Roche Protocol WA29961

(InterMune Protocol PIPF-028)

TITLE:	A 2-Year Observational Study to Describe the Characteristics and Progression of Patients Suffering from Idiopathic Pulmonary Fibrosis Treated with Esbriet® in the Conditions of Use Ancillary Study to PIPF-025 (PASSPORT): Post-Authorisation Safety Study of Esbriet® (Pirfenidone): A Prospective Observational Registry to Evaluate Long-Term Safety in a Real-World Setting
SPONSOR:	Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Version:	3.0
DATE:	10 November 2015 (including Amendment 1)

Approver's Name	**Title**	**Date and Time (UTC)**
[redacted]	Company Signatory	26-Nov-2015 04:28:09

PROTOCOL AMENDMENT APPROVAL

SCIENTIFIC COMMITTEE

The role of the Scientific Committee is:

- to validate the objectives and methodology of the study
- to review the results and provide input on data interpretations

The committee has 4 members:

Pr [redacted], Lyon

Pr [redacted], Bobigny

Pr [redacted], Paris

Mr [redacted], Lyon

This protocol was reviewed by Mr [redacted] on 17 October 2013 and by Pr [redacted], Pr [redacted] and Pr [redacted] on 22 October 2013.

Informational Contact:

_____

Dr [redacted]

Responsable Médical Respiratoire

Tel: [redacted]

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Roche SAS

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92650 Boulogne-Billancourt

PHYSICIAN SIGNATURE PAGE

I have read and approve this protocol. My signature, in conjunction with the signature of the sponsor representative, confirms the agreement of both parties that the French Ancillary Study (FAS) 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, and applicable privacy laws.

_____ _____

PHYSICIAN SIGNATURE Date

_____

PHYSICIAN NAME AND TITLE

SPONSOR:

_____ _____

NAME AND TITLE Date

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.
- A longer start-up period than was expected when the protocol was written.
- Adjustment of study goals and endpoints, to clarify and align with other Esbriet projects.
- The need to clarify unclear text and to correct grammatical or typographical errors.

The specific areas or items to be changed or added:

1. Data collection and management will use electronic data capture and eCRFs, not paper CRFs.
2. Most of the efficacy data will be collected retrospectively. These data are routinely collected in the clinical care chart in “real-time” but they will be collected from charts by study personnel retrospectively after the ongoing PASSPORT patient consents to participate in FAS as well.
3. Updating the number of sites and patients to be recruited.
4. Indicating that attempts will be made to collect data from subjects who are deceased or lost to follow up whenever possible and specify the process for contacting discontinued patients.
5. Updates the sample size section based on the revision to the primary endpoints.
6. Discussion of the possibility of an interim analysis.
7. The addition of details on the planned analyses, to bypass the need for a separate statistical analysis plan document.
8. Noting that data from the PASSPORT study will be combined with efficacy data collected in the FAS study for the FAS analyses, and updating the data collection section accordingly.

SUMMARY OF CHANGES MADE BY AMENDMENT 3 TO PROTOCOL PIPF-028

Page in Protocol Ver 2.0	**Topic**	**Previously Read**	**Now Reads**
Title Page	Protocol Number	PIPF-028	Roche Protocol WA29961 (InterMune Protocol PIPF-028)
Title Page	Protocol Name	Ancillary study to the PASSPORT study: Esbriet® post-authorisation study. Prospective observational study to evaluate the safety after two years in the conditions of use.	Ancillary study to PIPF-025 (PASSPORT): Post-Authorisation Safety Study of Esbriet® (Pirfenidone): A Prospective Observational Registry to Evaluate Long-Term Safety in a Real-World Setting
Title Page	Change in Marketing Authorization Holder (MAH) or Sponsor	InterMune France 62 Bis, Avenue Andre Morizel 92100 Boulogne France	Roche Registration Limited 6 Falcon Way Shire Park Welwyn Garden City AL7 1TW United Kingdom
Title Page	Version	2.0	3.0
Title Page	Date	02 October 2014	06 November 2015 (including Amendment 1)
2	first paragraph; first bullet	to validate the results	to review the results and provide input on data interpretations
2	Informational Contact	[redacted] MD VP Medical Affairs InterMune France 62Bis, Avenue André Morizet 92100 Boulogne France	Dr [redacted] Responsable Médical Respiratoire Tel: [redacted] [redacted] Roche SAS 30 cours de l'Ile Seguin 92650 Boulogne-Billancourt
3 (and all subsequent uses in protocol)	study name	ancillary study	French Ancillary Study (FAS)

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
3	Sponsor Signature	[redacted] MD VP Medical Affairs InterMune France	NAME AND TITLE
4,5	Table of Contents		UPDATED to reflect new page numbers
6	List of Abbreviations	CRF, DCF, DGS, DILD, JRS, MedDRA, pCRF, RCC, WHO – deleted	
6	List of Abbreviations		INSERTED: eCRF, electronic Case Report Form; FAS, French Ancillary Study; HCP, Health Care Professional; PIS, Patient Information Sheet
6	List of Abbreviations		FAS French Ancillary Study or PIPF-028
6	List of Abbreviations (and all subsequent references to paper CRFs)	pCRF Paper Case Report Form	eCRF Electronic Case Report Form
6	List of Abbreviations	Principle Investigator	Principal Investigator
7	Summary:		Study number Roche WA29961 (InterMune PIPF-028)
7	Summary: Study modalities	Ancillary study to the InterMune PASSPORT study (study number PIPF-025). The study is mandated by French authorities.	Designed as an ancillary study to Roche WB29908 (formerly InterMune PIPF-025 or PASSPORT). The PASSPORT study was mandated by the European Medicines Agency (EMA). This ancillary study is mandated by Haute Autorité de Santé and the Direction Générale de la Santé

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7	Summary: Study objectives	**Primary objective** Describe the clinical progression over two years of patients suffering from Idiopathic Pulmonary Fibrosis (IPF) treated with Esbriet® in the conditions of use. **Secondary objectives** - Describe the modalities of IPF diagnosis based on the results from high resolution computed tomography, histopathology and clinical characteristics discussed during the multidisciplinary meeting. - Describe the changes of the Gender, Age, Physiology (GAP) score, indicator of IPF severity, the complications, in particular exacerbations and pulmonary arterial hypertension. - Describe hospitalisations occurring during the study. - Collect progression-free survival data (time to onset of one of the following events: reduction of the predicted FVC ≥ 10%, reduction of the predicted DLco ≥ 15%, death) and mortality (all causes and linked to IPF) over the two years of follow-up.	**Primary objective** Describe the clinical progression over two years of patients suffering from IPF treated with Esbriet in the conditions of use. **Secondary objectives** 1. Describe the modalities used to determine IPF diagnosis. 2. Describe the changes in physiology and IPF complications, in particular, exacerbations and pulmonary arterial hypertension. 3. Summarize progression-free survival data.

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7	Summary: Endpoints	**Primary endpoints** - Change in % predicted FVC over 2 years - Change in % predicted DLco over 2 years - **Secondary endpoints** - Dyspnoea stage according to New York Heart Association (NYHA) classification - Categorical evaluation of the FVC (proportion of patients with a decline in % predicted FVC ≥ 10% over the duration of the follow-up) - Distance travelled during the Six minute walk test (6MWT) - GAP score - Number of episodes of exacerbations, hospitalisations and duration - Number of deaths	**Primary endpoints** Over total treatment time (up to 2 years): • Change in % predicted forced vital capacity (FVC) • Change in distance travelled during the six minute walk test (6MWT) **Secondary endpoints** 1. Modalities used to determine IPF Conclusion from Multidisciplinary Diagnosis Discussion on IPF diagnosis (certain, probable, possible or unclassifiable idiopathic diffuse interstitial lung disease) 2. Cases of IPF comorbidities, in particular acute exacerbation and pulmonary arterial hypertension Gender Age Physiology (GAP) score Dyspnoea stage according to New York Heart Association (NYHA) classification Number and duration of all-cause and respiratory related hospitalisations 3. Progression-free survival, defined as time from initiation of Esbriet treatment to the first occurrence of the following events: • An absolute decline in % predicted FVC ≥ 10% over the duration of the follow-up • An absolute decline in 6MWT distance ≥ 50 meters over the duration of the follow-up • Death from any cause

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7, 8	Summary: Methodology	The ancillary study will be conducted in the centres participating in the PASSPORT study (PIPF-025). During the inclusion period, the hospital pulmonologists will be asked to include patients meeting the inclusion criteria and consenting to participate in the study. The data will be collected at the same time in the PASSPORT study and in the ancillary study: at inclusion (after signing the informed consent form) and during normal follow-up visits (every 3 months +/- 4 weeks), during a 2 year follow-up period. As an observational study, this study will not change the patient/health professional relationship or the patient's treatment. The patients will remain in the study even if they miss a visit.	- The FAS will be conducted in the centres participating in the PASSPORT study (PIPF-025) who have enrolled at least one patient and who are located in France - All PASSPORT patients will be asked to enrol in the FAS as well - All FAS patients will sign a separate informed consent form (ICF) for FAS - Data will be collected at the same regularly scheduled visits as the PASSPORT study (approximately every 3 months +/- 4 weeks) - Because the FAS will start after PASSPORT has completed enrolment and patients have begun treatment, data will be captured retrospectively from the patient's records as well as prospectively as patients continue to receive treatment - Patients who have discontinued the PASSPORT study before the FAS begins may be contacted to ask for permission to use their clinical records to collect data retrospectively The FAS study is non-interventional and will not change the patient/health professional relationship or the patient's treatment. The observational nature of the study leaves any decision relating to the patient's treatment with Esbriet (pirfenidone) completely to the pulmonologist's discretion.
8	Summary: Number of patients; Number of centres	Up to 230 patients Up to 23[redacted]	Up to 214 patients Up to 22[redacted]

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8	Summary: Inclusion Criteria	**Inclusion criteria:** The following patients will be included in the study: - All patients enrolled in the PASSPORT study (PIPF-025) - Patients consenting to participate in the ancillary study and having completed and signed an informed consent form. The observational nature of the study leaves any decision relating to the patient's treatment with Esbriet® (pirfenidone) completely to the pulmonologist's discretion	The following patients will be included in the study: - All patients enrolled in the PASSPORT study (PIPF-025) at French sites - Patients consenting to participate in the FAS who have completed and signed an ICF. See Section 9.3 for exceptions - Patients who have had at least one dose of Esbriet during PASSPORT study

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8	Summary: Data Collection	The following information will be collected: **Inclusion Visit:** • Date of the visit • Date of Informed Consent • Inclusion criteria • Date of the Multidisciplinary meeting (or Multidisciplinary discussion) and conclusion: IPF certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease (DILD) • History of the IPF diagnosis - Clinical characteristics during diagnosis: the most recent FVC result, FEV1/FVC result, DLCO and NYHA dyspnoea stage - Other examinations at diagnosis: Distance travelled during the Six minute walk test and O2 saturation, calculated creatinine clearance • Description of concomitant pulmonary rehabilitation • IPF and IPF related co morbidities (particularly exacerbations, pulmonary arterial hypertension) • Other IPF treatments (medications, oxygen therapy)	he following information will be collected in FAS to supplement that already being collected in PASSPORT: **Baseline Visit:** • Date of Ancillary Informed Consent • Inclusion criteria • Date of the Multidisciplinary Diagnosis Discussion (MDD) and conclusion regarding IPF: certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease • History of the IPF diagnosis - Clinical characteristics during diagnosis: the most recent DL_{CO} result and NYHA dyspnoea stage - Other examinations at diagnosis: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer) • Other IPF treatments (medications, oxygen therapy) • Collection of information about hospitalisation and diagnosis-related groups (DRG)

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8		**Follow-up visits (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit:** • Date of the PASSPORT visit • Description of concomitant pulmonary rehabilitation • Clinical characteristics: the most recent FVC result, FEV1/FVC result, DLCO and NYHA dyspnoea stage • Other examinations: Distance travelled during the Six minute walk test and O2 saturation, calculated • creatinine clearance • IPF and IPF related co morbidities (particularly exacerbations, pulmonary arterial hypertension) • Collection of information linked to possible hospitalisation and diagnosis-related groups (DRG). **End of study:** • Date of the visit • Patient status (completed or early discontinued)	**Follow-up visits (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit:** • Clinical characteristics: the most recent FVC result, FEV1 result, DL_{CO} and NYHA dyspnoea stage • Other examinations: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer) **End of study:** Patient status (completed or early discontinuation)

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9	Summary: Statistical Methodology	**Objectives of the statistical analysis plan:** **Description of the study population :** The patients included in the study will be described according to their socio- demographics, their medical history and concurrent conditions. **Analysis of the primary objective :** - Long-term progress of patients with IPF will be described: changes of the FVC and DLCO as a percentage of their predicted value. **Analysis of secondary endpoints :** - Changes of the dyspnoea stage according to NYHA classification will be described. - Categorical changes of the FVC and the GAP score will be described. - Complications, particularly exacerbations and pulmonary arterial hypertension will be described. Hospitalisations will be described: respiratory causes or not, DRG and duration of hospitalisation. - Survival without progression and mortality data will be described. **Analysis methods :** - The statistical analyses will be descriptive. - The quantitative descriptive variables will be described in terms of mean, standard-deviation, median, 1st and 3rd quartiles, minimum and maximum, and amount of missing data. - The qualitative descriptive variables will be described in terms of number, percentage by modality and amount of missing data. - For the analyses per visit, the visits will be used as documented. The baseline value for all the analysed variables will be the value captured during the inclusion visit.	The study is descriptive in nature. No formal hypothesis testing will be performed. All patients who have met the entry criteria and enrolled in the study will be included in the analyses. **Description of the study population:** The patients included in the study will be described according to their socio- demographics, their medical history and concurrent conditions **Analysis methods for primary and secondary endpoints:** - The statistical analyses will be descriptive - The continuous variables will be summarized in terms of mean, standard-deviation, median, 1st and 3rd quartiles, minimum and maximum, and amount of missing data - The categorical variables will be summarized in terms of number and percentage - For the analyses per visit, visit windows will be utilized The baseline value for all the analysed variables will be the last, non-missing value captured up to an including the Baseline visit

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11	2. Justification of the Study	At the EMA's request, InterMune currently has a European post-marketing safety study in place, the PASSPORT study, which aims to evaluate the safety profile of long-term use of Esbriet® (pirfenidone) in patients with IPF and to monitor the potential or unknown risks over two years of treatment with Esbriet®. Given the necessity for improved understanding of the clinical outcomes in real life for patients with IPF treated with Esbriet®, InterMune implemented an observational study and an ancillary study to the PASSPORT study (PIPF-025) at the request of the French authorities (HAS and DGS). Data collected in the latter study will complement those obtained in the PASSPORT study and both studies will be conducted in parallel in the same patients by pulmonologists from the same centres of expertise.	At request of the EMA, InterMune (acquired by Roche) initiated a European post-marketing safety study, PIPF-025 or PASSPORT, to evaluate the safety profile of long-term use of Esbriet in patients with IPF and to monitor the potential or unknown risks over two years of treatment with Esbriet. Given the necessity for improved understanding of the clinical outcomes in real life for patients with IPF treated with Esbriet, Roche now plans to implement the FAS, an observational and ancillary study to the PASSPORT study at the request of the French authorities (Haute Autorité de Santé and Direction Générale de la Santé). Data collected in the FAS study will complement those obtained in the PASSPORT study and both studies will be conducted in parallel involving the same sites, patients and Principal Investigators (PI) as PASSPORT.
12	3. Objectives and Endpoints for the Study		UPDATED to match that as given in the synopsis summary.

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13	4.1 Study plan	The PASSPORT study, an observational, multicentre, prospective study of patients with IPF monitored for two years is being conducted in France. The ancillary study will be conducted in the centres participating in the same study. During the inclusion period, the participating pulmonologists will include patients meeting the selection criteria and consenting to be part of the ancillary study. Data will be collected at the same time in the PASSPORT study and in the ancillary study during inclusion (after signing the informed consent form) and as part of the scheduled follow-up visits depending on the patient's normal treatment, over a 2 years follow-up period (every 3 months +/- 4 weeks) (see Table 1). As this is an observational study, participation in this study will not change the relationship between the patient and the pulmonologist and will not influence prescription of medications or the patient's therapeutic treatments.	The PASSPORT study is an observational, multicentre, prospective safety study of patients with IPF who are treated with Esbriet and monitored for up to two years of treatment. The study is a post-authorization safety study (PASS) being conducted at the request of the EMA in 10 EU and Nordic countries, including France. The French Ancillary Study (FAS) is an auxiliary to the PASSPORT study to collect efficacy data requested by the French Regulatory Agency. The FAS is also a non-interventional study and will be conducted only in the French centres already participating in the PASSPORT study. The PASSPORT study has been ongoing in France since January of 2013. Enrolment is complete with 214 patients enrolled in 22 French sites. These patients will be approached by the Principal Investigator at each PASSPORT site and asked if they would consent to have Esbriet efficacy data collected in addition to their safety data. After meeting inclusion criteria and signing an informed consent form, efficacy data from ongoing or active PASSPORT patients will be collected retrospectively and prospectively as they complete up to 2 years of treatment with Esbriet. Patients who have discontinued PASSPORT will be contacted for permission to include the efficacy data already collected as part of their routine clinical visits in the FAS (see Table 1). Data from patients who have died or been lost-to-follow up will be included. The FAS is an observational study; participation will not change the relationship between the patient and the pulmonologist/PI and will not influence prescription of medications or the patient's therapeutic treatments.
13	Table 1 Schedule of Study Assessments	Follow-up visits 1 to 8	Follow-up visits 2 to 9

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13		Early discontinuation visit	DELETED (last visit completed is used if patient discontinues early)
13		Visit dates and Baseline FVC and FEV1	DELETED (as collecting in PASSPORT)
13	4.2 Selection criteria	• Patients included in the PASSPORT study.	• Patients included in the PASSPORT study in French sites
13		…completely to the pulmonologist's discretion.	ADDED: See Section 9.3 for exceptions..
13		…completely to the pulmonologist's discretion.	…completely to the treating pulmonologist's discretion.
14	4.4 Sample size	All patients meeting the eligibility criteria and consenting to participate will be included in the FAS. Up to 214 patients will be eligible for enrolment at up to 22 participating centres. The primary objective of the study is mainly descriptive; precision for a given frequency with a 95% confidence interval can be calculated using the following formula: $e = 1.96 \times \sqrt{\frac{p \times (1-p)}{n}}$ where e = the estimation precision, n = number of patients and p = evaluated proportion. The following table presents the absolute precision associated with frequencies between 5 and 50% for a sample size of 215 patients and a 95% confidence interval.	All patients meeting the eligibility criteria and consenting to participate will be included in the analyses. Up to 214 patients will be eligible for enrolment at up to 22 participating centres. The study is descriptive in nature. No formal hypothesis testing will be performed. For the primary endpoints and the change from baseline continuous secondary endpoints, the 95% confidence interval will be calculated using the following formula: Mean change from baseline ± *e*, where *e* = the estimation of precision, $e = t_{0\,025} \times s.d./\sqrt{n}$ s.d. = the standard deviation, and n = the sample size. The following table presents the precision expected for the primary endpoints using the standard deviations observed in the ASCEND study (PIPF-016) for potential FAS sample sizes of 180 and 214 patients and a 95% confidence interval.

<table>
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<tr><td>14</td><td>4.4 Sample size</td><td>
Table 1 Absolute precision associated with the different frequencies for sample sizes of 200 and 230 patients and a 95% confidence interval
<table>
<tr><th rowspan="2">Frequency</th><th colspan="2">Absolute precision</th></tr>
<tr><th>N = 200</th><th>N = 230</th></tr>
<tr><td>5 %</td><td>3.0 %</td><td>2.8%</td></tr>
<tr><td>10 %</td><td>4.2 %</td><td>3.9 %</td></tr>
<tr><td>20 %</td><td>5.5 %</td><td>5.2 %</td></tr>
<tr><td>30 %</td><td>6.4 %</td><td>5.9 %</td></tr>
<tr><td>40 %</td><td>6.8 %</td><td>6.3 %</td></tr>
<tr><td>50 %</td><td>6.9 %</td><td>6.5 %</td></tr>
</table>
A sample size of 200 to 230 patients guarantees acceptable precision for description of the long-term clinical results in patients with IPF treated with Esbriet® (pirfenidone) (between 2.8% and 6.9% for frequencies between 5 and 50%).
</td><td>
Table 2 Absolute precision associated with the different standard deviations for sample sizes of 180 and 214 patients and a 95% confidence interval
<table>
<tr><th rowspan="2">Variable</th><th rowspan="2">Standard Deviation</th><th colspan="2">Precision (e)</th></tr>
<tr><th>N = 180</th><th>N = 214</th></tr>
<tr><td>Change in Percent Predicted FVC</td><td>12.11</td><td>1.78</td><td>1.63</td></tr>
<tr><td>Change in Distance Walked in 6MWT</td><td>95.73</td><td>14.08</td><td>12.90</td></tr>
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14, 15	4.5 Collected Data	**Paper case report form / inclusion visit:** o Date of the visit o Date of Informed Consent o Inclusion criteria o Date of the Multidisciplinary meeting (or Multidisciplinary discussion) and conclusion: IPF certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease (DILD) o History of the IPF diagnosis o Clinical characteristics during diagnosis: the most recent FVC result, FEV1/FVC result, DLco and NYHA dyspnoea stage o Other examinations at diagnosis: Distance travelled during the Six minute walk test and O_2 saturation, calculated creatinine clearance o Description of concomitant pulmonary rehabilitation o IPF and IPF related co morbidities (particularly exacerbations, pulmonary arterial hypertension) o Other IPF treatments (medications, oxygen therapy, pulmonary rehabilitation)	**Visit 1: Baseline** • Patient Identification number (same as used in PASSPORT) • Date of Ancillary Informed Consent • Inclusion criteria • Date of the MDD and conclusion regarding IPF: certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease • Clinical characteristics during diagnosis: the most recent DL_{CO} result and NYHA dyspnoea stage (baseline FVC and FEV1 data have been collected in PASSPORT) • Other examinations at diagnosis: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer)

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		Paper case report form/Follow-up visits (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit: • Date of the PASSPORT visit • Description of concomitant pulmonary rehabilitation • IPF diagnosis o Clinical characteristics: the most recent FVC result, FEV1/FVC result, DLco and NYHA dyspnoea stage o Other examinations: Distance travelled during the Six minute walk test and O2 saturation, calculated creatinine clearance • IPF and IPF related co morbidities (particularly exacerbations, pulmonary arterial hypertension) • Collection of information linked to possible hospitalisation and diagnosis-related groups (DRG). **End of study visit:** • Date of the visit • Patient status (completed or early discontinued)	**Follow-up Visit (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit:** • Clinical characteristics: most recent FVC result, FEV1 result, DL_{CO} and NYHA dyspnoea stage • Other examinations: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer) • Collection of information about hospitalisation and DRG **End of Study:** • Patient status (completed or early discontinuation)

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15, 16	4.6 Processes for data management	A database will be programmed to receive the information collected in the CRF. Checking of automated edits will take place. The data entry screens and the edit checks will be validated using test data before the start of the study. A data processing manual including the specifications for edit checks, data entry guide, authorised corrections and locking procedure will be written as an operational guide. The pulmonologists will be asked to complete the CRF at different times. The quality controls will focus on the value ranges and missing data. When discrepancies are identified in the CRF, the data management group will issue requests for data correction by sending data change forms (DCFs). Resolution of these requests will require reauthorisation by the physician. The variables concerning the primary endpoint presenting with inconsistencies could be the subject of an additional request by telephone to the physician. At the end of the inclusion period, the interim database will be frozen and interim statistical analyses will be conducted at the same time as those for the PASSPORT study. Final validation of the database will be performed and the database will be frozen before performing the final statistical analysis.	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. Data for the study will be collected using a secure web-based electronic data capture (EDC) system. Where technical conditions prevent data entry via eCRF, paper CRFs may be used and sent to the MAH or designee for entry into the EDC system. A database will be programmed to receive the information collected in the eCRF. The data entry screens and the edit checks will be validated using test data before the start of the study. A data processing manual including the specifications for edit checks, data entry guide, authorised corrections and locking procedure will be written as an operational guide. Data will be checked with automated edits and by manual inspection of the eCRF site entries by off-site monitors. No imputations will be made for missing data. While effort will be made to try to avoid missing data, note that the majority of the study data will actually be collected retrospectively. As a result, data collection is constrained to what data are available. When discrepancies are identified in the eCRF, the data management group will issue requests for data clarification or correction by posting queries in the eCRF. Resolution of these requests will be documented in the eCRF.

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16	4.7 Statistical analysis	Statistical analysis will be performed using the SAS software. A statistical analysis plan (SAP) will be developed which will be validated by the Scientific Committee.	The statistical analysis will be descriptive using SAS software. No formal hypothesis testing will be performed. An interim statistical analysis may be conducted. The interim FAS data analysis will be scheduled to coincide with that done for the PASSPORT study. This will facilitate the combining of safety data from PASSPORT with efficacy data from the FAS. After the last patient has completed or terminated, a final validation of the FAS database will be performed and the database will be locked before performing the final statistical analysis.
16	4.7.1 Analysis populations	The main analysis population will be made up of all patients who have met entry criteria and have had at least one dose of Esbriet.	The analysis population will include all patients who have met entry criteria and enrolled in the study.
16	4.7.2 Sample of participating sites	The population of the centres having participated in the study will be described by the type of establishment, the geographical distribution.	The FAS patient enrolment counts will be summarized by study site.
16	4.7.3 Description of FAS population	Patients included in the study will be described according to their demographic characteristics (e.g., age, sex), history of the IPF and their clinical status at study entry.	Patients included in the study will be described according to their demographic characteristics (e.g., age, sex), history of the IPF and their clinical characteristics at study entry.
16	4.7.4 Response to primary objective	The clinical results at two years for patients with IPF will be described: changes of the clinical characteristics and respiratory function tests.	DELETED, as redundant with earlier sections.
16	4.7.5 Response to secondary objective	• The clinical characteristics of patients with IPF at the time of diagnosis will be described. Compliance with the multidisciplinary meeting will be described. • Monitoring of the GAP score will be measured. The incidence of associated comorbidities, complications (in particular exacerbations, pulmonary artery hypertension) and hospitalisations will be described	DELETED, as redundant with earlier sections.

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16	4.7.6 Analytical methods	The statistical analyses will be descriptive. The continuous variables of patients and treatments will be described by the mean, standard deviation, median, 1st and 3rd quartiles, extreme values (minimum and maximum) and amount of missing data. The categorical variables will be described by the total and percentage of each response modality and the amount of missing data. The primary and secondary endpoints will be estimated by their mean with 95% confidence interval for continuous variables and their frequency (percentage) with 95% confidence interval. The amount of missing data will be documented. The main analysis will focus on the population of all patients and sensitivity analysis restricted to patients with complete data will be performed. For the continuous endpoints, if strong asymmetry occurs, the estimations will be performed using the median and its confidence interval. For the analyses per visit, the visit will be used as documented. The baseline value for all analysed variables is the value captured during the inclusion visit.	The statistical analyses will be descriptive. The baseline value is defined as last observation on or before the Esbriet dosing start date collected in Study PIPF-025. With patients able to be on Esbriet for up to 4 weeks prior to the inclusion visit, “pre-Esbriet” values will also be summarized for lung function tests (LFT) and pulmonary function tests (PFT) variables. For the analyses by visit, the visits will be assigned based on target visit dates and visit windows, and the values collected closest to the target day used in the analysis. Continuous variables, including changes from baseline for continuous variables, will be summarized with means, standard deviations, medians, minimums and maximums, and amount of missing data. Categorical variables, including changes from baseline categories, will be summarized with counts and percentage of patients, and the amount of missing data. Kaplan-Meier estimates will be used to summarize the data for time-to-event variables. The primary and secondary endpoints will be estimated by the mean with 95% confidence interval for continuous variables (mean ± $t_{0.025}$ * sd / sqrt(n)) and the frequency (percentage) with 95% confidence interval for categorical variables (percentage (p) ± 1.96 * sd / sqrt($p*(1-p)/n$)). In addition, the magnitude of treatment benefit of Esbriet will be presented as the distribution (number and percentage) of patients across the following categories of the change from baseline over time.

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
			Change in % predicted FVC: • Decline of ≥ 10% or death • Decline of < 10% to 0% • No decline (change > 0%) Change in 6MWT distance: • Decline of ≥ 50 meters or death • Decline of < 50 m to 0m • No decline (change > 0m) Sensitivity analyses may be performed if deemed necessary to support the results of the analysis for the primary and secondary endpoints. Safety summaries of patient counts and percentages for adverse drug reactions (ADRs), ADRs with onset in the first 30 days, serious ADRs, ADRs leading to study drug discontinuation, and ADRs with outcome of death, by system organ class and preferred term, will be performed based on data collected in PASSPORT.
17	4.7.7 Missing data and lost to follow-up	The amount of missing data will be described for each variable. Missing data will not be imputed and will be addressed via analytical methods. Specifically, mixed models repeated measures (MMRM) analyses are valid even with imbalance and missing data, and Kaplan-Meier survival analyses can handle missing data as censored observations. The missing data are assumed to be random.	No data imputations or extrapolations will be done to replace missing values. The amount of missing data will be described for each variable.
17	5.1 Initiation of the site	Once all required regulatory authorisations have been obtained and the essential documents have been collected (i.e. confidentiality agreement, trial agreement, Curriculum Vitae (CV)), an Investigator Site File (ISF) will be sent to each pulmonologist identified/selected in preparation of the site initiation call.	Once all required regulatory authorisations have been obtained and the essential documents have been collected (i.e., confidentiality agreement, trial agreement, Curriculum Vitae), an Investigator Site File (ISF) will be sent to each pulmonologist previously identified for participation in PASSPORT, in preparation of the site initiation call for the FAS.

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
17	5.1 Initiation of the site	Upon receipt of the ISF, an initiation telephone call will be arranged by a Clinical Research Associate (CRA) to go through the study and provide explanations about the protocol, the CRF, data collection and certain practical aspects (i.e logistics and administration) of the study. Each call will be the subject of a written report. Site will fill pre-screening log forms.	Upon receipt of the ISF, an initiation telephone call will be arranged by a Clinical Research Associate (CRA) to review the study and answer questions about the protocol, the eCRF, data collection and other logistics. The CTA will document the agenda and items discussed for each initiation telephone call in a written report.
18	5.3 Follow-up visits	Data will be collected during the patient's normal treatment. During follow-up visits, the pulmonologist will complete the study follow-up CRF.	Data will be collected during the patient's routine treatment visits. During follow-up visits, the PI or site research staff will complete the study follow-up CRF.
18	5.5 Site monitoring	Monitoring will be based on that of the PASSPORT study. The CRA will contact the participating study coordinator by telephone during the study to monitor enrolment and return of study documents and resolve possible problems at the site or answer questions about the study.	Monitoring will be remote with any on-site visits coordinated with those done for PASSPORT. The CRA will contact the participating study coordinator by telephone during the study to monitor enrolment, update of study documents and resolution of site problems and questions.
18	6.1 Representativeness of the centres	The rare pulmonary disease reference centres, all the competence centres as well as a large majority of the [redacted] in France will participate in this ancillary study. All are PASSPORT sites	The rare pulmonary disease reference centres, all the competence centres as well as a large majority of the [redacted] in France are already PASSPORT sites and will be asked to participate in the FAS as well.
18	6.2 Patients lost to follow-up	The follow-up duration will be up to 2 years; consequently, the proportion of patients withdrawn from the study could be large given the progression of IPF. The characteristics of patients lost to follow-up will be described in the statistical analysis. Any other patient safety related information will be collected in the InterMune PASSPORT study.	The follow-up duration will be up to 2 years. Consequently, it is expected that a good proportion of patients will discontinue before study completion due to IPF progression or death. The characteristics of patients who discontinue early will be described in the statistical analysis.
19	9.1 Compliance with ethical standards	…and with all local applicable regulations.	…and with compliance to all local applicable regulations.
20	9.2.2 French committee of Scientific/Data Protection Agency	The patient will be informed of their right to access, objection and correction of data recorded during this study and of the fact that this right can be exercised at any time through their pulmonologist.	Patients will be informed of their right to access, object to, and correct any data recorded during this study and that this right can be exercised at any time through their pulmonologist.

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
20	9.3 Patient information and consent form	The pulmonologist will provide the patient with an information document and consent form during the inclusion visit. This form will contain information about the nature and subject of the study, the data collected, the individuals or legal entities receiving this data and the right to access the data, correction and opposition to their transfer which can be exercised by the patients (in accordance with the Data Protection Act dated 6 January 1978, amended version). Before implementation of any procedure associated with the study, the patient must read the patient information form and the consent form. The consent form must be signed and dated by the patient and the pulmonologist, in duplicate. One copy of the consent form will be kept by the patient (the copy) and the other (original) will be kept by the pulmonologist in the patient's medical records.	A patient information sheet (PIS) and ICF will be prepared for the ancillary study. These forms will contain information about the nature and subject of the study, the data collected, the individuals or legal entities receiving this data and the right to access the data, correction and opposition to their transfer which can be exercised by the patients (in accordance with the Data Protection Act dated 6 January 1978, amended version). The ICF must be signed and dated by the patient and the investigator in duplicate. One signed ICF will be kept by the patient and one will be kept by the site in the Investigator Site File. The local regulation requires that documentation of informed consent is recorded in the source document for each patient.
20	9.3 Patient information and consent form		The following process shall be followed by the investigative sites: 1. <u>PASSPORT study active patients</u> The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient will be asked to provide a signed ICF if he/she agrees to participate. 2. <u>Deceased patients</u> (i.e., patients who have died during the course of the PASSPORT study or after terminating or completing the study) The site shall keep a precise record of the patient's death in the patient's medical charts with as much information as possible regarding how this information was obtained. Date from deceased patients will be collected as permitted by the local regulations and no updated signed ICF is needed (Section 5.2).

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
			3. Discontinued patients from PASSPORT but still treated at the investigational site The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient will be asked to provide a signed informed consent if he/she agrees to participate. 4. Patient has discontinued from Passport and is no longer seen at the investigational site. The site should contact the patient by phone, email, letter or fax as preferred by the investigational site. a. The patient can be contacted The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient is required to sign the ICF if he/she agrees to participate. b. The patient can be contacted but is not able to come to the site (e.g., the health condition does not permit the patient to travel to the site) The investigator should inform the patient about the ancillary study on the phone and the PIS and ICF (twofold) are sent to the patient by post. The patient should be requested to sign both copies of the ICF and should return both by post. The investigator should then sign both copies and return one fully signed ICF to the patient. The process must be described clearly in the patient's medical records: date when the patient was informed by phone, date shipment PIS and ICF by post, date of patient's ICF signature, date of investigator's signature and date of fully signed ICF sent to the patient.

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
			The site shall call the patient a few days after the fully signed ICF was sent, in order to document the acknowledgment of receipt from the patient. c. <u>The patient is not reached after at least 3 attempts</u>, neither a family member was reached who could inform the site about the status of the patient i. The site shall contact the local HCP and try to get information about the patient (e.g., if patient is hospitalized, if patient has died, if patient has moved). If the site receives new contact details of patient, the site will contact the patient, then see 4a and 4b ii. The site shall contact the local HCP and try to get information about the patient (e.g., if patient is hospitalized, if patient has died, if patient has moved). If no additional information can be obtained, the site will contact the town hall of the patient's last residence. If the patient has died, the town hall will have this information available. 1. Patient has died. The patient can be included without an ICF signed (same as section 2). 2. No information available. The patient is declared "lost to follow-up". The patient

Page in Protocol Ver 2.0	Topic	Previously Read	Now Reads
			can be included without an ICF signed. Every contact that was made by the site to ascertain the patient's current status shall be noted in the patient's medical records.
20	10. FINAL REPORT AND PUBLICATIONS	At the end of the study, a final study report will be written which will be reviewed a Scientific Committee. This report will contain a description of the study objectives, the methodology, results and study conclusions. The final report will be made available six months after the study close-out. An addendum interim report to PASSPORT will be generated. The final statistical reports will be written in accordance with the detailed statistical analysis plan approved by InterMune and the Scientific Committee. A summary of the study results will be sent to the general medical community. The data will be declared in aggregated form to guarantee the confidentiality of patients and pulmonologists. The completed CRF and study reports must be processed as confidential property of InterMune and they cannot be communicated to unauthorised people in any form (publications or presentations) without express written authorisation from InterMune.	**9.4 Final report and publications** At the end of the study, a final study report will be written which will be reviewed the Scientific Committee. This report will contain a description of the study objectives, the methodology, results and study conclusions. The final report will be written in accordance with the SAP approved by Roche and the Scientific Committee. The data will be declared in aggregated form to guarantee the confidentiality of patients and pulmonologists. The final report will be submitted to the French Regulatory Agencies who requested the FAS within six months after the study close-out. The completed eCRF and study reports must be processed as confidential property of Roche and they cannot be communicated to unauthorised people in any form (publications or presentations) without express written authorisation from Roche.
20	11 STORAGE OF STUDY DOCUMENTATION	InterMune will keep the collected data (questionnaires and databases) for 5 years (or a longer period if it is specified and authorised) after the end of the study.	10. STORAGE OF STUDY DOCUMENTATION Roche will keep the collected data (questionnaires and databases) for 5 years (or a longer period if it is specified and authorised) after the end of the study.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

6MWT	Six Minute Walk Test
ALAT	Latin American Thoracic Association
ATS	American Thoracic Society
CCTIRS	Comité consultatif sur le traitement de l'information en matière de recherche dans le domaine de la santé (French Advisory Committee on Data Processing in Research in the Field of Health)
CNIL	Commission nationale française de l'informatique et des libertés (French Data Protection Authority)
CRA	Clinical Research Associate
CV	Curriculum Vitae
DL_{CO}	Diffusing capacity for carbon monoxide
DRG	Diagnosis-related groups
eCRF	electronic Case Report Form
EMA	European Medicines Agency
ERS	European Respiratory Society
FAS	French Ancillary Study or PIPF-028
FVC	Forced Vital Capacity
GAP	Gender, Age, Physiology
HAS	Haute Autorité de Santé (French National Authority for Health)
HCP	Health Care Professional
ICF	Informed Consent Form
IPF	Idiopathic Pulmonary Fibrosis
ISF	Investigator Site File
MDD	Multidisciplinary Diagnosis Discussion
NYHA	New York Heart Association
PI	Principal Investigator
PIS	Patient Information Sheet

1. SUMMARY

Study number	Roche WA29961 (InterMune PIPF-028)
Study title	A 2-year observational study to describe the characteristics and progression of patients suffering from idiopathic pulmonary fibrosis (IPF) treated with Esbriet in the conditions of use
Study modalities	Designed as an ancillary study to Roche WB29908 (formerly InterMune PIPF-025 or PASSPORT). The PASSPORT study was mandated by the European Medicines Agency (EMA). This ancillary study is mandated by Haute Autorité de Santé and the Direction Générale de la Santé
Study objectives	**Primary objective** Describe the clinical progression over two years of patients suffering from IPF treated with Esbriet in the conditions of use **Secondary objectives** 1. Describe the modalities used to determine IPF diagnosis 2. Describe the changes in physiology and IPF complications, in particular, exacerbations and pulmonary arterial hypertension 3. Summarize progression-free survival data
Endpoints	**Primary endpoints** Over total treatment time (up to 2 years): • Change in % predicted forced vital capacity (FVC) • Change in distance travelled during the six minute walk test (6MWT) **Secondary endpoints** 1. Modalities used to determine IPF Conclusion from Multidisciplinary Diagnosis Discussion on IPF diagnosis (certain, probable, possible or unclassifiable idiopathic diffuse interstitial lung disease) 2. Cases of IPF comorbidities, in particular acute exacerbation and pulmonary arterial hypertension Gender Age Physiology (GAP) score Dyspnoea stage according to New York Heart Association (NYHA) classification Number and duration of all-cause and respiratory related hospitalisations 3. Progression-free survival, defined as time from initiation of Esbriet treatment to the first occurrence of the following events: • An absolute decline in % predicted FVC ≥ 10% over the duration of the follow-up • An absolute decline in 6MWT distance ≥ 50 meters over the duration of the follow-up • Death from any cause

Methodology	- The FAS will be conducted in the centres participating in the PASSPORT study (PIPF-025) who have enrolled at least one patient and who are located in France. - All PASSPORT patients will be asked to enrol in the FAS as well - All FAS patients will sign a separate informed consent form (ICF) for FAS - Data will be collected at the same regularly scheduled visits as the PASSPORT study (approximately every 3 months +/- 4 weeks) - Because the FAS will start after PASSPORT has completed enrolment and patients have begun treatment, data will be captured retrospectively from the patient's records as well as prospectively as patients continue to receive treatment - Patients who have discontinued the PASSPORT study before the FAS begins may be contacted to ask for permission to use their clinical records to collect data retrospectively The FAS study is non-interventional and will not change the patient/health professional relationship or the patient's treatment. The observational nature of the study leaves any decision relating to the patient's treatment with Esbriet (pirfenidone) completely to the pulmonologist's discretion.
Number of patients Number of centres	Up to 214 patients Up to 22 French University Hospitals
Inclusion criteria	The following patients will be included in the study: - All patients enrolled in the PASSPORT study (PIPF-025) at French sites - Patients consenting to participate in the FAS who have completed and signed an ICF. See Section 9.3 for exceptions - Patients who have had at least one dose of Esbriet during PASSPORT study

Data collection	The following information will be collected in FAS to supplement that already being collected in PASSPORT: **Baseline Visit:** • Date of Ancillary Informed Consent • Inclusion criteria • Date of the Multidisciplinary Diagnosis Discussion (MDD) and conclusion regarding IPF: certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease • History of the IPF diagnosis - Clinical characteristics during diagnosis: the most recent DL_{CO} result and NYHA dyspnoea stage - Other examinations at diagnosis: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer) • Other IPF treatments (medications, oxygen therapy) **Follow-up visits (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit:** • Clinical characteristics: the most recent FVC result, FEV1 result, DL_{CO} and NYHA dyspnoea stage • Other examinations: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance • Concomitant pulmonary rehabilitation • IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer) • Collection of information about hospitalisation and diagnosis-related groups (DRG) **End of study:** • Patient status (completed or early discontinuation)

Statistical methodology	The study is descriptive in nature. No formal hypothesis testing will be performed. All patients who have met the entry criteria and enrolled in the study will be included in the analyses. **Description of the study population:** The patients included in the study will be described according to their socio-demographics, their medical history and concurrent conditions **Analysis methods for primary and secondary endpoints:** - The statistical analyses will be descriptive - The continuous variables will be summarized in terms of mean, standard-deviation, median, 1st and 3rd quartiles, minimum and maximum, and amount of missing data - The categorical variables will be summarized in terms of number and percentage - For the analyses per visit, visit windows will be utilized - The baseline value for all the analysed variables will be the last, non-missing value captured up to an including the Baseline visit
Scientific Committee	- Pr [redacted] (Lyon) - Pr [redacted] (Bobigny) - Pr [redacted] (Paris) - Mr [redacted] (Lyon)

2. JUSTIFICATION OF THE STUDY

Idiopathic pulmonary fibrosis is a chronic disease of unknown aetiology, characterised by the formation of scar tissue (fibrosis) inside the lungs [1]. IPF is one of the most common forms of interstitial lung disease and it is associated with significant morbidity and mortality (average survival of approximately three years from diagnosis) [2-5].

The epidemiology and the natural history of IPF are still not completely understood.

The incidence and prevalence of IPF are difficult to establish because it is only recently that uniform diagnostic criteria have been established [1]. The recently obtained data from subjects aged 50 years and over tends to indicate an incidence rate adjusted depending on age and sex between 8.8 cases per 100,000 person-years and 17.4 cases per 100,000 person-years in the USA. In the same population, the prevalence adjusted depending on age and sex was between 27.9 cases per 100,000 people and 63 cases per 100,000 people [6].

The familial form of IPF represents between 0.5 and 2% of all cases of IPF [7].

It appears that several environmental or occupational exposures are often part of the medical history of patients diagnosed with this disease (e.g., smoking) [8].

The onset of IPF symptoms is slow but the symptoms gradually get worse over time. The main symptoms are breathlessness during exertion and a chronic dry cough. Gastro-oesophageal acid reflux is present in close to 90% of the patients suffering from IPF but it is often asymptomatic [9].

Pulmonary auscultation during physical examination reveals Velcro-type crackling at the start of inspiration, mainly in the inferior and posterior section of the lungs. Clubbing of the digits is observed in approximately 50% of patients with IPF [10].

Establishing an exact diagnosis in patients presenting with interstitial lung disease is an essential component of treatment [1]. According to the guidelines of the American Thoracic Society, the European Respiratory Society, the Japanese Respiratory Society and the Latin American Thoracic Association (ATS/ERS/JRS/ALAT), diagnosis of IPF can only be considered as definitive with High Resolution Computed Tomography (HRCT) images and a surgical pulmonary biopsy if the clinical and HRCT examinations do not provide a definitive diagnosis of IPF [2].

The patient's medical records will be reviewed during a MDD) including specialists in pulmonology, radiology and pathological anatomy to establish a definitive diagnosis and establish treatment recommendations for patients with IPF.

Idiopathic pulmonary fibrosis presents significant associations with other conditions: cardiopulmonary, including coronary artery disease, pulmonary embolism, sleep apnoea, respiratory tract infections and lung cancer [11-15]. In addition, patients with IPF present with a risk of acute exacerbation of a defined clinical syndrome such as recurrent worsening (<1 month) of dyspnoea, recurrent observations of ground glass images on the HRCT and diffuse alveolar images on the histopathology examinations [16,17]. These acute exacerbations are responsible for 50% of the deaths of patients with IPF and can affect patients whose status was stable beforehand.

Because the clinical progression of IPF is very variable, treatment strategies must be individualised based on medical history and specific co morbidities of each patient.

Pharmacological treatments have consisted of the use of corticosteroids (e.g., prednisone) combined with an immunosuppressant (e.g, azathioprine or cyclophosphamide), in accordance with the recommendations of the ATS/ERS consensus for carefully selected patients with IPF [1]. Other pharmacological treatments have been evaluated without success: interferon gamma [18, 19], bosentan [20], high dose N-acetylcysteine associated with prednisone and azathioprine [21], etanercept [22] and more recently the triple therapy: prednisone, azathioprine, N-acetylcysteine [23] and warfarin [24].

Other suggested treatments have been oxygen therapy, respiratory physiotherapy and lung transplantation. Lung transplantation is the only treatment associated with demonstrated survival in IPF [25].

Pirfenidone, a new anti-fibrotic and anti-inflammatory agent, is the first medication having been recently authorised and indicated for treatment of adult patients with mild to moderate idiopathic pulmonary fibrosis in the European Union [26].

In two trials (PIPF-004 and PIPF-006), patients aged 40 to 80 with IPF (predicted FVC > 50% and predicted DL_{CO} > 35%) received pirfenidone or a placebo for a minimum of 72 weeks in 110 centres located in Australia, Europe and North America. A significant reduction of the FVC decline at all measurement points between week 24 and week 72 (PIPF-004 study) was observed whilst the difference was not significant at week 72 (PIPF-006). In addition, significant reduction of the distance decline during the 6MWT and reduced risk of disease progression were revealed [27].

In a new phase 3 study, ASCEND Study (PIPF-016) conducted at the FDA's request for approval in the USA, 555 patients with idiopathic pulmonary fibrosis were randomly assigned to receive either oral pirfenidone (2403 mg per day) or placebo for 52 weeks.

In the pirfenidone group, there was a relative reduction of 47.9% in the proportion of patients who had an absolute decline of 10 percentage points or more in the percentage of the predicted FVC or who died ($p<0.001$); there was also a relative increase of 132.5% in the proportion of patients with no decline in FVC ($p<0.001$). Pirfenidone reduced the decline in the 6MWT test ($p = 0.04$) and improved progression-free survival ($p<0.001$). There was no significant between-group difference in dyspnea scores ($p = 0.16$) or in rates of death from any cause ($p = 0.10$) or from idiopathic pulmonary fibrosis ($p = 0.23$). However, in a prespecified pooled analysis incorporating results from two previous phase 3 trials, the between-group difference favoring pirfenidone was significant for death from any cause ($p = 0.01$) and from IPF ($p = 0.006$) [28].

At request of the EMA, InterMune (acquired by Roche) initiated a European post-marketing safety study, PIPF-025 or PASSPORT, to evaluate the safety profile of long-term use of Esbriet in patients with IPF and to monitor the potential or unknown risks over two years of treatment with Esbriet.

Given the necessity for improved understanding of the clinical outcomes in real life for patients with IPF treated with Esbriet, Roche now plans to implement the FAS, an observational and ancillary study

to the PASSPORT study at the request of the French authorities (Haute Autorité de Santé and Direction Générale de la Santé).

Data collected in the FAS study will complement those obtained in the PASSPORT study and both studies will be conducted in parallel involving the same sites, patients and Principal Investigators (PI) as PASSPORT.

3. OBJECTIVES AND ENDPOINTS FOR THE STUDY

3.1 Primary objective

Describe the clinical progression over two years of patients suffering from IPF treated with Esbriet in the conditions of use.

3.2 Secondary objectives

1. Describe the modalities used to determine IPF diagnosis
2. Describe the changes in physiology and IPF complications, in particular, exacerbations and pulmonary arterial hypertension
3. Summarize progression-free survival data

3.3 Primary endpoints

Over total treatment time (up to 2 years):

- Change in % predicted FVC
- Change in distance travelled during the 6MWT

3.4 Secondary endpoints

1. Modalities used to determine IPF

   Conclusion from Multidisciplinary Diagnosis Discussion on IPF diagnosis (certain, probable, possible or unclassifiable idiopathic diffuse interstitial lung disease)

2. Cases of IPF comorbidities, in particular acute exacerbation and pulmonary arterial hypertension

   GAP score

   Dyspnoea stage according to NYHA classification
   Number and duration of all-cause and respiratory-related hospitalisations

3. Progression-free survival, defined as time from initiation of Esbriet treatment to the first occurrence of the following events:
   - An absolute decline in % predicted FVC ≥ 10% over the duration of the follow-up
   - An absolute decline in 6MWT distance≥ 50 meters over the duration of the follow-up
   - Death from any cause

4. METHODOLOGY

4.1 Study plan

The PASSPORT study is an observational, multicentre, prospective safety study of patients with IPF who are treated with Esbriet and monitored for up to two years of treatment. The study is a post-authorization safety study (PASS) being conducted at the request of the EMA in 10 EU countries, including France.

The FAS is an auxiliary to the PASSPORT study to collect efficacy data requested by the Haute Autorité de Santé and the Direction Générale de la Santé. The FAS is also a non-interventional study and will be conducted only in the French centres already participating in the PASSPORT study.

The PASSPORT study has been ongoing in France since January of 2013. Enrolment is complete with 214 patients enrolled in 22 French sites. These patients will be approached by the PI at each PASSPORT site and asked if they would consent to have Esbriet efficacy data collected in addition to their safety data.

After meeting inclusion criteria and signing an ICF, efficacy data from ongoing or active PASSPORT patients will be collected retrospectively and prospectively as they complete up to 2 years of treatment with Esbriet. Patients who have discontinued PASSPORT will be contacted for permission to include the efficacy data already collected as part of their routine clinical visits in the FAS (see Table 1 - Schedule of Supplemental Assessments Collected in FAS). Data from patients who have died or been lost-to-follow up may be included (See Section 9.3 for details).

The FAS is an observational study; participation will not change the relationship between the patient and the pulmonologist/PI and will not influence prescription of medications or the patient's therapeutic treatments.

Table 1 Schedule of Supplemental Assessments Collected in FAS

Evaluation	Visit 1 (Baseline)	Follow-up visits 2 to 9 (every 3 months ±4 weeks)	End of study
Ancillary Informed Consent	x		
Inclusion criteria	x		
MDD status and diagnosis	x		
Pulmonary function test (FVC, FEV1)		x	
Clinical characteristics (DL_{CO}, NYHA dyspnoea stage)	x	x	
6MWT	x	x	
Calculated Creatinine Clearance	x	x	
IPF and IPF-related comorbidities (acute exacerbation, CPFE, pulmonary arterial hypertension, sleep apnoea syndrome, lung cancer)	x	x	
Concomitant pulmonary rehabilitation	x	x	
Hospitalisations		x	
Patient's status (completed or early discontinuation)			x

4.2 Selection criteria

Inclusion criteria:

The following patients will be included in the study

- Patients included in the PASSPORT study in French sites
- Patients consenting to participate in the FAS and having completed and signed an ICF. See Section 9.3 for exceptions
- Patients who have had at least one dose of Esbriet during PASSPORT study

The observational nature of the study leaves any decision relating to the patient's treatment with Esbriet completely to the treating pulmonologist's discretion.

4.3 Physician selection

4.3.1 Type of physicians

The study will be conducted by hospital pulmonologists, known to treat and monitor patients with IPF (reference centres and competence centres for rare pulmonary diseases, University-Hospital centres) and already participating in the PASSPORT study.

4.3.2 Sampling

The FAS will be conducted in the centres participating in the PASSPORT study in France.

4.4 Sample size

All patients meeting the eligibility criteria and consenting to participate will be included in the analyses. Up to 214 patients will be eligible for enrolment at up to 22 participating centres.

The study is descriptive in nature. No formal hypothesis testing will be performed. For the primary endpoints and the change from baseline continuous secondary endpoints, the 95% confidence interval will be calculated using the following formula: Mean change from baseline ± *e*,

where *e* = the estimation of precision,

$$e = t_{0\,025} \times s.d./\sqrt{n}$$

s.d. = the standard deviation, and n = the sample size.

The following table presents the precision expected for the primary endpoints using the standard deviations observed in the ASCEND study (PIPF-016) for potential FAS sample sizes of 180 and 214 patients and a 95% confidence interval.

Table 2 Absolute precision associated with the different standard deviations for sample sizes of 180 and 214 patients and a 95% confidence interval

Variable	Standard Deviation	Precision (*e*)	
		N = 180	N = 214
Change in Percent Predicted FVC	12.11	1.78	1.63
Change in Distance Walked in 6MWT	95.73	14.08	12.90

4.5 Collected data

All data will be collected using an electronic case report form (eCRF) to supplement that already being collected in PASSPORT.

Visit 1: Baseline

- Patient Identification number (same as used in PASSPORT)
- Date of Ancillary Informed Consent
- Inclusion criteria
- Date of the MDD and conclusion regarding IPF: certain, probable, possible or unclassifiable idiopathic Diffuse Interstitial Lung Disease
- Clinical characteristics during diagnosis: the most recent DL_{CO} result and NYHA dyspnoea stage (baseline FVC and FEV1 data have been collected in PASSPORT)
- Other examinations at diagnosis: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance
- Concomitant pulmonary rehabilitation
- IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer)

Follow-up Visit (every 3 months +/- 4 weeks) for up to two years and early discontinuation visit:

- Clinical characteristics: most recent FVC result, FEV1 result, DL_{CO} and NYHA dyspnoea stage
- Other examinations: Distance travelled during the 6MWT and O_2 saturation, calculated creatinine clearance
- Concomitant pulmonary rehabilitation
- IPF and IPF-related comorbidities (e.g., exacerbation, emphysema, pulmonary hypertension, sleep apnoea, lung cancer)
- Collection of information about hospitalisation and DRG

End of Study:

- Patient status (completed or early discontinuation)

4.6 Processes for data management

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.

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

A database will be programmed to receive the information collected in the eCRF. The data entry screens and the edit checks will be validated using test data before the start of the study. A data processing manual including the specifications for edit checks, data entry guide, authorised corrections and locking procedure will be written as an operational guide. Data will be checked with automated edits and by manual inspection of the eCRF site entries by off-site monitors.

No imputations will be made for missing data. While effort will be made to try to avoid missing data, note that the majority of the study data will actually be collected retrospectively. As a result, data collection is constrained to what data are available.

When discrepancies are identified in the eCRF, the data management group will issue requests for data clarification or correction by posting queries in the eCRF. Resolution of these requests will be documented in the eCRF.

4.7 Statistical analysis

The statistical analysis will be descriptive using SAS software. No formal hypothesis testing will be performed.

An interim statistical analysis may be conducted. The interim FAS data analysis will be scheduled to coincide with that done for the PASSPORT study. This will facilitate the combining of safety data from PASSPORT with efficacy data from the FAS.

After the last patient has completed or terminated, a final validation of the FAS database will be performed and the database will be locked before performing the final statistical analysis.

4.7.1 Analysis populations

The analysis population will include all patients who have met entry criteria and enrolled in the study.

4.7.2 Sample of participating sites

The FAS patient enrolment counts will be summarized by study site.

4.7.3 Description of the FAS population

Patients included in the study will be described according to their demographic characteristics (e.g., age, sex), history of the IPF and their clinical characteristics at study entry.

4.7.4 Analytical methods

The statistical analyses will be descriptive.

The baseline value is defined as last observation on or before the Esbriet dosing start date collected in Study PIPF-025. With patients able to be on Esbriet for up to 4 weeks prior to the inclusion visit, “pre-Esbriet” values will also be summarized for lung function tests (LFT) and pulmonary function tests (PFT) variables.

For the analyses by visit, the visits will be assigned based on target visit dates and visit windows, and the values collected closest to the target day used in the analysis.

Continuous variables, including changes from baseline for continuous variables, will be summarized with means, standard deviations, medians, minimums and maximums, and amount of missing data.

Categorical variables, including changes from baseline categories, will be summarized with counts and percentage of patients, and the amount of missing data.

Kaplan-Meier estimates will be used to summarize the data for time-to-event variables.

The primary and secondary endpoints will be estimated by the mean with 95% confidence interval for continuous variables (mean ± $t_{0.025}$ * sd / sqrt(n)) and the frequency (percentage) with 95% confidence interval for categorical variables (percentage (p) ± 1.96 * sd / sqrt($p*(1-p)/n$)).

In addition, the magnitude of treatment benefit of Esbriet will be presented as the distribution (number and percentage) of patients across the following categories of the change from baseline over time

Change in % predicted FVC:

- Decline of ≥ 10% or death
- Decline of < 10% to 0%
- No decline (change > 0%)

Change in 6MWT distance:

- Decline of ≥ 50 meters or death
- Decline of < 50 m to 0m
- No decline (change > 0m)

Sensitivity analyses may be performed if deemed necessary to support the results of the analysis for the primary and secondary endpoints.

Safety summaries of patient counts and percentages for adverse drug reactions (ADRs), ADRs with onset in the first 30 days, serious ADRs, ADRs leading to study drug discontinuation, and ADRs with outcome of death, by system organ class and preferred term, will be performed based on data collected in PASSPORT.

4.7.5 Missing data and lost to follow-up

No data imputations or extrapolations will be done to replace missing values. The amount of missing data will be described for each variable.

5. STUDY CONDUCT

5.1 Initiation of the site

Once all required regulatory authorisations have been obtained and the essential documents have been collected (i.e., confidentiality agreement, trial agreement, curriculum vitae), an Investigator Site File (ISF) will be sent to each pulmonologist previously identified for participation in PASSPORT, in preparation of the site initiation call for the FAS.

The ISF contains the following elements:

- Study protocol
- Protocol summary
- Patient information note and consent form
- Working versions of the eCRF for inclusion and follow-up
- Instructions for the eCRF

Upon receipt of the ISF, an initiation telephone call will be arranged by a Clinical Research Associate (CRA) to review the study and answer questions about the protocol, the eCRF, data collection and other logistics. The CRA will document the agenda and items discussed for each initiation telephone call in a written report.

5.2 Inclusion of patients

During the enrolment phase, and for each patient, the investigator:

- Will check eligibility of each PASSPORT patient into this study
- Will explain the study (in particular the study objectives in addition to the PASSPORT study)
- Give an information note to the patient and a consent form and ask the patient to read and sign it to confirm they consent to participate in the study. Further details can be found in this protocol under section 9.3
- Complete the initial eCRF for the study

Before implementation of any procedure associated with the study, the ICF must be signed and dated by the patient.

5.3 Follow-up visits

Data will be collected during the patient's routine treatment visits. During follow-up visits, the PI or site research staff will complete the study follow-up eCRF.

5.4 Early discontinuation visit

Patients may withdraw consent and discontinue their FAS participation at any time, without prejudice. Physicians will complete the early discontinuation form.

5.5 Site monitoring

Monitoring will be remote with any on-site visits coordinated with those done for PASSPORT. The CRA will contact the participating study coordinator by telephone during the study to monitor enrolment, update study documents and resolve site problems and questions.

6. BIAS AND STUDY LIMITS

6.1 Representativeness of the centres

The rare pulmonary disease reference centres, all the competence centres as well as a large majority of the [redacted] in France are already PASSPORT sites and will be asked to participate in the FAS as well.

6.2 Patients lost to follow-up

The follow-up duration will be up to 2 years. Consequently, it is expected that a good proportion of patients will discontinue before study completion due to IPF progression or death. The characteristics of patients who discontinue early will be described in the statistical analysis.

7. SAFETY MANAGEMENT

All safety information will be collected within the PASSPORT study.

8. STUDY CALENDAR

The study will start when the protocol has been approved by HAS and regulatory authorisations have been obtained.

For patients included in the PASSPORT study before the start of this study, the data will be collected retrospectively from the patients' medical records.

9. ETHICAL CONSIDERATIONS

9.1 Compliance with ethical standards

The study must be conducted in accordance with the protocol, the Good Epidemiological Practice guidelines, ethical principles described in the Declaration of Helsinki revised in 2013 and with compliance to all local applicable regulations.

The participating physicians are assured by the study sponsor that this study will be conducted in accordance with the above regulatory terms and principles and that the laws and current practices will be used.

The data collected during the study will come from medical notes and information provided by the patients.

The study will have no impact on the treatment management of the patients and no invasive procedure or special monitoring measures will be required by the protocol.

9.2 Regulatory submission process

9.2.1 National Board of the French Medical Association (Conseil National de l'Ordre des Médecins/CNOM)

Under article L4113-6 of the French Public Health Code, Roche must submit the financial agreement established between Roche and each pulmonologist to the *Conseil national de l'ordre des médecins* with the current protocol for approval.

9.2.2 French Committee of Scientific Research/Data Protection Agency (Comité français de la recherche scientifique (CCTIRS) / Agence de protection des données (CNIL))

Due to the fact that personal data collected in this study is processed in France before being sent to the sponsor, this study is governed by chapter IX of the Data Protection Act dated 6 January 1978 (amended version). An authorisation request must be submitted to the French Advisory Committee on Data Processing in Research in the Field of Health (CCTIRS) and the French Data Protection Authority (CNIL).

The use of indirectly personal data is essential for the following reasons:

- This is patient follow-up with collection of longitudinal information
- It is essential to combine the data from the FAS and PASSPORT study for statistical analysis. These documents will therefore be identified with two numbers: the centre number and the patient number

Patients will be informed of their right to access, object to, and correct any data recorded during this study and that this right can be exercised at any time through their pulmonologist.

9.3 Patient information and consent form

A patient information sheet (PIS) and ICF will be prepared for the ancillary study. These forms will contain information about the nature and subject of the study, the data collected, the individuals or legal entities receiving this data and the right to access the data, correction and opposition to their transfer which can be exercised by the patients (in accordance with the Data Protection Act dated 6 January 1978, amended version).

The ICF must be signed and dated by the patient and the investigator in duplicate. One signed ICF will be kept by the patient and one will be kept by the site in the Investigator Site File. The local regulation requires that documentation of informed consent is recorded in the source document for each patient.

The following process shall be followed by the investigative sites:

1. PASSPORT study active patients
   The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient will be asked to provide a signed ICF if he/she agrees to participate.

2. Deceased patients (i.e., patients who have died during the course of the PASSPORT study or after terminating or completing the study)
   The site shall keep a precise record of the patient's death in the patient's medical charts with as much information as possible regarding how this information was obtained. Date from deceased patients will be collected as permitted by the local regulations and no updated signed ICF is needed (Section 5.2).

3. Discontinued patients from PASSPORT but still treated at the investigational site
   The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient will be asked to provide a signed informed consent if he/she agrees to participate.

4. Patient has discontinued from Passport and is no longer seen at the investigational site.
   The site should contact the patient by phone, email, letter or fax as preferred by the investigational site.

   a. The patient can be contacted
      The investigator should inform the patient about the ancillary study and the PIS should be given to the patient. The patient is required to sign the ICF if he/she agrees to participate.

   b. The patient can be contacted but is not able to come to the site (e.g., the health condition does not permit the patient to travel to the site)
      The investigator should inform the patient about the ancillary study on the phone and the PIS and ICF (twofold) are sent to the patient by post. The patient should be requested to sign both copies of the ICF and should return both by post. The investigator should then sign both copies and return one fully signed ICF to the patient.

      The process must be described clearly in the patient's medical records: date when the patient was informed by phone, date shipment PIS and ICF by post, date of patient's ICF signature, date of investigator's signature and date of fully signed ICF sent to the patient. The site shall call the patient a few days after the fully signed ICF was sent, in order to document the acknowledgment of receipt from the patient.

   c. The patient is not reached after at least 3 attempts, neither a family member was reached who could inform the site about the status of the patient

      i. The site shall contact the local health care professional (HCP) to obtain information about the patient (e.g., if patient is hospitalized, if patient has died, if patient has moved). If the site receives new contact details for the patient, the site will contact the patient (and follow 4a and 4b).

      ii. The site shall contact the local HCP to obtain information about the patient (e.g., if patient is hospitalized, if patient has died, if patient has moved). If no additional information can be obtained, the site will contact the town hall of the patient's last residence. If the patient has died, the town hall will have this information available.

         1. Patient has died. The patient can be included without an ICF signed (same as section 2).

2. No information available. The patient is declared “lost to follow-up”. The patient can be included without an ICF signed.

Every contact that is made by the site to ascertain the patient’s current status shall be noted in the patient’s medical records.

9.4 Final report and publications

At the end of the study, a final study report will be written which will be reviewed the Scientific Committee. This report will contain a description of the study objectives, the methodology, results and study conclusions.

The data will be declared in aggregated form to guarantee the confidentiality of patients and pulmonologists.

The final report will be submitted to the French Regulatory Agencies who requested the FAS within six months after the study close-out.

The completed eCRF and study reports must be processed as confidential property of Roche and they cannot be communicated to unauthorised people in any form (publications or presentations) without express written authorisation from Roche.

10. STORAGE OF STUDY DOCUMENTATION

Roche will keep the collected data (eCRFs and databases) for at least 5 years (or a longer period if it is specified and authorised) after the end of the study.

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