

# Experience with the Compassionate Use Program of nintedanib for the treatment of Idiopathic Pulmonary Fibrosis in Argentina

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## Abstract

**Introduction:** Idiopathic Pulmonary Fibrosis (IPF) is a diffuse lung disease (DLD) of unknown etiology that is chronic and progressive. It occurs in older adults; it is restricted to the lungs and it is associated with the anatomopathological and/or tomographic pattern of Usual Interstitial Pneumonia (UIP). The evolution of the disease is progressive and it is associated with a mean 5-year survival rate of 20%.

**Objectives:** to identify the clinical and pulmonary function characteristics in the group of patients with IPF included in the Compassionate Use Program (NPU, Named Patient Use); to identify the safety profile reported with nintedanib.

**Materials and methods:** a retrospective, descriptive and cross-sectional study including 54 patients enrolled in the NPU program from September 1<sup>st</sup>, 2015 to August 10<sup>th</sup>, 2016. Data were collected from the NPU program records.

**Results:** fifty-four patients with IPF were included in the NPU program, of whom 47 received nintedanib; the data from the latter were analyzed. Thirty-seven (78.72%) were males, with a mean age at the beginning of treatment of  $67.47 \pm 7.85$  years, and in 9 cases (19.14%) the diagnosis was confirmed by lung biopsy. The mean forced vital capacity (FVC) at the beginning of treatment was  $65.87 \pm 19.23$  and it is presented as the percentage of the predictive value; the mean carbon dioxide diffusing capacity (DLCO) presented as the percentage of the predictive value was  $38.74 \pm 3.09$ . The time of progression from the diagnosis of IPF to the beginning of the treatment with nintedanib was  $27.17 \pm 27.9$  months (median 17). Average drug exposure to cut-off point was  $9.92$  weeks  $\pm 2.15$  (median: 10 weeks). In 7 cases (31.91%) the FVC was over 80%, in 22 (46.80%) cases it was between 50 and 79% and in 10 cases (21.27%) it was below 49%. In total, 7 patients (14.89%) exhibited adverse events: Five (10.6%) patients exhibited weight loss, 4 (8.51%) diarrhea, 2 patients had nausea, 1 (2.12%) an increase of the liver enzymes and 1 (2.12%) pruritus. In most cases, the adverse events appeared during the first 2 weeks after beginning the treatment with nintedanib. In 3 (6.38%) cases it was imperative to suspend nintedanib permanently due to the adverse effects and in 4 (8.51%) cases the dose had to be titrated to 100 mg every 12 hours. Out of the total of patients, 6 (12.76%) passed away due to the progression of their underlying disease.

**Conclusions:** such as it was reported by other groups, nintedanib has a manageable and tolerable safety profile. In our series of 47 patients with IPF who received at least one dose of nintedanib, 14.89% had an adverse event that led to the permanent discontinuation of the drug in only 3 patients (6.38%).

**Key words:** IPF, idiopathic pulmonary fibrosis, nintedanib

## Introduction

Idiopathic Pulmonary Fibrosis (IPF) is a diffuse lung disease (DLD) of unknown etiology that is chronic and progressive. It occurs in older adults and it is associated with the anatomopathological and/or tomographic pattern of Usual Interstitial Pneumonia (UIP). It is more frequent in men and it is linked to smoking; it is usually accompanied by cough, bibasilar crepitant rales and clubbing in 30 to 40% of the cases. In every case, the determination of IPF requires the exclusion of other related forms of DLD, such as environmental exposure, systemic diseases and drugs<sup>1</sup>. Although it is an uncommon disorder with an estimated ratio of 4.6-6.8 / 100,000/ year, it is associated with high mortality and a mean 5-year survival rate of 20%<sup>2</sup>.

Recently, there has been new evidence related to the treatment of patients with IPF: results from the trials with nintedanib and pirfenidone were published, which allowed both drugs to be approved in Europe and the United States. In Argentina, nintedanib has been used as part of the compassionate use program (NPU) since August 2015. Nintedanib, formerly known as BIBF 1120, is a triple tyrosine kinase intracellular inhibitor with anti-fibroproliferative properties. The TOMORROW<sup>3</sup> study was a phase II, double-blind, randomized, placebo-controlled trial that analyzed 432 patients with IPF. The primary endpoint was a decline in the mean forced vital capacity (FVC). As a result, the 12-month treatment with nintedanib 150 mg twice daily was associated with a reduction in the decline of the FVC, less exacerbations and the preservation of a health-related quality of life. These results prompted the conduction of two simultaneous phase III, double-blind, randomized, placebo-controlled trials, INPULSIS-1 and INPULSIS-2, to evaluate the efficacy and safety of nintedanib 150 mg twice daily over 52 weeks in patients with IPF<sup>4</sup>. All the patients were randomized in a 3:2 ratio to receive nintedanib or placebo. In both trials, the annual rate of decline in the FVC was significantly lower in the nintedanib arm than in the placebo arm; and when analyzing both trials in combination, a significant benefit in the decline rate of the FVC was established with a difference of -109.9 mL/year in the annual rate [95% CI, 75.9 to -144.0]. In both trials, the most common adverse event was diarrhea (61.5% in the nintedanib-treated arm and 18.6% in the placebo

arm in INPULSIS-1, and 63.2% and 18.3% in INPULSIS-2). In more than 90% of the cases it was mild or moderate and in less than 5% of the patients it was a reason for discontinuation. In both studies, the number of patients with severe adverse events was similar for the nintedanib-treated arm and for the placebo arm (INPULSIS 1: 31.1% of the patients treated with nintedanib and 27.0% of the patients treated with placebo; INPULSIS-2: 29.8% and 32.9%, respectively). Another less frequently observed adverse event was the increase of the liver enzymes in less than 8%, which did not require a permanent discontinuation of the treatment in any of the cases.

## Objectives

To identify the clinical and pulmonary function characteristics in the group of patients with IPF included in the Compassionate Use Program (NPU); to identify the safety profile reported with nintedanib.

## Materials and Methods

We conducted a retrospective, descriptive and cross-sectional study that collected the data from the NPU program records. The data documented in the forms included the following: gender, age, FVC in liters, FVC presented as the percentage of the predictive value, DLCO presented as the percentage of the predictive value, diagnostic method (lung biopsy or high-resolution CT scan), time of progression of IPF up to the beginning of the treatment with nintedanib, and adverse events.

The statistical analysis was performed using the GraphPad Prism 4 software. To compare mean values, we used the T-test.

## Results

Fifty-four patients with IPF were included in the NPU from September 2015 to September 2016. Of these, 47 began treatment and their data was analyzed.

With reference to the population data, 37 (78.72%) were males, the mean age at the beginning of treatment was  $67.47 \pm 7.85$  years (median 68) and in 9 cases (19.14%) the diagnosis was confirmed by lung biopsy. The mean forced vital capacity (FVC) at the beginning of treatment was

65.87±19.23, presented as the percentage of the predictive value; the mean carbon dioxide diffusing capacity (DLCO) presented as the percentage of the predictive value was 38.11±17.97. The time of progression of IPF up to the beginning of treatment with nintedanib was 27.17± 27.9 months (median 17). Average drug exposure to cut-off point (10/31/16) was 6.78 months ± 4.74 and 26.08 ± 15.86 in weeks. In 15 cases (31.91%) the FVC was over 80%, in 22 (46.8%) cases it was between 50 and 79% and in 10 cases (21.27%) it was below 49% (see Table 1).

With reference to the adverse events, we documented a total of 12 adverse events in 7 patients (14.89%); in 3 of them (6.38%) it was imperative to suspend nintedanib permanently due to the adverse event. In 4 cases (8.51%) the dose had to be titrated to 100 mg every 12 hours. Five (10.6%) patients exhibited weight loss, 4 (8.51%) diarrhea, 2 (4.25%) patients had nausea, 1 (2.12%) an increase of the liver enzymes and 1 (2.12%) pruritus (see Figure 1). Out of the total of patients included in the NPU, 3 had to permanently discontinue treatment with nintedanib (2 due to diarrhea and one due to nausea and weight loss). In two cases, the dose had to be titrated to 100 mg every 12 hours (in one case due to a temporary increase of transaminases, in another due to nausea and weight loss). In most cases, the adverse events appeared early (before the first 2 weeks of the treatment with nintedanib).

Comparing the groups of patients with and without adverse effects, those who suffered from adverse effects had lower FVC values: 66.34 ± 3 vs. 34.71 ± 3.9 (p=0.0001) and this difference was absent when comparing DLCO values (see Table 2).

Out of the total of patients, 6 (12.76%) passed away due to the progression of their underlying disease. Mean FVC% in this group of patients was 47±8.85.

## Discussion

In both INPULSIS trials, the most common adverse event documented was diarrhea (61.5% in the nintedanib-treated arm and 18.6% in the placebo arm in INPULSIS-1, and 63.2% and 18.3% in INPULSIS-2). In more than 90% of the cases it was mild or moderate and in less than 5% of the patients it was a reason for discontinuation. Another less frequently observed adverse event was

the increase of the liver enzymes in less than 8%, which did not require a permanent discontinuation of the treatment in any of the cases<sup>4</sup>.

Corte T. published a study about the safety and tolerance of nintedanib in IPF by classifying the data from the patients included in INPULSIS, in which the permanent discontinuation of the drug due to adverse events comprised **19.3%** of the cases treated with nintedanib and **13%** of the cases in the placebo group. Diarrhea was the most common AE and it was reported in 62.4% of the patients treated with nintedanib vs. 18.4% of the patients in the placebo group; however, only 4.4% of the patients treated with nintedanib had to discontinue the treatment<sup>5</sup>. Table 3 shows the comparative data on the frequency of adverse events in the different publications.

Even though our study has limitations, such as the fact that it is a retrospective study and that the data included in the NPU forms were analyzed, as well as the fact that the number of patients

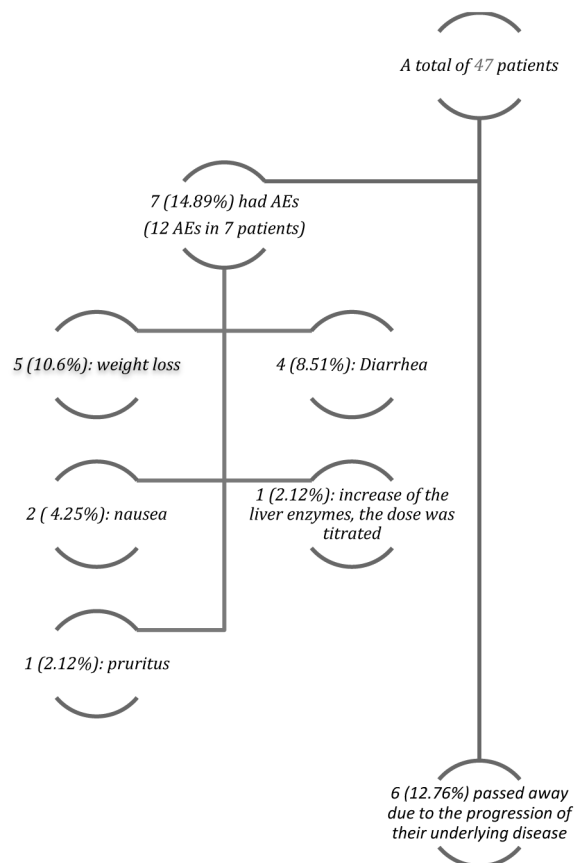


Figure 1

**TABLE 1.** Characteristics of the study population

Males % (n)	78.72 (37)	Mean time of progression of IPF up to the beginning of the treatment with nintedanib in months	27.17 ± 27.9 months (median 17)
Mean age at the beginning of treatment (years)	67.47 ± 7.85	Average drug exposure to cut-off point	Mean: 9.92 weeks ± 2.15
Diagnosis by biopsy % (n)	19.14 (9)	Patients with FVC over 80%	Median: 10 weeks 31.91 (15)
Mean FVC% at the beginning of treatment	65.87 ± 19.23	Patients with FVC between 50 and 79%	46.8 (22)
Mean %DLCO at the beginning of treatment	38.11 ± 17.97	Patients with FVC below 49%	21.27 (10)

**TABLE 2**

	Patients without adverse events	Patients with adverse events	P
Time of progression of IPF at the beginning of the NPU Mean in months ± SD	28.11 ± 4.8	22.14 ± 5.9	0.60
Age at the beginning of the NPU Mean in years ± SD	67.95 ± 1.3	64.86 ± 2.02	0.34
FVC presented as % Mean ± SD	66.34 ± 3	34.71 ± 3.9	0.0001
Time of exposure to nintedanib in weeks ± SD	10.06 ± 0.28	9.14 ± 1.38	0.30
Weight in Kg ± SD	82.08 ± 2.62	72.20 ± 5.25	0.14
DLCO presented as % ± SD	38.74 ± 3.09	34.71 ± 3.95	0.59

**TABLE 3**

	Inpulsis n = 638	Tomorrow + Inpulsis (data in combination) n = 723	NPU in Argentina n = 47
Diarrhea	62.4%	61.5%	8.51%
Nausea	24.5%	24.3%	4.25%
AE resulting in the discontinuation of nintedanib	19.3%	20.6%	6.38%

analyzed was low; it is one of the first local reports on the safety of the treatment with nintedanib in IPF. It should be noted that only adverse events reported spontaneously by prescriber physicians were documented, not dismissing the possibility that unreported adverse events could have been left out. More studies on this matter are imperative.

## Conclusions

Such as it was reported by other international groups, nintedanib has a manageable and tolerable safety profile. In our series of 47 patients with IPF, 14.89% had an adverse event that led to the permanent discontinuation of the drug in only 3 patients (6.38%).

**Conflict of interest:** The authors declare that this study was sponsored by Boehringer-Ingelheim Pharmaceuticals.

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