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CLINICAL STUDY REPORT NO: 1078250

STUDY INFORMATION

TITLE:	**A 2-YEAR OBSERVATIONAL STUDY TO DESCRIBE THE CHARACTERISTICS AND PROGRESSION OF PATIENTS SUFFERING FROM IDIOPATHIC PULMONARY FIBROSIS TREATED WITH ESBRIET® (PIRFENIDONE) IN THE CONDITIONS OF USE.** **ANCILLARY STUDY TO WB29908 (PIPF-025/PASSPORT): POST-AUTHORISATION SAFETY STUDY OF ESBRIET®: A PROSPECTIVE OBSERVATIONAL REGISTRY TO EVALUATE LONG-TERM SAFETY IN A REAL-WORLD SETTING**
PROTOCOL NUMBER:	WA29961 (Roche protocol number), formerly known as PIPF-028 (Intermune protocol number)
VERSION NUMBER:	1
RDR NUMBER:	1078250
STUDIED MEDICINAL PRODUCT:	Esbriet® (Pirfenidone)
COUNTRY OF STUDY POPULATION:	France
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1. SYNOPSIS/ABSTRACT

Title

Final Clinical Study Report - WA29961 (formerly known as PIPF-028) – A 2-Year Observational Study to Describe the Characteristics and Progression of Patients Suffering from Idiopathic Pulmonary Fibrosis treated with Esbriet® (Pirfenidone) in the Conditions of Use.

Ancillary Study to WB29908 (PIPF-025/PASSPORT): Post-Authorisation Safety Study of Esbriet®: A Prospective Observational Registry to Evaluate Long-Term Safety in a Real World Setting. June 2017.

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Keywords

Observational, non-interventional, registry, ancillary study

Research Question and Objectives

The primary objective of this French Ancillary Study (FAS) was to describe the clinical progression over 2 years of patients suffering from idiopathic pulmonary fibrosis (IPF) treated with Esbriet® in the conditions of use.

The secondary objectives were to:

- describe the modalities used to determine IPF diagnosis;
- describe the changes in physiology and IPF complications, in particular, exacerbations and pulmonary arterial hypertension;
- summarize progression-free survival (PFS) data.

Study design

The PASSPORT study (Roche protocol number WB29908; formerly known as PIPF-025 [Intermune protocol number]) was an observational, multicentre, prospective post-authorization safety study of patients with IPF who were treated with Esbriet and monitored for up to 2 years of treatment. The study was conducted at the request of the European Medicines Agency in 10 European Union (EU) countries, including France.

The FAS study (Roche protocol number WA29961; formerly known as PIPF-028 [Intermune protocol number]) was an ancillary to the PASSPORT study to collect real-world effectiveness data in IPF patients treated with Esbriet. The FAS was a non-interventional observational study conducted at the French centers already participating in the PASSPORT study; it did not change the patient/health professional relationship or the patient's treatment. The study was mandated by the French authorities [redacted].

The study involved primary data collection. All patients enrolled at the French PASSPORT sites were asked if they would consent to having effectiveness data collected in addition to their safety data. Effectiveness data from ongoing or active PASSPORT patients were collected retrospectively and, to a lesser extent, prospectively as they completed up to 2 years of treatment with Esbriet. Patients who discontinued PASSPORT were contacted for permission to include the effectiveness data already collected as part of their routine clinical visits. Data from

patients who had died or been lost-to-follow were collected as permitted by local regulations without the need for additional signed informed consent.

Target Population

The target population for the FAS was IPF patients in France who participated in the PASSPORT study, had taken at least one dose of Esbriet during the PASSPORT study and who, unless deceased or lost-to-follow up, provided additional written informed consent to participate in the FAS.

Study size

A total of 192 IPF patients were enrolled across 21 sites in France.

Studied medicinal product

Esbriet® (Pirfenidone)

Endpoints

- **Effectiveness endpoints:**
  - **Primary**
    - Change in percent predicted forced vital capacity (FVC) over total treatment time (up to 2 years)
    - Change in the distance travelled during the 6 minute walk test (6MWT) over total treatment time (up to 2 years)
  - **Secondary**
    - Gender Age Physiology (GAP) score
    - Dyspnoea stage according to New York Heart Association (NYHA) classification
    - Cases of IPF comorbidities, in particular acute exacerbation and pulmonary arterial hypertension
    - Number and duration of IPF-related hospitalizations
    - Progression-free survival (PFS)
  - **Exploratory**
    - Change in FVC, forced expiratory volume in one second (FEV1), and the diffusing capacity for carbon monoxide (DLco) over total treatment time (up to 2 years)
    - Overall survival
- **Additional secondary endpoints:**
  - Modalities used to determine IPF
  - IPF diagnosis according to Multidisciplinary Diagnosis Discussion (MDD)
- **Safety endpoint:** adverse drug reactions (ADRs)

Data Sources

All data were collected by review of patient medical files and using an electronic case report form (eCRF) to supplement that already being collected in PASSPORT. For ongoing or active PASSPORT patients, effectiveness data were collected retrospectively and prospectively as they completed up to 2 years of treatment with Esbriet. For patients who had discontinued PASSPORT or who had died or been lost-to-follow-up, existing effectiveness data were collected retrospectively. ADR data were collected within the PASSPORT study.

Statistical and Epidemiological Methods

All statistical analyses are descriptive. No formal hypothesis testing was performed.

All analyses were performed on the FAS enrolled population, which includes all patients who met the entry criteria and enrolled in the FAS study.

No data imputations or extrapolations were made to replace missing values. The amount of missing data is described for each variable.

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

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

Kaplan-Meier (KM) estimates were used to summarize the data for time-to-event variables.

For effectiveness analyses, the baseline date was the enrolment date recorded in PASSPORT. For safety analyses, ADRs were defined as events with onset on or after the first study dose of Esbriet through 28 days after last study dose of Esbriet.

Results

Patient Population and Demographics

Of the 192 patients enrolled in the FAS, 63 (32.8%) patients completed the PASSPORT study and 129 (67.2%) patients discontinued the PASSPORT study early. The most common primary reason for discontinuing the PASSPORT study early was experiencing an ADR related to Esbriet treatment.

The majority of patients were male (162/192 patients [84.4%]), the median age was 71.0 years, and the median duration of IPF since diagnosis was 0.58 years (range 0.01 to 12.23 years).

Effectiveness Results

The number of patients with non-missing assessments declined over the 2 years of treatment for all effectiveness endpoints due to the loss of patients from discontinuations and deaths. Post-baseline summaries should therefore be interpreted with caution, especially beyond Month 12.

Results of the primary effectiveness endpoint analyses are summarized in Table 1. The mean absolute change from baseline indicated that the percent predicted FVC remained relatively stable through Month 6 of Esbriet treatment and then declined. For the 6MWT, the mean change in distance walked remained positive at all time points through Month 12.

Table 1 Primary Effectiveness Endpoints: Mean (SD) Change in Percent Predicted FVC and Distance Walked in the 6MWT at Months 6, 12, 18, and 24 (Enrolled Population)

		Change from Baseline			
	Baseline	Month 6	Month 12	Month 18	Month 24
% predicted FVC	n=181	n=100	n=79	n=54	n=36
	71.72 (16.341)	0.71 (8.920)	-2.35 (12.444)	-3.17 (10.122)	-3.84 (11.219)
Distance walked in 6MWT (m)	n=99	n=31	n=30	n=10	n=13
	412.9 (130.54)	23.4 (94.77)	8.6 (103.52)	-2.2 (73.03)	3.1 (80.44)

FVC=forced vital capacity; 6MWT=6 minute walk test.

The results of the secondary effectiveness endpoint analyses were as follows:

- Of 96 patients with a NYHA dyspnoea stage assessment ≤III at baseline and with at least one post-baseline assessment, the highest stage post-baseline was the same or lower than at baseline for 56 (58.3%) patients and higher than at baseline for 40 (41.7%) patients.
- Of 64 patients with GAP Stage I or II at baseline and at least one post-baseline assessment, the highest stage post-baseline was the same or lower than at baseline for 46 (71.9%) patients and higher than at baseline for 18 (28.1%) patients.

- New or worsening acute IPF exacerbation, pulmonary arterial hypertension, lung cancer, and sleep apnoea were experienced by 38/190 (20.0%), 16/190 (8.4%), 9/190 (4.7%), and 1/190 (0.5%) patients, respectively. There were no reports of new or worsening emphysema.
- A total of 58 IPF-related hospitalizations in 41/192 (21.4%) patients were reported during the study. Most of the IPF-related hospitalizations were respiratory-related (50/58 hospitalizations in 36/41 patients). The majority of patients were hospitalized only once (29/41 patients).
- The KM estimated probability of surviving without progression through Months 6, 12 and 24 was 85%, 67%, and 46%, respectively. The 25th percentile for time to progression was 9.3 [95% CI: 6.9, 11.9] months and the median was 18.4 [95% CI: 12.9, not estimable] months.

The results of the exploratory effectiveness endpoint analyses were as follows:

- The KM estimated probability of surviving through Months 6, 12 and 24 was 98%, 92%, 83%, respectively. The 10th percentile for time to death was 15.4 months.
- Results for the change from baseline in FVC, FEV1, and DLco are shown in Table 2.

Table 2 Exploratory Effectiveness Endpoints: Mean (SD) Change in FVC, FEV1, and DLco at Months 6, 12, 18, and 24 (Enrolled Population)

		Change from Baseline			
	Baseline	Month 6	Month 12	Month 18	Month 24
Exploratory Endpoints					
FVC (mL)	n=182	n=100	n=79	n=54	n=36
	2677.3 (791.80)	20.9 (358.01)	-90.9 (523.00)	-121.1 (372.95)	-142.2 (462.65)
FEV1 (mL)	n=182	n=101	n=79	n=53	n=35
	2191.8 (623.95)	-45.5 (320.72)	-142.5 (380.47)	-137.4 (246.59)	-94.0 (364.53)
DLco (mmoL/min/kPa)	n=137	n=68	n=54	n=35	n=23
	3.69 (1.272)	-0.05 (1.088)	-0.28 (1.173)	-0.52 (0.891)	-0.36 (0.800)

FVC=forced vital capacity; FEV1= forced expiratory volume in one second; DLco= diffusing capacity for carbon monoxide.

Additional Secondary Endpoint Results

- The most common method of IPF diagnosis was high resolution computed tomography (146/192 patients [76.0%]).
- Of 156 patients who underwent a MDD, 114 (73.1%) were diagnosed with certain IPF, 28 (17.9%) were diagnosed with probable IPF, 11 (7.1%) were diagnosed with possible IPF, and 3 (1.9%) were diagnosed with unclassified diffuse interstitial lung disease.

Safety Results

- ADRs were reported following Esbriet treatment by 155/192 (80.7%) patients. A total of 482 events were reported overall; 461 non-serious ADRs in 154 (80.2%) patients and 21 serious ADRs in 13 (6.8%) patients. The most frequently reported ADR by preferred term was weight decreased (57 patients [29.7%]). A total of 178 ADRs in 81/192 (42.2%) patients had an onset in the first 30 days of Esbriet treatment
- ADRs led to discontinuation of Esbriet treatment in 61/192 (31.8%) patients. No patient experienced an ADR with a fatal outcome.

Conclusions

The key conclusions from this 2-year observational study in France of the clinical characteristics and progression of IPF patients treated with Esbriet® in a real world setting are as follows:

- Although there are limitations to the study due to missing data and the absence of a comparable control group, the effectiveness data obtained from the FAS are overall consistent with the published efficacy profile of Esbriet from Phase III clinical trials in IPF.
- The safety experience of patients in the FAS was consistent with the known safety profile of Esbriet. No new safety signals were observed.