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Boehringer Ingelheim
Clinical Trial Report
BI Trial No.: 1199.227
Synopsis

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Title of trial
A 12-week, double-blind, randomised, placebo-controlled, parallel-group trial followed by a single active arm phase of 40 weeks evaluating the effect of oral nintedanib 150 mg twice daily on change in biomarkers of extracellular matrix (ECM) turnover in patients with idiopathic pulmonary fibrosis (IPF) and limited forced vital capacity (FVC) impairment

Lay title
A study to better understand how nintedanib works in the cells and how this affects lung function of patients with idiopathic pulmonary fibrosis (IPF)

Coordinating investigator
Dr [REDACTED], PhD, [REDACTED], United Kingdom

Trial sites with randomised patients
Multinational trial in 86 sites (with entered subjects) in 13 countries in Oceania, Europe, Asia and America.

Publications


Clinical phase: IV

Objectives
This trial was conducted to examine for the first time the effects of nintedanib on biomarkers indicative of ECM turnover. This trial also aimed to confirm the association between the change in these biomarkers during the first 12 weeks and disease progression over 52 weeks, and to assess whether nintedanib treatment could alter this association or not.
### Methodology

The trial was a phase IV, multicentre, multinational, prospective trial comprising 2 treatment periods. The first period was a 12-week, randomised, double-blind, placebo-controlled, parallel-group period during which the effect of nintedanib (150 mg twice daily [bid]) on ECM biomarker turnover were compared with that of placebo. The second period was a 40-week, single arm, open-label, active treatment period during which all patients received nintedanib 150 mg bid. A 1:2 (nintedanib:placebo) randomisation ratio was used to increase the number of patients treated with placebo during the first 12 weeks of the trial, thereby increasing the statistical power for assessing the association between the changes in the ECM biomarkers during the first 12 weeks and disease progression over 52 weeks (see secondary objectives).

### Number of subjects

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<td>Entered: 347</td>
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<td>Nintedanib 150 mg bid:</td>
<td>Entered: 116 Treated: 116 Analysed (for primary endpoint): 116</td>
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<td>Entered: 231 Treated: 230 Analysed (for primary endpoint): 229</td>
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### Diagnosis

IPF

### Main criteria for inclusion

Male or female patients who were ≥40 years of age at Visit 1, had been clinically diagnosed with IPF (based on the American Thoracic Society/European Respiratory Society/Japanese Respiratory Society/Latin American Thoracic Association 2011 guideline) within 3 years of Visit 0, had a high-resolution computer tomography pattern consistent with the diagnosis of IPF (as assessed by central review) and had a FVC ≥80% of predicted normal at Visit 1.

**BI investigational product:** Nintedanib, capsule

**Dose:** 1 capsule of 150 mg bid with the possibility to reduce to 1 capsule of 100 mg twice daily to manage adverse events (AEs)

**Mode of administration:** Oral

**Comparator product:** Placebo, capsule

**Dose:** Not applicable

**Mode of administration:** Oral

### Duration of treatment

12 weeks of double-blind randomised treatment (nintedanib 150 mg bid or placebo) followed by a 40-week open-label active treatment (nintedanib 150 mg bid) period and a 4-week follow-up after trial medication termination.
Efficacy criteria for evaluation

The primary efficacy endpoint was the rate of change (slope) in blood C-reactive protein degraded by matrix metalloproteinase (MMP)-1/8 (CRPM) from baseline to Week 12.

The key secondary efficacy endpoint was the proportion of patients with disease progression as defined by absolute FVC (percentage of predicted) decline ≥10% or death up to Week 52 based on in-clinic supervised spirometry.

Additional secondary efficacy endpoints were:
- The rate of change (slope) in blood type I collagen degraded by MMP-2/9/13 (C1M) from baseline to Week 12
- The rate of change (slope) in blood type III collagen degraded by MMP-9 (C3M) from baseline to Week 12

Further endpoints are described in the clinical trial report body and include lung function and questionnaires regarding health-related quality of life in IPF patients (St. George’s Respiratory Questionnaire [SGRQ] and University of California, San Diego - Shortness of Breath Questionnaire [UCSD-SOBQ]), as well as investigations on 5 other biomarkers (biglycan degraded by MMP-2/9 [BGM], type III collagen degraded by ADAMTS1/4/8 [C3A], type V collagen degraded by MMP-2/9 [C5M], type VI collagen degraded by MMP-2/9 [C6M], and citrullinated vimentin degraded by MMP-2/8 [VICM]).

The pharmacokinetics (PK) endpoint was the predose plasma concentration of nintedanib and its metabolites (BIBF 1202 and BIBF 1202-glucuronide) at Visit 3 (Week 4), Visit 6 (Week 16), and Visit 10 (Week 52).

Safety criteria for evaluation

Safety parameters included AEs, clinical laboratory assessments (haematology, clinical chemistry, coagulation), urine pregnancy test, physical examinations, vital signs, and electrocardiograms (ECGs).

Statistical methods

The primary efficacy endpoint was analysed using a random coefficient regression (random slopes and intercepts) model including baseline CRPM, gender, age, and height as covariates.

The key secondary efficacy endpoint was analysed using logistic regression models. The following investigations were carried out on the key secondary endpoint (i.e. proportion of patients with disease progression):
1. The monthly rate of change in CRPM in the first 12 weeks as a prognostic biomarker in patients initially treated with placebo
2. The monthly rate of change in CRPM in the first 12 weeks as a predictive biomarker in patients initially treated with nintedanib versus patients initially treated with placebo
3. The difference between treatment groups
4. The contribution of the monthly rate of change in CRPM in the first 12 weeks to the difference between groups

In addition, investigations using C1M and C3M instead of CRPM were carried out. Analyses of additional secondary efficacy endpoints were performed repeating the primary endpoint analysis replacing baseline CRPM as covariate with baseline C1M or C3M.

Analyses of further endpoints are described in the clinical trial report body. Due to the non-normality of the biomarkers, a transformation was performed prior to any analysis.
SUMMARY – CONCLUSIONS
The patients initially treated with placebo are referred to as the “Placebo/Nint” group and the patients initially treated with nintedanib are referred to as the “Nint/Nint” group.

Trial subjects and compliance with the clinical trial protocol

Disposition
A total of 347 patients were randomised and 346 patients were treated (116 with nintedanib and 230 with placebo). In the study overall (double-blind and open-label periods), a slightly lower proportion of patients prematurely discontinued treatment in the Nint/Nint group (13.8%) than in the Placebo/Nint group (17.8%). The most frequent reason for premature treatment discontinuation was the occurrence of AEs (11.2% in the Nint/Nint group, 15.2% in the Placebo/Nint group).

At the conclusion of the double-blind treatment period, 96.2% of treated patients (96.6% of patients treated with nintedanib, 96.1% of patients treated with placebo) were still receiving study treatment and entered the open-label treatment period where all patients received nintedanib.

Important protocol deviations
The proportion of patients with IPDs during the study overall was higher in the Nint/Nint group (8.6%) than the Placebo/Nint group (3.9%), essentially due to a larger proportion of patients who did not meet entrance criteria (3.4% versus 0.9%). No per-protocol analysis was planned or performed.

Demographic and baseline characteristics
There were no major differences between the 2 randomised groups regarding baseline characteristics. The majority of patients were males (75.7%). Mean age was 70.3 years, with patients treated with nintedanib showing a slightly higher proportion of elderly patients (≥75 years) (32.8% versus 27.8% of patients treated with placebo) and a slightly lower proportion of patients between 65 to <75 years (47.4% versus 51.7% of patients treated with placebo). The majority of patients were ex- or current smokers (72.8% overall). The median time since diagnosis of IFP was approximately half a year in both groups and the majority of patients had IPF diagnosed within 1 year of study entry. Minor differences in baseline respiratory function were observed between groups: a higher percentage of patients treated with nintedanib had FVC <90% of predicted value (36.2% versus 27.4% of patients treated with placebo) and Hb-corrected DLCO <55% of predicted value (36.2% versus 32.6% of patients treated with placebo). The perceived clinical condition of patients did not seem to differ between groups with similar median SGRQ and UCSD-SOBQ total scores.

Extent of exposure
Median duration of exposure to trial medication was similar between groups in the double-blind period (12 weeks of either nintedanib treatment or placebo) and the open-label period (40 weeks of nintedanib treatment in both groups).

Efficacy/clinical pharmacology/other results
Primary endpoint
There was no statistically significant difference between nintedanib and placebo in the adjusted monthly rate of change in log_{10}-transformed CRPM from baseline to Week 12 (difference -0.00066 ng/mL/month; 95% CI -0.00621, 0.00488; p=0.8146).

Key secondary endpoint
Disease progression (defined as absolute FVC decline ≥10% predicted -based on in-clinic supervised spirometry- or death up to Week 52) was observed in 25.00% of subjects treated with nintedanib throughout and 30.43% of subjects treated with placebo for 12 weeks followed by nintedanib (odds ratio 0.769; 95% CI 0.46, 1.27; p=0.3116).
Efficacy/clinical pharmacology/other results (cont’d)

In patients initially treated with placebo, there was no significant association between the monthly rate of change in blood CRPM over 12 weeks and disease progression over 52 weeks (p=0.2084). However, when considering the rate of change in CRPM as a dichotomized covariate (slope >0 versus ≤0), there was a significant association between rising blood CRPM over 12 weeks and disease progression over 52 weeks (estimate 0.624; 95% CI 0.02, 1.23; p=0.0428).

Treatment with nintedanib did not have a significant effect on the association between the monthly rate of change in log_{10}-transformed CRPM over 12 weeks and disease progression over 52 weeks (interaction estimate -45.566; 95% CI -109.55, 16.37; p=0.1537). The adjustment for the rate of change in log_{10}-transformed CRPM over 12 weeks did not influence the effect of nintedanib versus placebo on disease progression over 52 weeks (odds ratio 0.772; 95% CI 0.46, 1.27; p=0.3175).

Other secondary endpoints

No statistically significant difference between nintedanib and placebo was detected regarding the adjusted monthly rate of change in C1M (negative reciprocal root-transformed) or C3M (log_{10}-transformed) from baseline to Week 12. No statistically significant association was found between the rate of change in C1M or C3M over 12 weeks and the risk of disease progression over 52 weeks.

Further endpoints

During the 12-week double-blind period, FVC remained stable in patients treated with nintedanib while it decreased in patients treated with placebo. Adjusted rates of change over 12 weeks (standard error [SE]) were +5.9 mL (18.5) and -70.2 mL (13.1) respectively, with a difference between groups over 12 weeks reaching 76.07 mL (95% CI 31.69, 120.44; p=0.0008).

Over 52 weeks, the annual rate of FVC decline did not differ between patients initially treated with nintedanib and patients initially treated with placebo, as measured by in-clinic spirometry (-88.8 mL per year in the Nint/Nint group versus -104.1 mL per year in the Placebo/Nint group, p=0.6027). A total of 8 patients had IPF exacerbations during the 52-week treatment period: 1 patient (0.9%) initially treated with nintedanib and 7 patients (3.0%) initially treated with placebo. All exacerbations occurred while on nintedanib treatment.

No clinically relevant difference between groups were observed regarding patient-reported outcomes. Health-related quality of life slightly worsened over 52 weeks, with a minor increase in mean SGRQ score in patients initially treated with nintedanib (+4.00) and in patients initially treated with placebo (+1.76). The perception of shortness of breath (UCSD-SOBQ) also slightly worsened after 52 weeks in both groups (mean score +3.45 and +4.72, respectively).

Of the 5 other biomarkers considered as further endpoints (BGM, C3A, C5M, C6M and VICM), only log_{10}-transformed VICM showed a statistically significant difference between nintedanib and placebo regarding the adjusted rate of change from baseline to Week 12. The adjusted difference between groups was -0.02463 ng/mL/month (95% CI -0.04694, -0.00231; p=0.0306).

Pharmacokinetics

Concentrations for nintedanib and its metabolites were similar between treatment regimens and across visits. GMean predose concentrations of nintedanib in the Nint/Nint group were 10.0, 8.4, and 7.0 ng/mL at Weeks 4, 16 and 52, respectively. Similarly, gMean predose concentrations of nintedanib in the Placebo/Nint group were 10.0 and 7.4 ng/mL at Weeks 16 and 52, respectively. Concentrations were found to have moderate-to-high inter-individual variability over all visits for both treatment groups (gCVs = 67.2 to 112%).

Metabolite concentrations for BIBF 1202 in the Nint/Nint group were 10.7, 8.6, and 7.5 ng/mL at Weeks 4, 16 and 52, respectively, and 10.2 and 7.5 ng/mL in the Placebo/Nint group at Weeks 16 and 52, respectively. BIBF 1202 glucuronide concentrations were 118, 114, and 111 ng/mL in the Nint/Nint group at Weeks 4, 16 and 52 and 157 and 128 ng/mL in the Placebo/Nint group at Weeks 16 and 52. Variability was high for both metabolites (gCVs: 72.9-97.8% for BIBF 1202 and 92.9-122% for BIBF glucuronide).
Concentrations and variability were consistent with what has been previously observed with nintedanib and its metabolites.

Safety results

Overall summary of adverse events

During the double-blind period, a higher proportion of patients treated with nintedanib had any AE (81.0%, versus 64.3% of patients treated with placebo), any drug-related AE (56.9% versus 27.8%), or any AE leading to permanent dose reduction (16.4% versus 3.5%). GI AE (such as diarrhoea and nausea) that led to dose reduction or treatment discontinuation were more frequent in patients treated with nintedanib: 9.5% of patients treated with nintedanib had a GI AE that led to permanent dose reduction (versus 1.7% of patients treated with placebo), and 4.3% of patients had a GI AE that led to treatment discontinuation (versus 3.9% of patients treated with placebo).

During the open-label treatment period, the patients initially treated with placebo switched treatment and started nintedanib. During this period, 15.2% of patients initially treated with nintedanib had an AE that led to permanent dose reduction (versus 29.4% of patients initially treated with placebo), and 5.4% of patients had an AE that led to treatment discontinuation (versus 12.2% of patients initially treated with placebo). The proportion of patients with drug-related AEs was relatively similar between patients initially treated with nintedanib and patients initially treated with placebo (74.1% versus 78.3%, respectively).

Over the 52-week treatment period, the most frequently reported AEs were related to (i) the GI system (83.6% in the Nint/Nint group, 78.7% in the Placebo/Nint group), mainly diarrhoea, nausea, vomiting and abdominal pain; (ii) the metabolic system (21.6% in the Nint/Nint group, 22.2% in the Placebo/Nint group), with decreased appetite and decreased weight; and (iii) the hepatobiliary system (21.6% in the Nint/Nint group, 20.9% in the Placebo/Nint group), mainly due to increased hepatic enzymes.

During the double-blind period, the incidence of diarrhoea was higher in patients treated with nintedanib (46.6% versus 18.3% in patients treated with placebo). None of the diarrhoea AEs were serious. Diarrhoea AEs were mostly mild in intensity and considered related to study treatment. None of the events led to permanent treatment discontinuation. Dose reduction was required in 14.8% of patients who had diarrhoea and were treated with nintedanib and 2.4% of patients who had diarrhoea and were treated with placebo. Diarrhoea AEs were observed primarily within the first 60 days of treatment, and most patients with diarrhoea AEs had 1 or 2 episodes.

During the 40-week open-label period, the incidence of diarrhoea was similar between patients initially treated with nintedanib (46.6% versus 18.3% in patients treated with placebo). None of the diarrhoea AEs were serious. Diarrhoea AEs were mostly mild in intensity and considered related to study treatment. None of the events led to permanent treatment discontinuation. Dose reduction was required in 14.8% of patients who had diarrhoea and were treated with nintedanib and 2.4% of patients who had diarrhoea and were treated with placebo. Diarrhoea AEs were observed primarily within the first 60 days of treatment, and most patients with diarrhoea AEs had 1 or 2 episodes.

During the 40-week open-label period, the incidence of diarrhoea was similar between patients initially treated with nintedanib (61.6%) and patients initially treated with placebo (66.1%). In the patients with diarrhoea, the event led to permanent dose reduction in 20.3% of patients initially treated with nintedanib and 26.0% of patients initially treated with placebo, and to permanent treatment discontinuation in few patients (1.4% and 4.8%, respectively).

Two bleeding AEs (lower GI haemorrhage of severe intensity, and rectal haemorrhage of mild intensity) were considered as serious. Both occurred during the open-label period in patients initially treated with placebo. Neither SAE was considered related to treatment and both patients recovered.

The AESIs prespecified in the protocol included AEs related to GI perforation and hepatic injury. No events of GI perforation were reported in any treatment group, whereas AESIs related to hepatic injury were reported in a lower proportion of patients in the Nint/Nint group (0.9% overall) than in the Placebo/Nint group (2.2% overall). All AESIs were reported during the open-label period.

There were 9 deaths in total during the study, all occurring during the open-label period. There was no difference in incidence between groups (2.7% in each group) and none of the deaths were considered drug-related.
Safety results (cont’d)

The incidence of SAEs was similar between patients treated with nintedanib and patients treated with placebo during the double-blind period (6.9% versus 7.8%). During the open-label period, the incidence of SAEs was lower in patients initially treated with nintedanib (13.4%) than in patients initially treated with placebo (22.6%), primarily due to AEs requiring hospitalization (7.1% versus 17.2%). No clear pattern explaining this difference between groups could be identified since the SAEs that required hospitalization were spread across various SOCs and PTs.

Laboratory measurements

There were no notable changes from baseline to Week 52 in mean values of haematology, chemistry or coagulation parameters for either group. PCSAs were rare, with no clinically relevant differences in incidence between treatment groups.

Increased liver enzymes, in particular AST, ALT and GGT, were relatively frequent. During the double-blind period, elevations in liver enzymes to above normal range were observed in 20-25% of patients treated with nintedanib (versus 5-8% of patients treated with placebo). During the open-label period, they were observed in 20-25% of patients initially treated with nintedanib and 30-35% of patients initially treated with placebo. Elevations in LDH to above normal range were also frequent during the double-blind period (23.5% of patients treated with nintedanib, 18.0% of patients treated with placebo) and the open-label period (32.7% of patients initially treated with nintedanib, 40.4% of patients initially treated with placebo). Differences between groups also included a lower incidence of ALP in the Nint/Nint group than the Placebo/Nint group during the open-label period (3.6% versus 14.0%).

Whereas no marked differences between groups were seen during the double-blind period, PCSAs in liver enzymes, bilirubin and other enzymes during the open-label period were less frequently reported in patients initially treated with nintedanib than in patients initially treated with placebo, especially changes in GGT (6.3% of patients initially treated with nintedanib, versus 13.8% of patients initially treated with placebo), changes in AST (0.9% versus 5.4%), changes in ALP (0% versus 2.3%), and changes in bilirubin (0% versus 2.7%).

Of the patients who had PCSAs in AST, ALT or bilirubin, normalization of the laboratory values was observed at the following visit in most cases.

There was one potential Hy’s law case in the Placebo/Nint group and abnormalities were detected after the start of nintedanib treatment during the open-label period. The patient had an SAE of hepatitis that was considered related and led to treatment discontinuation. The patient recovered without sequelae.

Vital signs

There were no clinically meaningful differences between the 2 treatment groups or changes from baseline to each measured time point in blood pressure or pulse rate values. The average body weight loss amounted to 0.7 kg and 3.2 kg after 12 and 52 weeks of treatment with nintedanib, respectively.

Conclusions

The trial did not show a statistically significant effect of nintedanib 150 mg bid on the monthly rate of change in CRPM, C1M, or C3M over 12 weeks in patients with IPF and well-preserved lung function. The rate of change in FVC over 12 weeks was lower in the patients treated with nintedanib than in those initially treated with placebo, consistent with the known effect of nintedanib on reducing FVC decline in patients with IPF.

The safety findings were consistent with the known safety profile of nintedanib, with no new safety signals. The most frequently reported AEs during treatment with nintedanib 150 mg bid were primarily events involving the GI tract (mainly diarrhoea), weight loss and decreased appetite, and increased liver enzymes.