

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205832Orig1s000

SUMMARY REVIEW

SUMMARY REVIEW OF REGULATORY ACTION

Date: October 10, 2014

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Products, CDER, FDA

Subject: Division Director Summary Review
NDA Number: 205832
Applicant Name: Boehringer Ingelheim Pharmaceuticals, Inc.
Date of Submission: May 2, 2014
PDUFA Goal Date: January 2, 2015
Proprietary Name: Ofev
Established Name: Nintedanib
Dosage form: Capsules
Strength: 150 mg and 100 mg
Proposed Indications: Treatment of patients with idiopathic pulmonary fibrosis (IPF)
Action: Approval

1. Introduction

Boehringer Ingelheim Pharmaceuticals, Inc. (BI) submitted this 505(b)(1) application for use of nintedanib 150 mg and 100 mg capsules for the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed dose is 150 mg twice daily for a total daily dose of 300 mg. Both a 150 mg and 100 mg capsule are proposed for marketing, as the product label advises that dose reduction to 100 mg twice daily may be necessary to manage adverse reactions. Nintedanib is a new molecular entity of the class of kinase inhibitor, and has been granted orphan drug, fast track, and breakthrough designations. The application is based on clinical efficacy and safety studies. This summary review provides an overview of the application, with a focus on the clinical efficacy and safety studies.

2. Background

IPF is a diffuse progressive parenchymal lung disease of unknown etiology, characterized by fibrotic interstitial infiltrates that are consistent with the histopathologic pattern of usual interstitial pneumonia.¹ It is the most common type of interstitial lung disease, estimated to affect 132,000 to 200,000 people in the United States. Approximately 50,000 new cases are diagnosed each year, and as many as 40,000 patients in America die from IPF each year. IPF is typically seen in older adults, more commonly in men than women, usually occurring between the ages of 50-70 years, and is characterized by

¹ ATS/ERS. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med. 2000;161:(2 Pt 1):646-64.

progressive dyspnea, non-productive cough, and progressive pulmonary insufficiency. The natural course of IPF is variable. As the interstitial fibrosis and architectural distortion advance, the lung becomes increasingly non-compliant, and the work of breathing and dyspnea increase. Patients with IPF typically experience slowly progressive worsening of lung function over time, but some experience rapid declines and frequent hospitalizations in the late stage of the disease.² While the course of the disease is variable, the prognosis is uniformly poor, with a median survival of about 3-5 years after diagnosis.

There are no medications approved for the treatment of IPF in the United States. IPF patients are often treated with corticosteroids and immunosuppressive agents, such as azathioprine and cyclophosphamide. No clinical trials have demonstrated a clear clinical benefit for these therapeutic agents and the use of these agents is not FDA-approved. In 2011, the American Thoracic Society issued a statement, citing evidence-based guidelines, that clinical benefit of any drug therapy used in IPF was weak.³ Interestingly, recent trials of historical standard-of-care treatment regimens in IPF have shown increased mortality.⁴ Historically, lung transplantation has been the only therapeutic option for patients with IPF. Nintedanib is not marketed anywhere in the world.

Pertinent regulatory interactions between BI and the Agency include a Pre-IND Meeting in August 2006, End-of-Phase 2 (EOP2) Meeting in December 2010, and a Pre-NDA meeting in October 2013. At the Pre-IND meeting the Division informed BI that there was a lack of non-clinical support for dosing in IPF patients. While the Division acknowledged the life-threatening nature of IPF, the serious nature of the disease was not considered sufficient to waive the requirement for non-clinical support because the findings in the animal toxicology studies and available human data from some oncology studies at that time raised the concern that the proposed doses may make some IPF patients ineligible for lung transplantation. At the Pre-IND and EOP2 meetings, the Division discussed forced vital capacity (FVC) as a primary endpoint in IPF trials and cautioned that a relationship between FVC and survival had not been established, and therefore, encouraged BI to explore numerous endpoints of relevance to IPF, including survival. BI conducted the phase 2 study outside the United States and had positive findings. With the positive findings in the phase 2 study, an IND was opened in the United States and phase 3 studies were conducted under the IND.

² Martinez FJ, Safrin S, Weycker D, et al. The clinical course of patients with idiopathic pulmonary fibrosis. *Ann Intern Med.* 2005;142 (12 Pt 1):963-7.

³ Raghu G, Collard HR, Egan JJ, et al. An official ATS/ERS/JRS/ALAT statement: idiopathic pulmonary fibrosis: evidence-based guidelines for diagnosis and management. *Am J Respir Crit Care Med.* 2011;183:788-824.

⁴ Raghu G, Anstrom KJ, King TE Jr, et al. Prednisone, azathioprine, and N-acetylcysteine for pulmonary fibrosis. *N Engl J Med.* 2012 May 24; 366(21):1968-77.

3. Chemistry, Manufacturing, and Controls

The proposed commercial drug product, Ofev (nintedanib) capsules, contains 150 mg or 100 mg of nintedanib (equivalent to 180.60 mg or 120.40 mg nintedanib ethanesulfonate, respectively) and standard compendial excipients. The drug product will be packaged in HDPE bottles of both 150 mg (60 count) and 100 mg (60 (b) (4) count) strength capsules. The active pharmaceutical ingredient will be manufactured at Boehringer Ingelheim (BI) Pharma GmbH in Germany. The drug product will be manufactured at (b) (4). The packaging will be performed at the BI Pharma site in Germany. All manufacturing and testing facilities associated with this application have acceptable inspection status. The various DMFs associated with the manufacture of the product are adequate. An expiry of 3 years is proposed and supported by submitted data.

4. Nonclinical Pharmacology and Toxicology

BI submitted a complete toxicology program that included general toxicology studies in mice, rats, and monkeys for up to 12 months; reproductive and developmental toxicology studies in rats and rabbits; and 2-year carcinogenicity studies in rats and mice. In the general toxicology studies, the target organs of toxicity were bone (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The chronic rat study identified a low-dose NOAEL of 5 mg/kg/day, and the chronic monkey study failed to identify a NOAEL. The only observation in monkeys at the low dose of 10 mg/kg/day was growth plate thickening, which is unlikely to be relevant to an older adult population. Development of nintedanib for IPF was allowed to proceed, despite the lack of adequate safety margins in non-clinical studies, due to the presence of adequate human clinical data. Nintedanib was negative in standard genotoxicity testing. Two-year carcinogenicity in rats and mice did not reveal any evidence of carcinogenic potential for nintedanib.

The reproductive and developmental toxicology studies demonstrated that nintedanib was a teratogen, causing embryofetal death and teratogenic effects in rats and rabbits at maternally non-toxic doses. Malformations included abnormalities in the vasculature, skeletal system, and urogenital systems. Nintedanib decreased female fertility in rats, as evidenced by increases in resorption and post-implantation loss, and a decrease in gestation index. Nintedanib had no effect on fertility in male rats. Nintedanib was also noted to decrease post-natal viability of rat pups during the early post-natal period. These findings support a pregnancy category D classification for this product, which is consistent with other kinase inhibitors.

5. Clinical Pharmacology and Biopharmaceutics

BI submitted a complete and adequate clinical pharmacology program for nintedanib. Nintedanib will be recommended for administration with food, as coadministration with food increased exposure (AUC and C_{max} by 20%). Of the absorbed fraction, nintedanib is extensively metabolized, primarily through the liver (hydrolytic cleavage by esterases followed by glucuronidation by UGT enzymes). The major metabolites are not active at clinically relevant concentrations. The terminal half-life of nintedanib is 10-15 hours,

which also supports twice-daily dosing. The majority of the administered dose (~93%) is excreted in the feces. Based on in vitro studies, nintedanib is not an inhibitor or inducer of CYP pathways. Nintedanib is a substrate of P-gp and to a minor extent CYP3A4. Labeling advises that P-gp and CYP3A4 inhibitors may increase exposure to nintedanib, while P-gp and CYP3A4 inducers may decrease the exposure; it is recommended that inducers be avoided. AUC decreased by 21% in current smokers, compared to patients who had stopped smoking or never smoked. Product labeling will advise against smoking while using nintedanib. No adjustment of the starting dose will be recommended for any intrinsic or extrinsic factors. Rather, it will be recommended that adverse reactions be managed through dose interruption or dose reduction.

Effect on the QT interval was evaluated in a study in patients with renal cell cancer. The study was not a thorough QT study and did not include a placebo group, positive control, or high dose level (due to ethical reasons). Nintedanib was administered at a dose of 200 mg BID. Frequent ECG measurements were performed at baseline, after the first administration of nintedanib, and at steady state. The study demonstrated the lack of effect of 200 mg nintedanib orally administered twice daily for 15 days on the QTcF interval as compared with baseline. The largest mean time-matched increase of QTcF at steady state was 3.1 ms (two-sided 90% CI: -0.2, 6.4).

No dedicated PK study with nintedanib was conducted for patients with hepatic impairment. As nintedanib is eliminated primarily by biliary/fecal excretion (>90%), hepatic impairment is likely to increase plasma nintedanib concentrations. Nintedanib clinical studies excluded patients with AST, ALT, or bilirubin greater than 1.5 x ULN. Therefore, the product label will recommend liver function monitoring and dose modification or discontinuation of nintedanib as needed for patients with mild hepatic impairment. Nintedanib will not be recommended in patients with moderate or severe hepatic impairment. BI will be asked to conduct a Post Marketing Requirement study in patients with hepatic impairment to evaluate the impact of hepatic impairment on nintedanib pharmacokinetics. BI has submitted this study protocol, and the study is ongoing.

6. Clinical Microbiology

The microbiological quality of the drug product is controlled by acceptable and suitable testing protocol.

7. Clinical and Statistical – Efficacy

a. Overview of the clinical program

Some characteristics of the relevant clinical studies that form the basis of review and regulatory decision for this application are shown in Table 1. The design and conduct of these studies are briefly described below, followed by efficacy findings and conclusions. Safety findings are discussed in the following section.

Table 1. Relevant clinical studies

ID Year*	Study Characteristics † - Patient age - Patient characteristics - Study objective, design - Study duration	Treatment groups ‡	N §	Primary efficacy endpoint ¶	Regions and Countries //
30 Study 1 [June 2010]	- ≥ 40 yr - DLco 30 to 79% and FVC ≥50% of predicted - Pivotal, R, DB, PC - 52 weeks	Nin 50 mg QD Nin 50 mg BID Nin 100 mg BID Nin 150 mg BID	87 86 86 86 87	Annual rate of decline in FVC from baseline to week 52	25 countries in Europe, Asia, South and Latin America, Australia, Canada, US: 0% of subject
32 Study 2 [Oct 2013]	- ≥ 40 yr - DLco 30 to 79% and FVC ≥50% of predicted - Pivotal, R, DB, PC - 52 weeks	Nin 150 mg BID Placebo	309 206	Annual rate of decline in FVC from baseline to week 52	13 countries in Americas, Europe, Asia, Australia, US: 14% of subject
34 Study 3 [Oct 2013]	- ≥ 40 yr - DLco 30 to 79% and FVC ≥50% of predicted - Pivotal, R, DB, PC - 52 weeks	Nin 150 mg BID Placebo	331 220	Annual rate of decline in FVC from baseline to week 52	17 countries in Americas, Europe, Asia, Australia, US: 16% of subjects
<p>* Study ID shown (top to bottom) as BI's study number, as references in the Ofev product label, and [Year study subject enrollment ended]</p> <p>† R=randomized, DB=double blind, PG=parallel group</p> <p>‡ Nin = Nintedanib, QD= daily, BID= twice daily</p> <p>§ Randomized</p> <p>¶ Statistical model for study was random coefficients linear regression with absolute change in FVC as the outcome, assuming linear decline over time</p> <p>// Study 30: Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, China, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Korea, Mexico, Netherlands, Portugal, Russia, S. Africa, Spain, Taiwan, Turkey, United Kingdom.</p> <p>Study 32: Australia, Belgium, China, Czech Republic, France, Germany, India, Ireland, Israel, Italy, Japan, United Kingdom, US</p> <p>Study 34: Canada, Chile, China, Finland, France, Germany, Greece, India, Japan, Korea, Mexico, Netherlands, Portugal, Russia, Spain, Turkey, US</p>					

b. Design and conduct of the studies

Studies 30, 32, and 34 were similar in design and conduct except for the treatment arms as noted in Table 1. All three studies were randomized, double-blind, placebo-controlled, parallel group in design, conducted in patients with a diagnosis of IPF, using acceptable diagnostic criteria. Patients with >1.5 times ULN of ALT, AST, or bilirubin, patients with a risk or predisposition for bleeding, patients receiving a full dose of anticoagulation treatment, and patients with a recent history of myocardial infarction or stroke were excluded from the studies. Concomitant treatments were for the most part prohibited, except for allowance for IPF exacerbation and progression of disease. In Studies 32 and 34, patients could be treated with a reduced dose (100 mg BID) to manage adverse events. Specific criteria were outlined for diarrhea and liver enzyme adverse event-driven dose reduction and subsequent dose re-escalation. In Study 30, dose reduction to the next lowest dose group occurred, with no provisions for re-escalation or re-challenge with a higher dose. The primary efficacy variable was the annual rate of decline in FVC from baseline to week 52 and was analyzed by random coefficient regression model, assuming linear decline over time. Important secondary efficacy variables included: time to first IPF exacerbation (defined as presence of all of the following: worsening or development of dyspnea, new diffuse pulmonary infiltrates, decrease in PaO₂ ≥10 mmHg or PaO₂/FiO₂ <225 (in Study 30); and exclusion of alternate causes, such as infection,

heart failure, pulmonary embolism), and change in St. George's Respiratory Questionnaire (SGRQ) score from baseline to week 52. Time to first IPF exacerbation was adjudicated in Studies 32 and 34, but investigator-reported only in Study 30. Time to death or mortality was an important exploratory efficacy variable. Time to first IPF exacerbation and time to death were analyzed by log-rank test and Kaplan-Meier estimates. Estimates of hazard ratios and confidence intervals were obtained by Cox's proportional hazards regression model. The SGRQ score was analyzed using a mixed model repeated measures approach. If the primary efficacy analyses from Studies 32 and 34 each showed efficacy, then the secondary outcome variable of time to death were to be analyzed using pooled data from both studies in addition to the individual study analyses. Safety assessments included recording of adverse events, vital signs, physical examination, clinical laboratory evaluation, and 12-lead ECG.

c. Efficacy findings and conclusions

The submitted clinical program supports efficacy of nintedanib at a dose of 150 mg BID.

Dose ranging in IPF patients was conducted in Study 30 (Table 1). From an efficacy standpoint, a dose-response relationship was observed for the annual rate of decline in FVC (-0.190, -0.174, -0.210, -0.162, -0.06 L/year for the placebo, 50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID groups, respectively). There was increased efficacy for the 150 mg BID compared to the 100 mg BID or lower doses. From a safety standpoint, gastrointestinal adverse reactions including diarrhea, nausea, abdominal pain, and decreased appetite tended to increase with increasing dose (occurring in 32% of patients in the placebo group and up to 74% of patients in the nintedanib 150 mg BID group). The proposed starting dose of 150 mg BID for phase 3 studies was reasonable because of the increased efficacy with respect to annual rate of decline in FVC for the 150 mg BID group compared to the 100 mg BID and other lower dose groups. Since there are no approved therapies for IPF patients, and the disease is progressive and fatal, maximizing efficacy is reasonable. Additionally, a higher proportion of subjects with greater than 3x ULN increase in ALT, AST, or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group. These data support BI's proposed dose reduction to 100 mg BID in order to manage these adverse events.

Results of the primary efficacy variable for the proposed to-be-marketed 150 mg BID dose for all three studies are shown in Table 2. The results showed statistically significant benefit of nintedanib compared to placebo in all three studies. A representative figure of FVC change over time is shown in Figure 1.

Table 2. Annual rate of decline in FVC (mL/year) at week 52

	Nintedanib 150 mg BID	Placebo	Difference from Placebo		
			Adjusted	[95% CI]	p-value
Study 30	-60	-191	131	[27, 235]	0.014
Study 32	-115	-240	125	[78, 173]	< 0.001
Study 34	-114	-207	94	[45, 143]	<0.001

Randomized set in Study 30; treated set in Studies 32 and 34
Rate of decline and difference are adjusted based on random coefficient regression model with fixed effects for treatment, gender, age,

	Nintedanib 150 mg BID	Placebo	Difference from Placebo		
			Adjusted	[95% CI]	p-value
height, and random effect of patient-specific intercept and time. Study 30 was based on an MMRM with similar fixed terms.					

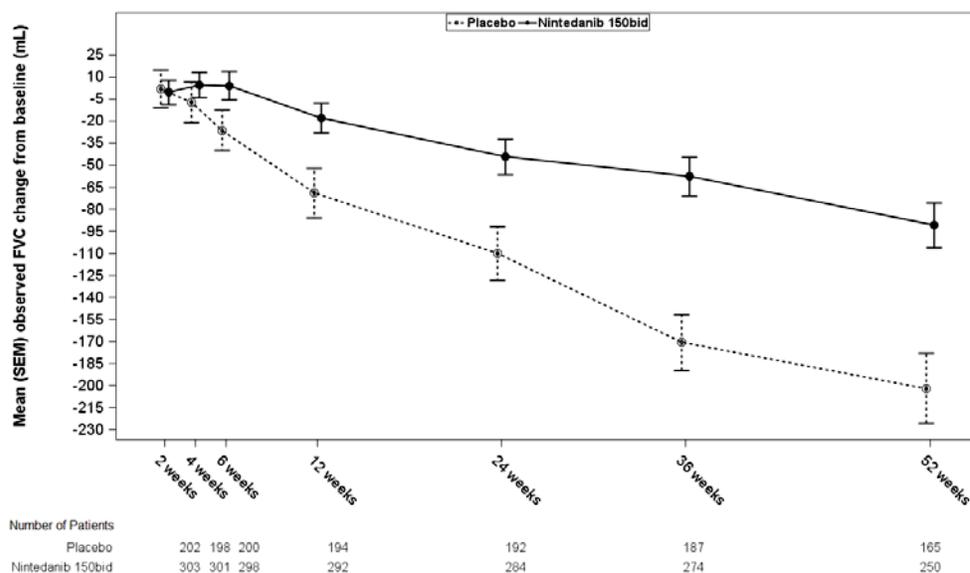


Figure 1. Mean observed FVC change from baseline in mL over time, Study 32.

The absolute effect size for FVC that can be considered clinically meaningful and correlates with mortality or other patient-centered outcomes is not known. According to scientific literature and the ATS Consensus Statement⁵, a $\geq 10\%$ increase in FVC over 3 to 6 months can be viewed as a favorable positive response. A continuous responder plot prepared by the Agency's statistical reviewer is shown in Figure 2. The x-axis shows the decline in % predicted FVC from baseline (or worsening) at week 52, and the y-axis shows the corresponding percentage of patients achieving the level of % predicted FVC decline or greater. The positive treatment effect of nintedanib was demonstrated by a consistent separation of the curves across all levels of response (Figure 2). Using an absolute decline in % predicted FVC of 10% or less to define a responder, the proportion of responders in study 32 were 71% and 57% in nintedanib group and placebo group, respectively. With the same definition, the proportion of responders in study 34 was 70% and 64% in nintedanib group and placebo group. Study 30 showed similar results.

⁵ American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. Am J Respir Crit Care Med 2000; 161: 646-664.

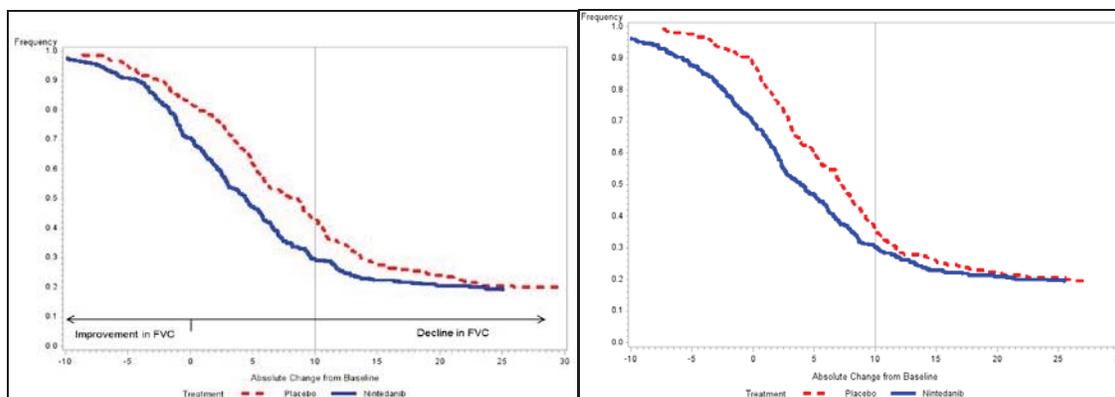


Figure 2. Cumulative distribution of relative change from baseline in percent predicted FVC, Study 32 shown in Left Panel, and Study 34 shown in Right Panel

Time to first acute IPF exacerbation was evaluated as a key secondary endpoint in the clinical development program. Studies 30 and 34 demonstrated a statistically significant difference for nintedanib compared to placebo as shown in Table 3.

Table 3. Time to first IPF exacerbation over 52 weeks, shown at number (percentage)

	Nintedanib 150 mg BID	Placebo	Difference from Placebo		
			Hazard Ratio	[95% CI]	p-value
Study 30	2 (2.3)	12 (13.8)	0.16	[0.04, 0.71]	0.016
Study 32*	7 (2.3)	8 (3.9)	0.55	[0.20, 1.54]	
Study 34*	5 (1.5)	16 (7.3)	0.20	[0.07, 0.56]	

*Adjudicated
Randomized set in Study 30; treated set in Studies 32 and 34
Estimated based on Cox regression model

SGRQ is a patient-reported outcome instrument that measures symptoms, activities, and the impact of disease on daily life, and has been predominantly used in patients with COPD. SGRQ was not developed specifically for use in IPF patients. For SGRQ score change from baseline to Week 52, Studies 30 and 34 demonstrated a statistically significant difference of nintedanib over placebo [Study 30 (LS mean difference -6.12; 95% CI: -10.57, -1.67), and study 34 (LS mean difference -2.69; 95% CI: -4.95, -0.43)]. In study 30 there was also a dose response for differences of nintedanib over placebo [LS mean difference -1, -3, -4, and -6 for 50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID, respectively]. Study 32 did not show a statistically significant difference between the two treatment groups [LS mean difference -0.1; 95% CI: -2.5, 2.4]. The minimal clinically important difference (MCID) for SGRQ, determined to be 4 for COPD patients, was reached in one study in the IPF program.

Mortality is the most relevant endpoint for IPF studies and is the ideal endpoint for assessing efficacy of IPF therapy. Mortality data were analyzed in various ways by BI and by the Agency. Results of all three studies individually and pooled are shown in Table 4. Mortality results are shown as vital status (all deaths that occurred during the total study period and defined study follow-up period regardless of whether patients

continued study treatment), and as on-treatment (deaths that occurred after the first dose and within 14 days of the last dose for study 30 and within 28 days of the last dose for studies 32 and 34). Respiratory-related deaths were similar to vital status except that all deaths were evaluated by a blinded adjudication committee to assign the cause of death. While both mortality results are important, vital status all-cause mortality is generally considered informative of the efficacy of a drug with respect to survival, and on-treatment mortality is generally considered informative of safety of a drug.

In the analysis of all-cause mortality measured at vital status, mortality benefit was not demonstrated for the three studies individually or pooled. The numerical trend generally favored nintedanib, but the confidence intervals were large. The trend in benefit in mortality as assessed in these studies supports FVC as the primary endpoint. Statistically significant benefit was seen in the on-treatment analysis of Study 30 and the pooled analysis of on-treatment mortality. This benefit was limited due to assessment while on treatment, and the post-hoc nature of both assessments, (b) (4)

Table 4. Mortality analysis from studies 30, 32, and 34

	Number of events (%)		Hazard Ratio (95% CI), p-value*
	Nintedanib 150 mg BID	Placebo	
All cause death, vital status at end of study			
Study 30	7 (8.1)	9 (10.3)	0.73 [0.27, 1.98], p=0.538
Study 32	13 (4.2)	13 (6.4)	0.63 [0.29, 1.36], p=0.288
Study 34	22 (6.7)	20 (9.1)	0.74 [0.40, 1.35], p=0.300
Study 32+34	35 (5.5)	33 (7.8)	0.70 [0.43, 1.12], p=0.140
Study 30+32+34	42 (5.8)	42 (8.3)	0.70 [0.46, 1.08], p=0.096
All cause death, on-treatment			
Study 30	1 (1.2)	8 (9.2)	0.14 [0.02, 1.11], p=0.034
Study 32	8 (2.6)	9 (4.4)	0.68 [0.26, 1.82], p=0.487
Study 34	16 (4.9)	17 (7.8)	0.68 [0.34, 1.35], p=0.221
Study 32+34	24 (3.8)	26 (6.1)	0.68 [0.39, 1.19], p=0.160
Study 30+32+34	25 (3.5)	34 (6.7)	0.57 [0.34, 0.97], p=0.027
Respiratory-related death, vital status at end of study			
Study 30	2 (2.3)	8 (9.2)	0.23 [0.05, 1.07], p=0.06
Study 32	10 (3.2)	10 (4.9)	0.61 [0.25, 1.47], p=0.352
Study 34	14 (4.3)	11 (5.0)	0.86 [0.39, 1.90], p=0.665
Study 32+34	24 (3.8)	21 (5.0)	0.74 [0.41, 1.34], p=0.344
Study 30+32+34	26 (3.6)	29 (5.7)	0.62 [0.37, 1.06], p=0.078
*Hazard ratio based on the Cox proportional hazard model with terms for treatment, sex, age, and height. P-value based on long-rank test			

Results of the clinical program show a consistent positive benefit of nintedanib in the treatment of IPF. Statistically significant differences in FVC were seen in all three studies. Benefit in FVC was supported by numerical trend in favor of mortality. There was also benefit noted in other secondary measures such as time to first IPF exacerbation.

8. Safety

a. Safety database

The safety assessment of nintedanib was primarily based on studies shown in Table 1. The total number of patients exposed to nintedanib is reasonable to assess safety.

b. Safety findings and conclusion

The submitted data support safety of nintedanib for the treatment of IPF. The major safety findings of note in the program were liver injury, and gastrointestinal adverse reactions.

Deaths, SAEs, and discontinuations due to AEs:

Deaths are discussed in detail in the efficacy discussion in 7c above. Generally, fewer patients in the nintedanib group than in the placebo group died due to any cause (34 [6.7%] vs 25 [3.5%], respectively). In both groups, IPF was the most common cause of death, occurring less often in the nintedanib group [nintedanib, n = 18 (2.5%) vs. placebo, n = 21 (4.1%)]. The most common adverse events leading to death in patients treated with nintedanib, more than placebo, were pneumonia (0.7% vs. 0.6%), lung neoplasm malignant (0.3% vs. 0%), and myocardial infarction (0.3% vs. 0.2%).

Non-fatal serious adverse events (SAEs) and discontinuations and drop out from adverse events (AEs) were balanced between nintedanib and placebo treatment groups. The proportions of patients who experienced at least one SAE were about 30% in both nintedanib and placebo treatment groups. The proportion of patients with an SAE is not surprising given the long duration of the studies and the older population with a severe disease and multiple co-morbidities. The three most frequently reported SAEs occurring more frequently in nintedanib versus placebo were bronchitis (1.2% vs. 0.8%), myocardial infarction (1.1% vs. 0.4%), and chest pain (1.0% vs. 0.8%).

More patients discontinued treatment early due to adverse events in the nintedanib treatment group (21%) than in the placebo group (15%). The most common AE leading to discontinuation was diarrhea (5.3% nintedanib vs. 0.2% placebo), followed by nausea (2.4% nintedanib, 0% placebo), decreased appetite (1.5% nintedanib, 0.2% placebo), and weight decreased (1.1% nintedanib, 0.2% placebo).

Common adverse events (AEs) were reported by 95% of patients treated with nintedanib and 90% of patients treated with placebo. The large frequency of AEs is not surprising given the long duration of the studies and the older patient populations. Common adverse events that occurred in $\geq 5\%$ and more frequently in nintedanib versus placebo-treated patient, in order of decreasing frequency, were: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, decreased weight, and hypertension.

AEs of interest:

The Applicant identified a set of AEs of interest for the IPF program based on class related mechanism of action, existing human data, and animal toxicology studies. The AEs that were identified as events of interest were liver-related adverse events, gastrointestinal adverse events, embryofetal toxicity, arterial thromboembolic events, risk of bleeding, gastrointestinal perforation, and hypothyroidism.

Liver-related adverse events:

Hepatic events that were SAEs were reported in 5 nintedanib-treated patients (0.7%) and no placebo-treated patients. None of the SAEs resulted in death. One patient was noted to be a potential Hy's law case, but liver enzymes and bilirubin were found to be elevated due to obstructive jaundice from a pancreatic head tumor, rather than nintedanib-related.

Liver enzymes were frequently monitored in all three studies with more frequent testing in the early months of treatment. In addition, dose modification guidelines based on liver enzyme abnormalities was also protocol-specified in all three studies. In the overall safety database, ALT and AST elevations were infrequent, but occurred in a larger proportion of patients on nintedanib than on placebo. For example, AST elevations 3 times or more of normal were reported in 3.2% and 0.2% in nintedanib and placebo treated patients, respectively; and ALT elevations 3 times or more of normal were reported in 4.1% and 0.6% in nintedanib and placebo treated patients, respectively. Elevation of AST or ALT along with elevation of bilirubin was not reported in the clinical program.

The Applicant initially proposed in labeling that liver enzymes be monitored as clinically indicated. The Division obtained consultation from the OSE regarding the liver safety signal, in order to better inform the labeling of nintedanib, as it was unclear if routine monitoring should be included in the labeling. After consultation with our OSE colleagues, the Division has decided that the monitoring is warranted. The label will propose checking ALT, AST, and bilirubin prior to initiation of treatment with nintedanib, then monthly for the first 3 months and every 3 months thereafter, and as clinically indicated. (b) (4)

This is consistent with what was done in the clinical program.

Gastrointestinal adverse events:

The most common GI adverse events reported more frequently in nintedanib patients when compared with placebo include diarrhea (62% vs. 18%), nausea (24% vs. 7%), and vomiting (12% vs. 3%). Overall, the GI events tended to be mild to moderate in severity, with few discontinuations (5% for diarrhea, 2% for nausea, and 1% for vomiting). Dose reductions were also required for some patients for these adverse events.

Embryofetal toxicity:

Animal reproductive and developmental toxicology studies demonstrated that nintedanib was a teratogen. The labeling will advise women of childbearing potential to avoid becoming pregnant and use adequate contraception while using nintedanib. The pregnancy category for nintedanib will be D.

Arterial thromboembolic events:

In clinical trials, arterial thromboembolic events were reported in 2.5% of patients treated with nintedanib and 0.8% of placebo-treated patients. Myocardial infarction was the most common adverse reaction under arterial thromboembolic events, occurring in 1.5% of nintedanib-treated patients compared to 0.4% of placebo-treated patients.

Risk of bleeding:

In clinical trials, bleeding events were reported in 10% of patients treated with nintedanib and in 7% of patients treated with placebo.

Gastrointestinal perforation:

In clinical trials, gastrointestinal perforation was reported in 0.3% of patients treated with nintedanib, compared to no cases in the placebo-treated patients.

Hypothyroidism:

In clinical trials, hypothyroidism as adverse events was in 1.1% (n=8) of patients treated with nintedanib (1 was reported as a SAE), compared to 0.6% (n=3) treated with placebo.

c. REMS/RiskMAP

No post-marketing risk evaluation and mitigation strategies are recommended.

9. Advisory Committee Meeting

A Pulmonary-Allergy Drugs Advisory Committee (PADAC) meeting was not held to discuss the nintedanib IPF application. The clinical program showed convincing benefit in FVC, which was supported by numerical trends in favor of mortality, and other secondary efficacy measures. Safety findings noted in the clinical program would not preclude approval of nintedanib for IPF, a life-threatening disease with no available medical treatment. Therefore a PADAC meeting was not deemed necessary as there was no uncertainty on the efficacy and safety data that would impact approval.

10. Pediatric

Specific pediatric studies are not necessary because IPF is a disease of adults and does not occur in the pediatric population. Furthermore, as an orphan drug program, pediatric studies are not required.

11. Other Relevant Regulatory Issues

a. DSI Audits

A high level DSI audit of the Applicant was requested during review of the NDA. Audit of individual sites were not done because the number of patients enrolled in any specific site was small and there were no outlier centers in the program. Final report of the DSI inspections revealed adherence to Good Clinical Practices. Minor deficiencies were noted, but these were isolated and deemed unlikely to impact data integrity and patient safety. During review of the submission, no irregularities were found that would raise concerns regarding data integrity. No ethical issues were present. All studies were performed in accordance with acceptable ethical standards.

b. Financial Disclosure

The applicant submitted acceptable financial disclosure statements. There are no issues with financial disclosures in the studies.

c. Others

There are no outstanding issues with consults received from OPDP, DMEPA, or from other groups in CDER.

12. Labeling

a. Proprietary Name

There are no issues with the proposed proprietary name Ofev. The proposed proprietary name was accepted by the DMEPA.

b. Physician Labeling

The applicant submitted a label in the Physician's Labeling Rule format. The labeling was reviewed by various disciplines of this Division, the DMPP, DRISK, DMEPA, SEALD, and OPDP. Various changes to different sections of the label submitted by the Applicant were made to reflect the data accurately and to better communicate the findings to the healthcare providers. The Division and the Applicant have a final agreed upon label.

c. Carton and Immediate Container Labels

These were reviewed by various disciplines of this Division and DMEPA, and found to be acceptable.

d. Patient Labeling and Medication Guide

Nintedanib will have patient labeling. There will not be a Medication Guide for nintedanib.

13. Action and Risk Benefit Assessment

a. Regulatory Action

The Applicant has submitted adequate efficacy data to support approval of nintedanib for the treatment of IPF. The recommended action on this application is Approval.

b. Risk Benefit Assessment

The overall risk benefit assessment supports approval of nintedanib for the treatment of IPF. Efficacy data show consistent positive benefit of nintedanib in the treatment of IPF. Statistically significant differences in FVC were seen in all three studies favoring nintedanib versus placebo. Benefit in FVC was supported by a numerical trend in favor of mortality. There was also benefit noted in other secondary measures such as IPF exacerbation. Safety data analysis show liver-related adverse events and gastrointestinal adverse events. For the most part, these appear to be patient tolerability issues, which can be managed by dose adjustment. Liver-related adverse events can occur in a small number of patients, but are outweighed by the benefit provided by nintedanib in IPF. Demonstration of efficacy for IPF, which is uniformly progressive and fatal, and for which there are currently no approved or effective therapies, firmly establishes a risk-benefit assessment in favor of the approval of nintedanib.

c. Post-marketing Risk Management Activities

None.

d. Post-marketing Study Commitments

The Office of Clinical Pharmacology recommends a Post Marketing Requirement for a hepatic impairment study to evaluate the impact of hepatic impairment on nintedanib pharmacokinetics so as to update the approved nintedanib labeling with recommendations for appropriate use of nintedanib in patients with hepatic impairment. This study protocol has been submitted, and the study is currently ongoing. The Applicant plans to submit the study results in the 3rd quarter of 2015.

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/s/

BADRUL A CHOWDHURY
10/10/2014