section 5.2.2.3.

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

5.2.6 Sensitivity and Supplementary Analyses

5.2.6.1 Sensitivity analyses for unmeasured confounding

To assess how robust an association is to potential unmeasured confounding, the 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 to all causes, would affect the existence of the primary measurements. To handle these terminal events in the primary analysis, the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use E9 (R1) addendum specifies several possible analysis approaches, including the treatment policy strategy, the composite endpoint strategy and the hypothetical strategy [57,78]. The strategy for the main analysis will be based on the treatment policy approach.

To provide an alternative perspective to the treatment effect, a composite strategy or a hypothetical approach will be applied. For the composite endpoint strategy, intercurrent events will be incorporated into the endpoint's definition. For the hypothetical approach, intercurrent events will be statistically adjusted by modelling missing endpoint data (e.g., by inverse probability of censoring weights) [79].

5.3 Data Reporting

A final analysis will be performed.

5.3.1 Final Analyses and Reporting

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

6. LIMITATIONS OF RESEARCH METHODS

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

The characteristics of patients who were eligible for INCREASE/INCREASE OLE trial may differ from those in the external comparator group (i.e., the exposed group and comparator group may not be exchangeable). This may lead to differences in potential outcomes [80]. To mitigate this, the study design and analytical approaches will be guided by the target trial emulation framework [34,35]. Key eligibility criteria from INCREASE/INCREASE OLE trials will be emulated and measured adjustment variables will be used for confounding control. However, residual differences may still exist due to unknown or unmeasured covariates. Thus,

to assess the robustness of the association to potential unmeasured confounding, the E-value will be calculated (see Section 5.2.6).

Trial patients (i.e., patients from INCREASE/INCREASE OLE trial) are more likely to be adherent to treatment. However, in RW practice patient decisions to use a particular medication can frequently change. The recordings of treatment initiation do not guarantee that the patient ingested the medication; they are an expression of the treating physician's intention to treat the patient with the drug. Misclassification of exposure in the external comparator group, may result in bias of effect measures.

The validity of any secondary data analysis depends on the accuracy and completeness of available information in the RW data sources. To minimise the risk of including inaccurate information, all retrieved data will be reviewed for possible inconsistences or implausible information. Furthermore, missing information may vary between individual RW data sources. In REHAR, the date of PH-ILD diagnosis and six-minute walk test (6MWT) is not captured. RHC is the gold standard for verifying a PH-ILD diagnosis [20], therefore the date of RHC will be used as the most appropriate proxy for date of PH-ILD diagnosis in REHAR. In addition, REHAR has provided specific instructions (e.g., record the closest 6MWT to the RHC date, omit 6MWT results done >6 months before the RHC, always perform 6MWT before treatment initiation) to clinicians in recording the results of the 6MWT. Thus, it will be assumed that all 6MWT were performed in the specified time window of 6 months before the index date. Missing covariate information will be handled as described in Section 5.2.5. Percentage of missing information will be reported.

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

Patients in routine clinical practice are not followed-up as closely and frequently as patients in clinical trials. Information on some outcome variables may not be collected, are only collected in some of the individual RW data sources (e.g., cardiopulmonary hospitalisation is only available in COMPERA), or outcome definition differs from trial patients (e.g., in COMPERA only hospitalisations related to PAH or PH are captured). Interval of 6MWT, pulmonary function tests, and laboratory measurements are expected to be less frequent in RW data. Further, loss to follow-up (e.g., in REHAR when a patient transfers from one region to another) may be a concern in RW data. A feasibility assessment of presence and frequency of assessments for outcomes will be conducted to understand whether differential capture of outcomes between the study groups can be expected [80].

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 RW comparators' outcome assessments differs markedly from INCREAS/INCREAS OLE trial patients in terms of measurement frequency, method of ascertainment, or definition [80].

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 [81]. Alignment of eligibility, beginning of treatment, and index date across trial and external comparator group is planned to avoid immortal time bias.

7. STUDY MANAGEMENT

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

7.1 Quality Control

The study will be conducted according to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology [82], the ENCePP Checklist for Study Protocols (see Appendix D), the International Society for Pharmacoepidemiology Good Pharmacoepidemiology Practice Guidelines (GPP) [2] 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 QC plan for the study will be developed and executed, which will include QC on the protocol in general, study methodology, SAP, programming, data management and analysis, and study report including study results and conclusions.

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

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

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

7.2 Data Management

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

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

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

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

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

R language v4.1.3 or later [83] (https://www.r-project.org), or SAS version 9.2 or later (SAS Institute Inc., Cary, NC, United States of America), or other statistical software as appropriate

will be used for managing data and creating the analysis database. Additionally, they will be used for statistical analysis to generate tabulations and graphics, as well as for statistical modelling.

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

In COMPERA, the patients are pseudonymised during data-entry by creating a new and unique study identification number. IQVIA will not have access to the key which links the individual identifiers to the study identification number, thus individuals cannot be directly identified. In REHAR and UKRB, all patient-level data accessible to IQVIA will have original personal identifies replaced with a study identification number. Thus, IQVIA will not have access to data that allow individuals to be directly identified. Ferrer will not have access to the registries' patient-level data at any time of the study.

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

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

7.3 Changes to the Protocol

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

7.4 Publication Policy

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

7.5 Disclosures

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

8. SAFETY REPORTING

8.1 Procedure for Reporting Adverse Events

Pursuant to the requirements for reporting of AEs for secondary data, according to Good Pharmacovigilance Practices (GVP) module VI, VI.C.1.2.1.2, AE reporting will not be conducted as part of this study given the study objectives will be met using secondary data [84].

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 [1], the Guidelines for GVP [85], the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations. IQVIA (who will perform the study on behalf of Ferrer) will take responsibility for obtaining necessary approvals (ethical or otherwise), and access to the study data.

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

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

9.2 Independent Ethics Committee / Institutional Review Board

This study does not require formal ethical approval by an Institutional Review Board but will seek favourable opinion from ethical committees for the conduct of the study and access to data from clinical registries. By being included in these registries, patients consented to the use of data for research purposes. The de-identified 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 (approval reference number 10944_BO_K_2023). For REHAR, a favourable opinion from the ethics committee of Hospital del Mar Clinical Research Ethics Committee was sought (approval reference number 2024/11380). For the UKRB, this study sought approval from the Health Research Authority (including Research Ethics

Committee review) via central Integrated Research Approval System (application reference number 335576).

10. REFERENCES

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

2 Public Policy Committee, International Society of Pharmacoepidemiology. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf*. 2016;25:2–10. doi: 10.1002/pds.3891

3 Humbert M, Kovacs G, Hoeper MM, *et al.* 2022 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Heart J*. 2022;43:3618–731. doi: 10.1093/eurheartj/ehac237

4 Dhont S, Zwaenepoel B, Vandecasteele E, *et al.* Pulmonary hypertension in interstitial lung disease: an area of unmet clinical need. *ERJ Open Res*. 2022;8:00272–2022. doi: 10.1183/23120541.00272-2022

5 Mandras SA, Mehta HS, Vaidya A. Pulmonary Hypertension: A Brief Guide for Clinicians. *Mayo Clin Proc*. 2020;95:1978–88. doi: 10.1016/j.mayocp.2020.04.039

6 Simonneau G, Montani D, Celermajer DS, *et al.* Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. doi: 10.1183/13993003.01913-2018

7 Wijeratne DT, Lajkosz K, Brogly SB, *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;11:e003973. doi: 10.1161/CIRCOUTCOMES.117.003973

8 Piccari L, Allwood B, Antoniou K, *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;13:e12213. doi: 10.1002/pul2.12213

9 Rich S, Haworth SG, Hassoun PM, *et al.* Pulmonary hypertension: the unaddressed global health burden. *Lancet Respir Med*. 2018;6:577–9. doi: 10.1016/S2213-2600(18)30268-6

10 Statista. Annual number of patients with pulmonary hypertension in the united kingdom (uk) from 2004 to 2021. 2022. https://www.statista.com/statistics/571912/patients-with-pulmonary-hypertension-in-the-united-kingdom-uk/ (accessed 6 August 2023)

11 NHS Digital. National Audit of Pulmonary Hypertension Great Britain, 2021-22. 13th Annual Report. 2023.

12 Handa T, Nagai S, Miki S, *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;46:831–7. doi: 10.2169/internalmedicine.46.6342

13 Todd NW, Lavania S, Park MH, *et al.* Variable prevalence of pulmonary hypertension in patients with advanced interstitial pneumonia. *J Heart Lung Transplant*. 2010;29:188–94. doi: 10.1016/j.healun.2009.07.025

14 Nikkho SM, Richter MJ, Shen E, *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;12:e12127. doi: 10.1002/pul2.12127

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

16 Heresi GA, Platt DM, Wang W, *et al.* Healthcare burden of pulmonary hypertension owing to lung disease and/or hypoxia. *BMC Pulm Med*. 2017;17:58. doi: 10.1186/s12890-017-0399-1

17 Heresi G, Castillo H, Lee H, *et al.* Burden of illness in patients with pulmonary hypertensiondue to interstitial lung disease: a real-world analysisusing US claims data. *CHEST*. 2021;160:A2322–3. doi: 10.1016/j.chest.2021.07.2017

18 Parikh R, Konstantinidis I, O'Sullivan DM, *et al.* Pulmonary hypertension in patients with interstitial lung disease: a tool for early detection. *Pulm Circ*. 2022;12:e12141. doi: 10.1002/pul2.12141

19 Slegg OG, Willis JA, Wilkinson F, *et al.* IMproving PULmonary hypertension Screening by Echocardiography: IMPULSE. *Echo Research & Practice*. 2022;9:9. doi: 10.1186/s44156-022-00010-9

20 Vitarelli A, Mangieri E, Terzano C, *et al.* Three-Dimensional Echocardiography and 2D-3D Speckle-Tracking Imaging in Chronic Pulmonary Hypertension: Diagnostic Accuracy in Detecting Hemodynamic Signs of Right Ventricular (RV) Failure. *J Am Heart Assoc*. 2015;4:e001584. doi: 10.1161/JAHA.114.001584

21 Montani D, Cifrián JM, Rojo RP, *et al.* Unmet need in PH-ILD: A clinician survey of real-world management of PH-ILD in Europe. *ERJ Open Research*. Published Online First: 1 January 2024. doi: 10.1183/23120541.00039-2024

22 Zare P, Heller D. Treprostinil. *StatPearls*. Treasure Island (FL): StatPearls Publishing 2023.

23 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Inhaled Treprostinil in Pulmonary Hypertension Due to Interstitial Lung Disease. *N Engl J Med*. 2021;384:325–34. doi: 10.1056/NEJMoa2008470

24 Waxman A, Restrepo-Jaramillo R, Thenappan T, *et al.* Long-term inhaled treprostinil for PH-ILD: INCREASE open-label extension study. *Eur Respir J*. 2023;2202414. doi: 10.1183/13993003.02414-2022

25 Raghu G, Behr J, Brown KK, *et al.* Treatment of idiopathic pulmonary fibrosis with ambrisentan: a parallel, randomized trial. *Ann Intern Med*. 2013;158:641–9. doi: 10.7326/0003-4819-158-9-201305070-00003

26 King TE, Behr J, Brown KK, *et al.* BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2008;177:75–81. doi: 10.1164/rccm.200705-732OC

27 King TE, Brown KK, Raghu G, *et al.* BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med*. 2011;184:92–9. doi: 10.1164/rccm.201011-1874OC

28 Idiopathic Pulmonary Fibrosis Clinical Research Network, Zisman DA, Schwarz M, *et al.* A controlled trial of sildenafil in advanced idiopathic pulmonary fibrosis. *N Engl J Med*. 2010;363:620–8. doi: 10.1056/NEJMoa1002110

29 Kolb M, Raghu G, Wells AU, *et al.* Nintedanib plus Sildenafil in Patients with Idiopathic Pulmonary Fibrosis. *N Engl J Med*. 2018;379:1722–31. doi: 10.1056/NEJMoa1811737

30 COMPERA. https://www.compera.org/ (accessed 6 June 2023)

31 ¿Que es REHAR? https://rehar.org/WEBPublica/QueesREHAR.htm (accessed 6 June 2023)

32 Dawes TJW, McCabe C, Dimopoulos K, *et al.* Phosphodiesterase 5 inhibitor treatment and survival in interstitial lung disease pulmonary hypertension: A Bayesian retrospective observational cohort study. *Respirology*. 2023;28:262–72. doi: 10.1111/resp.14378

33 Mack C, Christian J, Brinkley E, *et al.* When Context Is Hard to Come By: External Comparators and How to Use Them. *Ther Innov Regul Sci*. 2020;54:932–8. doi: 10.1007/s43441-019-00108-z

34 Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. *American Journal of Epidemiology*. 2016;183:758–64. doi: 10.1093/aje/kwv254

35 U.S. Food and Drug Administration. Considerations for the Design and Conduct of Externally Controlled Trials for Drug and Biological Products. 2023.

36 Gray CM, Grimson F, Layton D, *et al.* A Framework for Methodological Choice and Evidence Assessment for Studies Using External Comparators from Real-World Data. *Drug Saf*. 2020;43:623–33. doi: 10.1007/s40264-020-00944-1

37 Yap TA, Jacobs I, Baumfeld Andre E, *et al.* Application of Real-World Data to External Control Groups in Oncology Clinical Trial Drug Development. *Front Oncol*. 2021;11:695936. doi: 10.3389/fonc.2021.695936

38 Galiè N, Torbicki A, Barst R, *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;25:2243–78. doi: 10.1016/j.ehj.2004.09.014

39 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), *et al.* Guidelines for the diagnosis and treatment of pulmonary hypertension. *Eur Respir J*. 2009;34:1219–63. doi: 10.1183/09031936.00139009

40 Galiè N, Humbert M, Vachiery J-L, *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;37:67–119. doi: 10.1093/eurheartj/ehv317

41 Wakabayashi R, Hirano T, Laurent T, *et al.* 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;10:107–17. doi: 10.1007/s40801-022-00343-1

42 Hatswell AJ, Deighton K, Snider JT, *et al.* Approaches to Selecting 'Time Zero' in External Control Arms with Multiple Potential Entry Points: A Simulation Study of 8 Approaches. *Med Decis Making*. 2022;42:893–905. doi: 10.1177/0272989X221096070

43 Cordeiro R, Nunes A, Smith O, *et al.* Oxygen in interstitial lung diseases. *Breathe (Sheff)*. 2023;19:220271. doi: 10.1183/20734735.0271-2022

44 Jacobs SS, Krishnan JA, Lederer DJ, *et al.* Home Oxygen Therapy for Adults with Chronic Lung Disease. An Official American Thoracic Society Clinical Practice Guideline. *Am J Respir Crit Care Med*. 2020;202:e121–41. doi: 10.1164/rccm.202009-3608ST

45 Khor YH, Renzoni EA, Visca D, *et al.* Oxygen therapy in COPD and interstitial lung disease: navigating the knowns and unknowns. *ERJ Open Research*. 2019;5. doi: 10.1183/23120541.00118-2019

46 Wenger HC, Cifu AS, Lee CT. Home Oxygen Therapy for Adults With Chronic Obstructive Pulmonary Disease or Interstitial Lung Disease. *JAMA*. 2021;326:1738–9. doi: 10.1001/jama.2021.12073

47 Gall H, Felix JF, Schneck FK, *et al.* The Giessen Pulmonary Hypertension Registry: Survival in pulmonary hypertension subgroups. *J Heart Lung Transplant*. 2017;36:957–67. doi: 10.1016/j.healun.2017.02.016

48 Jang HJ, Woo A, Kim SY, *et al.* Characteristics and risk factors of mortality in patients with systemic sclerosis-associated interstitial lung disease. *Ann Med*. 2023;55:663–71. doi: 10.1080/07853890.2023.2179659

49 Zubairi ABS, Ahmad H, Hassan M, *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;12:1191–6. doi: 10.1111/crj.12650

50 Sangani RA, Lui JK, Gillmeyer KR, *et al.* Clinical characteristics and outcomes in pulmonary manifestations of systemic sclerosis: Contribution from pulmonary hypertension and interstitial lung disease severity. *Pulm Circ*. 2022;12:e12117. doi: 10.1002/pul2.12117

51 Shlobin OA, Kouranos V, Barnett SD, *et al.* Physiological predictors of survival in patients with sarcoidosis-associated pulmonary hypertension: results from an international registry. *Eur Respir J*. 2020;55:1901747. doi: 10.1183/13993003.01747-2019

52 Alhamad EH, Cal JG, Alrajhi NN, *et al.* Predictors of Mortality in Patients with Interstitial Lung Disease-Associated Pulmonary Hypertension. *J Clin Med*. 2020;9:3828. doi: 10.3390/jcm9123828

53 Rose L, Prins KW, Archer SL, *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;38:145–55. doi: 10.1016/j.healun.2018.09.011

54 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;12:1084–92. doi: 10.1111/crj.12631

55 Austin PC. Informing power and sample size calculations when using inverse probability of treatment weighting using the propensity score. *Statistics in Medicine*. 2021;40:6150–63. doi: 10.1002/sim.9176

56 Pocock SJ, Clayton TC, Altman DG. Survival plots of time-to-event outcomes in clinical trials: good practice and pitfalls. *Lancet*. 2002;359:1686–9. doi: 10.1016/S0140-6736(02)08594-X

57 International Conference on Harmonisation. GUIDELINE ADDENDUM ON ESTIMANDS AND SENSITIVITY ANALYSIS IN CLINICAL TRIALS TO THE GUIDELINE ON STATISTICAL PRINCIPLES FOR CLINICAL TRIALS E9(R1). https://www.ich.org/page/efficacy-guidelines#9-2

58 Wang A, Nianogo RA, Arah OA. G-computation of average treatment effects on the treated and the untreated. *BMC Medical Research Methodology*. 2017;17:3. doi: 10.1186/s12874-016-0282-4

59 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;34:3661–79. doi: 10.1002/sim.6607

60 Vaughan AS, Kelley CF, Luisi N, *et al.* 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;15:25. doi: 10.1186/s12874-015-0017-y

61 Brookhart MA, Wyss R, Layton JB, *et al.* Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6:604–11. doi: 10.1161/CIRCOUTCOMES.113.000359

62 Gökbuget N, Kelsh M, Chia V, *et al.* Blinatumomab vs historical standard therapy of adult relapsed/refractory acute lymphoblastic leukemia. *Blood Cancer J*. 2016;6:e473. doi: 10.1038/bcj.2016.84

63 Davies J, Martinec M, Delmar P, *et al.* Comparative effectiveness from a single-arm trial and real-world data: alectinib versus ceritinib. *J Comp Eff Res*. 2018;7:855–65. doi: 10.2217/cer-2018-0032

64 Thompson C, Lamm M, Yung Y-F. Causal Effect Estimands: Interpretation, Identification, and Computation. 2020.

65 Lee BK, Lessler J, Stuart EA. Weight Trimming and Propensity Score Weighting. *PLOS ONE*. 2011;6:e18174. doi: 10.1371/journal.pone.0018174

66 Zhang Z, Kim HJ, Lonjon G, *et al.* Balance diagnostics after propensity score matching. *Ann Transl Med*. 2019;7:16. doi: 10.21037/atm.2018.12.10

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;57:229–32. doi: 10.1198/0003130032314

71 Lavori PW, Dawson R, Shera D. A multiple imputation strategy for clinical trials with truncation of patient data. *Stat Med*. 1995;14:1913–25. doi: 10.1002/sim.4780141707

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;10:585–98. doi: 10.1002/sim.4780100410

75 Rubin DB, editor. *Multiple Imputation for Nonresponse in Surveys*. Hoboken, NJ, USA: John Wiley & Sons, Inc. 1987.

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;167:268. doi: 10.7326/M16-2607

78 European Medicines Agency. E 9 Statistical Principles for Clinical Trials. 2006.

79 David C. Hoaglin GD. The inverse-probability-of-censoring weighting (IPCW) adjusted win ratio statistic: an unbiased estimator in the presence of independent censoring. *Journal of Biopharmaceutical Statistics*. 2020;30:882–99. doi: https://doi.org/10.1080/10543406.2020.1757692

80 Seeger JD, Davis KJ, Iannacone MR, *et al.* Methods for external control groups for single arm trials or long-term uncontrolled extensions to randomized clinical trials. *Pharmacoepidemiol Drug Saf*. 2020;29:1382–92. doi: 10.1002/pds.5141

81 Suissa S. Immortal Time Bias in Pharmacoepidemiology. *American Journal of Epidemiology*. 2008;167:492–9. doi: 10.1093/aje/kwm324

82 ENCePP. ENCePP Checklist for Study Protocols (Revision 4). Published Online First: 15 October 2018. doi: https://encepp.europa.eu/encepp-toolkit/encepp-checklist-study-protocols_en

83 R Core Team. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria.

84 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.

85 Public Policy Committee IS of P. Guidelines for good pharmacoepidemiology practice (GPP). *Pharmacoepidemiol Drug Saf*. 2016;25:2–10. doi: 10.1002/pds.3891

11. APPENDICES

Appendix A. Eligibility criteria applied in the INCREASE and INCREASE OLE trials, and respective availability in RW data

Table 12: INCREASE clinical trial eligibility criteria

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

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

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
6	Subjects on a chronic medication for underlying lung disease (i.e., pirfenidone, nintedanib, etc.) must be on a stable and optimised dose for ≥30 days prior to randomisation	Not available	Partially available	Partially available	Patients on medication(s) for underlying lung disease (e.g., pirfenidone, nintedanib) are on stable dose with no dose modification in the last 30 days, before the index date
7	In the opinion of the investigator, the subject is able to communicate effectively with study personnel, and is considered reliable, willing and likely to be cooperative with protocol requirements, including attending all study visits	N/A	N/A	N/A	N/A
8	Subjects with CTD must have a Baseline FVC of <70%	Available	Available	Available	Patients with CTD 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	Available	Record of PAH at patient eligibility

NO.		Availability in COMPERA	Availability in REHAR	Availability in UKRB	Potential proxy
2	The subject has shown intolerance or significant lack of efficacy to a prostacyclin or prostacyclin analogue that resulted in discontinuation or inability to effectively titrate that therapy	Not available	Not available	Not available	N/A
3	The subject has received any PAH approved therapy including prostacyclin therapy (i.e., epoprostenol, treprostinil, iloprost, or beraprost; except for acute vasoreactivity testing), IP receptor agonist (selexipag), ERA, PDE5, SGC stimulator within 60 days of randomisation	Not available	Not available	Not available	A record of off-label PAH therapy before the index date, which would lead to exposure to the relevant drug in the time period of 60 days before the index date
4	The subject has evidence of clinically significant left-sided heart disease as defined by PCWP >15 mmHg LVEF <40%	Available	Available	Available	Record of a left-sided heart disease before or at index date with: PCWP >15 mmHg LVEF <40%
5	The subject is receiving >10 L/min of oxygen supplementation by any mode of delivery at rest at Baseline	Not available	Available	Available	Oxygen supplementation of >10 L/min at rest by any mode of delivery at index date (closest measurement to index date will be used, with a maximum look-back period of 6 months)

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

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

Abbreviations: 6MWD, six-minute walk distance; NO, number of order; COMPERA, Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CPFE, combined pulmonary fibrosis and emphysema; CT, computed tomography; CTD, connective tissue disease; ERA, endothelin receptor antagonist; FVC, forced vital capacity; ILD, interstitial lung disease; LVEF, left ventricular ejection fraction; mPAP, mean pulmonary arterial pressure; N/A, not available; PAH, pulmonary arterial hypertension; PCWP, pulmonary capillary wedge pressure; PDE5, phosphodiesterase type 5 inhibitor; REHAR, Spanish Registry of Pulmonary Hypertension Associated with Respiratory Disease; PH, pulmonary hypertension; PH-ILD, pulmonary hypertension - interstitial lung disease; RHC, right heart catheterisation; PVR, pulmonary vascular resistance; SGC, soluble guanylate cyclase; UKRB, The Royal Brompton Hospital PH registry in the United Kingdom; WHO, World Health Organization; WU, Wood units.

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

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

Table 13: INCREASE OLE clinical trial eligibility criteria

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

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

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

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

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

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

Table 14: Drug classes and active substances used off-label in the treatment of PH-ILD

Drug class and active substance	ATC code(s)
ERAs	
ambrisentan	C02KX02, C02KX52
bosentan	C02KX01
macintentan	C02KX04
PDE5i	
sildenafil	G04BE03
tadalafil	C02KX52, G04CB51, C02KX54, G04BE08, G04CA54
Prostanoids	
epoprostenol	B01AC09
iloprost	B01AC11
selexipag	B01AC27
treprostinil (study drug)	B01AC21
SGCs	
riociguat	C02KX05

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

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

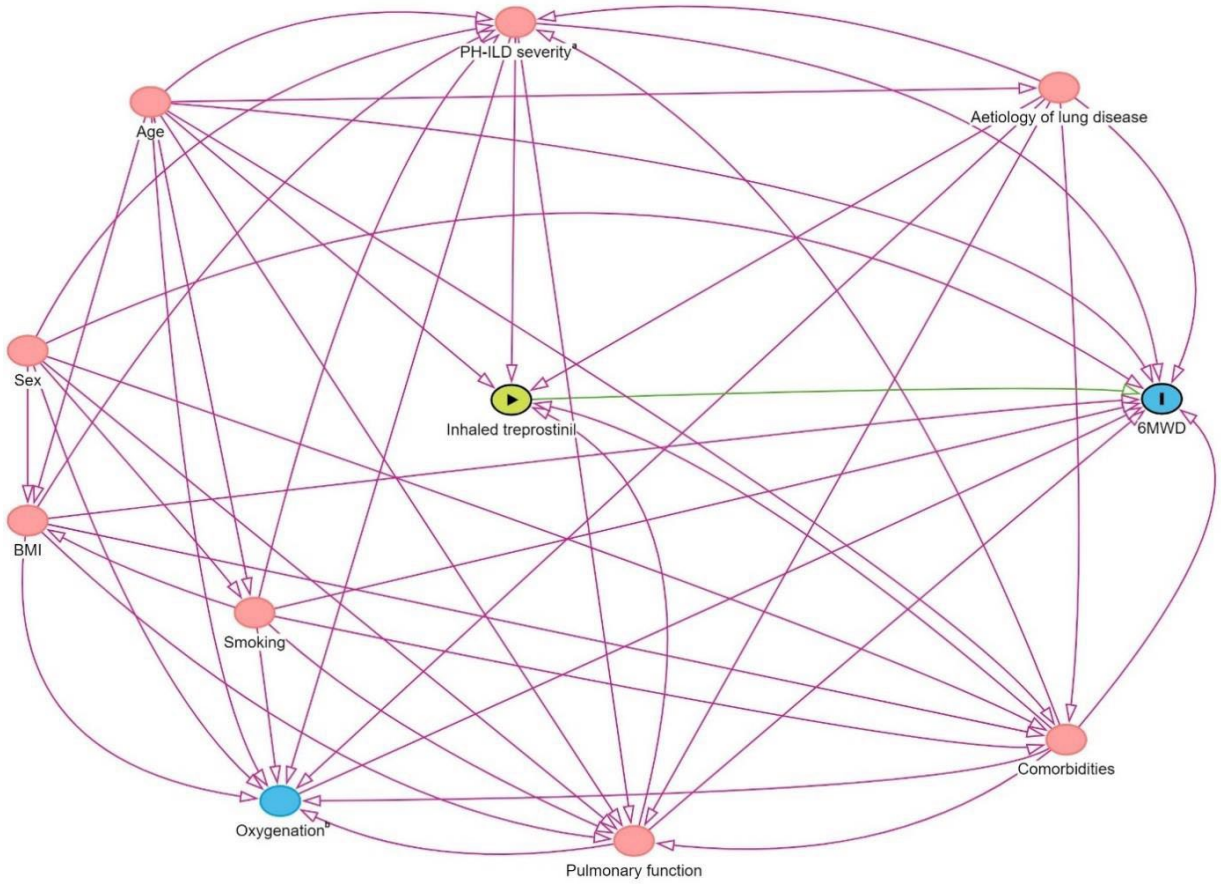

Figure 4: Directed Acyclic Graph for 6MWD

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

[a] PH-ILD severity will be defined by the PVR and time from PH-ILD diagnosis to index date.

[b] Oxygenation will be defined by the presence of hypoxia/hypoxemia and the use of supplemental oxygen therapy.

Appendix D. ENCePP checklist for study protocols

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

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

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

Comments:

-

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? (e.g., to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	2. Rationale
2.1.2 The objective(s) of the study?	☒	☐	☐	3. Objectives
2.1.3 The target population? (i.e., 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? (e.g., 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? (e.g., rate, risk, prevalence)	☒	☐	☐	3. Objectives 5.2.2.1 Descriptive statistics
3.4	Does the protocol specify measure(s) of association? (e.g., 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? (e.g., 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	☒	☐	☐	4.3.3 Follow-up
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g., 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? (e.g., operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	4.4 Exposure of interest
5.2	Does the protocol address the validity of the exposure measurement? (e.g., precision, accuracy, use of validation sub-study)	☒	☐	☐	4.4 Exposure of interest
5.3	Is exposure categorised according to time windows?	☐	☒	☐	-
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	-
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	4.4 Exposure of interest
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	4.4 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?	☒	☐	☐	4.5 Outcomes of interest
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	4.5 Outcomes of interest
6.3	Does the protocol address the validity of outcome measurement? (e.g., precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	-
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g., health-related quality of life, quality-adjusted life years, disability-adjusted life year, health care services utilisation, burden of disease or treatment, compliance, disease management)	☐	☐	☒	-

Comments:

-

Section 7: Bias	Yes	No	N/A	Section number
7.1 Does the protocol address ways to measure confounding? (e.g., confounding by indication)	☒	☐	☐	5.2.6 Sensitivity and Supplementary Analyses
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	4.3 Study population
7.3 Does the protocol address information bias? (e.g., 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? (e.g., collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	5.2.4 Subgroup analyses

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? (e.g., pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	4.7 Data sources and collection
9.1.2 Outcomes? (e.g., clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	4.7 Data Sources and Collection
9.1.3 Covariates and other characteristics?	☒	☐	☐	4.7 Data Sources and Collection
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g., date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☐	☒	☐	4.7 Data sources and collection

Section 9: Data sources	Yes	No	N/A	Section number
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☐	☒	☐	4.7 Data sources and collection
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☐	☒	☐	4.7 Data sources and collection
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical Classification System)	☒	☐	☐	4.7 Data sources and collection
9.3.2 Outcomes? (e.g., International Classification of Diseases, Medical Dictionary for Regulatory Activities)	☒	☐	☐	4.7 Data sources and collection
9.3.3 Covariates and other characteristics?	☒	☐	☐	4.7 Data sources and collection
9.4 Is a linkage method between data sources described? (e.g., 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?	☒	☐	☐	5.1 Sample size
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	5.2 Data Analyses
10.3 Are descriptive analyses included?	☒	☐	☐	5.2 Data Analyses
10.4 Are stratified analyses included?	☒	☐	☐	5.2.4 Subgroup analysis
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	5.2 Data Analyses
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	5.2 Data Analyses
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	5.2.5 Handling of missing data
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	5.2.6 Sensitivity and supplementary 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? (e.g., 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? (e.g., 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? (e.g., 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 considerations
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9. Ethical and regulatory considerations

Section 13: Ethical/data protection issues	Yes	No	N/A	Section number
13.3 Have data protection requirements been described?	☒	☐	☐	9. Ethical and regulatory considerations

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 (e.g., to regulatory authorities)?	☒	☐	☐	7.4 Publication Policy
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	7.4 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.

Name of the main author of the protocol: Urmeli Katus

Date: 09 July 2024

Signature: Signed by Urmeli Katus — Urmeli Katus — I approve this document 22-Jul-2024 | 9:30:44 PM JST — B24C3AE825CB465D90C1124223804336

DocuSign

Certificate Of Completion

Envelope Id: 4E61492628664A52993CC40A276E4653
Status: Completed
Subject: Ferrer PH-ILD TYVASO ECA protocol v2.0 2024-07-09_final.pdf
Country: Estonia
Document Type: Other – external document
Principal Investigator Name (e.g. Joseph Smith): Fabian Hoti
Project Code/ CRM Number (e.g. ABC12345): 2953067
Protocol Number (Format as in CTMS): NA
Site #: NA
Sponsor Name (Format as in CTMS): Ferrer
Source Envelope:
Document Pages: 87
Signatures: 7
Certificate Pages: 6
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Disabled
Time Zone: (UTC+02:00) Helsinki, Kyiv, Riga, Sofia, Tallinn, Vilnius

Envelope Originator:
Sylwia Damaszke
One IMS Way
Plymouth Meeting, PA 19462
sylwia.damaszke@iqvia.com
IP Address: 95.129.193.219

Record Tracking

Status: Original
09-Jul-2024 | 14:39
Holder: Sylwia Damaszke
sylwia.damaszke@iqvia.com
Location: DocuSign

Signer Events	Signature	Timestamp
Fabian Hoti fabian.hoti@iqvia.com Security Level: Email, Account Authentication (Required)	DocuSigned by Fabian Hoti [redacted] approve this document 09-Jul-2024 | 4:13:49 PM EEDT B63C1BB408A04080B6F32045ABC28A90	Sent: 09-Jul-2024 | 14:48 Viewed: 09-Jul-2024 | 16:13 Signed: 09-Jul-2024 | 16:14
	Signature Adoption: Pre-selected Style Signature ID: B63C1BB4-08A0-4080-B6F3-2045ABC28A90 Using IP Address: 185.76.230.249 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	
Electronic Record and Signature Disclosure: Accepted: 09-Jul-2024 | 16:13 ID: 3507afe8-63e6-4019-aa8b-7cdd078ba707		
Gabriela Silvina Bacchini Jeanneret gbacchini@ferrer.com Security Level: Email, Account Authentication (Required)	Gabriela Silvina Bacchini Jeanneret	Sent: 09-Jul-2024 | 14:48 Viewed: 10-Jul-2024 | 12:44 Signed: 10-Jul-2024 | 12:46
	Signature Adoption: Pre-selected Style Signature ID: 51AF2AA4-97CF-470B-93BD-FFAE2C8A4223 Using IP Address: 200.54.223.248 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Apruebo este documento	
Electronic Record and Signature Disclosure: Accepted: 08-May-2023 | 14:25 ID: 3297f55d-38ab-4f09-9aee-017c9ecd59bb		

Signer Events	Signature	Timestamp
Miriam Fernández Delgado mfernandezd@ferrer.com Senior Corporate Market Access Manager Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: E2C1F05C-0DA2-4AC2-B31D-E20595400A73 Using IP Address: 46.27.62.251 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Apruebo este documento	Sent: 09-Jul-2024 | 14:48 Viewed: 09-Jul-2024 | 15:17 Signed: 09-Jul-2024 | 15:20
Electronic Record and Signature Disclosure: Accepted: 19-Jan-2024 | 10:39 ID: dd15e723-89ed-494e-8164-e6fb025729a0		
Tania Nadal Boeufvé tnadal@ferrer.com Security Level: Email, Account Authentication (Required)	 Signature Adoption: Pre-selected Style Signature ID: B3B219CA-2803-43D6-97DC-BD3F6C211BE1 Using IP Address: 80.24.137.100 Signed using mobile With Signing Authentication via DocuSign password With Signing Reasons (on each tab): Apruebo este documento	Sent: 09-Jul-2024 | 14:48 Viewed: 09-Jul-2024 | 15:22 Signed: 09-Jul-2024 | 15:23
Electronic Record and Signature Disclosure: Accepted: 17-Jan-2024 | 14:57 ID: 7c37b6d6-8a0d-4cde-a65e-28a7375324dc		
Urmeli Katus urmeli.katus@iqvia.com Security Level: Email, Account Authentication (Required), Login with SSO	 Signature Adoption: Pre-selected Style Signature ID: B24C3AE8-25CB-465D-90C1-124223804336 Using IP Address: 185.76.228.248 With Signing Authentication via DocuSign password With Signing Reasons (on each tab): I approve this document I approve this document	Sent: 09-Jul-2024 | 14:48 Viewed: 22-Jul-2024 | 10:05 Signed: 22-Jul-2024 | 15:30
Electronic Record and Signature Disclosure: Accepted: 22-Jul-2024 | 11:49 ID: 1a807512-bc49-4728-855f-fecc727e2192		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	09-Jul-2024 | 14:48
Certified Delivered	Security Checked	22-Jul-2024 | 10:05
Signing Complete	Security Checked	22-Jul-2024 | 15:30
Completed	Security Checked	22-Jul-2024 | 15:30

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

ELECTRONIC RECORD AND SIGNATURE DISCLOSURE

From time to time, IQVIA – EU Part 11 (we, us or Company) may be required by law to provide to you certain written notices or disclosures. Described below are the terms and conditions for providing to you such notices and disclosures electronically through the DocuSign system. Please read the information below carefully and thoroughly, and if you can access this information electronically to your satisfaction and agree to this Electronic Record and Signature Disclosure (ERSD), please confirm your agreement by selecting the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

Getting paper copies

At any time, you may request from us a paper copy of any record provided or made available electronically to you by us. You will have the ability to download and print documents we send to you through the DocuSign system during and immediately after the signing session and, if you elect to create a DocuSign account, you may access the documents for a limited period of time (usually 30 days) after such documents are first sent to you. After such time, if you wish for us to send you paper copies of any such documents from our office to you, you will be charged a $0.00 per-page fee. You may request delivery of such paper copies from us by following the procedure described below.

Withdrawing your consent

If you decide to receive notices and disclosures from us electronically, you may at any time change your mind and tell us that thereafter you want to receive required notices and disclosures only in paper format. How you must inform us of your decision to receive future notices and disclosure in paper format and withdraw your consent to receive notices and disclosures electronically is described below.

Consequences of changing your mind

If you elect to receive required notices and disclosures only in paper format, it will slow the speed at which we can complete certain steps in transactions with you and delivering services to you because we will need first to send the required notices or disclosures to you in paper format, and then wait until we receive back from you your acknowledgment of your receipt of such paper notices or disclosures. Further, you will no longer be able to use the DocuSign system to receive required notices and consents electronically from us or to sign electronically documents from us.

All notices and disclosures will be sent to you electronically

Unless you tell us otherwise in accordance with the procedures described herein, we will provide electronically to you through the DocuSign system all required notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you during the course of our relationship with you. To reduce the chance of you inadvertently not receiving any notice or disclosure, we prefer to provide all of the required notices and disclosures to you by the same method and to the same address that you have given us. Thus, you can receive all the disclosures and notices electronically or in paper format through the paper mail delivery system. If you do not agree with this process, please let us know as described below. Please also see the paragraph immediately above that describes the consequences of your electing not to receive delivery of the notices and disclosures electronically from us.

How to contact IQVIA – EU Part 11:

You may contact us to let us know of your changes as to how we may contact you electronically, to request paper copies of certain information from us, and to withdraw your prior consent to receive notices and disclosures electronically as follows:
To contact us by email send messages to: kevin.sherman@iqvia.com

To advise IQVIA – EU Part 11 of your new email address

To let us know of a change in your email address where we should send notices and disclosures electronically to you, you must send an email message to us at kevin.sherman@iqvia.com and in the body of such request you must state: your previous email address, your new email address. We do not require any other information from you to change your email address.

If you created a DocuSign account, you may update it with your new email address through your account preferences.

To request paper copies from IQVIA – EU Part 11

To request delivery from us of paper copies of the notices and disclosures previously provided by us to you electronically, you must send us an email to kevin.sherman@iqvia.com and in the body of such request you must state your email address, full name, mailing address, and telephone number. We will bill you for any fees at that time, if any.

To withdraw your consent with IQVIA – EU Part 11

To inform us that you no longer wish to receive future notices and disclosures in electronic format you may:

i. decline to sign a document from within your signing session, and on the subsequent page, select the check-box indicating you wish to withdraw your consent, or you may;

ii. send us an email to kevin.sherman@iqvia.com and in the body of such request you must state your email, full name, mailing address, and telephone number. We do not need any other information from you to withdraw consent.. The consequences of your withdrawing consent for online documents will be that transactions may take a longer time to process..

Required hardware and software

The minimum system requirements for using the DocuSign system may change over time. The current system requirements are found here: https://support.docusign.com/guides/signer-guide-signing-system-requirements.

Acknowledging your access and consent to receive and sign documents electronically

To confirm to us that you can access this information electronically, which will be similar to other electronic notices and disclosures that we will provide to you, please confirm that you have read this ERSD, and (i) that you are able to print on paper or electronically save this ERSD for your future reference and access; or (ii) that you are able to email this ERSD to an email address where you will be able to print on paper or save it for your future reference and access. Further, if you consent to receiving notices and disclosures exclusively in electronic format as described herein, then select the check-box next to 'I agree to use electronic records and signatures' before clicking 'CONTINUE' within the DocuSign system.

By selecting the check-box next to 'I agree to use electronic records and signatures', you confirm that:

- You can access and read this Electronic Record and Signature Disclosure; and
- You can print on paper this Electronic Record and Signature Disclosure, or save or send this Electronic Record and Disclosure to a location where you can print it, for future reference and access; and
- Until or unless you notify IQVIA – EU Part 11 as described above, you consent to receive exclusively through electronic means all notices, disclosures, authorizations, acknowledgements, and other documents that are required to be provided or made available to you by IQVIA – EU Part 11 during the course of your relationship with IQVIA – EU Part 11.