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1. ABSTRACT

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Title of study:	<i>IPF Italian Observational Study (FIBRONET)</i>		
Keywords:	Idiopathic Pulmonary Fibrosis, clinical course, exacerbations, HRQoL, health care sector-related costs.		
Rationale and background:	Idiopathic Pulmonary Fibrosis (IPF) is a rare disease of unknown etiology that is characterized by progressive fibrosis of the interstitium of the lung, leading to decreasing lung volume and progressive pulmonary insufficiency [1][2], presenting more frequently in men than in women and is usually diagnosed in people over 50 years of age, particularly those with a history of cigarette smoking [2]. Idiopathic Pulmonary Fibrosis is usually associated with a poor prognosis: the clinical course of IPF can be unpredictable [3][4]. IPF progression is associated with an estimated median survival time of 2 to 5 years following diagnosis [1][2]. The 5-year survival for IPF ranges between 20% and 40% [4]. Recognizing IPF in clinical practice can be challenging as symptoms often appear similar to those of more common diseases. This contributes to delay the diagnosis which is usually made 6 to 24 months after initial symptoms [5][6]. An earlier diagnosis of IPF is a prerequisite for earlier treatment and, potentially, improvement of the long-term clinical outcome [1]. In 2011simplified and updated criteria for the diagnosis and management of IPF were published by the ATS, ERS, together with the Japanese Respiratory Society (JRS) and Latin American Thoracic Association (ALAT) [2]. It is possible to make the diagnosis of IPF by HRCT alone, obviating the need for surgical lung biopsy [1][2]. Except lung transplantation, that in a small portion of patients provides a chance of long-term survival, there is currently no therapy that reverses or cures the lung damage. Pirfenidone was the first product to receive EU and USA approval, as a treatment for mild to moderate IPF because in these cases it significantly reduces the decline of lung function. Nintedanib, a tyrosine kinase inhibitor was approved in EU and in USA for the treatment of patients with IPF. Nintedanib has shown to have a clinical benefit on slowing of deterioration in lung capacity with evidence of reduction of the rate of decline in lung function as indicated by absolute volume FVC.		
Research question and objectives:	Long-term data on the natural course of IPF in Italy are scarce. Further, there is limited information on IPF in terms of patient characteristics and disease management. The purpose of the present study was to evaluate the characteristics, management and clinical course of patients with IPF as treated under real-world in Italian Pulmonary Centres, in terms of symptoms, lung function and exercise tolerance during 12 months of observation. In particular, the study aimed to provide information on disease characteristics and treatment modalities (at enrollment) and on disease progression, HRQoL		

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and health care sector-related costs according to the Italian National Health Service (INHS) point of view (during 12 months of observation). OBJECTIVES Primary objective 1. In a sample of Italian IPF diagnosed patients to describe the clinical course during 12 months of observation, in terms of: • symptoms • lung function (VC, FVC, FEV1, TLC, DLCO, pO2, pCO2, SaO2, PaO2 and PaCO2 at rest) • exercise tolerance (6-minute walk distance test). Secondary objectives 1. Description of characteristics of IPF patients at enrollment in terms of: - o key (socio-) demographic data - o IPF risk factors, comorbidities - o IPF disease severity and manifestation (including lung function, cardiopulmonary exercise testing and/or exercise capacity if available, laboratory values) - o Methods used for IPF diagnosis - o IPF treatment modalities 2. To describe the frequency of exacerbations during 12 months of observation. 3. To describe HRQoL variation, measured with SGRQ, EuroQol (EQ) 5-dimension 5-level (EQ-5D-5L) descriptive system and EQ VAS, during 12 months of observation. 4. To describe health care sector-related costs from diagnosis up to the end of 12-month follow-up according to the Italian National Health Service (INHS) point of view.			
Study design:		This was an observational, multicenter prospective cohort study based on newly collected data. The enrolment period lasted 18 months. During this period, about 200 consecutive patients were included in agreement with the inclusion/exclusion criteria. Patients were followed up for 1 year, with 3 intermediate evaluations after 3 (+/-1), 6 (+/-1) and 9 (+/-1) months from baseline (such visits were referred as being the current clinical practice in Italy for IPF patients management).	
Setting:		Twenty Italian Pulmonary Centers highly experienced in the disease management of IPF were involved.	

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Subjects and study size, including dropouts:	Patients newly diagnosed with IPF less than 3 months before the patient's inclusion visit referring to pulmonary centers were consecutively enrolled according to the following criteria: <i>Inclusion Criteria</i> 1. Patients aged ≥ 40 years 2. Written informed consent to both participation in the study and privacy 3. Physician diagnosed IPF during the last 3 months based upon recent ATS/ERS/JRS/ALAT guidelines 2011 (see Tables A1-A2 for HRCT and histology criteria in FIBRONET CSR ANNEX 1 doc 2): • Exclusion of other known causes of ILD (e.g. domestic and occupational environmental exposures, connective tissue disease and drug toxicity) • Assessment of IPF based on HRCT or HRCT and surgical lung biopsy (for details see Tables A1-A2 in FIBRONET CSR ANNEX 1 doc 2) if available. 4. Patient with further follow-up possible with enrolling investigator during planned study period 5. Patients capable of discernment and able to read or write in Italian language. <i>Exclusion Criteria</i> 1. Inclusion in clinical trials or other IPF/ILD registries 2. Lung transplantation expected within the next 6 months 3. Pregnancy or breast feeding <i>Study-exit Criteria</i> 1. Inclusion in clinical trials 2. Consent withdrawal (from patient or legally accepted representative) 3. The patient was erroneously included in the study 4. Pregnancy or breast feeding 5. Any other reason as agreed to by the investigator and the BITSPA clinical monitor According to the volume of patients managed by the centers involved in this study, inclusion of 200 subjects (10 patients/center) with the characteristics defined at Inclusion/Exclusion criteria paragraphs was deemed reasonable for enrolment period (18 months). Assuming a drop-out rate ranging from of 20% to 40% , the total number of evaluable patients at 12-month follow-up visit was expected to range between 120 and 160 subjects. Drop-out rate was hypothesized by considering mortality rate in IPF patients and natural drop-out from studies.		

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Variables and data sources:	The following data were collected at baseline: eligibility criteria, socio-demographic information, information on IPF such as first symptoms and date of first diagnosis. At baseline, 3, 6, 9 and 12-month follow up the following data were collected: potential IPF risk factors, comorbidities, IPF Symptoms, functional assessment if available (lung function test, blood gas analysis, 6-minute walk distance test), exacerbations, pharmacological and non-pharmacological treatments, health-care resource consumption, survival status and adverse events. The following Diagnostic Tools/Patient Reported Outcomes were administered to patients: • Modified Medical Research Council Dyspnea Scale (mMRC); • Morisky medication Adherence Scale 4 items (MMAS-4); • EuroQol 5-dimension 5-level (EuroQoL-5D 5L); • Hospital Anxiety and Depression Scale (HADS); • Saint George Respiratory Questionnaire (SGRQ). The following procedures were applied at each study visit according to routine clinical practice: • Lung function test (FVC, FVC % predicted, FEV1, FEV1 % predicted, FEV1/FVC, VC, RV, TLC, DLCO, DLCO % predicted, SaO2, pO2, pCO2, PaO2 and PaCO2 at rest); • 6-minute walked distance test.		
Main summary measures:	Descriptive analysis were composed of means, medians, quantiles, proportions and contingency tables according to the nature of the variables. As a dispersion measurement the standard deviation and the interquartile range were calculated. The statistical analysis were done on all “evaluable patients at enrolment” defined as the patients satisfying all inclusion criteria, not violating any exclusion criteria and with available gender and at least one of the following evaluations at enrolment: IPF symptoms, Lung function, 6-minute walked distance test. Moreover, for analysis of follow up data only patients who performed V2 (3-months), V3 (6-months), V4 (9-months), V5 (12-months) follow up visit were considered. At each follow up visit patients who performed V2, V3, V4, V5 were defined as patients satisfying the following criteria: • Patients evaluable at enrollment (as previously defined) • Data collected at x-month follow-up (where x=3-, 6-, 9-, 12-) • Follow-up performed at x ±1.5 months from enrollment (where x=3-, 6-, 9-, 12-) • With available IPF symptoms evaluation at baseline and at x ±1.5 months		

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	from enrollment (where x=3-, 6-, 9-, 12-). Two interim statistical reports were performed (data extraction on March 13, 2017 and August 03, 2017 respectively). All “evaluable patients at enrolment” (as previously defined) entered on eCRF on the date of data extraction were analyzed. If analysis of follow up data were planned, data on the sub-sample of patients who already performed the 3-month follow up visit and recorded data on eCRF on data extraction were considered too.		
Results:	Two hundred and nine patients were enrolled in the FIBRONET study and all were evaluable for the analysis; 36 patients withdrew from the study. At enrollment 173 (82.8%) patients were males, mean (±SD) age of patients was 69.54 (±7.43) years. All patients (100%) were Caucasian/white. <u>Secondary objective #1: Description of characteristics of IPF patients at enrollment</u> At enrollment 171 (81.8%) patients had comorbidities, arterial hypertension (n=103, 49.3%), gastroesophageal reflux disease (n=49, 23.4%), diabetes mellitus (n=45, 21.5%), atherothrombotic disease (n=27, 12.9%) and benign prostatic hypertrophy (n=25, 12.0%) being the more frequently reported. Former and current smokers were 138 (66.0%) and 9 (4.3%) respectively; the median (25th -75th percentile) estimated amount of consumed tobacco by former and current smokers was 30.00 (14.00-40.00) packs/year for a median (25th-75th percentile) of 30.00 (20.00-40.00) years. Furthermore, 70 (34.0%) patients were exposed to environmental factors. The mean (±SD) age of IPF diagnosis was 69.46 (±7.43) years; the mean (±SD) number of years passed from first IPF symptoms was 2.14 (±2.45). IPF diagnosis was based on HRCT for all patients and mainly on the following procedures: spirometry (n=58, 27.8%), bronchoalveolar lavage (n=40, 19.1%), cryobiopsy (n=17, 8.1%), surgical lung biopsy (n=14, 6.7%) and transbronchial biopsy (n=11, 5.3%). Other methods (such as multidisciplinary discussion, test for autoimmunity exclusion, six minutes walking distance test and PET) were chosen for 4.8% of patients. At enrollment 71.4% (140 out of 196 evaluable patients with available FVC % predicted at baseline) were early diagnosed having a FVC of the predicted ≥ 70%; among them, 59 (30.1%) patients had FVC of the predicted ≥ 90%. <u>Primary objective: Clinical course of IPF during 12 months of observation</u> IPF symptom (cough, fatigue, dyspnea, dizziness, chest pain) frequency		

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decreased from baseline to 3-month follow-up and then remained stable. At baseline, 3-, 6-, 9- and 12-month follow up, 88.0% (184 out of 209 evaluable patients), 51.8% (99 out of 191 evaluable patients), 49.4% (85 out of 172 patients), 42.9% (69 out of 161 patients) and 45.4% (79 out of 174) patients had IPF symptoms, respectively. Among IPF symptoms, cough was present in 59.8%, 38.7%, 36.6%, 29.2% and 30.5% patients at baseline, 3-, 6-, 9- and 12-month follow up respectively, fatigue was reported in 54.1%, 35.1%, 33.1%, 26.1% and 32.2% patients and dyspnea (assessed by the clinician) in 18.2%, 6.3%, 2.3%, 3.7% and 4.6% patients at the five study visits respectively. Dizziness and chest pain were present in a minority of patients (<5% at the study visits). The frequency of IPF signs (bibasilar crackles and clubbing) decreased from baseline to 3-month follow-up and then remained stable. At baseline, 3-, 6-, 9- and 12-month follow up, 69.4% (145 out of 209 patients), 44.0% (84 out of 191 patients), 44.8% (77 out of 172 patients), 42.9% (69 out of 161 patients) and 43.7% (76 out of 174 patients) patients had bibasilar crackles, respectively, and clubbing was present in 11.0% (23 out of 209 patients), 7.9% (15 out of 191 patients), 6.4% (11 out of 172 patients), 6.2% (10 out of 161 patients) and 5.7% (10 out of 174 patients) patients, respectively. In the whole sample FVC % of the predicted remained stable over time: the mean (±SD) of the parameter was 80.01 (±19.23) at baseline and 82.17 (±20.93) % at 12-month follow up, respectively. Considering the relative change of FVC % of the predicted occurring at 12-month follow up as compared to the baseline, 70 out of 133 patients (52.6%) were decliners (relative change ≤0%) and 63 out of 133 patients (47.4%) non-decliners (relative change > 0%).Patient-perceived level of dyspnea appeared stable during observation: 42.2%, 41.8% and 37.3% of patients had mMRC dyspnea scale score ≥2 at baseline, 6- and 12-month follow up, respectively. The variation of other spirometry and blood gas analysis lung function parameters during observation was small. The mean (±SD) of FEV1 and DLCO of the predicted at baseline, 3-, 6-, 9- and 12-month follow up was 84.25 (±19.29) %, 85.20 (±18.41) %, 85.89 (±19.81) %, 87.57 (±19.39) %, 86.65 (±19.80) % and 51.68 (±13.52) %, 51.27 (±14.75) %, 49.71 (±13.23) %, 50.27 (±16.58) %, 50.91 (±15.65) % respectively. The mean (±SD) of PO2 and PCO2 at baseline, 3-, 6-, 9- and 12-month follow up was 73.82 (±12.11) mmHg, 73.13 (±12.20) mmHg, 75.53 (±13.62) mmHg, 73.07 (±15.85) mmHg, 72.70 (±14.92) mmHg and 39.25 (±4.06) mmHg, 40.94 (±3.39) mmHg, 41.87 (±5.9) mmHg, 42.50 (±4.46) mmHg, 40.35 (±3.97) mmHg respectively.			

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The mean (±SD) of 6-minute walked distance test at baseline, 3-, 6-, 9- and 12-month follow up was 395.70 (±121.70) meters, 398.20 (±137.60) meters, 417.40 (±110.20) meters, 402.10 (±126.30) meters, 411.70 (±108.90) meters respectively. <u>Secondary objective #2: Frequency of exacerbations during 12 months of observation</u> Exacerbations during observation occurred in 15 patients (total number of exacerbations: 18) and the 1-year probability of exacerbation was 6.5%. <u>Secondary objective #3: HRQoL variation during 12 months of observation</u> According to SGRQ scale the quality of life seemed better on IMPACTS ON DAILY LIFE component score and worse on SYMPTOMS and ACTIVITIES scores. The median (25th-75th percentile) SYMPTOMS scores were 42.26 (27.29-57.98) and 42.21 (24.72-56.08) at baseline and 12-month follow-up, respectively; the median (25th-75th percentile) ACTIVITIES scores were 54.39 (35.80-72.89) and 58.88 (35.47-77.85) at baseline and 12-month follow-up, respectively, and the median (25th-75th percentile) IMPACTS ON DAILY LIFE scores were 28.16 (12.26-47.09) and 27.32 (13.50-46.39) at baseline and 12-month follow-up, respectively. Considering the variation over time the quality of life appeared stable, the median (25th-75th percentile) SGRQ total score being 39.82 (23.40-56.49) at baseline and 39.60 (23.80-56.77) at 12-month follow up. Good quality of life with little variations during follow up was observed according to EuroQol. The mean (±SD) VAS score of EQ-5D-5L was, in fact, 67.01 (±18.29), 68.92 (±16.12) and 67.46 (±17.75) at baseline, 6- and 12-month follow up visits respectively. <u>Secondary objective #4: health care sector-related costs according to the Italian National Health Service point of view during 12 months of observation</u> Thirteen (6.2%) patients had 14 inward hospitalizations since diagnosis. Ten patients (4.8%) had 15 ER accesses. Thirty percent of patients (62 out of 209 patients) had at least one outpatient visits, the most frequent ones being GP (n=48, 23.0%) and lung specialist (n=23, 11.0%) visits; considering patients who had visits (users), the mean (±SD) number of GP and specialist visits per patient was 1.60 (±0.82) and 1.61 (±0.92) respectively. During study, 121 patients (57.9%) underwent laboratory tests examinations (especially liver function tests, blood count tests, HRCT and unscheduled spirometry).			

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<u>Further Endpoint(s)/Outcome(s)</u> <u>Level of anxiety and depression (HADS scale)</u> Low level of anxiety and depression with no relevant changes over time was observed. No anxiety or mild anxiety was present in 125 out of 177 patients (70.6%) and in 22 (12.4%) patients at baseline, respectively and no anxiety or mild anxiety was present in 80 out of 124 patients (64.5%) and in 24 (19.4%) patients at 12-month follow up, respectively. The median (25th-75th percentile) HADS anxiety score was 5.00 (2.00-8.00) at baseline and 5.00 (2.00-9.00) at 12-month follow up. No depression or mild depression was present in 123 (69.5%) and 28 (15.8%) patients at baseline, respectively and in 85 (68.5%) and 16 (12.9%) patients at 12-month follow up respectively. The median (25th-75th percentile) depression score was 5.00 (2.00-8.00) at baseline and 5.00 (2.17-9.00) at 12-month follow up. The HADS total score at baseline was 11.00 (5.00-17.00) and 10.00 (5.50-18.00) at 12-month follow up. <u>IPF pharmacological and not pharmacological therapies and lung transplantation</u> On average (±SD) 6.38 (±7.06) weeks elapsed between IPF diagnosis and start of therapy. At enrolment 15.8% of patients (n=33) were under pharmacological treatment for IPF and the frequency of treated patients increased during observation, being 72.3% (n=138), 80.8% (n=139), 83.9% (n=146) at 3-, 6- and 12-month follow-up respectively. Pirfenidone was administered to 11.5%, 44.5%, 48.3% and 50.0% of patients at baseline, 3-, 6- and 12-month follow-up, while Nintedanib to 4.3%, 27.7%, 32.6% and 33.9% of patients at the same study visits. Non-pharmacological therapy (mainly long-term oxygen therapy) was not frequent, with a proportion of treated patients of 3.3%, 8.4%, 8.1% and 8.6% at baseline, 3-, 6- and 12-month follow-up respectively. No patients were listed for lung transplantation at baseline; at 3-, 6-, 12-month follow up the frequency remained low, being 2.6% (n=5), 1.2% (n=2), 0.6% (n=1) respectively. <u>Patients’ adherence to Anti-IPF medications (MMAS-4)</u> Adherence to therapy was good with no relevant changes over time (mean (±SD) MMAS-4 score at baseline, 6- and 12-month follow up: 3.70 (±0.65), 3.65 (±0.74) and 3.56 (±0.75) respectively). <u>Adverse events/adverse drug reactions</u>			

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Eighty-six patients (41.1%) had at least one AE (total number of AEs: 125), 32 patients (15.3%) had at least one ADR (total number of ADRs: 39) and 16 patients (7.7%) had at least one SAE between diagnosis and end of observation. The total number of SAEs was 17 (11 fatal, causing study discontinuation). Narratives of SAEs observed during the observation period while the patient was in treatment with products marketed by Boheringer Ingelheim for IPF are reported below. For none of the cases, there was any reasonable causal relationship with any of the products marketed by Boehringer Ingelheim. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years had pulmonary thromboembolism of severe intensity, leading to hospitalization. It started 2.3 months after enrollment in the study and lasted 29 days. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 6th April 2017, end date: 10th June 2017); this therapy was not ongoing when the event occurred. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years had respiratory insufficiency of moderate intensity, leading to hospitalization. It started 5.5 months after enrollment in the study and lasted 17 days. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 18th October 2016 till the end of observation); this therapy was ongoing when the event occurred. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years had angina of severe intensity, immediately life threatening. It started 8.4 months after enrollment in the study and lasted 1 day. The same patient had fatal myocardial infarction 15 months after enrollment in the study. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 16th June 2017, end date: 12th October 2017 and start date: 20th October 2017 till the end of observation); this therapy was ongoing when the angina and myocardial infarction occurred. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years died 5.3 months after enrollment in the study. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 24th March 2017 till the end of observation); this therapy was ongoing when the event occurred. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years died 12.7 months after enrollment in the study. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 1st February 2017 till the end of observation); this therapy was ongoing when the event occurred. • A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years died 11.1 months after enrollment in the study. The patient assumed a product marketed by Boheringer Ingelheim during the study (start date: 1st February 2017 till the			

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end of observation); this therapy was ongoing when the event occurred. A [REDACTED] patient (patient ID: [REDACTED]) aged [REDACTED] years had fatal heart failure. It started 11.3 months after enrollment in the study and lasted 1 day. The patient assumed a product marketed by Boehringer Ingelheim during the study (start date: 9th September 2016 till the end of observation); this therapy was ongoing when the event occurred. Finally, beside the 11 patients with fatal SAEs, 2 more deaths occurred during the study observation period. These two patients had no treatment with products marketed by Boehringer Ingelheim during observation.			

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Discussion:		FIBRONET was aimed to evaluate the characteristics, management and clinical course of patients with IPF as treated under real-world in Italian Pulmonary Centres during 12 months of observation, filling the gap of long-term data on the natural course of IPF in Italy. Our study showed that FVC% predicted improved or remained stable or decreased <10% over 12 months in 84% of patients. These results are consistent with the ones observed in the sample of 624 IPF patients who met the criteria for enrolment in the CAPACITY or ASCEND trials and assigned to placebo group [7]: in the first 6 months after baseline, 91% of patients had FVC improved or stable or a <10% decline of the parameter. Another recent study on 80 Greek patients with IPF receiving pirfenidone [8] showed a significant improvement (>10%) over 12 months in FVC% in 25% of patients (vs 17% in the FIBRONET study). A marginal (5–10%) improvement, stability (–5 to 5%) or marginal (–5 to –10%) decline was observed in 40% (vs 66% in the FIBRONET study) and a significant decline (<–10%) in 35% (vs 17% in the FIBRONET). The higher quote of patients showing stability or marginal changes in FVC% predicted in the FIBRONET study and the lower quote showing a significant decline can be due to the better health status of patients enrolled in the FIBRONET vs the Greek patients. As far as 6-minute walked distance, its mean (±SD) measures observed in the FIBRONET study at baseline, 6- and 12-month follow up were 395.70 (±121.70), 417.40 (±110.20), 411.70 (±108.90) meters, respectively. The substantial stability of distance over time observed in our patients, was confirmed by the results of SWIGRIS study on a sample of subjects with IPF with moderate physiological impairment [9]. The 1-year probability of exacerbation observed in the FIBRONET study (6.5%) is in line with the 1-yr frequency of acute exacerbations found by Kim (8.5%) [10] and with the existing evidence showing the annual incidence of acute exacerbations of IPF ranging from approximately 5%–20% [11]. About QoL, the greatest impairment in the ACTIVITY component of the SGRQ observed in our study was already evident in a nationwide, real-world, observational registry of 623 patients with IPF [12], where mean (SD) TOTAL, SYMPTOMS, ACTIVITY, IMPACT SGRQ score were 48.3 (20.7), 57.2 (21.1), 62.3 (24.2), 37.9 (21.8), respectively. The scores observed in the FIBRONET study were indicative of a better health status at baseline with no significant changes over time; the median (25th-75th percentile) SGRQ TOTAL score at baseline was in fact 39.82 (23.40-56.49), while the median (25th-75th percentile) SYMPTOMS, ACTIVITIES and IMPACTS ON DAILY LIFE scores were 42.26 (27.29-	

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57.98), 54.39 (35.80-72.89) and 28.16 (12.26-47.09) respectively. The better QoL observed in the FIBRONET study compared to the study by Kreuter et al. [12] was probably due to the fact that enrolled patients in the insights-IPF registry were not newly diagnosed. About resource consumption, in a retrospective cohort study on insurance claims data collected in USA, Raimundo et al. [13] found that for respiratory-related conditions 19.5% of patients were hospitalized and 15.8% visited the ED at least once a year. Moreover, Kim et al [14] analyzed Korean nationwide data and found that from 24.9% to 28.9% of IPF patients were hospitalized at least once per year and 12.1~13.5% had an ER visit. In our study lower was the frequency of hospitalized patients (6.2%) and of patients admitted to ER (4.8%). The difference in results can be due to the worst health status of patients analyzed by Raimundo et al. compared to patients enrolled in the FIBRONET study and to the fact that Kim and collaborators [14] considered hospitalizations and ER admission for any cause (not only respiratory). Concerning the treatment of IPF, an earlier diagnosis of IPF is a prerequisite for earlier treatment and, potentially, improvement of the long-term clinical outcome [1, 15]. However, the question of when to start and when to stop treatment with antifibrotics is still debated. In IPF, particularly when the disease is diagnosed at an early stage, "wait and watch" behaviour is not rare to observe [16]. In the FIBRONET sample on average 6.38 weeks elapsed between IPF diagnosis and start of therapy and 1 year after diagnosis 83.9% of patients was under treatment with Nintedanib or Pirfenidone. This is a good result compared to that of a study on patients included in the Finnish and Swedish IPF-registries from 2014 through 2016 showing that during the 3-year follow up period, 29.6% Finnish and 69.4% Swedish patients, respectively, were initiated on treatment with an antifibrotic drug [17]. FIBRONET is one of the largest real-world series of Italian patients with IPF and one of the unique studies aimed to describe the clinical course in terms of symptoms and respiratory function of the disease in a real-life context.			
Marketing Authorisation Holder(s):	Not applicable		
Participating sites and principal investigators:	Principal Investigator	Participating sites	

[illegible]