Patterns of discontinuation in patients with IPF treated with open-label nintedanib: data from INPULSIS®-ON

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Introduction

- The results of the two Phase III placebo-controlled INPULSIS® trials showed that nintedanib reduced disease progression in patients with IPF by reducing the annual rate of decline in forced vital capacity.[1]
- Patients who completed the 52-week treatment period and follow-up visit 4 weeks later in an INPULSIS® trial were eligible to enter an open-label extension called INPULSIS®-ON. As in the INPULSIS® trials, dose reductions from 150 mg bid to 100 mg bid and treatment interruptions were allowed to manage adverse events. Dose re-escalation to 150 mg bid was permitted.

Aim

- To examine patterns of permanent discontinuation of nintedanib in INPULSIS®-ON.

Methods

- The first patient was enrolled into INPULSIS®-ON in July 2012. The database was locked on 12 September 2017.
- Patients received nintedanib in INPULSIS®-ON until they met a reason for discontinuation or until access to nintedanib was obtained outside the trial. Protocol-defined recommendations for discontinuation included:
  - Liver function impairment
  - Recurrence of diarrhoea (>4 stools/day) for ≥8 consecutive days, despite dose reduction and supportive care (e.g., treatment with loperamide)
  - Treatment interruption beyond defined periods
  - Pregnancy
  - Planned use of an investigational drug.
- Patients who permanently discontinued nintedanib in INPULSIS®-ON were classified as discontinuing due to one of the following reasons:
  - Death
  - Lung transplant
  - Adverse events related to IPF/worsening of IPF
  - Adverse events not related to IPF
  - Sponsor decision following local regulation request
  - Other reasons (e.g., lost to follow up, informed consent withdrawn).
- Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 20.1.
- Analyses were descriptive.

Results

- A total of 734 patients were treated in INPULSIS®-ON, of whom 430 continued nintedanib (having taken nintedanib in an INPULSIS® trial) and 304 initiated nintedanib (having taken placebo in an INPULSIS® trial). Baseline characteristics at the start of INPULSIS®-ON were similar between these groups (Table 1).

Table 1. *Baseline characteristics in INPULSIS®-ON*

	Continued nintedanib in INPULSIS®-ON (n=430)	Initiated nintedanib in INPULSIS®-ON (n=304)
Age, years, mean (SD)	66.8 (7.8)	67.7 (7.8)
Male, n (%)	350 (81)	237 (78)
Race, n (%)		
White	252 (59)	179 (59)
Asian	121 (28)	94 (31)
Black	2 (0)	0 (0)
Missing*	55 (13)	31 (10)
Ex or current smoker, n (%)	313 (73)	217 (71)
Weight, kg, mean (SD)	78.5 (16.3)	77.8 (16.1)
Body mass index, kg/m², mean (SD)	27.6 (4.4)	27.3 (4.5)
FVC, % predicted, mean (SD)	75.9 (18.3)	76.7 (20.1)

*In France, regulation did not permit the collection of data on race.

Exposure

- Median (minimum–maximum) exposure to nintedanib in INPULSIS®-ON in patients who continued and initiated nintedanib in INPULSIS®-ON was 32.8 (0.1–56.3) and 29.4 (0.0–55.0) months, respectively.

Discontinuations

- Over the course of the trial (July 2012 to September 2017), nintedanib was discontinued in 295 (68.6%) and 219 (72.0%) patients who continued and initiated nintedanib in INPULSIS®-ON, respectively.
- The most common reason for discontinuing nintedanib was adverse events not related to IPF (Table 2).
- Forty patients (5.4%) from Japan discontinued nintedanib following a local regulation request due to availability of commercial drug.
- Ninety-nine patients (13.5%) discontinued nintedanib due to other reasons, including switching to commercially available drug.

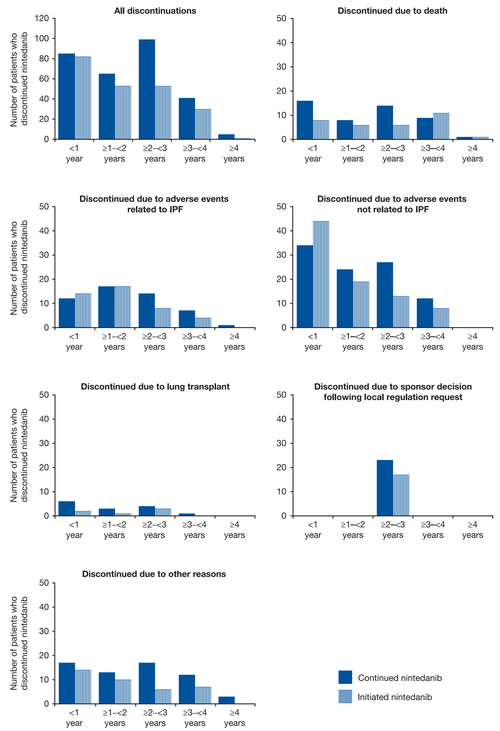
Table 2. *Nintedanib discontinuations in INPULSIS®-ON*

	Continued nintedanib in INPULSIS®-ON (n=430)	Initiated nintedanib in INPULSIS®-ON (n=304)
Discontinued nintedanib	295 (68.6)	219 (72.0)
Death	48 (11.2)	32 (10.5)
Adverse event related to IPF	51 (11.9)	43 (14.1)
Adverse event not related to IPF	97 (22.6)	84 (27.6)
Lung transplant	14 (3.3)	6 (2.0)
Sponsor decision following local regulation request	23 (5.3)	17 (5.6)
Other	62 (14.4)	37 (12.2)

Data are n (%) of patients.

- Nintedanib discontinuations were most frequent in the first year of INPULSIS®-ON (Figure 1).

Figure 1. *Patients who discontinued nintedanib in INPULSIS®-ON by reason and by year of discontinuation*

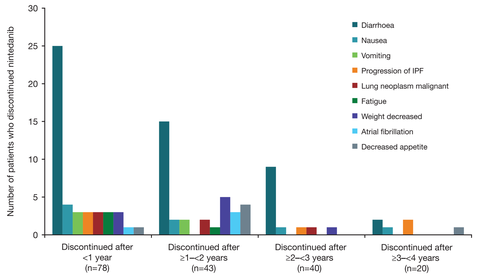


Some patients had >1 adverse event that led to discontinuation of nintedanib. Six patients who discontinued nintedanib due to adverse events not related to IPF had the MedDRA term 'IPF', which included disease worsening and acute exacerbations, recorded as an adverse event leading to nintedanib discontinuation.

Nintedanib discontinuations due to adverse events not related to IPF

- Diarrhoea was the most frequent adverse event not related to IPF that led to discontinuation of nintedanib. Diarrhoea led to discontinuation of nintedanib in 20 (4.7%) and 31 (10.2%) patients who continued and initiated nintedanib in INPULSIS®-ON, respectively.
- Discontinuations due to diarrhoea were most frequent in the first year of INPULSIS®-ON (Figure 2). In the first year of INPULSIS®-ON, discontinuations due to diarrhoea occurred in a greater proportion of patients who initiated than continued nintedanib (5.9% vs 1.6%).

Figure 2. *Most frequent adverse events not related to IPF* that led to discontinuation of nintedanib by year of discontinuation*



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Conclusions

- **In INPULSIS®-ON, the most common reason for discontinuing nintedanib was adverse events not related to IPF. These occurred most frequently in the first year.**
- **Diarrhoea was the most frequently reported adverse event not related to IPF that led to discontinuation of nintedanib, but the proportion of patients who discontinued nintedanib due to diarrhoea was low (6.9%). Discontinuations due to diarrhoea decreased over time.**
- **Close monitoring and proactive management of adverse events during nintedanib treatment, particularly in the first year, may help patients with IPF remain on therapy.**

Reference

1. Richeldi L et al. N Engl J Med 2014;370:2071–82.

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