CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OFFICE DIRECTOR MEMO

Office Director Decisional Memo

Date	October 15, 2014
From	Mary H. Parks, M.D.
Subject	Office Director Decisional Memo
NDA/BLA # **Supplement #**	205832
Applicant Name	Boehringer Ingelheim
Date of Submission	
PDUFA Goal Date	January 2, 2015
Proprietary Name / **Established (USAN) Name**	Ofev (nintedanib)
Dosage Forms / Strength	100 and 150 mg gelatin capsules
Proposed Indication(s)	Treatment of idiopathic pulmonary fibrosis
Action:	Approval

Material Reviewed/Consulted OND Action Package, including:	**Names of discipline reviewers**
Medical Officer Review	Miya Okada Paterniti
Statistical Review	Yongman Kim, David Petullo, Feng Zhou, Karl Lin
Pharmacology Toxicology Review	Luqi Pei, Marcie Woods, Tim McGovern, Carol Galvis, Grace Lee
CMC Review/OBP Review	Art Shaw, Craig Bertha, Edwin Jao
Microbiology Review	John Metcalfe, Bryan Riley
Biopharmaceutics	Kareen Riviere, Tapash Ghosh
Clinical Pharmacology Review	Jianmeng Chen, Satjit Brar
Pharmacometrics	Anshu Marathe, Liang Zhao
Pharmacogenomics	Robert Schuck, Christian Grimstein
OPDP	Roberta Szydlo
PLT	Twanda Scales
DGCPC	Anthony Orenica, Janice Pohlman, Susan Thompson
CDTL Review	Banu Karimi-Shah
OC	Linda Ng
OSE/DMEPA	Teresa McMillan, Lubna Merchant, Kendra Worthy
OSE/DRISK	Suzanne Robottom, Reeme Mehta
DMPP	Sharon Williams, LaShawn Griffiths, Melissa Hulett
OSE/OPE	John R. Senior,
Safety	Carol Hill/Sally Seymour
QT-IRT	Huifang Chen, Qianyu Dang, Li Zhang, Jian Liu, Michael Y Li
RPM	Jessica Lee, Ladan Jafari

Introduction
This new drug application is for nintedanib or tradename, Ofev, an inhibitor of multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs) developed for the treatment of idiopathic pulmonary fibrosis (IPF). Nintedanib inhibits platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FDFR) 1-3, vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3).

Idiopathic pulmonary fibrosis is a progressive disease of the lung parenchyma whose pathogenesis is incompletely understood. Patients are typically between 40 and 70 years and the disease occurs more commonly in men. Clinically, patients have progressive dyspnea with the median survival from diagnosis between 3 and 5 years.

There is currently no FDA-approved therapy for IPF. Pirfenidone, a small molecule with anti-fibrotic, anti-oxidant, and anti-inflammatory effects, is approved in Europe, Japan, India, and Canada. Anti-inflammatory agents such as corticosteroids and azathioprine have been tried in the past with little success.

Please see the multiple discipline reviews for this NDA, the cross-discipline team leader (CDTL) memo and division director's memo for a detailed account of the development program and data submitted in support of approval. No review disciplines have identified outstanding issues precluding approval and the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) is recommending approval. I concur with this overall recommendation and my memo will provide a highlight of the efficacy and safety results, discuss some labeling issues, and safety signals to monitor for in the post-marketing setting.

Regulatory History/Background
As summarized in Table 1 of Dr. Paterniti's review, the IND for this product was submitted in April 2011 with the results from a Phase 2 dose-ranging study supporting enrollment into two Phase 3 trials. This product was granted orphan and fast track designation for the indication sought. (b) (4) Breakthrough Designation was also granted.

The IND was opened after the results of a 52-week, dose-ranging Phase 2 study, conducted outside the U.S., were presented to the Division.

Clinical Efficacy
Trials Supporting Efficacy Determination
Clinical efficacy of nintedanib was based on the results from one Phase 2 trial and two Phase 3 trials. All three trials were 52 weeks in duration, randomized, double-blind and placebo-controlled. The two Phase 3 trials were identical in design and study objectives. The Phase 2 trial was a dose-ranging study which included a placebo and a 150 mg twice daily (bid) treatment group. The primary efficacy endpoint in all three trials was the rate in decline of forced vital capacity (FVC) from baseline to Week 52. The following table from Dr. Kim's review summarizes these three trials.

Table 1. Clinical Trials Reviewed

BI Trial No.	Phase	Design	Treatment Arms	Number of Patients	Dates
1199.32	3	52-week, randomized, double-blind, parallel-group, placebo-controlled	Nintedanib 150 mg bid Placebo	309 206	05/2011-10/2013
1199.34	3	same as 1199.32	Nintedanib 150 mg bid Placebo	331 220	05/2011-10/2013
1199.30	2	52-week, dose finding, proof-of concept, randomized, double-blind	Nintedanib 50 mg qd Nintedanib 50 mg bid Nintedanib 100 mg bid Nintedanib 150 mg bid Placebo	87 86 86 86 87	09/2007-06/2010

Source: Page 6, FDA statistical review of Dr. Yongman Kim

There were two secondary efficacy endpoints – time to first acute IPF exacerbation and change from baseline in St. George's Respiratory Questionnaire (SGRQ) score. How these two endpoints were defined and their clinical relevance to IPF are discussed in reviews of Dr. Chowdhury and Paterniti. In the two Phase 3 trials, hierarchical testing procedures to adjust for multiple endpoints included these two key secondary endpoints. The hierarchy for testing was primary endpoint> time to first acute exacerbation > SGRQ score with testing proceeding to the next level only after statistical significance at the 5% level was demonstrated. In the Phase 2 trial, the applicant used a closed testing procedure to adjust for multiple comparisons between each dose. There was no adjustment for secondary endpoints in Study 1199.30.

In addition to the primary and key secondary endpoints noted for the two Phase 3 trials, there were exploratory efficacy outcome variables not adjusted for in statistical testing. Of these, mortality was considered clinically relevant and will be discussed in this memo.

Patient Population

Please see Dr. Paterniti's review of a description of the key inclusion/exclusion criteria for all 3 clinical trials. Briefly, the patients studied were adults (≥40 years) with an IPF diagnosis within the past 5 years. An important exclusion criterion was hepatic impairment defined as transaminases > 1.5 x ULN or bilirubin > 1.5 x ULN which will impact the labeling and PMRs for this product.

Overall, the demographics of the study population reflected the IPF population and baseline characteristics were balanced between treatment groups.

Rate of Decline in FVC

The primary analysis in Studies 1199.32 and 1199.34 was performed on the Treated Set population defined as all randomized patients who received any amount of study drug. For Study 1199.30, the primary analysis population was the Intent-to-treat (ITT) population defined as all randomized patients regardless of actually received treatment. In all three trials, analyses were conducted on observed cases, assuming missing data was at random and was not imputed. Several sensitivity analyses were performed to assess for the impact of missing data. Please see Dr. Kim's review (page 9) for a detailed discussion of the different analyses. These

additional sensitivity analyses provided consistent results as observed with the primary analysis. The following table from Dr. Paterniti's review summarizes the results from all three trials.

Table 13. Annual Rate of FVC Decline: Studies 1199.32, 1199.34, 1199.30 (Treated Population)

	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=204 n (%)	Nintedanib 150 mg BID N=309 n (%)	Placebo N=219 n (%)	Nintedanib 150 mg BID N=329 n (%)	Placebo N=83 n (%)	Nintedanib 150 mg BID N=85 n (%)
Rate of decline in FVC (mL) over 52 weeks						
Adjusted rate (SE)	-240[1] (19)	-115 [1] (15)	-207 [1] (19)	-114 [1] (16)	-190 (36)	-60 (40)
95% CI	(-277,-203)	(-145, -85)	(-245, -169)	(-145, -83)	(-262, -119)	(-135, 16)
Comparison vs. Placebo						
Adjusted rate (SE)	125 (24)		94 (25)		131 (53)	
95% CI	(78, 173)		(45, 143)		(27, 235)[2]	

[1]Adjusted rate based on a random coefficient regression with fixed effects for treatment, gender, age, height and random effect of patient specific intercept and time. Within-patient errors were modelled by an unstructured variance-covariance matrix. Inter-individual variability was modelled by a variance-components variance-covariance matrix

[2] Nominal p-value 0.01, p-value from closed testing procedure 0.07

Source: Module 5.3.5.1, Study 1199.32 CSR, Table 11.4.1.1:1, p 109; SCE, Table 3.2.2.1:1 p 98.

In all three studies, the nintedanib group had a significantly lower rate of decline in FVC from baseline at Week 52 compared to placebo.

A continuous responder analysis was performed in all three trials and continuous responder curves for each treatment arm were plotted by Dr. Kim. A cut-point of at least a 10% relative decline in FVC was considered clinically relevant. In the two Phase 3 studies, the proportion of patients on placebo having a > 10% decline in FVC was higher than nintedanib (Figures 7 and 8 of Dr. Kim's review) and not appreciably different in the Phase 2 study (Figure 17).

Section 6.1.9 of Dr. Paterniti's review discusses persistence of efficacy. Of note, Study 30 had an option for patients to enroll into a dose-blinded active treatment extension period; placebo patients were rolled over to nintedanib 50 mg qd. This extension period provided controlled (albeit not placebo) data for an additional mean duration of 7 months. The nintedanib 150 mg bid group still had statistically significant treatment difference on rate of decline in FVC compared to the original placebo group (received 50 mg qd after 52 weeks).

Key Secondary Endpoints

As noted above, the two Phase 3 studies identified two key secondary endpoints, time to acute IPF exacerbation and SGRQ score, and included these in the hierarchical test for evaluating treatment on multiple endpoints. I note that the company was informed in December 2010 during an End-of-Phase 2 meeting that SGRQ was not developed for use in IPF; it is developed for use in chronic obstructive pulmonary disease (COPD).

As both Phase 3 trials showed a significant treatment effect on the primary endpoint, testing proceeded for the first key secondary endpoint, time to first acute exacerbation over 52 weeks. For this endpoint, a statistically significant effect of treatment was only observed in Study 34 (HR [95% CI]: 0.38 [0.19-0.77], p=0.005). As per hierarchical testing plan, SGRQ score was then evaluated and was found to be significantly lower in the nintedanib group over placebo. Dr. Kim also analyzed the SGRQ endpoint for Study 32 even though testing should have halted after the time to first acute exacerbation as there was no significant effect observed on that endpoint in Study 32. Regardless, no significant effect was note on SGRQ score in Study 32.

Although no secondary endpoints were considered in hierarchical testing in the Phase 2 trial (Study 30), Dr. Kim evaluated these endpoints and found a significant treatment. The Division does not recommend labeling for the SGRQ score given it is not specific to IPF. For time to acute exacerbation the individual study results of each of the 3 trials are proposed for labeling. Since the event characterized as an acute exacerbation was adjudicated in the Phase 3 studies, and representative of clinically meaningful outcome, I agree with the Division's approach.

Mortality

As discussed in the clinical reviews, a reduction in risk of mortality would be desirable. None of the efficacy trials was powered to show a survival benefit; however, an effect of treatment on mortality was evaluated as a secondary endpoint in a variety of ways – vital status (deaths occurring up to the time of end of study treatment period regardless of whether patients continued treatment) or on-treatment (within 28 days of treatment discontinuation). The following table provided by Dr. Banu Karimi-Shah summarizes the results across the different studies, individually and pooled, and by different survival analyses.

Table 7. Survival Analysis (Studies 30, 32, and 34)				
	Number of Events (%)			
Death	**Nintedanib 150 mg BID**	**Placebo**	**Hazard Ratio† (95% CI), p value‡**	**Pre-specified analysis**
Study 30	**N=86**	**N=87**		
Vital Status	7 (8.1)	9 (10.3)	0.73 [0.27, 1.98], p=0.538	Yes
On-treatment*	1 (1.2)	8 (9.2)	0.14 [0.02, 1.11], p=0.034	No
Study 32	**N=309**	**N=204**		
Vital Status	13 (4.2)	13 (6.4)	0.63 [0.29, 1.36], p=0.288	Yes
On-treatment	8 (2.6)	9 (4.4)	0.68 [0.26, 1.82], p=0.487	Yes
Study 34	**N=329**	**N=219**		
Vital Status	22 (6.7)	20 (9.1)	0.74 [0.40, 1.35], p=0.300	Yes
On-treatment	16 (4.9)	17 (7.8)	0.68 [0.34, 1.35], p=0.221	Yes
Pooled Studies 32, 34	**N=638**	**N=423**		
Vital Status	35 (5.5)	33 (7.8)	0.70 [0.43, 1.12], p=0.140	Yes
On-treatment	24 (3.8)	26 (6.1)	0.68 [0.39, 1.19], p=0.160	Yes
Pooled Studies 30, 32, 34	**N=723**	**N=508**		
Vital Status	42 (5.8)	42 (8.3)	0.70 [0.46, 1.08], p=0.096	No
On-treatment	25 (3.5)	34 (6.7)	0.57 [0.34, 0.97], p=0.027	No

† Hazard ratio was based on the Cox proportional hazard model with terms for treatment, sex, age, and height. Study 30 had terms for region instead of treatment.
‡ p-value based on log-rank test(unadjusted for Study 30), comparing nintedanib 150 mg BID to placebo.
*On treatment for study 30 was defined differently: including on AEs that leading to death with an onset date of the event reported during the treatment period plus the earliest of the following three options: 14 days, or first intake of trial drug in extension study, or date of last contact.

Across all the pre-specified analysis plans in all 3 trials, no reduction in risk of mortality was observed; however the lower rate in the nintedanib group consistently observed across all three trials is reassuring.

There has been much internal discussion on whether these negative findings should be allowed in labeling and if so, to what extent. The results based on pooling of all three trials were post-hoc and should not be included in labeling. Furthermore, the two Phase 3 trials were designed to confirm the findings observed in the Phase 2 trial. As Studies 32 and 34 were identical in design and conduct, pooling of these results is appropriate. The Division has proposed that text be included in labeling which states no statistically significant difference between treatment was observed on all-cause mortality and include the K-M estimate for the two Phase 3 trials. This curve would essentially display no discernible difference and will also include the HR and 95% CI. I concur with this approach.

Conclusion on Efficacy

The applicant was able to demonstrate efficacy based on the agreed-upon endpoint of rate of decline in FVC in two adequate and well-controlled trials confirming the findings in an earlier Phase 2 trial. Secondary endpoints supported the primary efficacy findings.

Safety

The main database for evaluating safety included the pooled Phase 2 and 3 trials since these were similarly designed. This safety group provided controlled data in 723 patients exposed to nintedanib 150 mg bid for a mean duration of 10 months and 508 patients exposed to placebo for a mean duration of 11 months. Evaluation of long-term safety included review of the extension periods of these trials. Please see Section 7 of Dr. Paterniti's review for a complete discussion of the safety findings from this program.

Adverse events leading to discontinuation were higher in nintedanib-treated patients than placebo with diarrhea being the most common reason for discontinuation, followed by nausea, decreased appetite, and weight decrease.

More deaths were reported in the placebo group than nintedanib and survival analyses have been discussed above as an exploratory efficacy endpoint. The majority of AEs leading to death fell into the SOC/PT category of 'Respiratory, thoracic, and mediastinal.'

Adverse Events of Special Interest

Adverse events of special interest (AESI) were identified based on non-clinical findings and previous experience with other tyrosine kinase inhibitors which have similar target of effects as nintedanib. Please refer to Table 30 from Dr. Paterniti's review which summarizes AESIs reported in > 2 patients in nintedanib group and at a higher rate than placebo. Abdominal pain and liver enzyme elevation were the most common AESIs reported. Of note, liver enzyme elevation was reported as 14.4% in the nintedanib group vs 2.6% placebo. There were no Hy's law cases and the majority of transaminase and bilirubin elevations were < 5x ULN and < 2x ULN, respectively.

FDA hepatologist, Dr. John Senior, reviewed the liver safety for nintedanib and provided his recommendations on labeling to the Division on September 22, 2014. This has been taken into consideration by the Division and for the most part, there is alignment on baseline monitoring and post-initiation monitoring albeit slight modification to the recommended frequency. Dr. Senior has recommended that the Warnings and Precautions section of labeling direct the prescriber to report liver test abnormalities to the sponsor. Such recommendation goes against the Preamble of the 2006 Final Rule on the Physician Labeling Rule, which in effect states that contact information for reporting adverse reactions shall be included only in the Highlights section of the label.

Other AESIs occurring at a higher rate in nintedanib-treated patients included events falling into the category of arterial thromboembolism, bleeding, GI perforation, hypothyroidism, hypertension, MACE, thromboembolic events, and venous thromboembolism. There was overlap in reporting of specific events across these categories (e.g., MI was reported under MACE and thromboembolic events). Except for (b) (4) the label in its current state includes discussion of these AESIs. (b) (4) The review team received follow-up information on the cases of hypothyroidism in this NDA and only one case (nintedanib) was reported as serious due to hospitalization. TSH levels were reportedly

elevated prior to drug initiation in this patient. The patient received LT4 and recovered without sequelae. While there was an imbalance in reports of hypothyroidism, given the lower incidence observed with nintedanib than what has been reported in the labels of other TK inhibitors, I believe it would be appropriate to describe this imbalance under the Adverse Reactions of labeling for the time being.

Conclusions on Safety

The overall database was adequate for evaluation of safety. The most common adverse events (GI) were, for the most part, non-serious, and were alleviated with dose reduction. More serious AEs were rare and can be mitigated through labeling such that prescribers can appropriately select patients for therapy or monitor for potential side-effects.

Postmarketing Activities

As nintedanib is eliminated primarily by biliary/fecal excretion, drug concentration will likely increase in patients with hepatic impairment. No such study was conducted in this development program; hence, a PK study evaluating safety and tolerability of nintedanib in patients with Child-Pugh Classification A and B and healthy subjects will be conducted as a PMR.

ODE Conclusions and Recommendations

The applicant has provided data from 2 adequate and well-controlled studies of similar design to support approval of nintedanib for the treatment of idiopathic pulmonary fibrosis. These studies were designed and conducted after evaluation of a Phase 2 dose-ranging study provided evidence of efficacy on the rate of decline FVC over placebo with nintedanib 150 mg bid dosing. All three studies provided consistent effect of treatment on this same primary endpoint and reassuring results on the secondary endpoint – time to acute IPF exacerbation – to support a conclusion of benefit. Although there was no significant reduction in mortality, a consistent finding of a HR that was < 1.0 in all three trials was also reassuring.

The program also provided data for an adequate safety evaluation. The most common ARs are GI-related and will more likely affect tolerability which might respond to dose reduction. Serious adverse events were rare and with appropriate labeling these risks may be mitigated through careful patient selection and monitoring while on therapy.

Overall, the effect of nintedanib on slowing the rate of decline in FVC and the acceptable safety profile support a recommendation for approval of this NDA to make available a treatment for this rare and devastating disease.

Pending agreement on product labeling, this NDA should be approved.

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/s/

MARY H PARKS
10/15/2014