# Roche Protocol WB29908
# (InterMune Protocol PIPF-025)

| | |
|---|---|
| **TITLE:** | Post-Authorisation Safety Study of Esbriet® (Pirfenidone): A Prospective Observational Registry to Evaluate Long-Term Safety in a Real-World Setting |
| **STUDY SPONSOR and MARKETING AUTHORIZATION HOLDER:** | Roche Registration Limited<br>6 Falcon Way<br>Shire Park<br>Welwyn Garden City<br>AL7 1TW<br>United Kingdom |
| **VERSION:** | 4.0 |
| **DATE:** | 02 December 2010 |

**DATES AMENDED**:

| | |
|---|---|
| Protocol Amendment 1.0: | 31 May 2012 |
| Protocol Amendment 2.0 | 10 Oct 2012 |
| Protocol Amendment 3.0 | 25 Apr 2014 |
| Protocol Amendment 4.0 | See electronic signature below. |

## PROTOCOL AMENDMENT APPROVAL

# TABLE OF CONTENTS

## LIST OF TABLES

## SPONSOR

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

Roche Registration Limited
6 Falcon Way
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## INFORMATIONAL CONTACTS:

[redacted], MD
Medical Monitor for Roche
[redacted]

[redacted], MD
EU QPPV for Roche
[redacted]

## PHYSICIAN SIGNATURE PAGE

I have read and approved this protocol. My signature, in conjunction with the signature of the MAH, confirms the agreement of both parties that the registry will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to, Good Pharmacoepidemiology Practices (GPP), the ethical principles that have their origins in the Declaration of Helsinki,[1] and applicable privacy laws.

PHYSICIAN SIGNATURE

Date

PHYSICIAN NAME AND TITLE

# RATIONALE FOR AMENDMENT TO THE PROTOCOL

This amendment addresses changes required by:

- The transfer of pirfenidone ownership from InterMune, Inc. to F. Hoffmann-La Roche, Ltd. requiring change of Marketing Authorization Holder and Sponsor of Study.
- The need to clarify unclear text and to correct grammatical or typographical errors.

# SUMMARY OF CHANGES MADE BY AMENDMENT 4 TO PROTOCOL WB29908 (INTERMUNE PIPF-025)

| **Page in Protocol with A3: 25 Apr 2014** | **Topic** | **Previously Read** | **Now Reads** |
|---|---|---|---|
| Title Page | Protocol Number | Protocol PIPF-025 | Protocol WB29908 (InterMune Protocol PIPF-025) |
| Title Page | Change in Marketing Authorization Holder (MAH) or Sponsor | InterMune UK Ltd<br>Grove House, 2nd Floor<br>248A Marylebone Road<br>London NW1 6JZ<br>United Kingdom | Roche Registration Limited<br>6 Falcon Way<br>Shire Park<br>Welwyn Garden City<br>AL7 1TW<br>United Kingdom |
| Title Page | Versions | | Page reformatted and Protocol Amendment 4 added |
| 4 | Sponsor | InterMune Ltd | Roche Registration Ltd |

| **Page in Protocol with A3: 25 Apr 2014** | **Topic** | **Previously Read** | **Now Reads** |
|---|---|---|---|
| 4 | Sponsor | InterMune UK Ltd<br>Grove House, 2nd Floor<br>248A Marylebone Road<br>London NW1 6JZ<br>United Kingdom | Roche Registration Limited<br>6 Falcon Way<br>Shire Park<br>Welwyn Garden City<br>AL7 1TW<br>United Kingdom |
| 4 | Informational Contacts | [redacted], MD<br>Senior Vice President/Drug Safety Risk Management<br>InterMune, Inc.<br><br>[redacted], MD<br>Medical Advisor & Advisory Board Member<br>NDA Regulatory Science Ltd.<br>EU QPPV for InterMune, Inc. | [redacted], MD<br>Medical Monitor for Roche<br>[redacted]<br><br>[redacted], MD<br>EU QPPV for Roche<br>[redacted] |
| 6 | List of Abbreviations | HLT, ICH, LFT, and NRP removed because they were not used in the protocol | PASS, Post-Authorisation Safety Study, was added. |
| 8 | Synopsis | | ADDED:<br>Protocol Number: WB29908 (InterMune PIPF-25) |
| 8 | Synopsis | Study Title | Protocol Title |
| 8 | Synopsis- Study Title | Post-Authorisations Safety Study (PASS) of Esbriet…. | Post-Authorisation Safety Study of Esbriet…. |
| 8 | Synopsis – Number of Registry Centres: | Up to 100… | Approximately 100… |
| 12 | Table 1: Table Header, column 3 | | ADDED:<br>± 4 weeks |
| 12 | Table 1: Row 15 | 0----------X | Information about and date of last Esbriet dose |
| 12 | Table 1: Row 16 | 0----------X | assessed throughout study |
| 12 | Table 1: Row 17 | 0----------X | assessed throughout study |
| 12 | Table 1: Row 18 | 0----------X | collected when associated with SADR or ADR of special interest |

| Page in Protocol with A3: 25 Apr 2014 | Topic | Previously Read | Now Reads |
|---|---|---|---|
| 12 | Table 1: Row 19 | 0----------X | collected as patient completes study or withdraws before completing study |
| 15 | 5.6 Patient Reconsent | | ADDED NEW SECTION. (all subsequent sections are renumbered)<br>All patients who are actively participating in the study will be asked to give verbal and written consent again, when the protocol is amended and changes are substantial (e.g., any change that impacts patient safety or the integrity of data). The informed consent will be updated to reflect the protocol changes. Patients who have discontinued will not be required to reconsent but they will be sent a letter from their study site to inform them of protocol or sponsor changes that could be relevant (e.g., a change of study sponsor/MAH or identification of a new, significant drug-related risk). |
| 16 | 6.2 Follow-up: Years 1 and 2 | The physician or other trained site staff will collect data via structured questionnaires administered to the patient during routine clinical visits. | The physician or other trained site staff will collect data from the patient during routine clinical visits. |
| 20 | 8.1 Schedule of Assessments | The currently authorised SPC for Esbriet® recommends liver function test (LFT) monitoring every month for the first 6 months of Esbriet® therapy and every 3 months thereafter. | The currently authorised SPC for Esbriet recommends liver function test monitoring prior to beginning Esbriet, every month for the first 6 months of Esbriet therapy, and every 3 months thereafter. |
| 21, 22 | 9.2.1 and 9.2.3 | | DELETED: high level term ( HLT) |
| 22 | 9.2.2. Baseline Assessment | Comparative demographic and baseline data will be summarized by treatments for IPF. | DELETED |
| 22 | 9.2.3. Primary Analyses | Comparative safety data will be summarized by treatments for IPF. | DELETED |

| Page in Protocol with A3: 25 Apr 2014 | Topic | Previously Read | Now Reads |
|---|---|---|---|
| 22 | 9.3. Missing Data | As explained in the ICFs, reasonable attempts will be made to contact patients to limit missing data. | Reasonable attempts will be made to contact patients who discontinue the study or who are lost to follow-up. |
| 23 | 10.1.2. Opinion of External Experts and Scientific Advisory Boards | The SAB will meet and review the registry data regularly and will make recommendations to the MAH. | The SAB will meet and review the registry data regularly and may make recommendations to the MAH about study conduct or data collection. |
| 25 | 11.3. Patient Files | …5 years after completion of the registry. | …15 years after completion of the registry. |
| **GLOBAL CHANGES** | | | |
| **Location** | **Action** | **Previously Read** | **Now Reads** |
| Header | changed | InterMune UK Ltd. Protocol PIPF-025: 02 Dec 2010<br>Pirfenidone Protocol Amendment 1.0: 31 May 2012<br>Protocol Amendment 2.0: 10 Oct 2012<br>Protocol Amendment 3.0: 25 Apr 2014 | Roche Registration, Ltd.<br>Pirfenidone<br>Protocol WB29908<br>InterMune Protocol PIPF-025 |
| text | changed | any statement referring to treatment of "2 years" | to "up to 2 years" |
| text | changed | from "certain" European Union Member States | to "selected" |
| text | changed | follow up | follow-up |
| text | changed | re-consent | reconsent |

# LIST OF ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| ADR | Adverse Drug Reaction |
| CHMP | Committee for Medicinal Products for Human Use |
| CRF | Case Report Form |
| CRO | Clinical Research Organization |
| eCRF | Electronic Case Report Form |
| EDC | Electronic Data Capture |
| EMA | European Medicines Agency |
| EU | European Union |
| GPP | Good Pharmacoepidemiology Practices |
| ICF | Informed Consent Forms |
| IEC | Independent Ethics Committee |
| IPF | Idiopathic Pulmonary Fibrosis |
| ISPE | International Society for Pharmacoepidemiology |
| MAH | Marketing Authorisation Holder |
| MedDRA | Medical Dictionary for Regulatory Activities |
| PASS | Post-Authorisation Safety Study |
| PT | Preferred Term |
| SAB | Scientific Advisory Board |
| SADR | Serious Adverse Drug Reaction |
| SAP | Statistical Analysis Plan |
| SOC | System Organ Class |
| SPC | Summary of Product Characteristics |

# 1. SYNOPSIS

| | |
|---|---|
| **Protocol Number:** WB29908 (InterMune PIPF-025) | |
| **Protocol Title**:<br>Post-Authorisation Safety Study of Esbriet® (Pirfenidone): A Prospective Observational Registry to Evaluate Long-Term Safety in a Real-World Setting | |
| **Condition/Disease**: Idiopathic Pulmonary Fibrosis | |
| **Number of Patients with IPF:** 1000 | **Number of Registry Centres:** Approximately 100 in selected EU Member States |
| **Duration of Patient Participation:** 2 years | **Duration of Registry:** 4 years |
| **Background and Rationale:**<br>Idiopathic pulmonary fibrosis (IPF) is a progressive illness with an extremely poor prognosis; median survival after diagnosis is 2-5 years. Esbriet® is an orally bioavailable small synthetic non-peptide molecule that attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors such as transforming growth factor-beta and platelet-derived growth factor. Esbriet is authorised for the treatment of mild to moderate IPF. Although data from the development programme including Phase 3 trials demonstrate that Esbriet has an acceptable risk benefit profile in the treatment of mild to moderate IPF, there is a need, in real-world clinical practice, to establish the long-term safety profile of Esbriet treatment. | |
| **Objective:** The objective of this study is to evaluate the long-term safety profile of Esbriet in patients with IPF and to monitor for any unknown or potential risks of treatment with Esbriet. | |
| **Design:**<br>This product registry is a multicentre, long-term, prospective, observational study to evaluate the long-term safety of Esbriet in patients with IPF. Patients will receive Esbriet at the discretion of their physicians and will be followed through the registry for up to 2 years after they begin treatment with Esbriet. This registry complies with the requirement of a post-authorisation safety study (PASS) and is a post-authorisation commitment, which has been approved by the Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA). | |
| **Registry Settings:**<br>The registry will initially enrol patients from approximately 100 pulmonary clinics throughout selected European Union (EU) Member States and is open to all patients who will receive Esbriet as part of normal clinical practice. The enrolment will be stopped when 1000 patients | |

with a diagnosis of IPF have been enrolled. It is estimated that the enrolment will be completed within approximately 24 months. The Marketing Authorisation Holder (MAH) will closely monitor enrolment and will keep the Rapporteur and Co-Rapporteur informed of progress with the registry at regular intervals. If progress is not satisfactory, then the MAH will discuss with the Rapporteur and Co-Rapporteur any contingency that might be considered in order to increase the recruitment level in the context of the overall usage of the product within the EU. These may include, but are not limited to, extending the registry into another Member State, opening up more sites and intensifying the communication plan.

Each patient will be followed for up to 2 years. The MAH will also closely monitor the retention of patients and will undertake all reasonable efforts and methods to minimize loss to follow-up for the entire 2 years of observation.

Treating physicians will collect pre-specified data at baseline and approximately every 3 months thereafter for the duration of the study. In the event that a patient discontinues Esbriet treatment, all serious adverse drug reactions (SADRs), and adverse drug reactions (ADRs) of special interest will be collected until 28 days after the last dose of Esbriet.

**Treatment:**

The registry is observational; therefore, all treatment decisions are at the discretion of the patient's health care provider and are not mandated by study design or protocol. Cooperation of health care professionals is based on goodwill and no contractual sanctions will be applied by the MAH.

**Inclusion Criteria:**

- A clinical decision has been made, prior to study enrolment, to prescribe Esbriet
- Patients who are newly prescribed Esbriet therapy
- Initiation of Esbriet therapy is not more than 30 days prior to study enrolment
- Patient or legal representative provides informed consent and/or informed assent according to local regulations

Esbriet is only indicated for the treatment of mild to moderate idiopathic pulmonary fibrosis in adults. The registry protocol does not encourage use of Esbriet for other conditions or in paediatric patients. However, if a physician, in collaboration with the patient and/or legal representative, makes an independent clinical decision to prescribe Esbriet outside the terms of the Summary of Product Characteristics (SPC), those patients may be included in the registry.

**Exclusion Criteria:**

- Patients receiving an investigational agent defined as any drug that has not been approved for marketing for any indication in the country of the participating site
- Patient has received Esbriet therapy 31 days or more prior to current treatment course (e.g., prior participation in clinical trials)

- Patient has any contraindication for the use of Esbriet, according to the current local version of the SPC
- Patient or legal representative refuses to provide informed consent and/or informed assent according to local regulations

**Data Collection (please see Table 1):**

- Baseline data collection:
  - Demographics
  - Medical history
  - Concurrent diseases
  - IPF history
  - Prior and concomitant treatments for IPF
  - Concomitant treatment with warfarin
  - Reason/indication for Esbriet therapy (other than IPF)
  - Initial prescribed dose of Esbriet
  - Other (concomitant medications, height, weight, liver function tests)
- Follow-up data collection:
  - Serious adverse drug reactions
  - Clinically significant ADRs of special interest: These ADRs of special interest encompass all "important identified risks" and "important potential risks" as defined in the Esbriet Risk Management Plan and include:
  - Photosensitivity reactions and skin rashes
  - Abnormal liver function tests
  - Dizziness
  - Weight loss
  - Gastrointestinal symptoms
  - Fatigue
  - Falls
  - Drug interactions (including smoking)
  - Increased platelet counts
  - Specific cardiac events: supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or

pulmonic valvular incompetence

- Blood dyscrasias: agranulocytosis, leukopenia, neutropenia
- Angioedema
- Any other clinically significant ADRs based on the judgment of the prescriber
- Relevant laboratory and clinical tests, Esbriet dose, and concomitant medications for reported ADRs
- Esbriet dose changes or discontinuation and reasons for change/discontinuation
- Concomitant treatments for IPF
- Concomitant treatment with warfarin
- Patient registry withdrawals

**Statistical Considerations:**

No formal hypotheses will be tested. The study population for analysis of safety will include any patient who receives at least one dose of Esbriet regardless of the length of follow-up for that patient. Descriptive analyses will include frequency and measures of central tendency, range, and dispersion of clinical characteristics of the study population. Frequencies and cumulative incidence of reported ADRs will be summarized.

**Ethical Considerations:**

The registry will be conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki,[1] applicable privacy laws, and local regulations for each participating site. This non-interventional study will be conducted in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP)[2] issued by the International Society for Pharmacoepidemiology (ISPE). When applicable, an independent ethics committee (IEC) will review and approve the protocol before any patient is enrolled. Appropriate informed consent and paediatric assent will be obtained from participating patients or their parents or legal representatives, if applicable.

## Table 1: Registry Schedule of Assessments

| Data Collected | Baseline | Follow-up visits (every 3 months ± 4 weeks) |
|---|---|---|
| Visit ID | 1 | 2-9 |
| Informed consent | X | - |
| Patient/legal representative and secondary contact information | X | X |
| Primary health care provider information | X | X |
| Demographics [age, gender, race/ethnicity (where allowed by local regulation), smoking history, alcohol use] | X | - |
| Medical history | X | - |
| Concurrent diseases | X | - |
| IPF history (date of diagnosis/duration of disease, method of diagnosis, pulmonary function at initiation of Esbriet®, oxygen supplementation) | X | - |
| Prior and concomitant treatments for IPF | X | X |
| Reason for Esbriet therapy (other than IPF) | X | - |
| Prescribed Esbriet treatment (initial dose, dose changes/discontinuation, reason for change/discontinuation) | X | X |
| Other (concomitant medications, height, weight, liver function tests) | X | - |
| Warfarin treatment | X | X |
| Esbriet discontinuation | information about and date of last Esbriet dose | |
| SADRs[a] | assessed throughout study | |
| ADRs of special interest[a] | assessed throughout study | |
| Relevant laboratory and clinical tests, Esbriet dose, and concomitant medications corresponding to reported ADRs | collected when associated with SADR or ADR of special interest | |
| Patient withdrawal from the registry[b] | collected as patient completes study or withdraws before completing study | |

[a] Patients will be interviewed at the specified time points to determine if any of these events have occurred since the last evaluation. However, the study physicians may report an event between evaluations if they become aware that such an event has occurred.

[b] Patients may withdraw from the registry at any time following enrolment.

# 2. BACKGROUND AND RATIONALE

Idiopathic pulmonary fibrosis (IPF) is characterized by shortness of breath and typical histologic findings of interstitial fibrosis, inflammatory infiltrate, and destruction of normal lung architecture, collectively termed usual interstitial pneumonia. This progressive illness has a very poor prognosis with median survival after diagnosis ranging from 2-5 years.[3,4]

Esbriet® is an orally bioavailable small synthetic non-peptide molecule that attenuates fibroblast proliferation, production of fibrosis-associated proteins and cytokines, and the increased biosynthesis and accumulation of extracellular matrix in response to cytokine growth factors, such as transforming growth factor-beta and platelet-derived growth factor. Esbriet is authorised for the treatment of mild to moderate IPF in adults. Although data from the development programme including Phase 3 trials demonstrate that Esbriet has an acceptable risk benefit profile in the treatment of mild to moderate IPF, there is a need, in real-world clinical practice, to establish the long-term safety profile of Esbriet treatment. The recommended dosage is 2403 mg/d given orally as three 267-mg capsules 3 times daily, after a 14-day dose escalation period.

In view of the recognised limitations of spontaneous reporting and the need to better define the long-term safety profile of Esbriet, as well as to monitor any unknown and potential risks, the Marketing Authorisation Holder (MAH) is conducting a Post-Authorisation Safety Study (PASS) in the form of an observational registry that will permit organised, prospective data collection to conduct pre-specified analyses. This multicentre, long-term, prospective study will collect data about the long-term safety profile of Esbriet. The design of this PASS registry is consistent with the principles of a non-interventional PASS as described in Volume 9A of The Rules Governing Medicinal Products in the European Union, Guidelines on Pharmacovigilance for Medicinal Products for Human Use, Part 1, Section 7.[5]

# 3. OBJECTIVE

The objective of this study is to evaluate the long-term safety profile of Esbriet in patients with IPF and to monitor for any unknown or potential risks of treatment with Esbriet.

# 4. REGISTRY DESIGN AND SETTING

## 4.1. Design

This product registry is a multicentre, long-term, prospective, observational study to evaluate the long-term safety profile as well as to monitor for any unknown or potential risks of treatment with Esbriet. Patients will receive Esbriet at the discretion of their physicians and will be followed through the registry for up to 2 years after they begin treatment with Esbriet. This registry constitutes a PASS and is a post-authorisation commitment, which has been approved by the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines

Agency (EMA). The registry will be set up, conducted, and closely monitored by the MAH, or a designee with oversight by a project specific Scientific Advisory Board (SAB).

## 4.2. Setting

The registry aims to initially enrol patients from approximately 100 pulmonary clinics throughout selected EU Member States and is open to all patients who will receive Esbriet. Enrolment will stop when 1,000 patients with a diagnosis of IPF have been enrolled. It is estimated that the enrolment will be completed within approximately 24 months. The MAH will closely monitor enrolment and will keep the Rapporteur and Co-Rapporteur informed of progress with the registry at regular intervals. If progress is not satisfactory, then the MAH will discuss with the Rapporteur and Co-Rapporteur any contingency that might be considered in order to increase the recruitment level in the context of the overall usage of the product within the EU. These may include, but are not limited to, extending the registry into another Member State, opening up more sites and intensifying the communication plan.

Each patient will be followed for up to 2 years. The MAH will also closely monitor the retention of patients and will undertake all reasonable efforts and methods to minimize loss to follow-up for the entire duration of the registry. Treating physicians will collect pre-specified data at the baseline and every 3 months thereafter, for the duration of the patients' participation in study.

# 5. SELECTION AND ENROLMENT OF PARTICIPANTS

When applicable, an independent ethics committee (IEC) must approve the protocol and informed consent forms (ICF) prior to patient enrolment. Each patient or legal representative must participate in the informed consent process and sign the ICF for this protocol before data collection is initiated. The registry requires that documentation of informed consent is recorded in the source document for each patient.

## 5.1. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for registry enrolment:

- A clinical decision has been made, prior to enrolment, to prescribe Esbriet; and
- Patient is newly prescribed Esbriet® therapy; and
- Initiation of Esbriet® therapy is not more than 30 days prior to study enrolment; and
- Patient or legal representative provides informed consent and/or informed assent according to local regulations

Esbriet is only indicated for the treatment of mild to moderate IPF in adults. The registry protocol will not encourage use of Esbriet for other conditions or in paediatric patients. However, if a physician, in collaboration with the patient and/or legal representative, makes an independent clinical decision to prescribe Esbriet outside the terms of the Summary of Product Characteristics (SPC), those patients may be included in the registry.

## 5.2. Exclusion Criteria

Patients are not eligible for this registry if they meet any of the following criteria:

- Patients receiving an investigational agent defined as any drug that has not been approved for marketing for any indication in the country of the participating site
- Patient has received Esbriet therapy 31 days or more prior to current treatment course (e.g., prior participation in clinical trials)
- Patient has any contraindication for the use of Esbriet, according to the current local version of the SPC
- Patient or legal representative refuses to provide informed consent and/or informed assent according to local regulations

## 5.3. Registry Enrolment

The registry initially aims to enrol patients from approximately 100 pulmonary clinics throughout selected EU Member States.

## 5.4. Physician Enrolment

The study will recruit pulmonologists and other physicians within the selected EU Member States who are likely to treat patients eligible for the registry.

## 5.5. Patient Enrolment

All patients undergoing treatment at any of the registry sites who meet the inclusion and exclusion criteria detailed above (Section 5.1 and Section 5.2) may be included in the registry. Patients who are enrolled in the registry in anticipation of Esbriet use, but are not treated with Esbriet within 6 months of enrolment will be considered screen failures and will require reconsent for enrolment at a later date.

## 5.6. Patient Reconsent

All patients who are actively participating in the study will be asked to give verbal and written consent again, when the protocol is amended and changes are substantial (e.g., any change that impacts patient safety or the integrity of data). The informed consent will be updated to reflect the protocol changes. Patients who have discontinued will not be required to reconsent but they will be sent a letter from their study site to inform them of protocol or sponsor changes that could be relevant (e.g., a change of study sponsor/MAH or identification of a new, significant drug-related risk).

## 5.7. Patient Withdrawal

Patients may withdraw consent and discontinue registry participation at any time, without prejudice. Physicians will complete a registry withdrawal case report form (CRF) and all reasonable efforts will be made to establish whether the reason for withdrawal was related to an ADR. Information collected during study participation will be retained for analysis unless the

patient specifically requests otherwise. In the event that a patient discontinues Esbriet treatment prior to registry withdrawal, all SADRs and ADRs of special interest will be collected until 28 days after the last dose of Esbriet or until registry withdrawal, whichever comes first.

# 6. DATA COLLECTION

Data collection is designed to minimize the burden on the participating physicians, sites, and patients, and to maximize information capture and patient retention. Electronic case report forms (eCRFs) for data entry have been designed to gather specific data consistent with the objectives of the study. If necessary, the physician may also retrieve medical record information from his/her own records and other health care settings. Normally, registry visits will be aligned with routine clinical visits.

## 6.1. Enrolment/Baseline

Data elements collected at baseline include:

1. Date of informed consent(s)/assent
2. Patient contact information, including secondary contacts and primary health care provider details, if other than enrolling physician
3. Demography [age, gender, race/ethnicity (where allowed by local regulation), smoking history, alcohol use]
4. Medical history and concurrent diseases [including but not limited to hepatic disease, diabetes mellitus, cardiovascular disease (including QT prolongation), kidney disease, other pulmonary diseases (secondary causes of pulmonary fibrosis)]
5. IPF history [date of diagnosis/duration of disease, method of diagnosis (surgical lung biopsy and clinical features, transbronchial biopsy and clinical features, clinical criteria including high resolution computed tomography features), pulmonary function at initiation of Esbriet, prior treatments, oxygen supplementation]
6. Medications used to treat IPF (including but not limited to steroids, immunosuppressive or cytotoxic agents such as cyclophosphamide, azathioprine, alternative therapies such as cyclosporin A, methotrexate, N-acetyl cysteine, sildenafil citrate, bosentan, and interferons)
7. Reason for Esbriet therapy (other than IPF)
8. Initial prescribed dose of Esbriet
9. Concomitant medications
10. Concomitant treatment with warfarin
11. Height and weight
12. Liver function tests

## 6.2. Follow-up: Years 1 and 2

Data are collected every 3 months (±4 weeks) during follow-up. The physician or other trained site staff will collect data from the patient during routine clinical visits. The physician will also enter data as necessary from the patient's medical record. In the event that the registry visit does not coincide with a routine clinical visit, the physician, trained site staff, MAH or designated clinical research organization (CRO) registry staff may administer follow-up questionnaires via phone interviews.

The data elements to be collected at follow-up are:

1. Updated contact information
2. Status of prescribed Esbriet treatment (ongoing/dose change/discontinued/reason for change or discontinuation)
3. Changes/additions to other medications used to treat IPF
4. Changes to or addition of warfarin
5. All SADRs and ADRs of special interest (that are considered at least possibly related to Esbriet) and associated information including but not limited to Esbriet dose, concomitant medications, relevant laboratory, clinical, and other test results (See Section 7.2)

## 6.3. Registry Discontinuation

In discussion and agreement with the EMA and CHMP, the MAH may suspend or terminate the registry or part of the registry at any time for any reason.

## 6.4. Patients Lost to Follow-up

For patients who discontinue registry participation without notification, before considering a patient lost to follow-up, the physician/site staff will make all reasonable attempts to contact the patient to ensure that the inability to contact the patient is not related to an ADR. If there is no response within a month of the scheduled follow-up visit, site staff, MAH or designated CRO registry staff will contact any other known health care providers to determine if the lack of response is health related and to determine the health status of the patients. If unable to obtain any follow-up data from the other provider(s), site staff, MAH or designated CRO registry staff will contact the secondary patient contact to obtain vital status. The informed consent process and forms outline these procedures, including the possibility of contacting other health care providers. Any data collected prior to loss to follow-up will be included in all analyses.

# 7. SAFETY EVALUATION AND REPORTING

Any patient who receives at least one dose of Esbriet as part of the registry will be included in the evaluation of safety. When a serious adverse reaction or adverse reaction of special interest is reported, appropriate follow-up measures will be conducted to obtain further information.

## 7.1. Definition of Adverse Drug Reactions and Serious Adverse Drug Reactions

An ADR is a noxious and unintended response to a medicinal product related to any dose in which a causal relationship between the medicinal product and the adverse event is at least a reasonable possibility. Therefore all SADRs and events of interest that are considered at least possibly related to Esbriet will be defined and collected as ADRs.

An SADR is defined as any ADR meeting the following criteria at any dose:

- Results in death;
- Is life threatening (i.e., the patient was, in the opinion of the physician, at immediate risk of death from the event as it occurred); it does not refer to an event which hypothetically might have caused death if it were more severe;
- Requires or prolongs patient's hospitalization;
- Results in persistent or significant disability/incapacity (i.e., the event causes a substantial disruption of a person's ability to conduct normal life functions);
- Results in a congenital anomaly/birth defect;
- Is an important and significant medical event that may not be immediately life threatening or resulting in death or hospitalization but, based upon appropriate medical judgment, may jeopardize the patient or may require intervention to prevent one of the outcomes listed above.

If there is doubt as to whether the event under consideration is a SADR, the event should be treated as a SADR. If the onset of an event occurred before the patient entered the registry in the context of any pre-planned hospitalization (e.g., for cosmetic treatments or for a pre-existing condition) the event should be classified as serious only if in the view of the physician the hospitalization was prolonged or the pre-existing condition worsened as a result of Esbriet treatment.

## 7.2. Safety Data Collection

The following will be collected from the point of the first dose with Esbriet and will continue through the end of the follow-up period (2 years):

1. SADRs
2. Clinically significant ADRs of special interest: These ADRs of special interest encompass all "important identified risks" and "important potential risks" as defined in the Esbriet Risk Management Plan and include:
    - Photosensitivity reactions and skin rashes
    - Abnormal liver function tests
    - Dizziness
    - Weight loss

- Gastrointestinal symptoms
- Fatigue
- Falls
- Drug interactions (including smoking)
- Increased platelet counts
- Specific cardiac events: supraventricular tachyarrhythmia, atrioventricular block/sick sinus syndrome, ventricular arrhythmia, bundle branch block, aortic or pulmonic valvular incompetence
- Blood dyscrasias: agranulocytosis, leukopenia, neutropenia
- Angioedema
- Any other clinically significant ADRs based on the judgment of the prescriber

3. Information to be collected in association with reported ADRs (including, but not limited to):
   a. Prescribed Esbriet dose changes and reasons for change
   b. Concomitant medications including treatments for IPF (those stopped or started within 28 days prior to the event). The following minimum data elements will be collected:
      – Medication name
      – Dose and duration of exposure
      – Indication for use
   c. Relevant laboratory and clinical tests

In the event that a patient discontinues Esbriet treatment, all SADRs, and ADRs of special interest will be collected until 28 days after the last dose of Esbriet. All serious and reportable ADRs will be followed until resolution or until the end of the follow-up period, whichever comes first.

### 7.2.1. Other Reportable Information

Pregnancy and/or lactation exposure to Esbriet will be recorded, reported, and followed up. Reportable information includes entire course of pregnancy, delivery, and perinatal and neonatal outcomes, even if there are no abnormal findings. Both maternal and paternal exposures are considered reportable information. For exposure involving the female partner of a male patient, the previously listed information must be collected from the patient with consideration for the partner's right to confidentiality.

## 7.3. Adverse Drug Reaction Recording and Reporting

Each participating site will be trained on the recording and reporting of SADRs, and ADRs of special interest to the MAH, or designee. Prescribers should follow the local regulations of

reporting ADRs and SADRs to local and national authorities. Reportable ADRs include those that are observed by or reported to site personnel by the patient from the time of enrolment through patient discontinuation from the registry (or 28 days after the last dose of Esbriet, whichever is later). The physician or site staff should instruct patients to report ADRs during this time period.

Each patient interview will begin with simple open-ended questions designed to collect information regarding specific reactions of interest. Directly observed ADRs or those reported by patient to the physician or site staff, from time of enrolment (i.e., informed consent has been obtained and patient has received one dose of Esbriet), will be assessed and recorded as appropriate within the CRFs. If a patient is seen by a non-study physician, the study physician and/or trained site staff should make every effort to follow-up with the relevant concerned health care provider to obtain all information necessary for the accurate reporting of the ADR in a timely manner.

Reportable ADRs identified by the physician and/or site staff will be recorded in the ADR eCRF. All SADRs should be promptly reported to the MAH within 24 hours of the learning of the ADR. Upon receipt of a SADR or an ADR of special interest, a designated MAH, site or CRO registry staff will initiate appropriate follow-up. All ADRs reported on the ADR eCRF by the reporting physician will be assessed through a follow-up algorithm with the reporting and/or treating physician. If death were to be reported as a suspected ADR, cause of death will need to be ascertained as accurately as possible.

### 7.3.1. Safety Reporting to Competent Authorities and Ethics Committees

As noted in Section 7.4.2 of Volume 9A of The Rules Governing Medicinal Products in the European Union-Guidelines on Pharmacovigilance for Medicinal Products for Human Use,[5] it is the MAH's responsibility to report all SADRs that occurred within the EU to the Competent Authority of the Member States on whose territory the SADR occurred; this report must be made no later than 15 calendar days following the receipt of information regarding an SADR.

The study physician will be provided with instructions to help comply with all site-specific requirements regarding SADR and ADR reporting, including prompt notification to their IEC of any safety reports and filing of copies of all related correspondence in the patients' notes. Unless otherwise requested by particular IECs, the MAH will normally aim to submit reports to the IECs in the same time frame that these reports are provided to the EMA and CHMP.

# 8. REGISTRY PROCEDURES

All treatment decisions, including medications, are at the sole discretion of the treating physician in accordance with their usual care. Registry participation does not entail dispensing of study medication or protocol-specified procedures.

## 8.1. Schedule of Assessments

The currently authorised SPC for Esbriet recommends liver function test monitoring prior to beginning Esbriet, every month for the first 6 months of Esbriet therapy, and every 3 months

thereafter. Scheduled registry visits will occur at baseline and at 3-month intervals for the duration of follow-up. The registry will permit a window of ±4 weeks around the scheduled visit date. SADRs, ADRs of special interest, Esbriet discontinuations, and registry withdrawals should be reported in a continuous ongoing manner at any time during follow-up.

# 9. DATA ANALYSIS AND STATISTICAL CONSIDERATIONS

## 9.1. Sample Size

The registry aims to enrol 1,000 patients with IPF across participating EU Member States. The sample size was selected in order to have sufficient statistical precision as expressed by a 2-sided, 95% confidence limit around the expected incidence rate for each ADR.

The incidence of ADRs during the 75 weeks of exposure among 789 unique patients treated with Esbriet in Phase 3 studies and 2 open-label studies ranged from 2.5% to 22%.

Table 2 shows the precision with a sample size of 1000 for varying rates of ADRs. Precision is defined as half the width of the 95% confidence interval. For example, if the expected proportion of abnormal LFT is 2.5% for a sample size of 1,000, the precision is 0.97%. The precision shown in the table was calculated based on 95% normal approximation confidence interval. The calculation of the confidence intervals was performed using PASS software[6].

**Table 2: Precision for Estimates of ADRs of Varying Proportions with Sample Size of 1000**

| Expected proportion | Precision |
|---|---|
| 0.5% | 0.44% |
| 2.5% | 0.97% |
| 5.0% | 1.35% |
| 7.5% | 1.63% |
| 10.0% | 1.86% |
| 15.0% | 2.21% |
| 20.0% | 2.48% |
| 25.0% | 2.68% |

## 9.2. Data Analyses

### 9.2.1. General Considerations

A detailed Statistical Analysis Plan (SAP) will be prepared and approved by the MAH prior to implementation. All SADRs, and ADRs of special interest will be recorded and coded using Medical Dictionary for Regulatory Activities (MedDRA) terms and presented by system organ class (SOC) and preferred term (PT). Anonymised characteristics of patients who are screened

for enrolment, but do not participate in the study, will be collected in screening logs and reviewed on an ongoing basis for the purposes of understanding enrolment trends.

### 9.2.2. Baseline Assessment

The demographic and clinical profile of the registry population will be described using baseline data. Continuous variables will be reported using appropriate measures of dispersion and central tendency and categorical variables will be summarized as number and percentage of the total registry population.

### 9.2.3. Primary Analyses

Cumulative incidence of SADRs, and ADRs of special interest will be calculated as the number of patients who have a specific event starting during the study period, divided by the number of patients enrolled, multiplied by 100.

Risk of SADRs, and ADRs of special interest will be estimated as number of events over cumulative time at risk. Time at risk will be defined as the time between dates of first dose of Esbriet to end of follow-up (completion of follow-up / registry withdrawal). Case narratives will be provided for each SADR.

Tables with counts of SADRs, and ADRs of special interest summarized by MedDRA SOC and PT, and stratified by fatal or non-fatal outcome will be provided. Analysis will be conducted, if possible, for subgroups of patients including: predisposing conditions for liver disease; concomitant immunosuppressive therapy and other therapy for IPF; advanced stages of IPF; secondary cause of pulmonary fibrosis; QT prolongation; underlying cardiac, hepatic and other forms of pulmonary disease; Esbriet use for conditions other than IPF; paediatric patients, and patients who have stable warfarin anticoagulation at the beginning of pirfenidone treatment.

## 9.3. Missing Data

Reasonable attempts will be made to contact patients who discontinue the study or who are lost to follow-up. However, no imputations will be made for missing data. Details on handling of missing data will be included in the SAP.

# 10. ETHICAL, SCIENTIFIC AND REGULATORY ASPECTS

## 10.1. Good Practice and Scientific Advise

### 10.1.1. Guiding Principles

The registry complies with Volume 9A of the Rules Governing Medicinal Products in the European Union-Guidelines on Pharmacovigilance for Medicinal Products for Human Use-Part 1 Section 7, Company-Sponsored Post-Authorization Safety Studies.[5]

To ensure the quality and integrity of research, the conduct of this registry will be governed by the Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International

Society for Pharmacoepidemiology, the Declaration of Helsinki[1] and its amendments, and any applicable national guidelines.[1,2]

### 10.1.2. Opinion of External Experts and Scientific Advisory Boards

A SAB, consisting of pulmonologists with expertise in fibrotic lung diseases and other experts (e.g., hepatologists and dermatologists, if necessary) will be identified and recruited to assist in study execution and interpretation. The SAB will meet and review the registry data regularly and may make recommendations to the MAH about study conduct or data collection.

## 10.2. Patient Information and Informed Consent

Informed consent is an unconditional prerequisite for patient participation in the registry. For paediatric patients, written informed consent will be required from a parent/legal representative. Underage patients, as defined by local regulations in each country, will be required to provide assent for participation. Underage patients who reach the local legal age for providing informed consent during follow-up will be reconsented at the next follow-up time point.

Prior to any registry-related data collection activities, the study physician will obtain informed consent and contact information for treating physician(s) other than themselves and obtain permission to access hospital records. As permitted by local regulations, the form may include consent for direct contact with the patient or parent/legal representative, and retrieval of information or supportive documentation from health care providers and/or administrative sources other than the study physician.

At the time of recruitment, the study physician will be required to provide patients or legal representatives/parents with an information sheet in their local language that contains adequate information on risks of registry participation specifically communication of personal identifiers and health information. If permissible under local regulations, provision of verbal and written information for the purpose of obtaining consent may be performed by a trained designee of the study physician. The original informed consent document will be maintained at the site and a copy provided to each patient or legal representative/parent.

## 10.3. Patient Identification and Privacy

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing patient data. By signing the protocol, the institution and/or physician commit to complying with all related applicable local laws and regulations as well as any applicable EU regulations, such as the EU Data Protection Act, Directive 95/46/EC and Safe Harbour privacy principles.

Each patient will be unambiguously identified by a code, which allows the identification of all the data reported for each patient. Should a patient be withdrawn from the study, his or her unique identification number will not be reallocated.

## 10.4. Compensation to Patients and Physicians

Retaining patients and physicians over multiple years and minimizing loss to follow-up are critical to meet registry goals. The main component of patient retention is the rapport between study physician and patient or legal representative/parent. If permitted by the local IEC, additional strategies to facilitate patient retention, including, for example, distribution of educational materials about IPF and feedback to patients about the registry progress, will be implemented where possible.

Study physicians will be compensated for time spent in completing registry requirements consistent with local prevailing conditions. This compensation schedule will be determined in accordance with national and local IEC guidelines.

## 10.5. Independent Ethics Committees

IEC approval consistent with local regulations will be obtained for each site. Prior to enrolment of patients at a given site, the registry protocol will be submitted together with its associated documents (e.g., ICF, questionnaires, and communication materials) to the responsible IEC for its review. The written favourable opinion/approval of the IEC will be provided to each study physician, and a copy will be filed in the Registry Master File maintained by the MAH. Patient enrolment will not start at any site before the MAH has obtained written confirmation of a favourable opinion/approval from the concerned IEC. This must not interfere with normal prescribing of Esbriet. The IEC will be asked to provide documentation of the date of the meeting at which the favourable opinion/approval was given, and of the members and voting members present at the meeting. Written evidence of favourable opinion/approval that clearly identifies the registry, the protocol version, and the Patient Information and Consent Form version reviewed will be provided.

Before implementation of any substantial changes to the protocol, protocol amendments will also be submitted to the relevant IEC in a manner consistent with local regulations. Pertinent safety information will be submitted to the relevant IECs during the course of the registry in accordance with local regulations and requirements.

## 10.6. Regulatory Authorities

The approved protocol will be submitted to the Competent Authorities in accordance with the regulations of the countries involved in the registry, and in compliance with Volume 9A of The Rules Governing Medicinal Products in the European Union (Guidelines on Pharmacovigilance of Medical Products for Human Use)[5] as it applies to PASS.

# 11. MANAGEMENT OF THE REGISTRY

## 11.1. Operations

Each participating site will receive appropriate training, which describes all processes that the study physician or representative must understand. The information will outline all processes required for a clinic to become a registry site, enrolling patients, providing follow-up data on

enrolled patients, maintaining registry documents or files, reporting ADRs, and closing the registry. All site staff who participate in enrolling patients, collecting, or entering data for the registry will be required to undergo appropriate training.

## 11.2. Data Entry

Data for the study will be collected using a secure web-based electronic data capture (EDC) system. Where technical conditions or site preference prevent data entry via eCRFs, paper CRFs may be used and sent to the MAH or designee for entry into the EDC system.

## 11.3. Patient Files

The physician should maintain source documents for each patient enrolled in the study. Source documents such as patient charts and doctors' notes will be kept as part of the patients' medical records. Patient files including medical records and signed patient ICFs must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 15 years after completion of the registry.

## 11.4. Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (substantial, significant) amendments will usually require agreement with the CHMP and then submission to the relevant IECs for approval or favourable opinion. In such cases, the amendment will be implemented only after approval or favourable opinion has been obtained. Minor (nonsubstantial) protocol amendments, including administrative changes, will be filed by the MAH and/or designee and at each participating site. The amendments will be submitted to the relevant IEC or to Competent Authorities where required by pertinent regulations. Any amendment that could have an impact on the patient's agreement to participate in the registry, for example, changing the nature of the data collected, requires the patient's or parent/legal representative's informed consent prior to implementation.

## 11.5. Publication Policy

Regular communications on the progress of the study will be provided to participating physicians. The MAH's decision to publish or otherwise publicly communicate the results of this study will be made in accordance with all applicable laws, regulations, and MAH policies regarding publication and communication of study results. Publications and authorship will be guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journals Editors, updated October 2008.[7]

# 12. REFERENCES

**1.** Declaration of Helsinki 59th World Medical Association General Assembly, Seoul, October 2008. Available at: http://www.wma.net/e/policy/b3.htm.

**2** Pharmacoepidemiology ISF. (ISPE) Guidelines for good pharmacoepidemiology practices (GPP), revision 2. April 2007. Available at: http://www.pharmacoepi.org/resources/guidelines_08027.cfm.

**3.** Katzenstein AL, Myers JL. Nonspecific interstitial pneumonia and the other idiopathic interstitial pneumonias: classification and diagnostic criteria. *Am J Surg Pathol.* Jan 2000;24(1):1-3.

**4.** Bjoraker JA, Ryu JH, Edwin MK, et al. Prognostic significance of histopathologic subsets in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med.* Jan 1998;157(1):199-203.

**5.** EMEA. EudraLex VOLUME 9A of The Rules Governing Medicinal Products in the European Union Guidelines on Pharmacovigilance for Medicinal Products for Human Use. September 2008.

Available at: http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol9_en.htm.

**6.** Hintze JL. PASS Power Analysis and Sample Size System. Published by NCSS Kaysville, Utah. 2008.

**7.** International Committee of Medical Journal of Editors (ICMJE). Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publications. October 2008.

Available from http://www.icmje.org/urm_full.pdf.