

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

205832Orig1s000

MEDICAL REVIEW(S)

Hepatology Consultation

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF SURVEILLANCE AND EPIDEMIOLOGY
OFFICE OF PHARMACOVIGILANCE AND EPIDEMIOLOGY

DATE: 22 September 2014
FROM: John R. Senior, M.D.
Associate Director for Science (Hepatology)
Office of Pharmacovigilance and Epidemiology (OPE)
Office of Surveillance and Epidemiology (OSE)

TO: Badrul Chowdhury, M.D., Director, Division of Pulmonary, Allergy, and
Rheumatology Products (DPARP)
Sally Seymour, M.D., Deputy Director for Safety, DPARP
Banu Karimi-Shah, M.D., Clinical Team Leader, DPARP
Miya Paterniti, M.D., Clinical Reviewer, DPARP

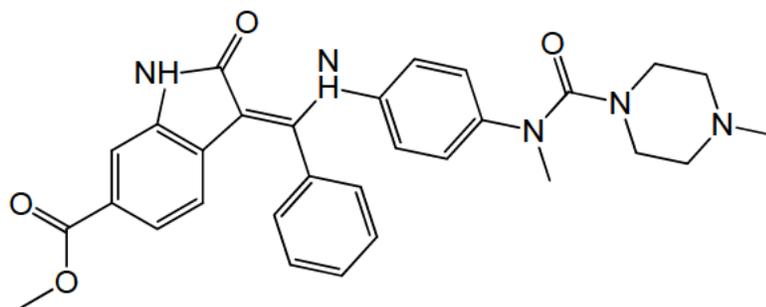
VIA: Solomon Iyasu, M.D., Director, OPE

SUBJECT: Hepatic effects of nintedanib, NDA 295832, submitted 2 May 2014 for treatment of
idiopathic pulmonary fibrosis (IPF)

Documents reviewed:

- 1) Consultation request from DPARP dated 11 August 2014 asking for review of findings related to liver toxicity, desired response date 25 August 2014;
- 2) Draft labeling submitted by Boehringer Ingelheim
- 3) Medical review by Mita Paterniti, M.D. of 3 September 2014
- 4) Selected pertinent medical literature articles

Nintedanib is a synthetic indolinone compound developed by Boehringer Ingelheim (BIBF 1120) that inhibits vascular endothelium growth factor receptor (VEGFR), fibroblast growth factor receptor (FGFR) and platelet-derived growth factor receptor (PDGFR), a group of tyrosine kinase inhibitors, under study as an anti-cancer agent, and also for slowing progression of IPF.



nintedanib (BIBF 1120)

The novel agent BIBR 1120 was a triple angiokinase inhibitor found to have good antitumor efficacy and sustained receptor blockade (Hilberg et al. 2008). It was proposed (Antoniou and Kolb, 2010) as a treatment for idiopathic pulmonary fibrosis (IPF) and studied by Richeldi et al., (2011) soon after in a phase II study dubbed TOMORROW. They carried out a dose-ranging study that showed 150 mg twice daily was needed to slow significantly progression of IPF, despite causing adverse effects of diarrhea, nausea and vomiting. The potential usefulness of nintedanib was noted by Woodcock et al. (2013). A pair of trials was set up by Richeldi and colleagues (INPULSIS I and II) to compare that dose to placebo more in than a 1000 IPF patients, results of which were reported 29 May 2014. Boehringer Ingelheim submitted a new NDA 205832 on 4 May 2014, almost simultaneous (three weeks earlier) with the re-submission of NDA 022535 on 23 May for pirfenidone that also showed very promising efficacy, but with frequent gastrointestinal effects, mainly nausea and vomiting. Both drugs also appeared to cause serum aminotransferase activity elevations in some patients, but with no serious drug-induced hepatotoxicity to date.

Comment: Because it is likely that both drugs will be approved in coming months for this highly lethal and previously untreatable disease, the request for consultation was focused on labeling for both drugs, and later consideration of the hepatotoxicity issues. It was announced in August in the Wall Street Journal (Rockoff and Plumridge) that Roche Diagnostics bought InterMune, the sponsor of pirfenidone, for \$8.3 billion, and expects a profitable return. This may be a major game-changer, with two large pharmaceutical companies battling to market their products, and intense competition. Both agents have similar efficacy, better than placebo but not curative, and with only a hint so far of possible improvement in mortality. They both have distressing adverse gastrointestinal effects, nintedanib more diarrheal, and pirfenidone more nausea and vomiting. Both NDAs were submitted within three weeks in May, and both are considered priority agents for accelerated approval. Both agents have caused a modest number of patients to show serum transaminase elevations, mostly without major symptoms and without liver dysfunction, and none serious so far, but drug exposure has been limited to a few hundred patients. Nintedanib 150 mg twice daily was given to 723 patients and placebo to 508 in dose-ranging and INPULSIS trials. In the three studies of pirfenidone, effective doses of 2403 mg were randomized for administration to 174, 171, and 278 patients in trials PFIF-004,-006, and -016 (total 633), while 634 were treated with placebo. Thus, effective doses of both agents have been given to only 1356 patients with IPF, placebo to 1142, and placebo-controlled trials will not be possible after FDA approval of both agents.

Effects in slowing progression of IPF by both drugs suggest that possibly they may be used together as well as separately. With approval of both agents, it will no longer be ethical to conduct placebo-controlled studies. This is an exciting time, but the enthusiastic celebrations should be tempered by humility because of the limited data. Neither drug cures or completely stops the relentless progression of IPF, at least so far. Both drugs are likely to be promoted aggressively and competitively to tens or hundreds of thousands of IPF patients worldwide. But a great deal remains to be learned about how to use these drugs, singly or in combination, how to optimize their beneficial effects and minimize the very uncomfortable gastrointestinal adverse effects. How labeling may be used to encourage prescribers to continue to study and report to the sponsors the results in patients is problematical; recommendations can be made but not enforced. There is a reasonable aim to harmonize the labeling for both drugs so that neither

company can derive a marketing advantage. At present there is not much to claim about a marketing advantage for the efficacy of either agent, and there are as yet almost no data on head-head comparisons, or of use of combinations.

The situation with respect to possible liver injury and dysfunction is that both pirfenidone and nintedanib have been found apparently to cause at least transient elevations of aminotransferase activities indicating probable hepatocellular injury, with a few also showing some functional disturbance as indicated by rising serum bilirubin concentration, but no cases of liver failure have yet been attributed to the drug. It is a little reassuring that despite marketing of pirfenidone in Japan, South Korea, and Taiwan since 2008, in India since 2010, in Europe since 2011, and in China since 2013, that no cases have been published in which liver failure was probably caused by the drug. There is no post-marketing experience with nintedanib in IPF patients, but perhaps some in patients with cancers treated with it, a different population.

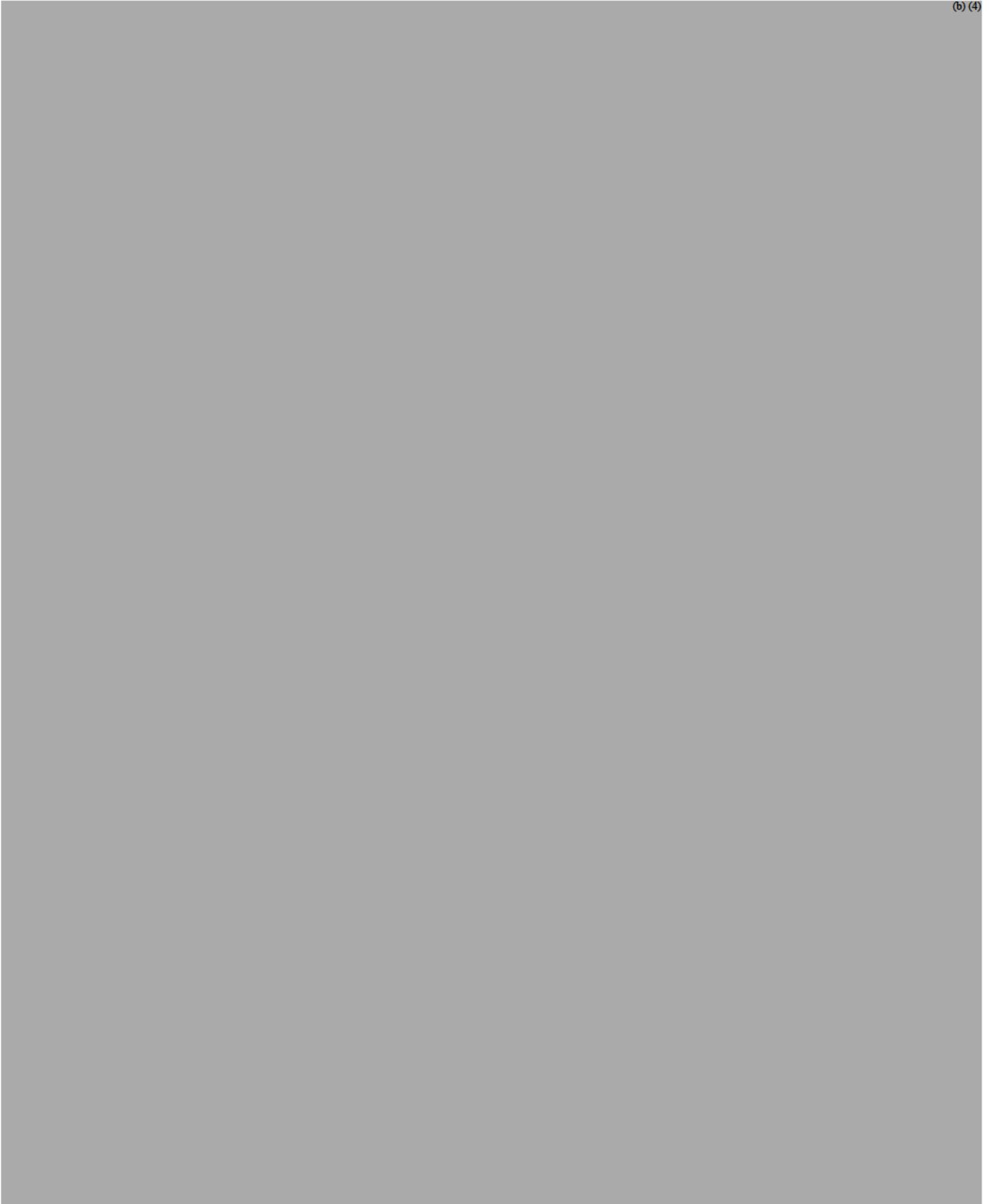
It may be considered useful to recall the experience with another drug important for prevention of another serious disease, tuberculosis. Isoniazid was found to cause frequent elevations of AST activities in about 15% of patients started on it, and could cause liver failure and death if used for too long in certain patients (Black et al., 1975; Kopanoff et al., 1978). A key observation leading to understanding was made by Mitchell et al. (1975) who showed that even drug-induced AST elevations $>10\times\text{ULN}$ with bilirubin $>2.5\times\text{ULN}$ was reversible despite continuing administration, presumably by liver adaptation to the drug. It is well known that the human liver can regenerate after 2/3 of it is resected or damaged, but it became understood the hepatocytes can also change and adapt to chemicals even with less injury than resection or total necrosis. Four decades later we appreciate that of the 10-20% of patients who show serum transaminase elevations after starting isoniazid, almost all of them can adapt to the drug if given time, and only 1 or 2 per thousand (0.1-0.2%) cannot do so, and must have the isoniazid permanently stopped.

After much concern and controversy, it was finally realized (Nolan et al., 1999) that the drug could be used safely if patients on isoniazid preventative treatment were carefully monitored for signs or symptoms of hepatotoxicity (anorexia, nausea, vomiting, jaundice, progressive rise of serum AST $>5\times\text{ULN}$, and resolution of findings after interrupting treatment with isoniazid). Because pirfenidone and nintedanib frequently cause anorexia, nausea, vomiting, the symptoms cannot be counted upon to indicate hepatotoxicity, so reliance must be placed on laboratory measures and very early detection of whole liver dysfunction. Rising bilirubin or prothrombin time (or INR) must be used to indicate early dysfunction. It may also be possible to recognize the adaptation phenomenon whereby the liver can change and become tolerant of a drug that initially causes hepatocellular injury and mild dysfunction, when using a drug important for suppressing a bad disease such as IPF or cancer.

Both sponsors have recognized that at least mild liver injury may be caused by these new drugs for treating IPF, and have proposed labeling to detect it, with action taken to prevent continuing the drug in the rare patient who is liver-intolerant of the drug or whose liver is unable to adapt. A draft suggestion for labeling is provided on the following page, to be discussed when clinical reviews have been completed.

Proposed uniform labeling to prevent serious liver injury for both drugs:

(b) (4)



It goes beyond the question of possible hepatotoxicity (how to detect it, how to prevent it from becoming serious, and how to avoid it) to say that it is clear that much is yet to be learned about these drugs and how best to use them. It has been recommended (Ryerson et al., 2014) that a worldwide registry of patients with IPF be established, including centers for treatment where special expertise exists, and I strongly agree with that idea. (b) (4)

(b) (4)
Ideally all patients with IPF should be enrolled in a registry and followed from before initiation of treatment until death, with as much on-treatment information obtained, reported, and available for analyses as possible.

There are limitations to how much the practice of medicine can be proscribed by labeling, and reliance should not be placed on labeling alone. Active educational programs for treating physicians seem to be a good idea in everyone's best interest: physicians need to learn more about this disease, more data may show true reduction in mortality rates to stimulate sales further, regulatory bodies may get data needed, and certainly patients will be better served. In addition to recommending dosing and monitoring, labeling should instruct physicians and encourage close observation of patients treated, and reporting, promptly and completely of the results noted. Because another new agent, nintedanib, is also about to be approved for treatment of the same disease, there is nothing to prevent physicians from using both together or in some sequence, to determine if better results may be found. In the competitive marketing of these two now agents, it may be too much to ask sponsors eager for return on investment to work together constructively, but at least they should not oppose it.

Because there is little to suggest that nintedanib is better or worse than pirfenidone, the careful wording of the labeling for both new agents should not confer a marketing advantage on one or the other, so pretty much the same labeling should be developed, negotiated, and approved for both agents. I shall be glad to participate in those discussions if desired and as possible.

John R. Senior, M.D.

*Please go to PubMed and enter: **Ahluwalia N 2014 fibrosis**, (PMID 25090037), click on the AJRCCM box to open and read, print, or save. Look carefully at the diagram on page 34/34. (I was unable to copy and insert it here).*

REFERENCES

- Ahluwalia N, Shea BS, Tager AM. New therapeutic targets in idiopathic pulmonary fibrosis: aiming to rein in runaway wound healing responses. *Am J Respir Crit Care Med*. 2014 Aug 4; Epub ahead of print. PMID 25090037
- Antoniou SA, Kolb MR. Nintedanib, a triple kinase inhibitor of VEGFR, FGFR, and PDGFR for the treatment of cancer and idiopathic pulmonary fibrosis. *IDrugs* 2010 May; 13(5):332-45. PMID 20433291
- Chakraborty S, Chopra P, Ambi SV, Datsidar SG, Ray A. Emerging therapeutic interventions for idiopathic pulmonary fibrosis. *Expert Opin Investig Drugs*. 2014 Jul; 23(7):893-910. PMID 24766571
- Hilberg F, Roth GJ, Krssak M, Kautschitsch S, Sommergruber W, Tontsch-Grunt U, Garin-Chesa P, Bader G, Zoephel A, Quant J, Heckel A, Rettig W. BIBF 1120: triple angikinase inhibitor with sustained receptor blockade and good antitumor efficacy *Cancer Res*. 2008 Jun 15; 68(12):4774-82. PMID 18559524
- Hunninghake GM. A new hope for idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29; 370(22):2142-3. PMID 24836311
- King TE Jr, Bradford WZ, Castro-Bernardini S, Fagan EA, Glaspole I, Glassberg MK, Gorina E, Hopkins PM, Kardatzke D, Lancaster L, Lederer DJ, Nathan SD, Pereira CA, Sahn SA, Sussman R, Swigris JJ, Noble PW, for the ASCEND Study Group. A phase 3 trial of pirfenidone in patients with idiopathic pulmonary fibrosis. *N Engl J Med*. 2014 May 29; 370(22):2083-92. PMID 24836312
- Kopanoff DE, Snider DE Jr, Caras GJ. Isoniazid-related hepatitis: a U.S. public health service cooperative surveillance study. *Am Rev Respir Dis*. 1978 Jun; 117(6):991-1001. PMID 666111
- Mitchell JR, Long MW, Thorgeirsson UP, Jollow DJ. Acetylation rates and monthly liver function tests during one year of isoniazid preventative therapy. *Chest* 1975 Aug; 68(2):181-90. PMID 1080096
- Black M, Mitchell JR, Zimmerman HJ, Ishak KG, Epler GR. Isoniazid-associated hepatitis in 114 patients. *Gastroenterology* 1975 Aug; 69(2):289-302. PMID 1150039
- Noble PW, Albera C, Williamson ZB, Costabel U, Glassberg MK, Kardatzke D, Talmadge ET Jr, Lancaster L, Sahn SA, Schwarzeberg J, Valeyre D, du Bois RM, for the CAPACITY Study Group. Pirfenidone in patients with idiopathic pulmonary fibrosis (CAPACITY): two randomized trials. *Lancet* 2011 May 21; 1760-9. PMID 21571362
- Nolan CM, Goldberg SV, Buskin SE. Hepatotoxicity associated with isoniazid preventative therapy: a 7-year survey from a public health tuberculosis clinic. *JAMA*. 1999 Mar; 281(11):1014-18. PMID 10086436

Novelli L, Alberti S, Pesci A. Dyspnea in crackling lungs. *Eur J Intern Med.* 2014 Jul 3; pii Epub ahead of print. PMID 24998757

Richeldi L, Cottin V, Flaherty KR, Kolb M, Inoue Y, Raghu G, Taniguchi H, Hansell DM, Nicholson AG, Le Mauf F, Stowasser S, Collard HR. Design of the INPULSIS trials: two phase 3 trials of nintedanib in patients with idiopathic pulmonary fibrosis. *Respir Med.* 2014; 108:1023-30. PMID24834811

Richeldi L, Costabel U, Selman M, Kim DS, Hansell DM, Nicholson AG, Brown KK, Flaherty KR, Noble PW, Raghu G, Brun M, Gupta A, Juhel N, Kluglich M, du Bois RM. Efficacy of a tyrosine kinase inhibitor in idiopathic pulmonary fibrosis. *N Engl J Med.* 2011 Sep 22; 365(12):1079-87. PMID 21992121

Richeldi L, du Bois RM, Raghu G, Azuma A, Brown KK, Costabel U, Cottin V, Hansell DM, Inoue Y, Kim DS, Kolb M, Nicholson AG, Noble PW, Selman M, Taniguchi H, Brun M, LeMauf F, Girad M, Stowasser S, Schlenker-Herceg R, Disse B, and Collard HR, for the INPULSIS trial investigators. Efficacy and safety of nintedanib in idiopathic pulmonary fibrosis. *N Engl J Med.* 2014 May 29; 370(22):2071-82. PMID 24836310

Richeldi L (King TEJr). Treatments for idiopathic pulmonary fibrosis. (Replies to comments by Koczulla, Izumi-Iikura-Sugiyama, Ohkubo-Takeda-Niimi, Thabaut-Crestani) *N Engl J Med.* 2014 Aug 21; 371(8):781-4. PMID 25140967

Rockoff JD, Plumridge H. Roche bets \$8.3 billion on new lung drug. *Wall Street Journal.* 2014 Aug 25: B1-B2.

Ryerson CJ, Corte TJ, Collard HR, Richeldi L. A global registry for idiopathic pulmonary fibrosis: the time is now. *Eur Respir J.* 2014 Aug; 44(2):273-6. PMID 25082902

Wells AU, Kokosi M, Karagiannis K. Treatment strategies for idiopathic interstitial pneumonias. *Curr Opin Pulm Med.* 2014 Sep; 20(5):442-8 PMID 25032814

Woodcock HV, Molyneaux PL, Maher TM. Reducing lung function decline in patients with idiopathic pulmonary fibrosis: potential of nintedanib. *Drug Design Devel Ther.* 2013 Jun 19; 7:503-10. PMID23818761

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

JOHN R SENIOR
09/23/2014

CLINICAL REVIEW

Application Type	NDA
Application Number(s)	205832
Priority or Standard	Priority
Submit Date and Received Date	May 2, 2014
PDUFA Goal Date	January 2, 2014
Division / Office	DPARP/ODEII/OND/CDER/FDA
Reviewer Name(s) Through CDTL	Miya Okada Paterniti, M.D. Banu Karimi-Shah, M.D.
Review Completion Date	September 3, 2014
Established Name (Proposed) Trade Name	Nintedanib Ofev [®]
Therapeutic Class Applicant	Tyrosine Kinase Inhibitor Boehringer Ingelheim
Formulation(s) Dosing Regimen	150 mg Soft Gelatin Capsule 150 mg Twice Daily
Indication(s)	Treatment of idiopathic pulmonary fibrosis
Intended Population(s)	Adults with idiopathic pulmonary fibrosis

Template Version: [March 6, 2009](#)

Table of Contents

1	RECOMMENDATIONS/RISK BENEFIT ASSESSMENT.....	8
1.1	Recommendation on Regulatory Action	8
1.2	Risk Benefit Assessment	8
1.3	Recommendations for Postmarket Risk Evaluation and Mitigation Strategies.....	13
1.4	Recommendations for Postmarket Requirements and Commitments	13
2	INTRODUCTION AND REGULATORY BACKGROUND.....	13
2.1	Product Information.....	13
2.2	Tables of Currently Available Treatments for Proposed Indications	13
2.3	Availability of Proposed Active Ingredient in the United States	14
2.4	Important Safety Issues with Consideration to Related Drugs.....	14
2.5	Summary of Pre-submission Regulatory Activity Related to Submission.....	14
2.6	Other Relevant Background Information	15
3	ETHICS AND GOOD CLINICAL PRACTICES	15
3.1	Submission Quality and Integrity.....	15
3.2	Compliance with Good Clinical Practices.....	15
3.3	Financial Disclosures.....	16
4	SIGNIFICANT EFFICACY/SAFETY ISSUES RELATED TO OTHER REVIEW DISCIPLINES.....	17
4.1	Chemistry Manufacturing and Controls	17
4.2	Clinical Microbiology.....	17
4.3	Preclinical Pharmacology/Toxicology	17
4.4	Clinical Pharmacology	18
4.4.1	Mechanism of Action	18
4.4.2	Pharmacodynamics.....	18
5	SOURCES OF CLINICAL DATA.....	21
5.1	Tables of Studies/Clinical Trials	21
5.2	Review Strategy.....	22
5.3	Discussion of Individual Studies/Clinical Trials	23
5.3.1	Studies 1199.32 and 1199.34	23
5.3.2	Study 1199.30	38
6	REVIEW OF EFFICACY	43
	Efficacy Summary	43
6.1	Indication	45
6.1.1	Methods.....	45
6.1.2	Demographics	46
6.1.3	Subject Disposition	52
6.1.4	Analysis of Primary Endpoint.....	55

6.1.5 Analysis of Secondary Endpoints(s).....	61
6.1.6 Other Endpoints	65
6.1.7 Subpopulations	71
6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations	72
6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.....	75
6.1.10 Additional Efficacy Issues/Analyses.....	77
7 REVIEW OF SAFETY	77
7.1 Methods	79
7.1.1 Studies/Clinical Trials Used to Evaluate Safety.....	79
7.1.2 Categorization of Adverse Events	79
7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence	80
7.2 Adequacy of Safety Assessments	80
7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations	80
7.2.2 Explorations for Dose Response	81
7.2.3 Special Animal and/or In Vitro Testing	83
7.2.4 Routine Clinical Testing.....	83
7.2.5 Metabolic, Clearance, and Interaction Workup.....	83
7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class	83
7.3 Major Safety Results	84
7.3.1 Deaths	84
7.3.2 Nonfatal Serious Adverse Events.....	85
7.3.3 Dropouts and/or Discontinuations.....	86
7.3.4 Significant Adverse Events	87
7.3.5 Submission Specific Primary Safety Concerns	88
7.4 Supportive Safety Results.....	94
7.4.1 Common Adverse Events	94
7.4.2 Laboratory Findings	100
7.4.3 Vital Signs	102
7.4.4 Electrocardiograms (ECGs)	103
7.5 Other Safety Explorations	103
7.5.1 Dose Dependency for Adverse Events	103
7.5.2 Time Dependency for Adverse Events.....	106
7.5.3 Drug-Demographic Interactions.....	106
7.5.4 Drug-Disease Interactions	108
7.5.5 Drug-Drug Interactions	109
7.6 Additional Safety Evaluations	112
7.6.1 Human Carcinogenicity.....	112
7.6.2 Human Reproduction and Pregnancy Data	112
7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound.....	112
7.7 Additional Submissions / Safety Issues.....	113
7.7.1 120-day Safety Update.....	113

7.7.2 Long-term safety	113
7.7.3 Other indications	128
8 POSTMARKETING EXPERIENCE	129
9 APPENDICES	129
9.1 Literature Review/References	129
9.2 Labeling Recommendations	130
9.3 Advisory Committee Meeting	131

Table of Tables

Table 1. Regulatory History.....	14
Table 2. Sources of clinical data.....	21
Table 3. Schedule of Assessments: Studies 1199.32 and 1199.34.....	26
Table 4. Concomitant Medication Exclusions: Studies 1199.32 and 1199.34.....	29
Table 5. Treatment groups: Studies 1199.32 and 119.9.34.....	29
Table 6. Management of Liver Enzyme Elevations: Studies 1199.32 and 1199.34.....	32
Table 7. Protocol Violations (Treated population): Studies 1199.32 and 1199.34.....	38
Table 8. Period 1 Schedule of Assessments: Study 1199.30.....	40
Table 9. Baseline demographics: Studies 1199.32, 1199.34 and 1199.30 combined (Treated Population).....	46
Table 10. Baseline demographics: Individual results for Studies 1199.32, 1199.34 and 1199.30 (Treated Population).....	47
Table 11. Baseline IPF disease characteristics: Studies 1199.32, 1199.34, and 1199.30 (Treated population).....	48
Table 12. Subject disposition: Studies 1199.32, 1199.34, and 1199.30 (Randomized population).....	54
Table 13. Annual Rate of FVC Decline: Studies 1199.32, 1199.34, 1199.30 (Treated Population).....	56
Table 14. Primary efficacy endpoint sensitivity analysis populations: Study 1199.32 (Randomized population).....	59
Table 15. Results for key secondary efficacy endpoints: Study 1199.32, 1199.34, (Treated population) and Study 1199.30 (Randomized Population).....	62
Table 16. Results for Time to Death over 52 weeks: Studies 1199.32, 1199.34, and 1199.30 (Treated Set).....	64
Table 17. Secondary endpoints: Study 1199.32 and 1199.34 (Treated population).....	66
Table 18. Dose reductions/increases (Studies 1199.32, and 1199.34; Treated population. Study 1199.30; Randomized Population).....	72
Table 19. Primary Efficacy Results for All Doses: Study 1199.30 (Randomized Population)....	74
Table 20. Rate of Decline in FVC (mL) for All Doses: Study 1199. 30 Period 1 + Period 2 (~ 80 weeks, Randomized Population).....	75
Table 21. Change from baseline in FVC (mL): Study 1199.33 (Treated population).....	76
Table 22. Safety Groupings.....	80
Table 23. Overall duration of exposure to nintedanib for SG-1: Studies 1199.32, 1199.34, and 1199.30.....	81
Table 24. Exposure with Dose reductions: SG 1.1 - Studies 1199.32 and 34.....	82
Table 25. Dose reductions: SG 1.2 - Study 1199.30.....	82
Table 26. AEs leading to death: SG 1- Studies 1199.32, 1199.34, and 1199.30.....	84
Table 27. SAEs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	85
Table 28. AEs leading to premature treatment discontinuation reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	87

Table 29. AEs leading to permanent dose reduction reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	88
Table 30. AESIs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group and associated AESIs : SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	89
Table 31. Malignancies SMQ: SG 1 - Studies 1199.32, 1199.34, and 1199.30 (Randomized Population).....	92
Table 32. Frequency of patients with Neoplasms benign, malignant and unspecified (incl cysts and polyps) and Malignancy AEs ¹ for Study 1199.30 (Treated population).....	93
Table 33. Common AEs reported in ≥ 5% patients in the nintedanib group and > 1% greater than the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	94
Table 34. Diarrhea AEs: intensity, clinical consequences and outcome: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	95
Table 35. Diarrhea AE: time to onset, number, and duration of episodes: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	96
Table 36. Nausea AEs: intensity, clinical consequences and outcome: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	97
Table 37. Nausea AE: time to onset, number, and duration of episodes: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population,).....	98
Table 38. Summary of individual patients liver enzyme and bilirubin worse value on treatment: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population).....	100
Table 39. Marked changes in blood pressure: SG 1.1 - Study 1199.32 and 1199.34 (Treated population).....	102
Table 40. Adverse events occurring in ≥ 10% of patients in any treatment group: Study 1199.30 (all doses, Treated population).....	104
Table 41. AEs leading to discontinuation of study medication >2% of patients in any group: Study 1199.30 (Treated population).....	105
Table 42. Treatment groups: Study 1199.31 (Randomized and Treated population).....	110
Table 43. Gastrointestinal and Investigations AEs for the nintedanib150 mg BID treatment group more common than placebo: Study 1199.31 (Randomized and treated population).....	110
Table 44. Schedule of Assessments: Study 1199.30 Period 2.....	116
Table 45. Subject Disposition: Study 1199.30 Period 2.....	117
Table 46. Schedule of Assessments: Study 1199.35.....	118
Table 47. Subject Disposition: Study 1199.35.....	120
Table 48. Schedule of Assessments: Study 1199.33.....	121
Table 49. Subject Disposition: Study 1199.33 (Treated Population).....	122
Table 50. Overall duration of exposure to nintedanib for the long-term safety studies: Studies 1199.30 Period 2, 1199.35, and 1199.33 (Treated population).....	123
Table 51. Patients with liver enzyme or bilirubin values analyzed as multiples of the ULN (Studies 1199.30 Period 2, 1199.35, and 1199.33).....	128
Table 52. Labeling recommendations.....	130

Table of Figures

Figure 1. Nintedanib clinical development program flow of studies.....	22
Figure 2. Study Design: Studies 1199.32 and 1199.34.....	25
Figure 3. Management of Mild to Moderate Diarrhea: Studies 1199.32 and 1199.34	30
Figure 4. Management of Severe Diarrhea: Studies 1199.32 and 1199.34	31
Figure 5. Mean observed FVC change from baseline (mL) over time: Study 1199.32 (Treated population)	57
Figure 6. Mean observed FVC change from baseline (mL) over time: Study 1199.34 (Treated population)	58
Figure 7. Mean (SEM) observed FVC change from baseline (L) over time: Study 1199.30 (Randomized population).....	59
Figure 8. Sensitivity analysis of the rate of decline in FVC (ml/year) over 52 weeks: Study 1199.32.....	60
Figure 9. Sensitivity analysis of the rate of decline in FVC (ml/year) over 52 weeks: Study 1199.34.....	61
Figure 10. Cumulative distribution of relative change from baseline in SGRQ total score: Studies 1199.32 and 1199.34.....	63
Figure 11. Cumulative distribution of relative change from baseline in FVC: Study 1199.32	68
Figure 12. Cumulative distribution of relative change from baseline in FVC: Study 1199.34	69
Figure 13. Cumulative distribution of relative change from baseline in FVC: Study 1199.30	69
Figure 14. Mean (SEM) observed FVC change from baseline (mL) over time by dose intensity (>90%, <= 90%) - Pooled 1199.32 and 1199.34	73
Figure 15. Rate of decline in FVC (L/year) at 52 weeks	74
Figure 16. The relationship of proportions of patients with diarrhea with steady state AUC: Study 1199.30, all doses.....	105

1 Recommendations/Risk Benefit Assessment

1.1 Recommendation on Regulatory Action

Based on my review of the risk-benefit assessment, my recommendation is **Approval** of nintedanib 150 mg twice daily for the treatment of idiopathic pulmonary fibrosis (IPF), pending revisions to the label.

1.2 Risk Benefit Assessment

In order to frame the discussion regarding risk-benefit assessment, a brief summary of the efficacy and safety of nintedanib is provided below.

Introduction

Boehringer Ingelheim (BI) submitted a 505(b)(1) New Drug Application (NDA 205832) for nintedanib capsules for the treatment of patients with idiopathic pulmonary fibrosis (IPF). IPF is a chronic progressive, diffuse parenchymal lung disease of unknown etiology. It is characterized by scarring of the lungs, non-productive cough, and progressive dyspnea. Median survival time in patients with IPF is estimated to be from 3 to 5 years, with respiratory failure being the most frequent cause of death. IPF affects approximately 100,000 patients in the United States and therefore has been granted orphan drug designation. The published worldwide incidence rate ranges from 0.6 to 17.4 per 100,000 person years.¹

Currently, there are no FDA-approved therapies for an IPF indication. Hence, there is no regulatory precedent for an IPF clinical development program. While mortality has been encouraged as the ideal primary endpoint for IPF clinical programs, powering studies for this endpoint has been challenging. In the current development program, the Applicant studied the annual rate of decline in lung function (forced vital capacity, FVC). There has been much debate as to whether FVC is an appropriate primary efficacy endpoint, as it has not been established as a validated clinical surrogate for clinically important outcomes. Additionally, there is a lack of information on what difference is considered clinically important. However, in a disease that is marked by a progressive decline in lung function, FVC appears to be a logical primary endpoint, and was therefore considered acceptable for this clinical development program. Due to the uncertainty around several aspects of the primary endpoint, clinically important secondary endpoints and evaluation of mortality are also factored into the evaluation, in order to support the primary endpoint.

Summary of Clinical Findings

Summary of Efficacy

Boehringer Ingelheim (BI) submitted the results of three 52-week, double-blind, randomized, placebo-controlled, clinical trials in patients with IPF (Studies 1199.30, 1199.32 and 1199.34) to

support the efficacy of nintedanib to treat IPF. Studies 1199.32 and 1199.34 were replicate, confirmatory, phase 3 studies of nintedanib 150 mg twice daily (BID) compared to placebo. Study 1199.30 was a phase 2 dose-ranging study of similar design. Although Study 1199.30 was designated as supportive data by the Applicant, due to the similar design/duration and inclusion of the treatment arms of interest, the nintedanib 150 mg BID and placebo treatment arms of Study 1199.30 were evaluated by this reviewer as pivotal study data to support the efficacy of nintedanib.

The pivotal studies enrolled patients aged ≥ 40 years of age with a diagnosis of IPF (ATS/ERS/JRS/ALAT criteria) for <5 years. Diagnoses were centrally adjudicated based on radiologic and, if applicable, histopathologic confirmation. Patients were required to have mild to moderate disease, with an FVC $\geq 50\%$ of predicted and a carbon monoxide diffusing capacity (DLCO, corrected for hemoglobin) 30% to 79% of predicted. Patients with relevant airways obstruction (i.e., pre-bronchodilator FEV1/FVC <0.7) or, in the opinion of the investigator, likely to receive a lung transplant during the studies were excluded (being listed for lung transplant was acceptable for inclusion). For the most part, concomitant medications being used to treat IPF were prohibited; allowances were made in the case of acute IPF exacerbation and progression of disease.

A total of 1231 patients with IPF were randomized into the 3 studies. The phase 3 studies (1199.32 and 1199.34) enrolled the majority of patients (n=423 on placebo and n=638 on nintedanib 150 mg BID). The phase 2 study (1199.30) enrolled 85 patients in each of the nintedanib 150 mg BID and placebo treatment groups.

For all 3 studies, the baseline characteristics were balanced across treatment groups. The mean age was 67 years (range: 42 to 89 years), with 39% of patients < 65 years of age. Most patients were male (79%), Caucasian (60%) or Asian (30%), and current or former smokers (72%). The majority of patients were enrolled outside the US (87%).

For the phase 3 studies, approximately 97-98% of patients met criteria for definite IPF on high-resolution computed tomography scan (HRCT). All patients with a possible diagnosis of IPF had their diagnosis confirmed by lung biopsy. Baseline mean percent predicted FVC was 80%. A total of 76% of patients completed the study without discontinuing trial medication. An additional 5% of patients completed the planned observation time despite early treatment discontinuation.

The primary efficacy endpoint was the annual rate of decline in FVC. All three studies achieved statistical significance for the primary endpoint in favor of nintedanib. The treatment difference (nintedanib – placebo) in trials 1199.30, 1199.32 and 1199.34 was 131mL/year (95% CI: 27, 235mL), 125mL/year (95% CI: 78, 173mL), and 94mL/year (95% CI: 45, 143 mL), respectively.

The statistical reviewer conducted a continuous responder analyses to provide the relative benefit of nintedanib across the entire range of response over 52 weeks. The positive treatment effect of nintedanib was demonstrated by consistent separation of the curve across different levels of

response in all 3 studies. As an example, only 35% of nintedanib-treated patients had a 10% or greater decline in FVC compared to 50% of placebo-treated patients.

Key secondary endpoints included time to IPF exacerbation and St. George's Respiratory Questionnaire (SGRQ) score absolute change from baseline compared to placebo. IPF exacerbation was defined as unexplained worsening or development of dyspnea or new diffuse pulmonary infiltrates on CXR and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities), and exclusion of alternative causes. SGRQ is a disease-specific patient-reported instrument which measures symptoms, activities, and its impact on daily life.

Time to IPF Exacerbation in two studies (1199.30 and 1199.34) demonstrated statistical significance of nintedanib compared to placebo [Study 1199.30 (HR 0.16; 95% CI: 0.04, 0.71) and Study 1199.34 (HR 0.38; 95% CI: 0.19, 0.77)]. For Study 1199.32, nintedanib did not demonstrate a statistically significant difference compared to placebo [HR -1.2; 95% CI: 0.5, 2.4].

For SGRQ score change from baseline to Week 52 Studies 1199.30 and 1199.34 also demonstrated a statistically significant difference of nintedanib over placebo in the change from baseline to Week 52 in SGRQ total score [Study 1199.30 (HR -6.12; 95% CI: -10.57, -1.67) and Study 1199.34 (HR -2.69; 95% CI: -4.95, -0.43)]. Study 1199.32 did not show a statistically significant difference between the two treatment groups for SGRQ [HR -0.1; 95% CI: -2.5, 2.4].

Mortality was an additional efficacy endpoint. Mortality (time to death) was assessed on treatment (within 14 days of treatment discontinuation) and vital status was obtained for patients who discontinued (vital status at the end of study). Cause of death was adjudicated. The majority of deaths were due to respiratory causes. Survival was analyzed in a number of ways. None of the individual studies demonstrated a survival benefit; however, they were not powered to examine this endpoint. Each of the three studies demonstrated a numerical trend for survival benefit in favor of nintedanib compared to placebo. The rates for all-cause mortality for nintedanib versus placebo in Studies 1199.32, 1199.34, and 1199.30 were: 4.2% vs. 6.4%, 6.7% vs. 9.1%, and 8.2% vs. 10.6%, respectively. In a pre-specified integrated analysis of Studies 1199.32 and 1199.34, there were numerically fewer deaths in the nintedanib group (5.5%) compared to the placebo group (7.8%), however the integrated analysis did not achieve statistical significance [HR 0.7; 95% CI 0.43, 1.12]. A post-hoc analysis in which all three studies were pooled also demonstrated similar non-significant, but numerically favorable results [HR 0.7; 95% CI 0.46, 1.08].

Overall, the efficacy of nintedanib for the treatment of IPF has been demonstrated. Three studies showed a statistically significant difference in the primary efficacy endpoint of annual rate of FVC decline. Efficacy is further supported by the key secondary endpoints of time to IPF exacerbation and SGRQ score, which demonstrated statistically significant differences in 2 of the 3 studies. Although not powered for survival, a numerical trend favoring nintedanib was seen for survival in both pre-specified and sensitivity analyses.

Summary of Safety

The safety evaluation of nintedanib similarly relies on data from Studies 1199.30 (Phase 2), 1199.32, and 1199.34. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar (1199.32 and 1199.34 were identical) in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of nintedanib received. Safety assessments in these 3 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. Each of these studies had associated long-term safety studies (1199.30 period 2, 1199.33, and 1199.35) that did not reveal any additional safety signals.

There were a total of 723 patients treated with nintedanib 150 mg BID and 508 patients treated with placebo. The mean treatment duration was similar between the treatment groups (10-11 months). Subjects could dose reduce from 150 mg BID to 100 mg BID or dose interrupt for adverse events. In the phase 3 studies, the majority of dose reductions occurred due to an adverse event and were more common in the nintedanib treated patients (28%) compared to placebo (4%). A total of 98% of placebo and 76% of nintedanib treated patients finished the study at the full dose, resulting in a dose intensity (actual amount of drug received over the study divided by the amount of drug planned) of 99% in the placebo treated subjects and 94% of nintedanib treated subjects. Similar dose reduction results were seen in Study 1199.30.

Overall, there were numerically fewer deaths in the nintedanib treated patients (5.3%) vs. placebo- treated patients (8.5%). The most common AE leading to death was IPF (4.1% placebo vs. 2.5% nintedanib), followed by pneumonia (0.6% placebo vs. 0.7% nintedanib). Deaths are discussed in further detail in the efficacy summary above.

The overall occurrence of serious adverse events (SAEs) was equally distributed across treatment groups (~30%). The 3 SAEs that were reported more frequently in the nintedanib group as compared with placebo were myocardial infarction (1.1% nintedanib, 0.4% placebo), diarrhea (0.7% nintedanib, 0.2% placebo), and transient ischemic attack (0.4% nintedanib, 0% placebo).

AEs leading to discontinuation were slightly more frequent in the nintedanib-treated patients (20.6%) compared to placebo (15.0%). Diarrhea was the most common reason for discontinuation (5.3% nintedanib vs. 0.2% placebo). The next most frequent adverse events leading to discontinuation more frequently in the nintedanib-treated patients compared to placebo-treated patients were nausea, decreased appetite, and weight decreased.

The overall rates of patients with AEs leading to permanent dose reduction were higher in the nintedanib group (16.3%) than in the placebo group (1.4%). The rates were highest in patients with adverse events in the system organ class (SOC) of GI Disorders (13.3% nintedanib vs. 0% placebo). The common AEs (>2 patients) that led to dose reduction that were reported more frequently by patients treated with nintedanib than placebo included diarrhea, nausea, abdominal

pain, decreased appetite, hepatic function abnormal, weight decreased, and transaminase increased.

Before unblinding, the Applicant identified a number of clinically important adverse events of special interest (AESI). These AESI were identified based upon relevant non-clinical findings, human experience in previously conducted nintedanib IPF clinical trials, and potential class effects of tyrosine kinase inhibitors including the effects on the platelet derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR). Abdominal pain (15.2% nintedanib vs. 6.1% placebo) and liver enzyme elevation (14.4% nintedanib vs. 2.6% placebo) were the most common AESIs. Arterial thromboembolic events, major adverse cardiovascular events (MACE), thromboembolic events, and venous thromboembolism were overlapping AESI's and were all more frequent in the nintedanib group. Myocardial infarction was the most common AE within these groups occurring in 1.5% of nintedanib-treated patients vs. 0.4% of patients in the placebo group. In the case of hepatic laboratory abnormalities, there were no Hy's law cases. Liver enzyme elevations were more frequent (14% nintedanib vs. 2.6% placebo), led to more frequent early discontinuations (2.1% nintedanib vs. 0.4% placebo), and permanent dose reductions (1.5% nintedanib vs. 0.2% placebo) in nintedanib treated patients compared to placebo treated patients. The majority of elevated liver enzymes and bilirubin events were $\leq 3x$ ULN and $\leq 1.5x$ ULN, respectively. Most patients returned to within the normal range by the end of treatment.

Common adverse reactions that occurred at a frequency of $\geq 5\%$ and more commonly than placebo include: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, and weight decreased.

The safety database is adequate to assess the safety of nintedanib. The safety findings should be factored into the risk-benefit assessment of nintedanib treatment in patients with IPF.

Risk-Benefit Assessment

The nintedanib clinical development program has demonstrated robust efficacy, with all three studies demonstrating a statistically significant benefit on the annual rate of decline in FVC, support from two key secondary endpoints (IPF exacerbation and SGRQ), and a numerically favorable trend towards survival benefit. While there are numerous safety signals that will need to be closely followed in these patients, the majority center on gastrointestinal tolerability which can be addressed in most patients with symptom management, dose modification, or temporary treatment interruptions.

IPF is a disease with no known effective therapies, in which lung function progressively declines and patients have a median survival of 3 to 5 years after diagnosis. Given the severity of the disease, and the unmet medical need in this patient population, the risk-benefit profile supports the approval of nintedanib for treatment of patients with IPF.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

No postmarket risk evaluation and mitigation strategies are recommended at the time of this review.

1.4 Recommendations for Postmarket Requirements and Commitments

The Office of Clinical Pharmacology recommends one Post Marketing Requirement (PMR) study to evaluate the impact of hepatic impairment on nintedanib pharmacokinetics. Hepatic impairment has been shown to increase the exposure of nintedanib, which is predominantly metabolized by the liver. The goal of this study is to provide information regarding dose adjustment in a population with hepatic impairment, such that the population for whom this drug is indicated may be safely broadened; currently, nintedanib is not recommended for patients with moderate to severe hepatic impairment.

2 Introduction and Regulatory Background

2.1 Product Information

Nintedanib (tradename Ofev®) is a new molecular entity in an established pharmacologic class of kinase inhibitors. Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is necessary for the proliferation, migration, and transformation of fibroblasts. These pathways have been proposed as essential mechanisms in IPF pathology. In addition, nintedanib inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of FLT3 and nRTK inhibition to IPF efficacy is unknown.

The proposed indication is the treatment of patients with idiopathic pulmonary fibrosis (IPF). The proposed dosing regimen is 150 mg by mouth twice daily, with the option to reduce to 100 mg twice daily in the case of intolerance or adverse reactions.

2.2 Tables of Currently Available Treatments for Proposed Indications

Currently, there are no FDA-approved treatments for any aspect of IPF. Esbriet (pirfenidone) is approved outside the U.S for the treatment of IPF.

2.3 Availability of Proposed Active Ingredient in the United States

Nintedanib is a new molecular entity and is not currently marketed in the United States or elsewhere.

2.4 Important Safety Issues with Consideration to Related Drugs

Pazopanib is a kinase inhibitor that shares similar targets with nintedanib (VEGFR, PDGFR, FGFR, and Lck). Pazopanib was approved in 2009 and is indicated for the treatment of patients with advanced renal cell carcinoma and advanced soft tissue sarcoma who have received prior chemotherapy. In the approved package insert of Pazopanib, the following are listed in the Warnings and Precautions section: elevated liver enzymes, bilirubin, cardiac dysfunction including prolonged QT intervals and torsades de pointes, fatal hemorrhagic events, arterial thromboembolic events, venous thromboembolic events, thrombotic microangiopathy, gastrointestinal perforation, reversible posterior leukoencephalopathy syndrome (RPLS), hypertension, proteinuria, infection, and embryofetal toxicity.

Per the package insert, the most common adverse reactions in patients with advanced renal cell carcinoma ($\geq 20\%$) are diarrhea, hypertension, hair color changes (depigmentation), nausea, anorexia, and vomiting. The most common adverse reactions in patients with advanced soft tissue sarcoma ($\geq 20\%$) are fatigue, diarrhea, nausea, decreased weight, hypertension, decreased appetite, hair color changes, vomiting, tumor pain, dysgeusia, headache, musculoskeletal pain, myalgia, gastrointestinal pain, and dyspnea.

2.5 Summary of Pre-submission Regulatory Activity Related to Submission

Prior to submission of this NDA, this product has been the subject of multiple regulatory interactions (as IND 74683). Key regulatory milestones and meetings are summarized below in Table 1.

Table 1. Regulatory History		
Date	Interaction	Highlights of Discussion
Aug 2006	Pre-IND meeting	-FVC cannot be used as a surrogate for survival -No non-clinical support for proposed doses
Dec 2010	End-of-Phase 2	-Requested specification on addressing lung transplant in the phase 3 program -Discussion regarding the use of SGRQ in the phase 3 program; Division stated that SGRQ was not developed for use in IPF
Apr 2011	IND 74, 683 opened	-2 international, replicate P3 trials begun
Jun 2011	Orphan Designation	-Granted

Table 1. Regulatory History		
Date	Interaction	Highlights of Discussion
May 2013	Fast Track Designation	-Granted
Jul 2013	Type C meeting	-Phase 3 protocols require modification to handle missing data -The Division emphasized importance of a mortality endpoint
Nov 2013	Pre-NDA written responses	-Safety database deemed acceptable -Sponsor stated that they did not plan to submit a REMS -Sponsor informed Division of plans to submit Expanded Access Protocol in early 2014
Apr 2014	Expanded Access Protocol opened	500 patients, 150 mg BID (100 mg option for intolerance)
May 2014	Breakthrough Designation Request	Granted

2.6 Other Relevant Background Information

There is no further relevant background information.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

This submission was appropriately indexed and complete to permit review. A high level DSI audit of the sponsor has been completed. While the final review is pending, preliminary reports indicate that there are no inspection issues which require action.

3.2 Compliance with Good Clinical Practices

The Applicant certified that all clinical investigations in this NDA were performed in compliance with the principles of the Declaration of Helsinki, and studies in the US conducted under IND 74,683 were conducted in compliance with 21 CFR Subchapter D, part 312, part 50, and part 56. All study site personnel received training on all aspects of the conduct of the studies and in good clinical practices (GCP).

3.3 Financial Disclosures

The Applicant's compliance with the Final Rule on Financial Disclosure by Clinical Investigators is attested to in Module 1.3.4 of this NDA application. Details of the financial disclosure are outlined below:

Covered Clinical Studies (Name and/or Number): 1199.30, 1199.32, and 1199.34

Was a list of clinical investigators provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request list from applicant)
Total number of investigators identified: <u>1444</u>		
Number of investigators who are sponsor employees (including both full-time and part-time employees): <u>0</u>		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): <u>2</u>		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: <u>1</u> Significant payments of other sorts: <u>1</u> Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request details from applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request information from applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) <u>0</u>		
Is an attachment provided with the reason:	Yes <input checked="" type="checkbox"/>	No <input type="checkbox"/> (Request explanation from applicant)

The applicant submitted FDA Form 3454 (v.10/09) certifying investigators and their spouses/dependents were in compliance with 21 CFR Part 54. In Trial 1199.30 there were 2 principal investigators with disclosable interests. (b) (6) (also involved in Trial 1199.34) disclosed that (b) (6) was employed by (b) (4) working as a local clinical monitor in the cardiovascular and metabolic therapeutic areas. (b) (6) was a back-up investigator. (b) (6)

(b) (6) became an investigator for Trial 1199.30. (b) (6) received \$28,000 for consultation. (b) (6) was not directly involved in the clinical evaluation of patients. The sponsor was unable to obtain financial disclosures from 170 investigators. In Trial 1199.30, financial disclosure information was not collected for 31 investigators. The reasons for not collecting financial disclosure on the remaining 139 investigators in Trials 1199.30, 1199.32, and 1199.34 included no enrolled patients, did not participate, no longer at site, and retired.

No potentially conflicting financial interests were identified.

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

The study drug was supplied as soft, liquid-filled, gelatin capsules in either 150 mg or 100 mg capsules. The target dose is 150 mg by mouth twice daily, however some patients could be dose modified to 100 mg twice daily by mouth for intolerance/adverse reactions. Both dosage strengths are intended for market. Each nintedanib capsule contains the following excipients: titanium dioxide, (b) (4) triglycerides, hard fat, lecithin, gelatin, (b) (4) (b) (4) ferric oxide. The liquid-fill formulation (b) (4) was used in the phase 1-3 trials. The capsule intended for the market differs from the capsules used in clinical trials in the color of the capsule shell, the imprint, and the capsule size. Dissolution profile comparisons showed that the formulations are similar. The to-be-marketed capsules are peach-colored (100 mg) or brown (150 mg) and imprinted with the unit strength (i.e. '100' or '150') and the BI company logo.

The CMC reviewer, Dr. Arthur Shaw, recommends approval. From a CMC perspective, there are no lists of deficiencies or post-marketing commitments/requirements.

4.2 Clinical Microbiology

Dr. John Metcalfe from the product quality microbiology review team reviewed the microbial limits and found them to be acceptable.

4.3 Preclinical Pharmacology/Toxicology

The general toxicity of nintedanib was studied in multiple nonclinical species with treatment durations up to 3, 6 and 12 months in mice, rats, and monkeys, respectively. These studies revealed that the target organs of nintedanib toxicity include the bones (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system included adrenal glands, bone marrow, spleen, and thymus.

Changes in the bone included dentopathy and thickened epiphyseal cartilage in mice and rats, and thickening of growth plate in monkeys. The dentopathy in rodents includes teeth fractures and gum inflammation. Changes in the liver included the presence of extra-medullary hematopoiesis. Changes in the kidney included PAS-positive hyaline droplets, tubular casts, fat droplets in tubular epithelium, and tubular pigment. Changes in the ovaries included increases/decreases in the number of corpora lutea, mature corpora lutea and decrease in the size of corpora lutea. Changes in the adrenal glands included cortical peliosis/angiectesia in rats and cortical hypertrophy in mice. Changes in the bone marrow included cellular depletion. Changes in the spleen included extra-medullary hematopoiesis and lymphoid cell depletion. Changes in the thymus included cellular depletion.

In vitro and *in vivo* studies indicated that nintedanib is neither genotoxic or carcinogenic. Nintedanib tested negative in the following genetic toxicity tests: a bacterial gene mutation assay *in vitro*, a mammalian cell chromosomal aberration assay in mouse lymphoma cells *in vitro*, and in a *in vivo* micronucleus test in rats. Two 2-year oral (gavage) carcinogenicity studies in rats and mice did not reveal any evidence of carcinogenicity in either sex or species.

Nintedanib is a potent teratogen and reproductive toxicant. It is embryocidal and teratogenic when pregnant animals are exposed to the drug. Nintedanib causes implantation loss, resorptions, and malformations at maternally non-toxic doses in rats and rabbits. It also causes sex ratio changes in rabbits and decreases female fertility in rats.

Per. Dr. Luqi Pei's review, the nonclinical program is adequate to support the approval of nintedanib in patients with IPF. For further details, refer to Dr. Pei's nonclinical review.

4.4 Clinical Pharmacology

4.4.1 Mechanism of Action

Nintedanib is a small molecule tyrosine kinase inhibitor including the receptors platelet derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1- 3, and vascular endothelial growth factor receptor (VEGFR). Nintedanib binds competitively to the ATP binding pocket of these receptors and blocks the intracellular signaling which is necessary for the proliferation, migration, and transformation of fibroblasts. These pathways have been proposed to be involved in IPF pathophysiology. In addition, nintedanib inhibits Flt-3, Lck, Lyn, and Src kinases and blocking the subsequent signaling cascade of IL-6. The impact of non-receptor tyrosine kinase on IPF pathophysiology is no known.

4.4.2 Pharmacodynamics

A thorough QT study was conducted for nintedanib and reviewed by the QT Interdisciplinary Review Team. The QT study was conducted as part of the clinical development program in patients with renal cell cancer. In this study, single oral doses of 200 mg as well as multiple oral doses of 200mg nintedanib were administered for 15 days. No significant QTc prolongation

effect of nintedanib 200 mg BID was detected. The largest upper bound of the 2-sided 90% confidence interval (CI) for the mean change from baseline in QTcF was 6.4 ms, observed on Day 15.

4.4.3 Pharmacokinetics

Basic pharmacokinetic (PK) data were derived from 6 studies in healthy volunteers, including 2 drug-drug interaction studies. The PK profile of nintedanib was further characterized in patients with cancer, based on 5 phase 1 monotherapy trials, 3 phase 3 monotherapy trials, 7 phase I combination therapy trials, 3 phase 2 combination therapy trials, and 2 phase 3 combination therapy trials. Pharmacokinetic data for nintedanib in patients with IPF are available from 2 phase 3 trials (1199.32 and 1199.34), from the phase 2 trial 1199.30, and from the Japanese phase 2a trial 1199.31.

IPF vs. Healthy

- The PK properties of nintedanib were similar in healthy volunteers, patients with IPF, and cancer patients.

Absorption

- The absolute bioavailability of nintedanib under fed conditions is about 5%
- Systemic exposure ($AUC_{0-\infty}$) and peak plasma concentration (C_{max}) increased in proportion to the dose in the dose range of 150 to 300 mg BID.
- T_{max} was reached by approximately 2-4 hours following oral administration under fed conditions. In several studies, a second peak in plasma was observed around 5-6 hours following oral administration of nintedanib, suggesting entero-hepatic circulation.
- Coadministration with food increased exposure ($AUC_{0-\infty}$ and C_{max}) was increased by 20%.
- Upon multiple dosing, steady-state was reached by one week with 1.4 fold accumulation.
- Nintedanib is a substrate of P-gp transporter.

Distribution

- Plasma protein binding for nintedanib is high, primarily to albumin, with bound fraction of 97.8%.
- The volume of distribution at steady-state (V_{ss}) is approximately 1050 liters, indicating extensive tissue distribution.

Metabolism and Transporters

- Nintedanib was extensively metabolized, primarily through hydrolytic cleavage by esterases (result in BIBF1202) followed by glucuronidation by UGT enzymes (result in BIBF1202 glucuronide).
- At steady state, the major metabolite in blood is BIBF1202 glucuronide, which is 5-9 fold higher compared to nintedanib. The major metabolites are not active at clinical relevant concentrations.
- Based on in vitro studies, nintedanib is not an inhibitor or inducer of CYP pathways.

- Based on in vitro studies, at therapeutic concentrations, nintedanib has low potential for inhibition of OCT1, P-gP, and BCRP.
- Based on in vitro studies, BIBF1202 is a substrate of OATP-1B1, OATP-2B1. BIBF1202 glucuronide is a substrate of MRP1 and BCRP.

Elimination

- Approximately 93.4% of administered dose gets excreted in feces and less than 1% is eliminated by urine.
- The terminal half-life of nintedanib is 10-15 hours.

Special Populations

- No dose adjustments are recommended based on weight, age, race and gender.
- No dedicated PK study was conducted in patients with renal impairment or end stage renal disease. No dose adjustments are recommended for mild and moderate renal impairment patients because of negligible elimination of nintedanib and its metabolites in urine. The safety and efficacy of nintedanib have not been established in patients with severe renal impairment.
- No dedicated PK study was conducted for patients with hepatic impairment patients. As Nintedanib is eliminated primarily by biliary/fecal excretion (>90%), hepatic impairment is likely to increase plasma nintedanib concentrations. Clinical studies excluded patients with AST or ALT greater than 1.5 x ULN. Patients with total bilirubin greater than 1.5 x ULN were also excluded. Therefore, the recommendation is to monitor for adverse reactions and consider dose modification or discontinuation of nintedanib as needed for patients with mild hepatic impairment, and nintedanib is not recommended in patients with moderate or severe hepatic impairment.

The Clinical Pharmacology Team recommends approval. Refer to the clinical pharmacology review by Dr. Dinko Rekić for further details.

5 Sources of Clinical Data

5.1 Tables of Studies/Clinical Trials

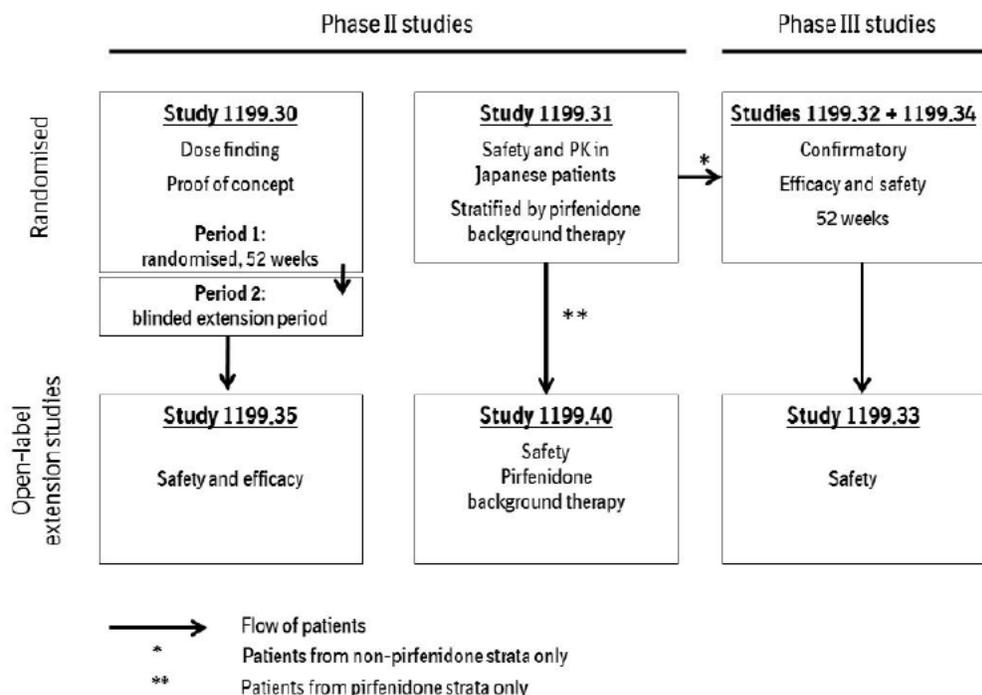
Table 2. Sources of clinical data						
Study	Design	Study Duration	Treatment Arms	N ¹	Population ³	Objective
Phase 2 studies						
1199.30 <i>Sept 2007 to June 2010</i>	DB, R, PC, PG	52 weeks	Nint 50 mg daily Nint 50 mg BID Nint 100 mg BID Nint 150 mg BID Placebo	87 86 86 86 87	IPF patients	Dose-finding, safety and efficacy
1199.35 <i>Ongoing: Aug 2010 to Jul 2013 (data lock)</i>	OL roll-over from 1199.30	22 months ²	Nint 50 mg daily Nint 50 mg BID Nint 100 mg BID Nint 150 mg BID	64 51 45 38	IPF patients from study 1199.30	Safety
1199.31 <i>May 2010 to Mar 2011</i>	DB, R, PC	14-28 days	Nint 50 mg BID Nint 50 mg BID + Pirfenidone Nint 100 mg BID Nint 100 mg BID + Pirfenidone Nint 150 mg BID Nint 150 mg BID + Pirfenidone Placebo Pirfenidone	2 4 4 4 11 13 7 5	Japanese IPF patients stratified by pirfenidone ²	Safety and PK with and without pirfenidone
1199.40 <i>Ongoing: Sept 2011 to Oct 2013 (data lock)</i>	OL roll-over from 1199.31	18 months ³	Nint 150 mg BID	20	Japanese IPF patients from study 1199.31	Safety with pirfenidone
Phase 3 studies						
1199.32 <i>May 2011 to Oct 2013</i>	R, DB, PC, PG	52 weeks	Nint 150 mg BID Placebo	309 206	IPF patients	Efficacy and Safety
1199.34 <i>May 2011 to Oct 2013</i>	R, DB, PC, PG	52 weeks	Nint 150 mg BID Placebo	331 220	IPF patients	Efficacy and Safety

Table 2. Sources of clinical data						
Study	Design	Study Duration	Treatment Arms	N ¹	Population ³	Objective
1199.33 <i>Ongoing: July 2012 to Sept 2013(data lock)</i>	OL- rollover from 1199.32 and 1199.34	6 months ³	Nint 150 mg BID ⁴	680	IPF patients from study 1199.32 and 1199.34	Safety

R=randomized, DB=double-blind, PC=placebo-controlled, PG=parallel-group, OL=open label, BID=twice daily, Nint = nintedanib
¹Number randomized
²Pirfenidone doses ranged from 600-1800mg/day
³Mean treatment duration at time of data lock – patients continued until they met discontinuation criteria
⁴100 mg option for low tolerance
 Source: Trial 1199 30 CSR, Table 15.1.1, p 198; Trial 1199 35 CSR, Table 15.1.1, p 129; Trial 1199.33 CSR, Table 10.1:1, p 59

The flow of clinical studies is displayed in Figure 1.

Figure 1. Nintedanib clinical development program flow of studies



Source: Module 2.7.4, SCS, p 25.

5.2 Review Strategy

This clinical review focuses on the three randomized, double-blind, placebo-controlled 52-week studies: the phase 2 dose-ranging study (1199.30) and the two confirmatory phase 3 studies

(Study 1199.32 and Study 1199.34). The discussion of the phase 2 study focuses on the comparison of placebo to the 150 mg BID treatment arm, which was carried forward to the phase 3 studies. The long-term extension studies for each of the 3 studies (Study 1199.33 (from 1199.32 and 1199.34) and Study 1199.35 (from 1199.30)) provide supportive safety information and are discussed separately in Section 7.7.2 Long-term safety. Additionally there was a second active-treatment only blinded period in the phase 2 study (1199.30 period 2) that is also discussed in Section 7.7.2 Long-term safety. The PK study (Study 1199.31) is briefly reviewed in Section 7.5.5 Drug-Drug Interactions as this study provides unique data for concomitant treatment with pirfenidone (another drug with the proposed indication to treat IPF with its NDA currently under review).

Section 5.3 Discussion of Individual Studies/Clinical Trials describes the protocols in detail for each individual study. Section 6 Review of Efficacy reviews the efficacy results for each individual study. This section includes efficacy results from all treatment arms of Study 1199.30 (Section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects).

Section 7 Review of Safety describes pooled safety for all 3 studies (focusing only on the 150 mg BID treatment and placebo arms of Study 1199.30). The safety results for the other treatment arms of Study 1199.30 are described in Section 7.5.1 Dose Dependency for Adverse Events. Finally, the sponsor submitted clinical study safety data for nintedanib for the treatment of non-small cell cancer and ovarian cancer. This data is briefly discussed in Section 7.7.3 Other indications.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Studies 1199.32 and 1199.34

Study 1199.32 and 1199.34 were identically designed trials. The following section outlines the protocol for these studies.

Administrative Information

Study 1199.32

- **Study title:** A 52-week, double-blind, randomized, placebo-controlled trial evaluating the effect of oral nintedanib, 150 mg twice daily, on annual Forced Vital Capacity (FVC) decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)
- **Study dates:** May 9, 2011 to October 9, 2013
- **Study sites:** 98 centers in 13 countries
- **Study report date:** April 8, 2014

Study 1199.34

- **Study title:** A 52-week, double-blind, randomized, placebo-controlled trial evaluating the effect of oral nintedanib, 150 mg twice daily, on annual Forced Vital Capacity (FVC) decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)

- **Study dates:** May 3, 2011 to October 15, 2013
- **Study sites:** 107 centers in 17 countries
- **Study report date:** April 8, 2014

Objectives/Rationale

Primary Objectives

- To investigate the efficacy and safety of nintedanib 150 mg twice daily (bid) versus placebo in patients with IPF over 52 weeks.

Study Design and Conduct

Overview

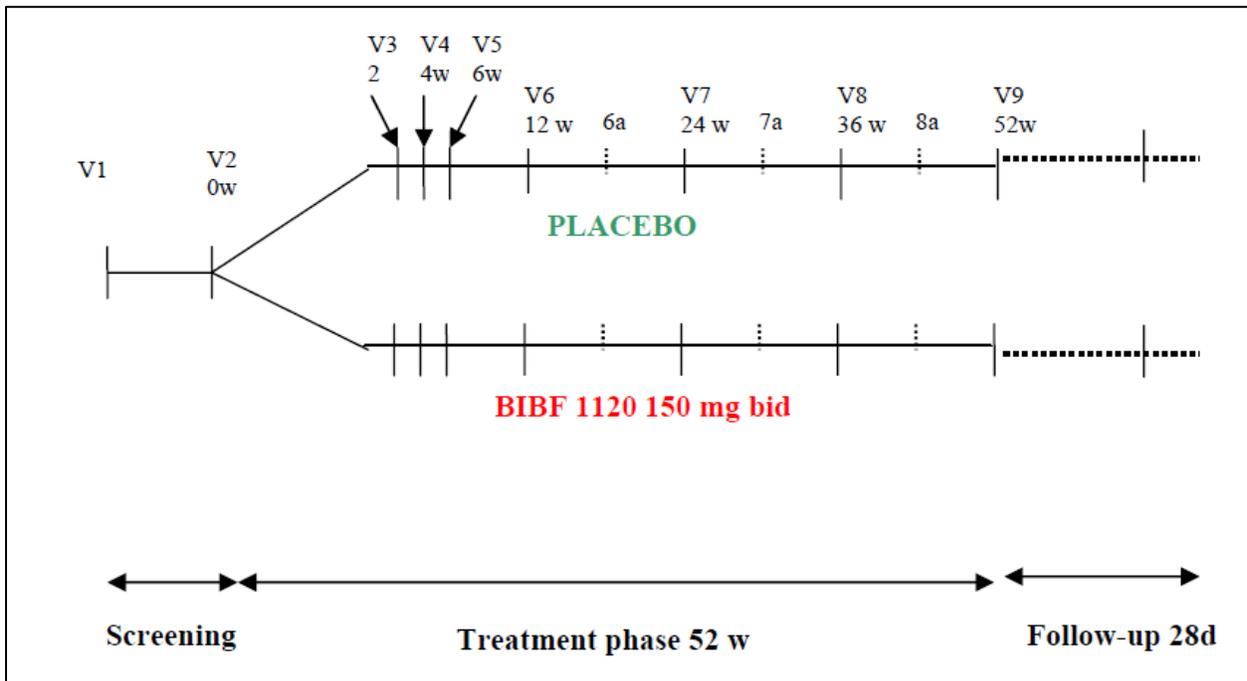
Study 1199.32 and 1199.34 were replicate, confirmatory, phase 3, 52-week, randomized, double-blind, placebo-controlled, multinational, multicenter study of nintedanib 150 mg twice daily compared to placebo in patients with IPF.

Patients were screened up to 4 days prior to the baseline randomization visit. At the baseline visit, patients were randomized 2:1 to nintedanib 150 mg twice daily or placebo. Nine study visits occurred through the 52-week treatment period, with a follow-up visit after 4 weeks.

Subjects could continue into an open-labeled safety study (Study 1199.33) after completion of the blinded studies (further details of this protocol can be found in Section 7.7.2 Long-term safety, Study 1199.33).

The study design for both studies is depicted in Figure 2.

Figure 2. Study Design: Studies 1199.32 and 1199.34



Source: Module 5.3.5.1, Study 1199.32 CSR, Figure 3.1:1, p 19; Study 1199.34 CSR, Figure 9.1:1, p 45.

The schedules of assessments are shown in Table 3.

Table 3. Schedule of Assessments: Studies 1199.32 and 1199.34

Visit		1	2	3	4	5	6	6a	7	7a	8	8a	9	FU
	Screening		Treatment											FU
Weeks of treatment				2	4	6	12	18	24	30	36	44	52	+4
Day	Before or at the latest at Visit 1	≥4 days before Visit 2	1	15	29	43	85	127	169	211	253	309	365	+28
Time window (days)				±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	+7
Informed consent	X*													
HRCT sent to central review	X													
Biopsy sent to central review, if available	X													
Demographics		X												
Medical history		X												
Inclusion/exclusion criteria		X	X											
Physical examination, vital signs		X	X	X	X	X	X		X		X		X	X
Laboratory test		X	X	X	X	X	X	X ¹	X	X ¹	X	X ¹	X	
PK sample ²				X					X					
HCRU assessments			X	X	X	X	X		X		X		X	
Pregnancy test		X	X	X	X	X	X		X		X		X	X
Spirometry (FVC)		X	X	X	X	X	X		X		X		X	X
SpO ₂		X	X				X		X		X		X	
DLCO			X						X				X	
12-lead ECG		X	X ³		X				X				X	
SGRQ, SOBQ, CASA-Q(CD)			X			X	X		X				X	
EQ-5D			X				X		X				X	
PGI-C							X		X				X	
Exacerbations		X	X	X	X	X	X		X		X		X	X
Randomisation			X											
IXRS call/notification		X ⁴	X		X		X		X		X		X	
Administer 1 st trial medication at the clinic			X											
Dispense trial medication			X		X		X		X		X			
Collect trial medication					X		X		X		X		X	
Compliance / drug accountability				X	X	X	X		X		X		X	
Adverse events, concomitant medications		X	X	X	X	X	X		X		X		X	X
Assessment of lung transplant qualification					X	X	X		X		X		X	
Trial medication termination													X ⁵	
Vital status assessment ⁶													X	
Conclude patient participation														X

FU = follow-up

* Informed consent was to be signed before any procedure related to the trial took place. When it was signed before Visit 1, e.g. to allow shipment of images for central review, all AEs and concomitant treatments occurring after the Informed consent were to be recorded.

¹ Laboratory test only for liver transaminases. This did not necessarily need to be a site visit.

² At Visits 4 and 7; just before drug administration and for Japanese centres, 2 to 4 hours after administration of the study drug, but within 30 minutes after completion of ECG measurement at Visit 4 and 7

³ Only if abnormal at Visit 1, except in Japan, where ECG was always performed at Visit 2

⁴ IXRS was to be notified at the latest by Visit 1 but could be notified upon informed consent's signature

⁵ Trial Termination page was a separate eCRF page from Visit 9

⁶ Vital status at 52 weeks was to be available for all patients. Patients who withdrew prematurely from the trial were to attend visits as planned until 52 weeks.

Note: In case of dose change (reduction or re-escalation) a visit was to be included

Source: Module 5.3.5.1, Study 1199.32 CSR, Flow Chart, p 72; Study 1199.34 CSR, Flow Chart, p 71.

Subjects who discontinued prematurely were asked to complete all study visits through week 52. In subjects who did not comply, every attempt was made to obtain vital status at week 52.

Population

The patient population was adult patients with IPF.

Key Inclusion Criteria

1. Age \geq 40 years
2. IPF diagnosed, according to most recent 2013 ATS/ERS/JRS/ALAT IPF guideline² for diagnosis and management, within 5 years.
3. Chest HRCT performed within 12 months (reviewed by independent expert radiologist)
4. Combination of HRCT pattern, and if available surgical lung biopsy pattern, as assessed by independent expert/ histopathologist reviewers, consistent with diagnosis of IPF
5. DLco (corrected for Hb) 30%-79% predicted of normal
6. FVC \geq 50% predicted of normal

Key Exclusion Criteria

1. AST, ALT $>$ 1.5 x ULN.
2. Bilirubin $>$ 1.5 x ULN.
3. Relevant airways obstruction (i.e. pre-bronchodilator FEV1/FVC $<$ 0.7).
4. In the opinion of the Investigator, patient likely to have lung transplantation during study (but being on transplantation list was acceptable for participation).
5. Cardiac disease
 - Myocardial infarction within 6 months of visit 2.
 - Unstable angina within 1 month of visit 2.
6. Bleeding risk
 - Known genetic predisposition to bleeding.
 - Patients who required fibrinolysis, full-dose therapeutic anticoagulation (e.g. vitamin K antagonists, dabigatran, heparin, hirudin, etc.), or high dose antiplatelet therapy. Prophylactic low dose heparin or heparin flush as needed for maintenance of an indwelling intravenous device (e.g. enoxaparin 4000 I.U.

SC per day), as well as prophylactic use of antiplatelet therapy (e.g. acetyl salicylic acid up to 325 mg/d, or clopidogrel at 75 mg/d, or equivalent doses of other antiplatelet therapy) was **not** excluded. History of hemorrhagic CNS event within 12 months of visit 2.

- Any of the following within 3 months of visit 2:
 - Hemoptysis or hematuria.
 - Active gastro-intestinal bleeding or ulcers.
 - Major injury or surgery.
7. Thrombotic risk
 - Known inherited predisposition to thrombosis.
 - History of thrombotic event (including stroke and transient ischemic attacks) within 12 months of visit 2.
 - Coagulation parameters: International normalized ratio (INR) > 2, prolongation of prothrombin time (PT) and partial thromboplastin time (PTT) by > 50% of institutional ULN.
 8. Known hypersensitivity to the trial drug or its components.
 9. Other disease that may interfere with testing procedures or in the judgment of the Investigator may interfere with trial participation or may put the patient at risk when participating in this trial.
 10. Life expectancy for disease other than IPF < 2.5 years (Investigator assessment).
 11. Previous treatment with nintedanib (except short term treatment of up to four weeks).
 12. Concomitant therapies
 - Other investigational therapy (participation in research trial) received within 8 weeks of visit 1.
 - NAC, prednisone > 15mg/day or equivalent received within 2 weeks of visit 1.
 - Pirfenidone, azathioprine, cyclophosphamide, cyclosporine A received within 8 weeks of visit 1.
 13. Surgical procedures (describe) planned to occur during trial period.
 14. Pregnant women or women who are breast feeding or of child bearing potential not using two effective methods of birth control (one barrier and one highly effective non-barrier) for at least 1 month prior to enrolment (and until 3 months after treatment end).
 15. Sexually active males not committing to using condoms during the course of the study (except if their partner is not of childbearing potential) and 3 months after end of treatment.
 16. Active alcohol or drug abuse.

Reviewer comment: The trial design and inclusion/exclusion criteria are appropriate. The exclusion criteria address potential risks due to mechanism of action and known adverse events such as bleeding, venous thrombosis, arterial thrombosis, embryofetal toxicity, elevated liver enzymes, poor wound healing, and gastrointestinal perforation.

Concomitant medication exclusions

Medications that were excluded or had limited use during Studies 1199.32 and 1199.34 are summarized in Table 4.

Table 4. Concomitant Medication Exclusions: Studies 1199.32 and 1199.34	
Medication	Exclusion Details
Pirfenidone and any other experimental IPF therapy	Not allowed during with 8 weeks of treatment and during treatment period. Patients were discontinued if taken.
Fibrinolysis	Not allowed during treatment period. If medically indicated, a 4-week washout of nintedanib occurred prior to their use
Full-dose therapeutic ¹ anticoagulation	
High-dose antiplatelet therapy ²	
Azathioprine	Not allowed during first 6 months of treatment period, except for acute IPF exacerbation. Allowable after 6 months, in the case of deterioration.
Cyclosporine A	
Cyclophosphamide	
N-Acetylcysteine (NAC)	
Prednisone at < 15 mg/day	
Bronchodilators	Washout prior to spirometric assessment
¹ Low dose heparin or heparin flush as needed for maintenance of catheters was allowed.	
² Prophylactic antiplatelet therapy (e.g. aspirin 325mg/day or Plavix 75mg/day) was allowed.	
Source: Module 5.3.5.1, Study 1199.32 CSR, p 59-61; Study 1199.34 CSR, p 60-2.	

In case of acute IPF exacerbation or deterioration, all treatment options were allowed and could be freely initiated or increased, except pirfenidone. Patients were also allowed to interrupt treatment of trial medication for up to 8 weeks if this was considered necessary.

Treatment groups

Treatment groups are outlined in Table 5.

Table 5. Treatment groups: Studies 1199.32 and 119.9.34		
Substance	Nintedanib	Placebo
Pharmaceutical form	Soft gelatin capsule	
Source	BI Pharma GmbH & Co. KG	
Unit strength	150 mg, 100 mg	-
Frequency	Twice daily	
Route of administration	Oral (swallowed)	
Source: Module 5.3.5.1, Study 1199.32 CSR, p 28; Study 1199.34 CSR, p 53.		

Treatments were administered every 12 hours with 250 mL of water and after food intake (due to possible stomach discomfort). To maintain blinding, the 100 mg and matching placebo were the same color (peach). The 150 mg nintedanib capsule was also the same color as its matching placebo (brown).

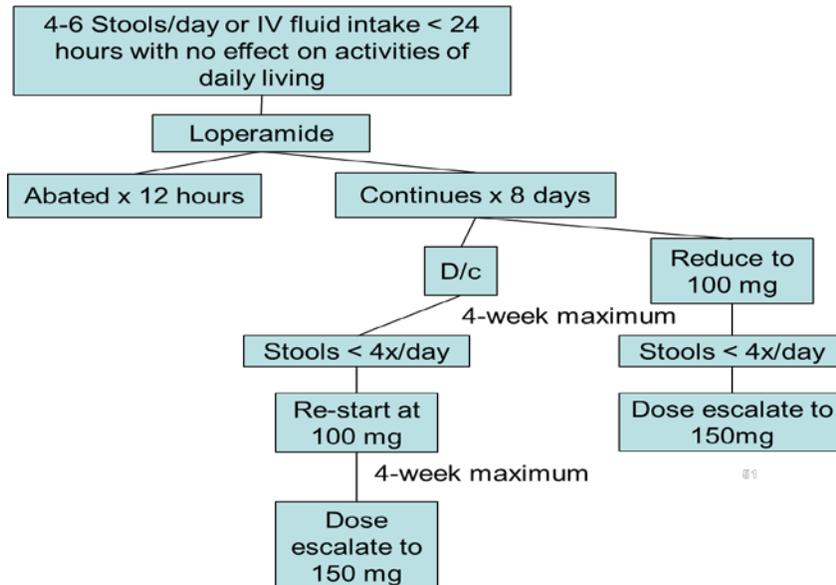
Dose-reduction

Subjects could be treated with a reduced dose (100 mg) due to an AE. Specific criteria were outlined for diarrhea and liver enzyme adverse event-driven dose reduction (as outlined below). If the reduced dose was well-tolerated, re-escalation was possible within 4 weeks. If the AE was considered non-treatment related, re-escalation could occur after 8 weeks. Non-treatment related AEs included acute IPF exacerbations. It was necessary to interrupt treatment with trial medication for up to 8 weeks if prohibited concomitant therapies such as full anti-coagulation were medically indicated. A 4-week washout period was required before use of full dose anticoagulation or high dose antiplatelet therapy.

Management of Diarrhea

The general management of mild to moderate diarrhea is outlined in Figure 3. If diarrhea continued for more than 8 days, despite loperamide treatment, patients could be either discontinued from treatment or their dose reduced to 100 mg BID. There was no clear delineation between which patients would be discontinued or dose-reduced (investigator judgment). If diarrhea re-occurred after this algorithm, patients could be treated with loperamide again, however if diarrhea continued for 8 days despite loperamide, subjects were permanently discontinued.

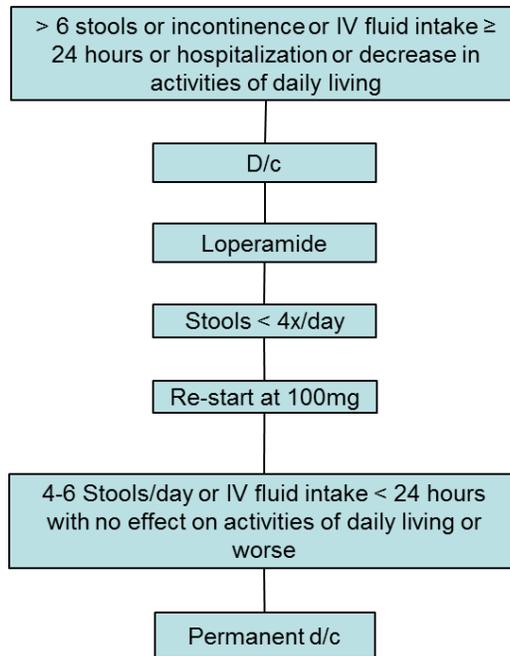
Figure 3. Management of Mild to Moderate Diarrhea: Studies 1199.32 and 1199.34



Source: Module 5.3.5.1, Study 1199.32 CSR, p 28.

The general management of severe diarrhea is outlined in Figure 4.

Figure 4. Management of Severe Diarrhea: Studies 1199.32 and 1199.34



Source: Module 5.3.5.1, Study 1199.32 CSR, p 28.

Management of Liver Enzyme Elevations

The protocol-defined management of liver enzyme elevations is listed in Table 6.

Table 6. Management of Liver Enzyme Elevations: Studies 1199.32 and 1199.34

	AST or ALT increase to				
	1.5x to <3x ULN	3x to <5x ULN	5x to <8x ULN	≥ 3x ULN and signs of severe liver damage ¹	≥ 8x ULN
Visit 1 (screening)	Do not randomize!	Do not randomize!	Do not randomize!	Do not randomize!	Do not randomize!
Visit 2 (randomization)	Withdraw treatment or justify continuation ²	Withdraw treatment!	Withdraw treatment!	Withdraw treatment!	Withdraw treatment!
Any other visit	Continue as planned ³	Reduce dose or interrupt treatment ⁴	Interrupt treatment	Withdraw treatment!	Withdraw treatment!
		Close observation ⁵	Close observation ⁵		
		Monitor at 48-72hrs, at 7 days, at 2 weeks	Monitor at 48-72hrs, at 7 days, at 2 weeks		
After 2 weeks or any time later	< 3x ULN	≥ 3x ULN	< 3x ULN	≥ 3x ULN	
	Reduced: return to initial dose. Interrupted: restart at reduced dose. Monitor bi-weekly for at least 8 weeks	Withdraw treatment!	Restart at reduced dose Monitor weekly for 4 weeks, then bi-weekly for at least 8 weeks	Withdraw treatment!	

¹ Signs of severe liver damage

- Symptoms: Increase of liver transaminases is paralleled by appearance of fatigue, nausea, vomiting, right upper abdominal quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%) or
- Total bilirubin > 1.5xULN or
- INR > 1.5xULN

² Investigator to confirm in writing that continuation is justified (e.g. intermittent fluctuation of transaminases).

³ According to visit schedule (at 2, 4, 6, 12, 18, 24, 30, 36, 44, 52 weeks). Consider additional control visits as adequate.

⁴ To be decided by Investigator, based on individual risk assessment.

⁵ It is recommended to ensure close observation as follows:

- Monitor 2x to 3x per week all of the following: ALT, AST, alkaline phosphatase, total bilirubin, eosinophils
- Frequency of retesting can decrease to once a week or less if abnormalities stabilize or the trial drug has been discontinued and the subject is asymptomatic.
- Re-query detailed history of symptoms and prior or concurrent diseases.
- Re-query history of concomitant drug use (including non-prescription medications and herbal and dietary supplement preparations), alcohol use, recreational drug use, and special diets.
- Rule out all of the following: acute viral hepatitis types A, B, C, D, and E; autoimmune hepatitis; alcoholic hepatitis; NASH (non-alcoholic fatty hepatitis); hypoxic/ischemic hepatopathy; and biliary tract disease.
- Re-query about exposure to environmental chemical agents.
- Consider additional tests to evaluate liver function, as appropriate (e.g., INR, direct bilirubin).
- Consider gastroenterology or hepatology consultations.

Source: Module 5.3.5.1, Study 1199.32 CSR, Table 19.4.1.; p 73-4.

Acute IPF Exacerbation

Subjects were allowed to interrupt nintedanib treatment for up to 8 weeks and restart at the full 150 mg BID dose.

Adverse Events

For those adverse events considered to be drug-related, nintedanib was to be discontinued for up to 4 weeks, and then restarted at 100 mg BID. Re-escalation to 150 mg BID was to occur within 4 weeks of re-start.

For those AEs considered unrelated to treatment, treatment was to be discontinued for up to 8 weeks and then restarted at 150 mg BID.

Efficacy Endpoints

Primary Endpoint

- Annual rate of decline in FVC

Key Secondary Endpoints

- Change from baseline in SGRQ total score
- Time to first acute IPF exacerbation

Other Secondary Endpoints:

Further Analyses on FVC

- Absolute and relative change from baseline in FVC (mL) and FVC% predicted
- Absolute categorical change of FVC% predicted
 - >5% decrease, >5% increase, and change within ≤ 5%

- > 10% decrease, > 10% increase, and change within $\leq 10\%$
- Proportion of FVC responders using 5% or 10% threshold
 - defined as patients with absolute decline in FVC% predicted $\leq 5\%$ or $\leq 10\%$ AND with an FVC evaluation at 52 weeks

Vital sign/Lung function

- SpO₂ change from baseline
- DLco change from baseline

Patients reported outcomes (PRO)

- Proportion of SGRQ responders
 - Absolute change from baseline at 52 weeks in SGRQ total score ≤ -4 points
- SGRQ change from baseline
- SGRQ-I (IPF specific version of SGRQ) change from baseline
- Shortness of breath questionnaire (SOBQ) change from baseline
- Cough impact and cough symptoms of the Cough Sputum Assessment Questionnaire (CASA-Q[CD]) score
- Proportion of Patient's Global Impression of Change (PGI-C) responders
- EuroQol 5-Dimensional Quality of Life Questionnaire (EQ-5D) health state

Acute Exacerbation

- Risk of an acute IPF exacerbation

Survival analyses

- Time to death
- Time to death due to respiratory cause
- Time to on-treatment death
- Time to death or lung transplant
- Time to death or lung transplant as qualifying for lung transplant
 - Qualifications for lung transplant: FVC < 45% predicted or DLco < 30% predicted or SpO₂ < 88% at rest

Efficacy Endpoint Parameters

Primary Efficacy Parameter

FVC

Spirometry performance was centrally reviewed and met ATS/ERS criteria. Spirometry was performed at roughly the same time of day and patients were to refrain from strenuous activity for at least 12 hours, and smoking for 30 minutes.

Reviewer comment: ATS/ERS Spirometry criteria (2005) recommend avoiding smoking \geq 1 hour prior to spirometry assessment, however this discrepancy (30 min vs. 1 hours) is unlikely to have an impact on spirometry results.

Secondary Efficacy Parameters

Acute IPF Exacerbation

Defined as otherwise unexplained clinical features including all of the following:

1. Unexplained worsening or development of dyspnea within 30 days
2. New diffuse pulmonary infiltrates on CXR and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities)
3. Exclusion of alternative causes
 - a. Infection
 - b. Left heart failure
 - c. Pulmonary embolism
 - d. Identifiable cause of acute lung injury

PRO

Questionnaires were completed in the following order:

- SGRQ, SOBQ, CASA-Q(CD) (Weeks 0, 6, 12, 24, 52)
- PGI-C (Weeks 12, 24, 52)
- EG-5D (Weeks 0, 12, 24, 52)

DLco

- % predicted corrected for Hemoglobin
- Measured at Weeks 0, 24, and 52.

Compliance Parameters

The patients will be instructed to bring all study medication to the clinic at each visit. The Investigator will be responsible for the assessment of patient compliance with study medication at each visit, by physical count of returned study medication.

Safety Parameters

The safety analysis was based on the reported AEs, vital signs, physical exam, and review of laboratory data. The safety assessor was the Principal Investigator.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

For Study 1199.32, Site 10001 was closed due to serious non-compliance. No further details are provided.

Statistical Plan

Primary endpoint:

The primary endpoint was analyzed using a random coefficient regression model (random slopes and intercepts) including gender, age, and height (usual predictors of FVC) as covariates. All data, from baseline up to the follow-up visit were included. Follow-up visit data was not included (except for patients who prematurely discontinued and did not complete the planned observation time). An unstructured variance-covariance structure was used to model the within patient measurements. Significance tests were based on a 2-sided $\alpha=0.05$ (2-sided 95% CI).

Secondary endpoints:

SGRQ: Mixed Effects Model for Repeated Measures (MMRM) analysis including treatment and visit as fixed effects and baseline total score as a covariate, treatment-by-visit and baseline-by-visit as interaction terms.

Time to first acute IPF Exacerbation: Cox's proportional hazards model, adjusted for gender, height, and age, and a log-rank test.

A hierarchical procedure was used for the secondary endpoints (1-sided 2.5% level in favor of nintedanib). For the US analysis, Time to first acute IPF exacerbation was first, followed by SGRQ. It was reversed for the EU and the rest of the world registration analyses.

Analyses Population

The **treated set** was used for efficacy and safety analyses. The treated set was defined by patients who were dispensed study medication AND were documented to have taken at least one dose.

Sensitivity analysis

The sensitivity analysis challenged the linearity assumptions for the decline in FVC. Several alternative models were used. Some included efficacy evaluations following lung transplant. The potential effect of missing data was investigated using multiple imputation approaches, based on the following patient classifications:

1. Patients with a 52-week FVC value who received trial drug until Week 52
2. Patients with a 52-week FVC value who prematurely discontinued trial drug but were followed up until Week 52, i.e. completed planned observation time
3. Patients without a 52-week FVC value who were alive at Week 52
4. Patients without a 52-week FVC value who died before Week 52

The statistical reviewer found that the sponsor's sensitivity analyses with multiple imputations based on various patterns of availability of data such as completers, retrieved dropouts, live dropouts, and dead dropouts provided useful information on the impact of missing data on the results. For further details regarding the statistical analysis, See Dr. Yongman Kim's statistical review.

Protocol Results

Study 1199.32 and 1199.34 Protocol Amendments

Amendment 1 (November 17, 2011)

No notable changes were included.

Amendment 2 (September 4, 2012)

- Addition of analyses of exploratory biomarkers related to IPF pathology and prognostic markers of disease in subset of patients who gave specific informed consent.
- Addition of pharmacogenomics analysis
- Addition of eCRF pages for diarrhea to better specify the event and collect grading, diagnostic procedure and therapy.

Reviewer comment: The protocol changes do not affect data interpretation.

Protocol Deviations

For Study 1199.32, a total of 56 (18%) patients in the nintedanib group and 25 (12%) patients in the placebo group had major protocol deviations. For Study 1199.34, a total of 31 (9%) of patients in the nintedanib group and 24 (11%) of patients had major protocol deviations. Major protocol deviations were pre-defined in the statistical analysis plan. The major protocol deviations in these studies are outlined in Table 7.

Table 7. Protocol Violations (Treated population): Studies 1199.32 and 1199.34				
	Study 1199.32		Study 1199.34	
	Placebo	Nintedanib 150 mg BID	Placebo	Nintedanib 150 mg BID
	N=204	N=309	N=219	N=329
	N (%)		N (%)	
Patients with at least 1 important protocol violation	25 (12)	56 (18)	24 (11)	36 (11)
Patients with ≥ 1 efficacy related major protocol violation	22 (11)	48 (16)	24 (11)	31 (9)
Entrance criteria not met	6 (3)	6 (2)	4 (2)	5 (2)
Trial medication and randomization	8 (4)	24 (8)	9 (4)	13 (4)
Prohibited concomitant therapy	8 (4)	12 (4)	9 (4)	10 (3)
Missing data	3 (2)	12 (4)	5 (2)	5 (2)
Patients with ≥ 1 safety related important protocol violation	13 (6)	24 (8)	11 (5)	24 (8)
Entrance criteria not met	0	4 (1)	1 (<1)	0
Trial medication and randomization	2 (1)	5 (2)	0	3 (1)
Prohibited concomitant therapy	8 (4)	12 (4)	9 (4)	10 (3)
Missing data	1 (<1)	0	0	0
Informed consent	1 (<1)	3 (1)	1 (<1)	2 (<1)
Incorrect timing	1 (<1)	1 (<1)	0	0

Source: Module 5.3.5.1, Study 1199.32, Table 10.2:1, p 98; Study 1199.34, Table 10.2:1, p 98.

The most common major protocol violation overall (adding efficacy and safety groupings together) was prohibited concomitant therapy, occurring similarly across treatment groups. These therapies included prednisone 15 mg/day, warfarin, bivalirudin, dexamethasone, prednisolone, metasulfabenzate sodium, methylprednisolone, dalteparin, prednisolone, tinzaparin sodium, dabigatran etexilate mesilate, enoxaparin, urokinase, acenocoumarol + nadroparin calcium, and cyclosporin. In Study 1199.32, three patients from the nintedanib group received incorrect trial medication (placebo), for durations ranging from 2 days to 5 months. In Study 1199.34, two patients (1 nintedanib and 1 placebo) received incorrect trial medication. The patient randomized to placebo received nintedanib for 84 days. No AES occurred during this time. The nintedanib patient received a placebo kit, but it was not used.

5.3.2 Study 1199.30

Study 1199.30 was designed, conducted, and analyzed very similarly to Studies 1199.32 and 1199.34. Any important/relevant differences will be highlighted here.

Administrative Information

Study 1199.30

- **Study title:** A 52 week, double-blind, randomized, placebo-controlled trial evaluating the effect of oral nintedanib, administered at oral doses of 50 mg daily, 50 mg twice daily (BID), 100 mg BID, and 150 mg BID, on annual Forced Vital Capacity (FVC) decline, in patients with Idiopathic Pulmonary Fibrosis (IPF)
- **Study dates:** September 14, 2007 to June 10, 2010
- **Study sites:** 92 centers in 25 countries
- **Study report date:** February 25, 2011

Objectives/Rationale

Primary Objectives

- To investigate the efficacy and safety of 4 dose strategies of nintedanib treatment for 52 weeks compared to placebo in patients with IPF.

Study Design and Conduct

Overview

Study 1199.30 was a phase 2, 52-week, randomized, double-blind, placebo-controlled, multinational, multicenter study of 4 doses of nintedanib compared to placebo in patients with IPF.

The trial used a dose-escalation scheme, with the next highest dose only possible after a Data Monitoring Committee (DMC) decision of the safety of the previous cohort. All patients had the opportunity for 1 step dose reduction for intolerance. Subjects could continue on their current blinded therapy (placebo rolled into 50 mg daily in a blinded fashion) until the end of the trial (52 weeks after the last patient was randomized). Thus, total treatment duration ranged from ~ 1-3 years. Treatment up to 52 weeks was considered period 1 and treatment beyond 52 weeks was considered period 2. In addition, subjects had the option to roll over into an open-label extension study (Study 1199.35) after the database lock and unblinding of Study 1199.30. The active-treatment blinded extension of this study (period 2) and the long term safety study (Study 1199.35) are discussed further in Section 7.7.2 Long-term safety (Study 1199.30 Period 2, Study 1199.33)

The schedule of assessments for Study 1199.30 period 1 is shown in Table 8.

Table 8. Period 1 Schedule of Assessments: Study 1199.30

	Scr	Treatment										
Visit	1	2	3	4	5	6	6a	7	7a	8	8a	9
Days	Before -4	1	15	29	43	85	127	169	211	253	309	365
Weeks of treatment			2	4	6	12	18	24	30	36	44	52
Time window allowed (days)	Before -4		±3	±3	±3	±3	±7	±7	±7	±7	±7	±7
Informed Consent, Demographics, Medical History	X											
Inclusion / Exclusion criteria	X	X										
Diagnosis confirmation (HRCT/lung biopsy according to ERS/ATS guidelines)	X											
Randomisation		X										
Physical examination, vital signs	X	X	X	X	X	X		X		X		X
AE, concomitant medication, exacerbations	X	X	X	X	X	X		X		X		X
Laboratory tests	X ¹	X	X	X	X	X	X*	X	X*	X	X*	X
Pharmacogenetics		X										
Urinary pregnancy test	X	X				X		X		X		X
Resting 12-lead ECG	X		X	X		X		X		X		X
FVC, FEV ₁ (spirometry)	X	X	X	X	X	X		X		X		X
SpO ₂ (resting)	X	X		X		X		X		X		X
Body plethysmography		X						X				X
6-Minute Walk Test		X						X				X
DL _{CO}		X						X				X
Arterial blood gases (PaO ₂ , PaCO ₂)		X										X
SGRQ, MRC dyspnoea scale		X				X		X				X
Blood biomarkers	X	X		X				X				X
Blood sampling for PK ²		X		X				X				X
Study drug dispensation		X		X		X		X		X		X
Study drug administration at clinic (morning dose)		X		X				X				X
Compliance check			X	X	X	X		X		X		X
Dispensation of laboratory test kit if needed						X		X		X		

* Visit 6a, 7a and 8a: only lab test for transaminases. May not have required visit at study site.

¹ Laboratory test at visit 1 should have been within 6 weeks before randomization.

² Visit 2, 4: before and at 2 hours (± 60 minutes) after study drug administration.

Visit 7 and 9: before and at 2 hours (± 60 minutes) and 4-10 hours after study drug administration.

EOT: at trough.

Source: Module 5.3.5.1, Study 1199.30 CSR, Flow Chart, p 84

Population

The patient population was adult patients with IPF.

Key Inclusion Criteria

Inclusion criteria in trial 1199.30 were the same as the phase 3 studies (1199.32 and 1199.34), with 1 additional criterion:

- PaO₂ ≥55 mmHg (sea level to 1500 m) or 50 mmHg (above 1500 m) room air.

Also, in Study 1199.30 diagnosis of IPF was to be based on the version of ATS/ERS diagnostic criteria available at the time (2000)⁷.

Reviewer comment: Study 1199.30 used the 2000 ATS/ERS IPF diagnostic criteria compared to the phase 3 studies that used the 2011 criteria. The most notable difference is that the 2000 criteria mostly required surgical lung biopsy to make the diagnosis of IPF. In 2011, there was a greater understanding of HRCT interpretation, as well as better quality images, which led to the establishment and acceptance of HRCT criteria for IPF diagnosis. As a result, surgical lung biopsy was no longer considered a requirement for diagnosis.

Key Exclusion Criteria

In general, exclusion criteria in Study 1199.30 were the same as for Studies 1199.32 and 1199.34. In addition, patients who required continuous oxygen supplementation at randomization (defined as 15 or more hours per day) were not allowed to participate in Study 1199.30. Although treatment with pirfenidone, azathioprine, cyclophosphamide, NAC, and high dose prednisone was not an exclusion criterion, the use of these medications was restricted in Study 1199.30 (see Table 4).

Concomitant medication exclusions

Study 1199.30 followed similar restrictions of concomitant medication as the phase 3 studies (see Table 4).

Treatment groups

Except for the dose strength options (50 mg daily, 50 mg twice daily, 100 mg twice daily, or 150 mg twice daily) the treatments were the same as the phase 3 studies. To maintain the blind, all patients took the same number of capsules per dose.

Dose-reduction

Subjects could be treated with a reduced dose (reduction by 50 mg daily for those patients in the 50 mg daily or bid group, and by 50 mg BID for those patients in the 100 mg or 150 mg BID group) due to an adverse event (AE). Once a patient had undergone a nintedanib dose reduction, there was no provision for re-escalation or re-challenge with a higher dose. Dose reduction had to occur in a blinded fashion, so any reduced dose took the form of one fewer capsule in the morning and one fewer capsule in the evening.

Study 1199.30 followed similar criteria as the phase 3 studies for diarrhea and liver enzyme adverse enzyme-driven dose reductions (see Section 5.3.1 Studies 1199.32 and 1199.34 Treatment groups).

Efficacy Endpoints

The primary efficacy endpoint was the same as for the phase 3 studies. The key secondary of time to acute IPF exacerbation and SGRQ score, as well as survival endpoints, were also included in Study 1199.30. Multiple other secondary endpoints were also included, but will not be discussed further in this review.

Efficacy Endpoint, Compliance, and Safety Parameters

These were all similar to the phase 3 studies.

Ethics

An Independent Ethics Committee reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Statistical Plan

The primary endpoint analysis was performed on the randomized set, but including only patients with 2 on-treatment FVC evaluations. For further details regarding the statistical analysis, See Dr. Yongman Kim's statistical review.

Protocol Results

Protocol Amendments

Amendment 1 (November 13, 2007)

No notable changes were included.

Amendment 2 (December 15, 2009)

- Maintained patients in the trial after database lock until inclusion in a roll-over
- Corrected the period of follow-up of AES after drug discontinuation from 7 to 14 days.

Protocol change that did not trigger an amendment: Approximately May 2008 (8 months after study start)

- IPF diagnosis was to be confirmed by central review of HRCT and available biopsy before each patient randomization. At study start, only patients with “definitely not” UIP were withdrawn, even if the investigator diagnosis according to ATS/ERS criteria was IPF. About eight months after study start, the control of IPF was strengthened and patients with “possible UIP” diagnosis were not allowed anymore in order to avoid the inclusion of patients with uncertain borderline IPF diagnosis. According to the sponsor, this change did not require an amendment.

Reviewer comment: The protocol changes do not affect data interpretation for the 150 mg BID group. Notably, there were no patients with possible UIP in the nintedanib 150 mg BID group because their inclusion in the study was stopped before the introduction of the 150 mg BID dose in the randomization scheme.

Protocol Deviations

The proportion of subjects with at least 1 major protocol deviation was similar to the phase 3 studies and across treatment groups, ranging from 7-16%. Major protocol deviations were pre-defined in the statistical analysis plan.

6 Review of Efficacy

Efficacy Summary

Boehringer Ingelheim (BI) submitted the results of three 52-week, double-blind, randomized, placebo-controlled, clinical trials in patients with IPF (Studies 1199.30, 1199.32 and 1199.34) to support the efficacy of nintedanib to treat IPF. Studies 1199.32 and 1199.34 were replicate, confirmatory, phase 3 studies of nintedanib 150 mg twice daily (BID) compared to placebo. Study 1199.30 was a phase 2 dose-ranging study of similar design. Although Study 1199.30 was designated as supportive data by the Applicant, due to the similar design/duration and inclusion of the treatment arm of interest, the nintedanib 150 mg BID and placebo treatment arms of Study 1199.30 were evaluated by this reviewer as pivotal study data to support the efficacy of nintedanib.

The pivotal studies enrolled patients aged ≥ 40 years of age with a diagnosis of IPF (defined by ATS/ERS/JRS/ALAT criteria) for < 5 years. Diagnoses were centrally adjudicated based on radiologic and, if applicable, histopathologic confirmation. Patients were required to have mild to moderate disease, with an FVC $\geq 50\%$ of predicted and a carbon monoxide diffusing capacity (DLCO, corrected for hemoglobin) of 30% to 79% of predicted. Patients with relevant airway obstruction (i.e., pre-bronchodilator FEV1/FVC < 0.7) or, in the opinion of the investigator, likely to receive a lung transplant during the studies were excluded (being listed for lung transplant was acceptable for inclusion). For the most part, concomitant medications being used to treat IPF were prohibited; allowances were made in the case of acute IPF exacerbation and progression of disease.

A total of 1231 patients with IPF were randomized into the 3 studies. The phase 3 studies (1199.32 and 1199.34) enrolled the majority of patients (n=423 on placebo and n=638 on nintedanib 150 mg BID). The phase 2 study (1199.30) enrolled 85 patients in both the nintedanib 150 mg BID and placebo treatment groups.

For all 3 studies, the baseline characteristics were balanced across treatment groups. The mean age was 67 years (range: 42 to 89 years), with 39% of patients < 65 years of age. Most patients

were male (79%), Caucasian (60%) or Asian (30%), and current or former smokers (72%). The majority of patients were enrolled outside the US (87%).

For the phase 3 studies, approximately 97-98% of patients met criteria for definite IPF on high-resolution computed tomography scan (HRCT). All patients with a possible diagnosis of IPF had their diagnosis confirmed by lung biopsy. Baseline mean percent predicted FVC was 80%. A total of 76% of patients completed the study without discontinuing trial medication. An additional 5% of patients completed the planned observation time despite early treatment discontinuation.

The primary efficacy endpoint was the annual rate of decline in FVC. All three studies achieved statistical significance for the primary endpoint in favor of nintedanib. The treatment difference (nintedanib – placebo) in trials 1199.30, 1199.32 and 1199.34 was 131mL/year (95% CI: 27, 235mL), 125mL/year (95% CI: 78, 173mL), and 94mL/year (95% CI: 45, 143 mL), respectively.

The statistical reviewer conducted a continuous responder analyses to provide the relative benefit of nintedanib across the entire range of response over 52 weeks. Consistent with the primary endpoint, nintedanib demonstrated a positive treatment effect of nintedanib as shown by consistent separation of the curves across different levels of response in all 3 studies. As an example, only 35% of nintedanib-treated patients had a 10% or greater decline in FVC compared to 50% of placebo-treated patients.

Key secondary endpoints included time to IPF exacerbation and St. George's Respiratory Questionnaire (SGRQ) score absolute change from baseline compared to placebo. IPF exacerbation was defined as unexplained worsening or development of dyspnea or new diffuse pulmonary infiltrates on CXR and/or new HRCT parenchymal abnormalities with no pneumothorax or pleural effusion (new ground-glass opacities), and exclusion of alternative causes. SGRQ is a disease-specific patient reported instrument which measures symptoms, activities, and its impact on daily life.

For time to IPF exacerbation, two studies (1199.30 and 1199.34) demonstrated statistical significance of nintedanib compared to placebo [Study 1199.30 (HR 0.16; 95% CI: 0.04, 0.71) and Study 1199.34 (HR 0.38; 95% CI: 0.19, 0.77)]. For Study 1199.32, nintedanib did not demonstrate a statistically significant difference compared to placebo [HR -1.2; 95% CI: 0.5, 2.4].

For SGRQ score change from baseline to Week 52, Studies 1199.30 and 1199.34 also demonstrated a statistically significant difference of nintedanib over placebo [Study 1199.30 (HR -6.12; 95% CI: -10.57, -1.67) and Study 1199.34 (HR -2.69; 95% CI: -4.95, -0.43)]. Study 1199.32 did not show a statistically significant difference between the two treatment groups for SGRQ [HR -0.1; 95% CI: -2.5, 2.4].

Mortality was an additional efficacy endpoint. Mortality (time to death) was assessed on treatment (within 14 days of treatment discontinuation) and vital status was obtained for patients

who discontinued (vital status at the end of study). Cause of death was adjudicated. The majority of deaths were due to respiratory causes. Survival was analyzed in a number of ways. None of the individual studies demonstrated a survival benefit; however, they were not powered to examine this endpoint. Each of the three studies demonstrated a numerical trend for survival benefit in favor of nintedanib compared to placebo. The rates for all-cause mortality for nintedanib versus placebo in Studies 1199.32, 1199.34, and 1199.30 were: 4.2% vs. 6.4%, 6.7% vs. 9.1%, and 8.2% vs. 10.6%, respectively. In a pre-specified integrated analysis of Studies 1199.32 and 1199.34, there were numerically fewer deaths in the nintedanib group (5.5%) compared to the placebo group (7.8%), however the integrated analysis did not achieve statistical significance [HR 0.7; 95% CI 0.43, 1.12]. A post-hoc analysis in which all three studies were pooled also demonstrated similar non-significant, but numerically favorable results [HR 0.7; 95% CI 0.46, 1.08].

Overall, the efficacy of nintedanib for the treatment of IPF has been demonstrated. Three studies showed a statistically significant difference in the primary efficacy endpoint of annual rate of FVC decline. Efficacy is further supported by the key secondary endpoints of time to IPF exacerbation and SGRQ score, which demonstrated statistically significant differences in 2 of the 3 studies. Although not powered for survival, a numerical trend favoring nintedanib was seen for survival in both pre-specified and sensitivity analyses.

6.1 Indication

The Applicant proposes nintedanib for the treatment of IPF (b) (4).

Reviewer comment: The Applicant has shown efficacy on multiple aspects of the disease (b) (4) (as measured by lung function). Efficacy is also supported by IPF exacerbations and health-related quality of life (SGRQ). Therefore, the Division recommends that the proposed indication include the broader statement of "treatment of IPF", (b) (4).

6.1.1 Methods

The pivotal efficacy data is derived from Studies 1199.32, 1199.34, and 1199.30. Studies 1199.32 and 1199.34 were replicate, confirmatory, phase 3, 52-week, randomized, double-blind, placebo-controlled, multinational, multicenter studies of nintedanib 150 mg twice daily (BID) compared to placebo in patients with IPF. Study 1199.30 was a phase 2, 52-week, double-blind, placebo-controlled, dose-ranging study in IPF patients which contributed 85 patients at the proposed dose of 150 mg BID compared to 85 placebo-treated patients. While Study 1199.30 was designated as a phase 2 dose ranging study, the design/duration/conduct of this study was similar to the confirmatory phase 3 studies. Therefore, the efficacy information from Study 1199.30 is also considered as pivotal in the efficacy evaluation. For Study 1199.30, discussion of efficacy will focus on period 1 (the placebo-controlled, 52-week period) and the 150 mg BID and placebo treatment arms, unless otherwise specified.

Efficacy analyses performed by both the applicant and the Agency will be presented in this section. The Agency has no specific issue with the way in which the pre-specified analyses were conducted; however, different statistical models and imputation strategies were utilized by the Agency as sensitivity analyses to explore the robustness of the data. A summary of these varied methods will be presented in the following review of efficacy. For full details of these sensitivity analyses, refer to the Biometrics Review by Dr. Yongman Kim.

6.1.2 Demographics

Baseline demographics were balanced across treatment groups. The mean age for all 3 studies was 67 years, with 39% of patients < 65 years. Most patients were male (79%), Caucasian (60%) or Asian (30%), and current or former smokers (72%). The demographics for the combined study population are displayed in Table 9.

Table 9. Baseline demographics: Studies 1199.32, 1199.34 and 1199.30 combined (Treated Population)			
	Placebo N=508	Nintedanib 150 mg BID N=723	Total N=1231
Sex, n (%)			
Male	397 (78)	572 (79)	969 (79)
Female	111 (22)	151 (21)	262 (21)
Race, n (%)			
Caucasian	313 (62)	421 (58)	734 (60)
African American	0	2 (<1)	2 (<1)
Asian	148 (29)	218 (30)	366 (30)
Missing	47 (9)	82 (11)	129 (11)
Age in Years			
Mean (SD)	67 (8)	67 (8)	67 (8)
Median	67	67	67
Min-Max	42-88	42-89	42-89
Age in class, n (%)			
< 65 years	186 (37)	296 (41)	482 (39)
≥ 65 years to < 75 years	249 (49)	299 (41)	548 (45)
≥ 75 years	73 (14)	128 (18)	201 (16)
Weight (kg)			
Mean (SD)	78 (16)	79 (16)	79 (16)
Height in cm			
Mean (SD)	168 (9)	168 (9)	168 (9)
Body mass index (kg/m²)			
Mean (SD)	28 (4)	28 (5)	28 (4)
Body surface area (m²)			
Mean (SD)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)
Smoking history, n (%)			
Never smoked	150 (30)	199 (28)	349 (28)
Ex-smoker	334 (66)	493 (68)	827 (67)
Currently smokes	24 (5)	31 (4)	55 (5)

Table 9. Baseline demographics: Studies 1199.32, 1199.34 and 1199.30 combined (Treated Population)

Source: \Module 1.11.3, Response to information request 6.20.14, Table 18.1 1 2, p 45-46

In the phase 3 studies, the distribution of patients by age category showed some imbalances, with a higher proportion of younger (< 65 years) and elderly (<75 years) patients in the nintedanib group compared to placebo. Demographic information for the treated population for each individual study is summarized in Table 10.

Table 10. Baseline demographics: Individual results for Studies 1199.32, 1199.34 and 1199.30 (Treated Population)

	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=204	Nintedanib 150 mg BID N=309	Placebo N=219	Nintedanib 150 mg BID N=329	Placebo N=85	Nintedanib 150 mg BID N=85
Sex, n (%)						
Male	163 (80)	251 (81)	171 (78)	256 (78)	63 (74)	65 (77)
Female	41 (20)	58 (19)	48 (22)	73 (22)	22 (26)	20 (24)
Race, n (%)						
Caucasian	135 (66)	198 (64)	131 (52)	162 (49)	65 (77)	61 (72)
African American	0	0	0	2 (<1)	0	0
Asian	41 (20)	66 (21)	86 (39)	128 (39)	20 (24)	24 (28)
Missing	28 (14)	45 (15)	19 (9)	37 (11)	0	0
Age in Years						
Mean (SD)	66.9 (8)	66.9 (8)	67 (8)	66 (8)	65 (9)	65 (8)
Median	68	68	68	66	65	66
Min, Max	45, 87	42, 85	42, 88	42, 89	45, 84	43, 81
Age in class, n (%)						
< 65 years	71 (35)	119 (39)	74 (34)	139 (42)	-	-
≥ 65 years to < 75 years	102 (50)	130 (42)	114 (52)	133 (40)	-	-
≥ 75 years	31 (15)	60 (19)	31 (14)	57 (17)	-	-
Weight (kg)						
Mean (SD)	81.2 (16.3)	82.0 (16.8)	76.2 (16.4)	76.6 (15.9)	77.3 (13.3)	74.9 (14.6)
Height in cm						
Mean (SD)	169.5 (8.3)	168.8 (9.2)	167.0 (9.7)	166.3 (9.2)	167.8 (8.7)	167.8 (9.5)
Body mass index (kg/m²)						
Mean (SD)	28.1 (4.6)	28.6 (4.5)	27.2 (4.5)	27.6 (4.6)	27.4 (3.8)	26.4 (3.9)
Body surface area (m²)						
Mean (SD)	1.9 (0.2)	1.9 (0.2)	1.8 (0.3)	1.8 (0.2)	1.8 (0.2)	1.8 (0.2)
Smoking history, n (%)						
Never smoked	51 (25)	71 (23)	71 (32)	103 (31)	28 (33)	25 (29)
Ex-smoker	144 (71)	217 (70)	139 (64)	218 (66)	51 (60)	58 (68)
Currently smokes	9 (4)	21 (7)	9 (4)	8 (2)	6 (7)	2 (2)

"-" = data not provided

Source: Module 5.3.5.1, Study 1199.32, Table 11.2.1:1, p 96; Study 1199.34, Table 11.2.1:1, p 102; SCE, Table 3.1.2.2.1, p 65; Study 1199.30,

Table 10. Baseline demographics: Individual results for Studies 1199.32, 1199.34 and 1199.30 (Treated Population)

Table 15.1.4.1, p 415; Module 1.11.3, Response to information request 6.20.14, Table 18.1.1.2, p 45.

Reviewer comment: The patient population is fairly representative of the IPF patient population as a whole.

Baseline IPF characteristics

Baseline IPF disease characteristics were generally balanced between groups within studies, as summarized below in Table 11.

Table 11. Baseline IPF disease characteristics: Studies 1199.32, 1199.34, and 1199.30 (Treated population)

	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=204	Nintedanib 150 mg BID N=309	Placebo N=219	Nintedanib 150 mg BID N=329	Placebo N=85	Nintedanib 150 mg BID N=85
Time since IPF diagnosis (years)						
Mean (SD)	1.59 (1.4)	1.66 (1.4)	1.55 (1.3)	1.64 (1.3)	1.4 (1.5)	1.0 (1.2)
Median	1.22	1.26	1.2	1.3	0.8	0.5
Min, Max ¹	0, 5.0	0, 5.2	0.1, 5.0	0, 4.9	0, 5.0	0, 5.0
Time since IPF diagnosis by class, n (%)						
≤ 1 year	92 (45)	133 (43)	101 (46)	141 (43)	48 (55)	57 (67)
> 1 year to ≤ 3 years	75 (37)	115 (37)	79 (36)	128 (39)	21 (25)	21 (25)
> 3 years to ≤ 5 years	37 (18)	58 (19)	39 (18)	60 (18)	16 (19)	7 (8)
> 5 years ¹	0	3 (1)	0	0	0	0
Centrilobular emphysema, n (%)						
Yes	78 (38)	118 (38)	88 (40)	136 (41)	19 (22)	23 (27)
Radiological assessment, n (%)						
Not evaluable	0	0	0	0	0	0
Consistent with UIP	198 (97)	301 (97)	215 (98)	321 (98)	81 (96)	85 (100)
Possible UIP	6 (3)	8 (3)	4 (2)	8 (2)	4 (5)	0
Definitely not UIP	0	0	0	0	0	0
Missing	0	0	0	0	0	0
Pulmonary assessment Mean (SD)						
FVC (L)	2.84 (0.82)	2.76 (0.74)	2.62 (0.79)	2.67 (0.78)	2.79 (0.77)	2.72 (0.80)
FVC (% predicted)	80.5 (17.3)	79.5 (17.0)	78.1 (19.0)	80.0 (18.1)	81.7 (17.6)	79.1 (18.5)
FEV1/FVC	80.8 (6.1)	81.5 (5.4)	82.4 (5.7)	81.8 (6.3)	81.7 (17.6)	79.1 (18.5)
SpO2 (%)	95.9 (1.9)	95.9 (2.0)	95.7 (2.1)	95.8 (2.6)	95.3 (2.2)	95.6 (1.7)
DLco (mmol/min/kpa) ²	3.96 (1.11)	3.96 (1.2)	3.75 (1.3)	3.77 (1.2)	3.8 (1.1)	3.7 (1.0)
SGRQ						

Table 11. Baseline IPF disease characteristics: Studies 1199.32, 1199.34, and 1199.30 (Treated population)						
	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=204	Nintedanib 150 mg BID N=309	Placebo N=219	Nintedanib 150 mg BID N=329	Placebo N=85	Nintedanib 150 mg BID N=85
Total score	39.8 (18.5)	39.6 (17.6)	39.4 (18.7)	39.5 (20.5)	41.2 (17.9)	40.1 (18.3)
Symptoms component	45.2 (22.9)	45.7 (22.0)	43.8 (21.6)	43.0 (23.5)	42.2 (21.6)	43.1 (25.2)
Activities component	52.1 (21.2)	52.2 (20.6)	52.8 (21.3)	51.8 (23.4)	54.2 (22.2)	53.9 (21.6)
Impact component	30.3 (19.4)	30.1 (18.7)	29.7 (20.9)	30.8 (21.9)	33.1 (19.7)	30.8 (19.0)

¹Inclusion criteria was IPF diagnosis within 5 years of first day of treatment (Visit 2)
²Corrected for Hemoglobin
 Source: Module 5.3.5.1, Study 1199.32, Table 11.2.2:1, 11.2.3:1, p 103-4; Study 1199.34, Table 11.2.2:1, p 103, Table 11.2.3:1, p 104; SCE, Table 3.1.2.2.2:1 p 66; Table 3.1.2.2.3:1, p 67; Study 1199.30, Table 15.1.4:6 478-9.

For the phase 3 studies, the mean time since IPF diagnosis was 1.6 years, with the majority of patients being diagnosed between 1-3 years from randomization. The phase 2 study had a slightly shorter period of time from IPF diagnosis (1-1.4 years) and most patients were diagnosed ≤ 1 year from study start. Baseline FVC was generally balanced across groups and within studies. In Study 1199.32, mean baseline FVC in placebo group (2845 mL) was higher than that in nintedanib group (2757 mL). The imbalance was mainly due to lower mean baseline FVC among Asian nintedanib group (2586 mL) compared to those in other race-by-treatment groups (2803 mL – 2830 mL). However, per the sensitivity analysis by the statistical reviewer on FVC adjusting for the baseline FVC, the apparent imbalance had no impact on the statistical significance.

Reviewer comment: The difference in baseline FVC, favoring nintedanib in Study 1199.34 is very small and not likely to result in a falsely increased treatment difference.

For the phase 3 studies, most patients had radiologic assessments consistent with usual interstitial pneumonia (UIP) (97-98%). Notably, no patients had radiologic assessments that were not evaluable, definitely not UIP, and/or missing. The diagnosis of UIP was based on the following conditions:

- Condition A = Honeycomb lung destruction with basal and peripheral predominance
- Condition B = Presence of reticular abnormality and traction bronchiectasis consistent with fibrosis with basal and peripheral predominance
- Condition C = Atypical features are absent – specifically: nodules and consolidation. Ground glass opacity, if present, is less extensive than reticular opacity pattern

Overall, for 53.4% of patients 'consistent with UIP' was determined by the presence of definite honeycomb lung destruction with basal and peripheral predominance (conditions A, B, and C or A and C). For 44.1% of patients, no honeycombing was present on the HRCT scans and 'consistent with UIP' was determined by the presence of reticular abnormality and traction bronchiectasis (conditions B and C). In total, 12.3% of patients (130 out of 1061) had an HRCT

fulfilling conditions B and C and their diagnosis confirmed by a lung biopsy, with a 'definite UIP', 'probable UIP', or 'possible UIP' outcome of the lung biopsy review. Overall, 31.9% of patients (338 out of 1061) had an HRCT fulfilling conditions B and C and no biopsy. All patients with a 'possible UIP' outcome of the HRCT central review had their diagnosis confirmed by a lung biopsy, with a 'definite UIP' or 'probable UIP' outcome of the lung biopsy review.

The phase 2 study did include 4 subjects with “possible UIP” based on results of the central reviewed HRCT and lung biopsy if available in the placebo group. These patients were enrolled before the protocol change to exclude these subjects. The sponsor did not state whether the diagnosis of these 4 subjects was supported by lung biopsy. Lung biopsy was available for 22% and 34% of patients on placebo and nintedanib, respectively.

Concomitant therapies

The ranges listed in this section represent results from Study 1199.32 and Study 1199.34 only, as the Applicant’s originally submitted pooled safety analysis included these studies. The pooled analysis of Studies 1199.32, 1199.34, and 1199.30 (placebo and 150 mg BID treatment arms only) was submitted after the original application, per request from the Agency, and did not include pooled data for concomitant therapies. Reviewing the data as presented by the sponsor, all 3 studies had similar concomitant therapy profiles.

Baseline therapies

Studies 1199.32 and 1199.34

Most patients were on at least one baseline therapy (86-88%). There were no noteworthy differences between the study arms with respect to the type and frequency of treatments for baseline therapies. The most common were P-glycoprotein inhibitors (47-48%), proton pump inhibitors/H₂-receptor antagonists (35-42%), anti-platelet (25-33%), bronchodilators (19%), and systemic corticosteroids (21-22%). N-Acetylcysteine was taken by 0.6 - 1.2% of patients in the nintedanib group and by 1.5-2.3% of patients in the placebo group.

Study 1199.30

Most patients were on at least one baseline therapy (70%). Overall baseline therapies were balanced between groups. Numerical differences between the treatment groups were observed for P-gp inhibitors (placebo: 46%, nintedanib: 35%), systemic corticosteroids (38% nintedanib vs. 32%), antiplatelet agents (25% vs.15%), and antioxidants/expectorants (14% vs. 5%).

On-treatment concomitant therapies

Studies 1199.32 and 1199.34

In Study 1199.32, nearly all patients received at least one on-treatment concomitant therapy (96%). In Study 1199.34 most patients (74%) received at least one concomitant on-treatment therapy. The types of treatments were similar to those at baseline. In the phase 3 studies, an expected imbalance was seen in anti-diarrheal therapies (34-35% nintedanib: 4-6% placebo) due to higher diarrhea AEs reported in the nintedanib group. In Study 1199.32 a difference was also

noted in the use of proton pump inhibitors/H₂-receptor antagonists (61% nintedanib; 53% placebo) and N-acetylcysteine (4% nintedanib, 11% placebo). These differences were not seen in Study 1199.34. Similarly, the phase 2 study (1199.30) showed an increased use in nintedanib group of anti-diarrheal therapies (25% nintedanib vs. 4% placebo), and proton pump inhibitors/H₂ receptor antagonists (25% nintedanib vs. 11% placebo).

Overall, 15-20% of patients received at least one restricted therapy at baseline or on-treatment (12-18% nintedanib; 20-24% placebo). Restricted therapies are outlined in Table 4. The proportion of patients receiving at least one restricted therapy within the first 6 months after randomization was balanced between the treatment groups (8.1% nintedanib; 9.8% placebo) in Study 1199.32, and slightly higher in the placebo group for Study 1199.34 (9.1% nintedanib; 13.2% placebo). The most commonly used restricted therapy during the first 6 months was systemic corticosteroids at a dose equivalent to >15mg/day of prednisone (6% nintedanib; 5-9% placebo). The use of restricted therapies after 6 months after randomization was higher in the placebo group (16-18%) compared with nintedanib (9-13%) and the most commonly used restricted therapy during this time was also systemic corticosteroids at a dose equivalent to >15mg/day of prednisone (6-8% nintedanib; 7-11% placebo).

For the phase 3 studies, overall, 34-43% of patients received a potential forbidden concomitant therapy at any point during the trial i.e. at baseline, on-treatment, and post-trial drug discontinuation. This was balanced between treatment groups. Potential forbidden concomitant therapies are outlined in Table 4. The majority of patients (29-37%) received anti-platelet therapies and this was balanced between treatment groups. According to the protocol, patients could take potentially forbidden concomitant therapies if medically indicated, with a 4-week washout of nintedanib prior to their use. In Study 1199.32, pifrenidone was received by 2 patients in the nintedanib group and 5 patients in the placebo group. In Study 1199.34, 3 patients in the nintedanib group and 4 patients in the placebo group received pifrenidone. In all cases pifrenidone was taken post-trial drug discontinuation, except for 2 patients (one in each study) in the placebo group who took pifrenidone while on treatment.

Studies 1199.30

In Study 1199.30, nearly all patients received at least one on-treatment concomitant therapy (96%). In Study 1199.34 most patients (74%) received at least one concomitant on-treatment therapy. The types of treatments were similar to those at baseline.

Restricted therapies were used more frequently in the placebo group (9%) compared to the nintedanib group (5%). In the first 6 months after randomization, acetylcysteine was the only restricted therapy that was used by at least 2 patients in either treatment group. The use of acetylcysteine was more frequent in the placebo arm (4.7%) than the nintedanib arm (1.2%). Later than 6 months after randomization, the use of acetylcysteine had increased to 7.1% in the placebo group and 2.4% in the nintedanib group. Restricted oral steroids were not analyzed for this study as restricted medication doses were not collected.

A total of 65% of patients received potentially forbidden concomitant therapies in Study 1199.30. This was balanced across treatment groups. The time period these therapies were given was not provided and therefore could have been within the >6 month allowable window. No patients received pirfenidone.

Lung Transplant

In Study 1199.32, out of 60 patients who qualified for a lung transplant, a total of 5 patients (4 nintedanib; 1 placebo) received a lung transplant post-trial discontinuation. In Study 1199.34, 2 patients in the placebo group received a lung transplant post-trial discontinuation. The efficacy analysis excluded patient data after lung transplant. No subjects received a lung transplant in Study 1199.30.

Reviewer comment: The concomitant medications taken during the study are not expected to affect the efficacy and safety analysis. There are no approved therapies for IPF, therefore none of the concomitant medications would be considered to affect efficacy evaluations.

Concomitant Diseases

Studies 1199.32 and 34

Most patients had a baseline condition (94%). There were no noteworthy differences between the treatment arms with respect to previous diseases. The most common baseline conditions, by preferred term, were hypertension (29% nintedanib; 45% placebo) and GERD (19-28% nintedanib; 22-27% placebo).

Studies 1199.30

Similarly, most patients had a baseline condition (86% (147/170)). The most common baseline conditions, by PT, were hypertension (44% nintedanib; 42% placebo) and GERD (13% nintedanib; 5% placebo).

Reviewer comment: Baseline disorders are consistent with what would be expected with an IPF population.

6.1.3 Subject Disposition

Disposition:

Study sites

Study 1199.32

A total of 98 centers enrolled 718 subjects. The centers were located in **Australia, Belgium, China, Czech Republic, France, Germany, India, Ireland, Israel, Italy, Japan, the United Kingdom, and the United States**. The countries in **bold font** contributed the most patients (i.e. ≥ 10 patients in either treatment group). The United States centers enrolled 14% of all subjects.

Study 1199.34

A total of 107 centers enrolled 794 subjects. The centers were located in Canada, Chile, **China**, Finland, **France**, **Germany**, **Greece**, India, **Japan**, **Korea**, Mexico, **Netherlands**, **Portugal**, Russia, **Spain**, **Turkey**, and the **US**. The countries in **bold font** contributed the most patients (i.e. ≥ 10 patients in either treatment group). The United States centers enrolled 16% of all subjects.

Study 1199.30

A total of 92 centers enrolled 679 subjects. The centers were located in Argentina, Australia, Belgium, Brazil, Bulgaria, Canada, Chile, China, Czech Republic, **France**, **Germany**, Greece, Hungary, Ireland, **Italy**, Korea, Mexico, Netherlands, Portugal, Russia, South Africa, Spain, Taiwan, Turkey, and the United Kingdom. The countries in **bold font** contributed the most patients (i.e. $\geq 10\%$ of the total number of patients enrolled). All centers were outside the US.

Patients

Study 1199.32

Out of 718 enrolled patients, 515 (72%) were randomized (3:2) into the study, with 206 randomized to placebo and 309 randomized to nintedanib 150 mg BID. The treated population, defined as patients who were dispensed study medication AND were documented to have taken at least one dose, consisted of 513 patients (204 subjects on placebo and 309 subjects on nintedanib 150 mg BID). A total of 114 patients prematurely discontinued trial medication (36 (18%) on placebo and 78 (25%) on nintedanib). Of those, 42 (36%) patients completed the planned 52-week observation period.

Study 1199.34

Out of 794 enrolled patients, 551 (69%) were randomized (3:2) into the study. The treated population, defined as patients who were dispensed study medication AND were documented to have taken at least one dose, consisted of 548 patients (219 subjects on placebo and 329 subjects on nintedanib 150 mg BID). A total of 114 patients prematurely discontinued trial medication (24% on placebo and 20% on nintedanib). Of those, 83% patients completed the planned 52-week observation period.

Study 1199.30

Out of 679 enrolled patients, 432 (64%) were randomized, with equal numbers in each treatment group. The treated population, defined as patients who were dispensed study medication AND were documented to have taken at least one dose, consisted of 428 (99%) patients (85 subjects on placebo and 343 subjects on nintedanib). In the high dose treatment group (150 mg BID) 53 subjects (62%) completed the study on treatment. Out of the remaining 32 subjects, 11 completed the study visits despite prematurely discontinuing treatment, resulting in 64 (74%) of subjects completing the study.

Patient disposition for all 3 studies is summarized in Table 12.

Table 12. Subject disposition: Studies 1199.32, 1199.34, and 1199.30 (Randomized population)						
	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=206 n (%)	Nintedanib 150 mg BID N=309 n (%)	Placebo N=220 n (%)	Nintedanib 150 mg BID N=331 n (%)	Placebo N=87 n (%)	Nintedanib 150 mg BID N=86 n (%)
Treated population ¹	204 (99)	309 (100)	219 (100)	329 (100)	85 (100)	85 (100)
Treated with ≥ 2 FVC measurements ²	-	-	-	-	83 (98)	84 (99)
Completed Study and did not prematurely discontinue trial medication	163 (80)	229 (74)	175 (80)	251 (76)	61 (72)	53 (62)
Completed planned observation time despite prematurely discontinuing trial medication ³	11 (5)	31 (10)	10 (5)	26 (8)	5 (6)	11 (13)
Completed planned observation time	174 (85)	260 (84)	179 (82)	272 (83)	66 (76)	64 (74)
Prematurely discontinued trial medication	36 (18)	78 (25)	44 (20)	78 (24)	-	-
Non-Safety	12 (6)	13 (4)	9 (4)	17 (5)	-	-
Protocol non-compliance	3 (2)	2 (<1)	1 (<1)	3 (1.0)	-	-
Subject decision to discontinue medication	7 (3)	9 (3)	6 (3)	11 (3)	-	-
Lost to follow-up	0	0	1 (<1)	0	-	-
Other	2 (1)	2 (<1)	1 (<1)	3 (1)	-	-
Safety	24 (12)	65 (21)	35 (16)	62 (19)	-	-
Adverse Event ⁴	24 (12)	65 (21)	35 (16)	62 (19)	-	-
Prematurely discontinued from study⁴	30 (15)	49 (16)	40 (18)	57 (18)	24 (28)	32 (38)
Non-Safety	15 (7)	24 (8)	10 (5)	15 (5)	1 (1)	1 (1)
Protocol non-compliance	2 (1)	0	0	2 (<1)	1 (1)	0
Subject decision to discontinue study	12 (6)	23 (7)	7 (3)	9 (3)	0	0
Lost to follow-up	0	0	1 (<1)	2 (<1)	0	0
Other	1 (<1)	1 (<1)	2 (<1)	2 (<1)	0	1 (1)
Safety	15 (7)	25 (8)	30 (14)	42 (13)	21 (25)	27 (32)
Adverse Event ⁴	15 (7)	25 (8)	30 (14)	42 (13)	21 (25)	27 (32)

¹ Used for efficacy and safety analysis
² Population used for Study 1199.30 primary efficacy analysis
³ Patients who prematurely discontinued trial medication continued planned observation time through 52-weeks
⁴ Deaths were reported as AEs.
“-” = data not provided
Source: Module 5.3.5.1, Study 1199.32, Table 10.1:1, p 96; Study 1199.34, Figure 10.1:1, p 95, Table 10.1:1, p96; Study 1199.30, Table 10.1:1, p 115, Table 15.1.1:5, p 406

Reviewer comment: As expected, in both of the phase 3 studies, the number of patients who discontinued trial medication due to an adverse event is higher in the treatment group compared to placebo. While the difference favors placebo over treatment, the risk benefit remains in favor of nintedanib treatment for this fatal condition (see Section 1.2 Risk Benefit Assessment for a full discussion of risk benefit). This difference is not seen in the patients who discontinued the study (patients were encouraged to continue study assessments despite discontinuing treatment) due to an adverse event.

Compliance

Compliance was high and balanced across all treatment groups for all 3 studies (96-98%). Missing data occurred in 3% of subjects for all 3 studies (Study 1199.32: 5% (n=14) nintedanib; 1% (n=2) placebo; Study 1199.34: 3% (n=9) nintedanib; 3% (n=7) placebo; Study 1199.30: <1% (n=2) nintedanib 150 mg BID, 2% (n=4) placebo).

6.1.4 Analysis of Primary Endpoint

Primary Efficacy Results

The primary endpoint for all 3 studies was the rate of decline in FVC (mL) over 52 weeks. Details for each study are summarized below.

Study 1199.32

The adjusted annual rate of decline in FVC was lower in the nintedanib group (-115 ml/year) than in the placebo group (-240 mL/year). The adjusted difference between nintedanib and placebo was statistically significant: 125 mL/year (95% CI: 78, 173).

Study 1199.34

The adjusted annual rate of decline in FVC was also lower in the nintedanib group (-114 ml/year) than in the placebo group (-207 ml/year). The adjusted difference between nintedanib and placebo was slightly numerically lower than in Study 1199.32, but still statistically significant: 94 mL/year (95% CI: 45, 143).

Study 1199.30

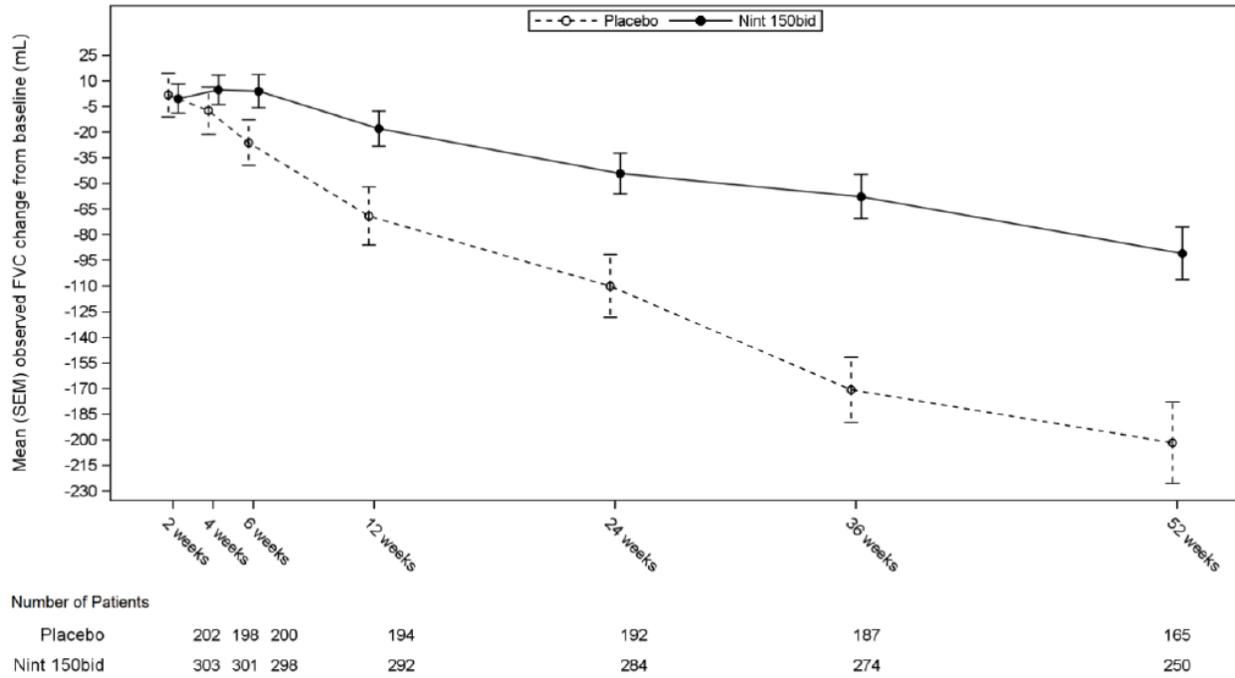
As in the phase 3 studies, the adjusted annual rate of decline in FVC was also lower in the 150 mg BID nintedanib group (-60 ml/year) than in the placebo group (-190 ml/year). The adjusted difference between nintedanib and placebo was slightly higher than the phase 3 studies at 131 mL/year (95% CI: 27, 235). The 150 mg bid dose reached nominal significance ($p=0.0136$, hierarchical testing procedure specified in the pre-specified statistical analysis plan as a sensitivity analysis.). Protection of alpha (type I error) was not achieved for the multiplicity correction procedure ($p=0.0639$). These results are summarized in Table 13.

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.						

Reviewer comment: When comparing overall, the magnitude of the treatment effect across studies was comparable.

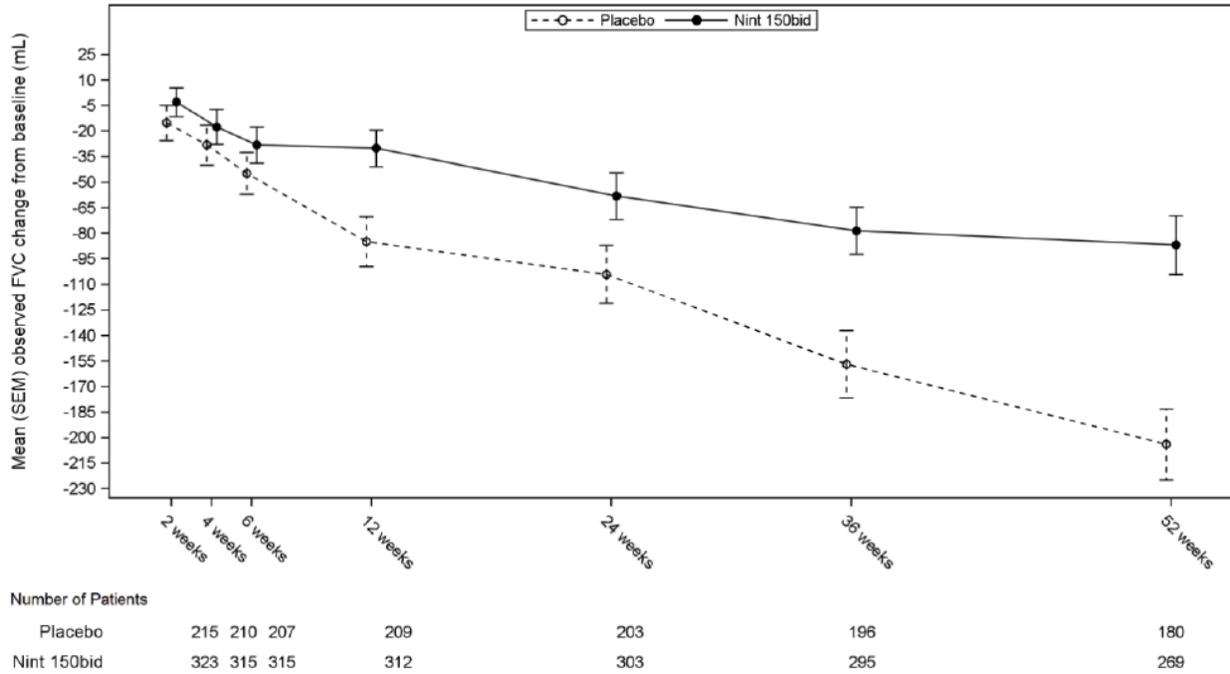
Graphical presentation of the mean observed change from baseline in FVC for both treatment groups is presented in Figure 5 (Study 1199.32), Figure 6 (Study 1199.34), and Figure 7 (Study 1199.30). The figures illustrate that the curves separate early and gradually over 52 weeks.

Figure 5. Mean observed FVC change from baseline (mL) over time: Study 1199.32 (Treated population)



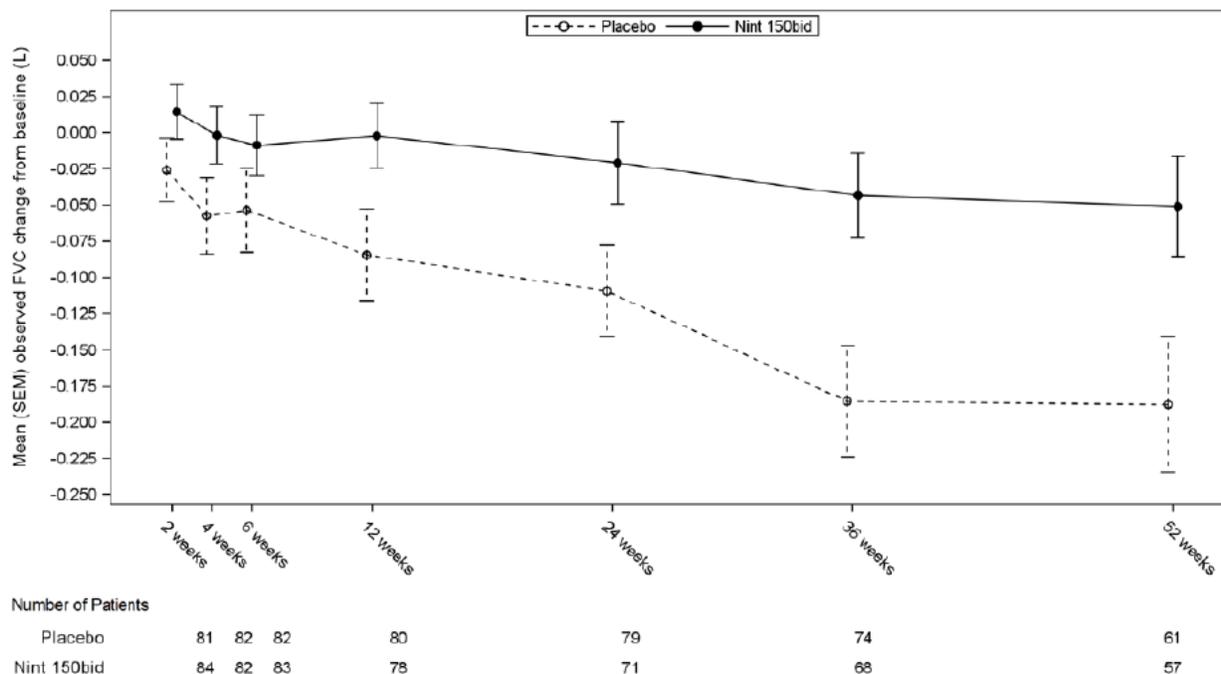
Source: Module 5.3.5.1, Study 1199.32 CSR, Figure 11.4.1.1:1, p 111.

Figure 6. Mean observed FVC change from baseline (mL) over time: Study 1199.34 (Treated population)



Source: Module 5.3.5.1, Study 1199.34 CSR, Figure 11.4.1.1:1, p 110.

Figure 7. Mean (SEM) observed FVC change from baseline (L) over time: Study 1199.30 (Randomized population)



Source: Module 2.7.3, SCE, Figure 3.2.2.1:1, p 99.

Sensitivity Analysis

For the phase 3 studies, the sponsor conducted multiple sensitivity analyses using patterns based on patient populations as outlined in Table 14.

Table 14. Primary efficacy endpoint sensitivity analysis populations: Study 1199.32 (Randomized population)					
Analysis population	Population description	Study 1199.32		Study 1199.34	
		Placebo N=206 n (%)	Nintedanib 150 mg BID N=309 n (%)	Placebo N=220 n (%)	Nintedanib 150 mg BID N=331 n (%)
Primary Analysis	Treated population ¹	204 (99)	309 (100)	219 (100)	329 (100)
Pattern 1	Patients with an FVC value at 52-weeks and did NOT prematurely discontinue trial medication	163 (80)	229 (74)	175 (80)	251 (76)
Pattern 2	Patients with an FVC value at 52-weeks despite prematurely discontinuing trial medication	11 (5)	31 (10)	10 (5)	26 (8)
Pattern 3	Patients withOUT an FVC value at 52-weeks, but were alive at week	17 (8)	33 (11)	26 (12)	18 (5)

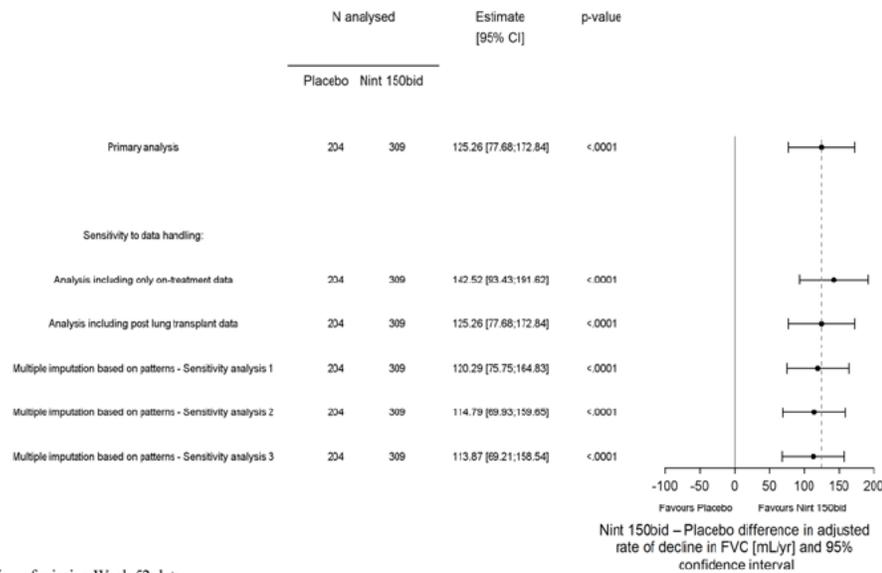
Table 14. Primary efficacy endpoint sensitivity analysis populations: Study 1199.32 (Randomized population)

	52	Study 1199.32		Study 1199.34	
Pattern 4	Patients withOUT an FVC value at 52-weeks who died before week 52	13 (6)	14 (5)	22 (10)	19 (6)

Source: Module 5.3.5.1, Study 1199.32, Figure 11.4.1.1:2, p 113, Statistical methods interim analysis, Table 6.2.1.6, p 546; Study 1199.34, Figure 11.4.1.1:2, p 116.

The results of the sensitivity analyses based on the above populations were consistent with the primary efficacy analysis, as depicted in Figure 8 (Study 1199.32) and Figure 9 (Study 1199.34).

Figure 8. Sensitivity analysis of the rate of decline in FVC (ml/year) over 52 weeks: Study 1199.32

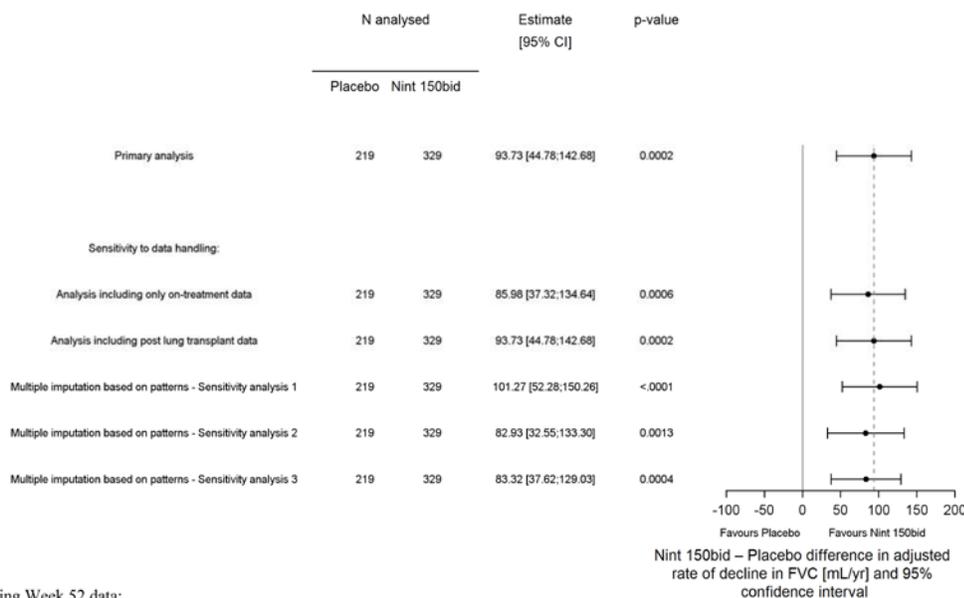


Multiple imputation of missing Week 52 data:

Sensitivity analysis 1: Imputation in pattern 3 is based on the slope (SE) estimates in drug and placebo in patients of pattern 2. Imputation in pattern 4 is based on the slope (SE) estimates in placebo patients of pattern 2, but using a truncated distribution. **Sensitivity analysis 2:** Imputation in pattern 3 is based on the slope (SE) estimates in placebo patients of pattern 2. Imputation in pattern 4 is based on the slope (SE) estimates in placebo patients of pattern 2, but using a truncated distribution. **Sensitivity analysis 3:** Imputation in pattern 3 is based on the slope (SE) estimates in placebo patients from the primary analysis model. Imputation in pattern 4 is based on the slope (SE) estimates in all placebo patients, but using a truncated distribution. **Pattern 1:** Patients with a 52-week FVC value who received trial drug until Week 52. **Pattern 2:** Patients with a 52-week FVC value who prematurely discontinued trial drug but were followed up until Week 52, i.e. completed planned observation time. **Pattern 3:** Patients without a 52-week FVC value who were alive at Week 52 **Pattern 4:** Patients without a 52-week FVC value who died before Week 52.

Source: Module 5.3.5.1, Study 1199.32, Figure 11.4.1.1:2, p 113

Figure 9. Sensitivity analysis of the rate of decline in FVC (ml/year) over 52 weeks: Study 1199.34



Multiple imputation of missing Week 52 data:

Sensitivity analysis 1: Imputation in pattern 3 is based on the slope (SE) estimates in drug and placebo in patients of pattern 2. Imputation in pattern 4 is based on the slope (SE) estimates in placebo patients of pattern 2, but using a truncated distribution. **Sensitivity analysis 2:** Imputation in pattern 3 is based on the slope (SE) estimates in placebo patients of pattern 2. Imputation in pattern 4 is based on the slope (SE) estimates in placebo patients of pattern 2, but using a truncated distribution. **Sensitivity analysis 3:** Imputation in pattern 3 is based on the slope (SE) estimates in placebo patients from the primary analysis model. Imputation in pattern 4 is based on the slope (SE) estimates in all placebo patients, but using a truncated distribution. **Pattern 1:** Patients with a 52-week FVC value who received trial drug until Week 52. **Pattern 2:** Patients with a 52-week FVC value who prematurely discontinued trial drug but were followed up until Week 52, i.e. completed planned observation time. **Pattern 3:** Patients without a 52-week FVC value who were alive at Week 52. **Pattern 4:** Patients without a 52-week FVC value who died before Week 52.

Source: Module 5.3.5.1, Study 1199.34, Figure 11.4.1.1:2, p 112

A number of sensitivity analyses were also performed on the primary endpoint for Study 1199.30 which supported the primary endpoint analyses.

The statistical reviewer, Dr. Yongman Kim, confirmed the sponsor’s primary analysis. Dr. Yongman Kim also conducted sensitivity analyses on the primary endpoint for all 3 studies that supported the primary analysis.

Further discussion of efficacy can be found in Dr. Youngman Kim’s statistical review.

6.1.5 Analysis of Secondary Endpoints(s)

Key secondary endpoints were SGRQ score at 52 weeks and time to acute IPF exacerbation. Survival analysis will also be discussed here due to its clinical importance, although it was not designated as a key secondary endpoint.

Results for the key secondary efficacy endpoints are summarized in Table 15.

Table 15. Results for key secondary efficacy endpoints: Study 1199.32, 1199.34, (Treated population) and Study 1199.30 (Randomized Population)

	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo N=204	Nintedanib 150 mg BID N=309	Placebo N=219	Nintedanib 150 mg BID N=329	Placebo N=87	Nintedanib 150 mg BID N=85
SGRQ						
Baseline, Mean (SD)	39.8 (18.5) N=202	39.6 (17.6) N=298	39.4 (19.7) N=217	39.5 (20.5) N=326	-	-
Week 52, Mean (SD)	42.4(21.4) N=163	42.7 (20.2) N=240	42.2 (21.1) N=179	40.3 (22.0) N=267	-	-
Absolute change from baseline to Week 52						
Mean (SD)	3.7 (15.4)	3.9 (16.0)	5.3 (16.1)	2.2 (15.2)	5.2 (1.6)	-0.4 (1.5)
Adjusted ¹ mean (SE)	4.4 (1.0)	4.3 (0.8)	5.5 (0.9)	2.8 (0.7)	5.5 (1.7)	-0.7 (1.7)
95% CI	(2.5, 6.3) N=161	(2.8, 5.9) N=233	(3.7, 7.2) N=178	(1.4, 4.2) N=264	(2.1, 8.9) N=79	(-4.0, 2.7) N=75
Comparison vs. placebo						
Adjusted mean (SE)	-0.1 (1.3)		-2.7 (1.2)		-6.1 (2.3)	
95% CI	(-2.5, 2.4)		(-5.0, -0.4)		(-10.6, -1.7)	
Time to first acute IPF exacerbation over 52 weeks						
Probability of being event free	0.94	0.93	0.90	0.96	-	-
Patients with events ² , n (%)	11 (5)	19 (6)	21 (10)	12 (4)	12 (14)	2 (2)
Hazard ratio ³	1.2		0.4		0.16	
95% CI	(0.5, 2.4)		(0.2, 0.8)		(0.04, 0.71)	

¹ Based on MMRM, with fixed effects for treatment, visit treatment-by-visit, baseline SGRQ total score, baseline SGRQ total score-by-visit and random effect for patient. Within-patient errors were modelled by compound symmetry covariance matrix. Adjusted mean was based on all analyzed patients in the model (not only patients with a change from baseline to Week 52).
²Number of patients at risk is the total treated population
³Based on a Cox's regression model with terms for treatment, gender, age, and height
 -- " = data not provided
 Source: Module 5.3.5.1, Study 1199.32, Tables 11.4.1.2, p 113; Table 11.4.1.3:1, p 118; Study 1199.34, Tables 11.4.1.2, p 113; Table 11.4.1.3:1, p 117; Module 2.7.3 SCE, Table 3.2.2.2:1, p 100, Table 3 2 2 3:1, p 102

SGRQ score at 52 weeks

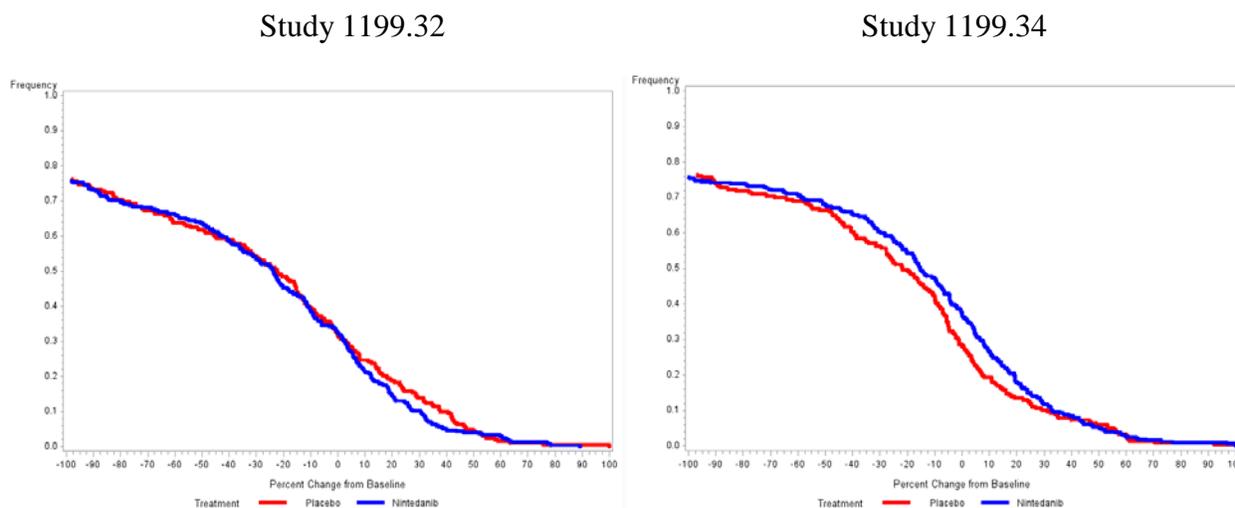
In Study 1199.32, the adjusted mean change from baseline to Week 52 in SGRQ total score was comparable between nintedanib (4.3) and placebo (4.4). The difference between treatment groups was -0.1 (95% CI: -2.5, 2.4). In Study 1199.34, the adjusted mean change from baseline to Week 52 in SGRQ total score favored nintedanib (nintedanib 2.8 vs. placebo 5.5). The adjusted mean difference in the change from baseline to Week 52 in SGRQ total score showed a statistically significant difference between nintedanib and placebo of -2.7 (95% CI: -5.0, -0.4).

Study 1199.30 also demonstrated a statistically significant difference between nintedanib and placebo with an adjusted mean difference of -6.1 (95% CI: -10.6, -1.7).

Reviewer comment: For patients with chronic obstructive pulmonary disease (COPD) the minimal clinically important difference (MCID) of 4 has been established for SGRQ, but the SGRQ MCID is not known for patients with IPF.

A cumulative distribution curve analyses for SGRQ, conducted by the statistical reviewer with worse score imputation for missing data showed separation of curves in Study 1199.34, but not in Study 1199.32 (Figure 10).

Figure 10. Cumulative distribution of relative change from baseline in SGRQ total score: Studies 1199.32 and 1199.34



The sponsor also conducted a cumulative distribution analyses for SRGQ responders (other PRO endpoints are under Section 6.1.6 Other Endpoints). In Study 1199.32, no significant difference between nintedanib and placebo was observed for the SGRQ responders at 52 weeks. In Study 1199.34, the proportion of SGRQ responders at 52 weeks, defined by a change from baseline of ≤ -4 points, was greater for nintedanib (25.2%) than placebo (16.9%). The odds ratio was 1.67 (95% CI: 1.08, 2.57) and was statistically significant.

Time to acute IPF exacerbation

In Study 1199.32, the proportion of patients with at least one acute IPF exacerbation over 52 weeks, based on all investigator-reported adverse events, was generally low and similar between groups. The time to event analysis yielded a hazard ratio of 1.2 (95% CI: 0.5, 2.4), indicating no significant difference in the risk of first acute IPF exacerbation between the treatment groups. However, in Study 1199.34, more subjects in the placebo group had at least one acute IPF exacerbation. The time to event analysis yielded a hazard ratio of 0.4 (95% CI: 0.2; 0.8), indicating that nintedanib was statistically better than placebo with respect to the time to first

acute IPF exacerbation. Study 1199.30 also demonstrated a statistically significant treatment difference in favor of nintedanib with a hazard ratio of 0.16 (95% CI: 0.04, 0.71).

A sensitivity analyses for the SGRQ score and time to first acute IPF exacerbation for Studies 1199.34 and 1199.30 supported the primary analysis.

All key secondary endpoints were confirmed by the statistical reviewer. Further discussion of the key secondary endpoint analyses can be found in Dr. Youngman Kim's statistical review.

Survival analyses

The Applicant conducted an analysis comparing all-cause mortality between the treatment groups for all 3 studies. Kaplan-Meier estimates were used to summarize survival time up to the end of the study treatment period. Survival time is measured by time from randomization to death. Treatment differences were analyzed using the log-rank test. The hazard ratio (HR) was determined based on the Cox proportional hazard model, with sex, age, and height as factors. Time to death for all 3 studies is summarized in Table 16.

Table 16. Results for Time to Death over 52 weeks: Studies 1199.32, 1199.34, and 1199.30 (Treated Set)						
Individual Study Results						
	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=87 n (%)	Nintedanib 150 mg BID N=85 n (%)
Deaths, n (%)	13 (6)	13 (4)	20 (9)	22 (7)	9 (10)	7 (8)
HR ^{1,2}	0.63		0.74		0.73	
95% CI	(0.29, 1.36)		(0.40, 1.36)		(0.27, 1.98)	
Pooled Study Results						
	Study 1199.32 and 1199.34				-	
	Placebo N=423 (%)		Nintedanib 150 mg BID N=638 (%)		-	
Deaths, n (%)	33 (8)		35 (6)		-	
HR ^{1,2}	0.70				-	
95% CI	(0.43, 1.12)				-	
	Placebo N=508 (%)			Nintedanib 150 mg BID N=723 (%)		
Patients with event, n (%)	42 (8)			42 (6)		
HR ^{1,2}	0.70					
95% CI	(0.46, 1.08)					
¹ Based on data collected up to 372 days after randomization (52 weeks + 7 days margin)						
² Based on a Cox's regression model with terms for treatment, gender, age, and height. Study 1199.30 also used terms for region.						
-- " " = data not provided						
Source: Module 5.3.5.1, Study 1199.32, Table 11.4.1.5.6:1, p 136; Study 1199.34, Table 11.4.1.5.6:1, p 133; Module 2.7.3 SCE, Table 3.2.1.5:1, p 92;						

There was a numerical trend in favor of nintedanib for time to death for all 3 studies.

For Studies 1199.32 and 1199.34, all time-to-event survival endpoints (time to death, time to death due to respiratory cause, time to on-treatment death, time to death or lung transplant, time to death or lung transplant or qualifying for a lung transplant) showed a lower proportion of patients experiencing an event in the nintedanib group than in the placebo group (data now shown). The proportion of patients who died over 52 weeks was numerically lower in the nintedanib group compared to the placebo group for both studies (Study 1199.32, 4% vs. 6%; Study 1199.34, 7% vs 9%, respectively). The hazard ratio for time to death over 52 weeks was 0.63 (95% CI: 0.29, 1.36) for Study 1199.32 and 0.74 (95% CI: 0.40, 1.36) for Study 1199.34. The pooled analysis of Studies 1199.32 and 1199.34 for time to death resulted in a HR of 0.70 (95% CI: 0.43, 1.12). Following adjudication, the majority of deaths were considered to be due to respiratory cause.

In Study 1199.30, time to death numerically favored nintedanib with a hazard ratio of 0.73 (95% CI: 0.27, 1.98) for the 150 mg BID treatment group. The proportion of patients who died over 52 weeks was numerically lower in the nintedanib group compared to the placebo group (8.2% vs. 10.6%, respectively). For on-treatment time to death (including only AEs leading to death with an onset date of the event reported during the treatment period plus 14 days, but for which the death may have occurred after the 52 weeks period.), a dose-dependent decrease in the number of deaths was observed: 12, 10, 4, 5 and 1 patient died in the placebo, 50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID dose groups, respectively (data now shown). Following adjudication, the majority of deaths were considered to be due to respiratory cause.

As the number of deaths was expected to be low, a pre-specified pooled analysis of the phase 3 studies (1199.32 and 1199.34) was performed on survival endpoints. The hazard ratio for time to death over 52 weeks numerically favored nintedanib (0.70 [95% CI: 0.43, 1.12]). A post-hoc pooled analysis (Cox's proportional hazards model, adjusted for gender, height, and age) for all 3 studies, time to death was also lower in the nintedanib-treated group compared to placebo with a similar hazard ratio of 0.70 (95%: CI 0.46, 1.08), that was not statistically significant.

The survival analysis was confirmed by the statistical reviewer. Further discussion of the survival analysis can be found in Dr. Youngman Kim's statistical review.

Reviewer comment: The individual studies were not powered to look at mortality as an endpoint; however the numerical trend in favor of nintedanib in all survival endpoints supports the primary efficacy endpoint.

6.1.6 Other Endpoints

Multiple other secondary efficacy endpoints were analyzed. The focus of Study 1199.30 was to support the primary and key secondary endpoints, and therefore Study 1199.30 will not be included in this section of the review. The other secondary endpoints for the phase 3 studies are grouped under the following categories: further analyses on FVC, patients reported outcomes

(PRO), acute exacerbation, and vital signs. Secondary endpoints will be presented in this section under their respective categories.

Further Analyses on FVC

Secondary endpoints for further analyses on FVC are summarized in Table 17.

Table 17. Secondary endpoints: Study 1199.32 and 1199.34 (Treated population)				
	Study 1199.32		Study 1199.34	
	Placebo	Nintedanib 150 mg BID	Placebo	Nintedanib 150 mg BID
	N=204	N=309	N=219	N=329
Absolute change from baseline in FVC (mL) over 52 weeks				
Baseline, Mean (SD)	2845 (820) N=204	2757 (735) N=309	2618 (787) N=219	2673 (812) N=329
Week 52, Mean (SD)	2664 (834) N=165	2669 (772) N=250	2513 (821) N=180	2637 (812) N=269
Change from baseline to Week 52, Mean (SD)	-202 (306)	-91 (243)	-204 (281)	-87 (283)
Adjusted ¹ mean (SE)	-205 (17)	-95 (14)	-205 (17)	-95 (14)
95% CI	(-238, -173) N=165	(-123, -67) N=250	(-237, -172) N=180	(-123, -67) N=269
Comparison vs. placebo	110 (20) 95% CI (71, 149)		110 (20) 95% CI (71, 149)	
Absolute change from baseline in FVC (% predicated) over 52 weeks				
Baseline, Mean (SD)	80.5 (17.3) N=204	79.5 (17.0) N=309	78.1 (19.0) N=219	80.0 (18.1) N=329
Week 52, Mean (SD)	75.7 (18.1) N=165	76.6 (17.5) N=250	73.6 (20.5) N=180	77.9 (19.0) N=269
Change from baseline to Week 52, Mean (SD)	-5.9 (8.8)	-2.7 (7.1)	-6.1 (8.0)	-2.8 (8.7)
Adjusted ¹ mean (SE)	-6.0 (0.5)	-2.8 (0.4)	-6.2 (0.5)	-3.1 (0.4)
95% CI	(-6.9, -5.1) N=165	(-3.6, -2.0) N=250	(-7.1, -5.2) N=180	(-4.0, -2.2) N=269
Comparison vs. placebo	3.2 (0.6) 95% CI (2.1, 4.3)		3.1 (0.6) 95% CI (1.9, 4.3)	
Proportion of FVC responders using 5% and 10% threshold at 52 weeks				
5%				
Number of FVC responders (%)	78 (38.2)	163 (52.7)	86 (39.3)	175 (53.2)
95% CI	(31.8, 45.1)	(47.2, 58.3)	(33.0, 45.9)	(47.8, 59.5)
Comparison vs. placebo, odds ratio	1.8		1.8	
95% CI	(1.3, 2.7)		(1.3, 2.6)	
10%				
Number of FVC responders (%)	116 (56.9)	218 (70.6)	140 (64.0)	229 (70.0)

Table 17. Secondary endpoints: Study 1199.32 and 1199.34 (Treated population)				
	Study 1199.32		Study 1199.34	
	Placebo	Nintedanib 150 mg BID	Placebo	Nintedanib 150 mg BID
	N=204	N=309	N=219	N=329
95% CI	(50.0, 63.5)	(65.2, 75.4)	(57.4, 70.0)	(64.4, 74.3)
Comparison vs. placebo, odds ratio	1.9		1.3	
95% CI	(1.3, 2.8)		(0.9, 1.9)	
¹ Based on MMRM, with fixed effects for treatment, visit, gender, age, height, treatment-by-visit, baseline FVC, baseline FVC-by-visit and random effect for patient. Within-patient errors were modelled by compound symmetry covariance matrix. Adjusted mean was based on all analyzed patients in the model (not only patients with a change from baseline to Week 52). ² Number of patients at risk is the total treated population. Source: Module 5.3.5.1, Study 1199.32, Tables 11.4.1.5.1:1, p 122; Table 11.4.1.5.2:1, p 123; Table 11.4.1.5.3:1, p 125; Study 1199.34, Tables 11.4.1.5.1:1, p 121; Table 11.4.1.5.2:1, p 122; Table 11.4.1.5.3:1, p 125				

For both studies, the adjusted mean absolute change from baseline to Week 52 in FVC was lower in the nintedanib group compared to the placebo group (-205 mL). The adjusted mean difference between the treatment groups was statistically significant. The adjusted mean absolute change from baseline to Week 52 in FVC% predicted was lower in the nintedanib group compared to the placebo group. The adjusted mean difference between the treatment groups was statistically significant. This outcome supports the results of the primary endpoint of the annual rate of decline in FVC.

FVC Responders

The proportion of FVC responders at 52 weeks, defined as patients with no decline in absolute change from baseline in FVC% predicted >5% was statistically significantly greater for nintedanib both studies. Dropouts were considered non-responders. The proportion of FVC responders at 52 weeks, defined as patients with no decline in absolute change from baseline in FVC% predicted >10% was only statistically significantly greater for nintedanib compared to placebo in Study 1199.32. With 10% threshold in Study 1199.32, proportion of responders was 71% and 57% in nintedanib group and placebo group, respectively. Again with the 10% threshold in Study 1199.34, proportion of responders was 70% and 64% in nintedanib group and placebo group, respectively.

Dr. Yongman Kim also conducted a continuous responder analyses to provide the relative benefit of nintedanib across the entire range of response over 52 weeks. In each study, continuous responder curves for each treatment arm were plotted. In these plots, all patients who drop out from treatment due to any reason, including death, were considered non-responders (i.e. highest decline in FVC). The x-axis shows the relative decline in FVC from baseline (or worsening) at Week 52, and the y-axis shows the corresponding percentage of patients achieving that level of FVC decline or greater. The positive treatment effect of nintedanib was demonstrated by consistent separation of the curve across different levels of response in Study 1199.32. As an example, only 35% of nintedanib-treated patients have 10% or greater decline in FVC compared to 50% of placebo-treated patients (Figure 11). If we interpret '10% or less decline' as response, then the proportion of responders was 65% and 50% in nintedanib group

and placebo group, respectively. With the same definition, the proportion of responders was 64% and 54% in nintedanib group and placebo group, respectively in Study 1199.34 (Figure 12). For Study 1199.30 the separation between curves of two groups was shown mostly in 10% or less relative decline (Figure 13). This responder analysis confirmed the primary analysis result for all 3 studies.

Figure 11. Cumulative distribution of relative change from baseline in FVC: Study 1199.32

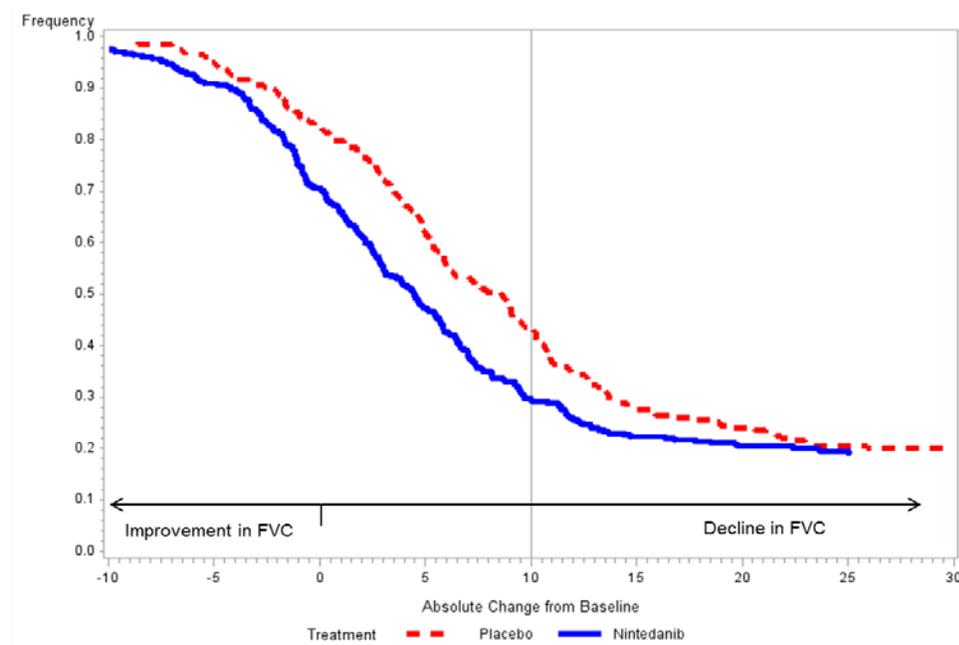


Figure 12. Cumulative distribution of relative change from baseline in FVC: Study 1199.34

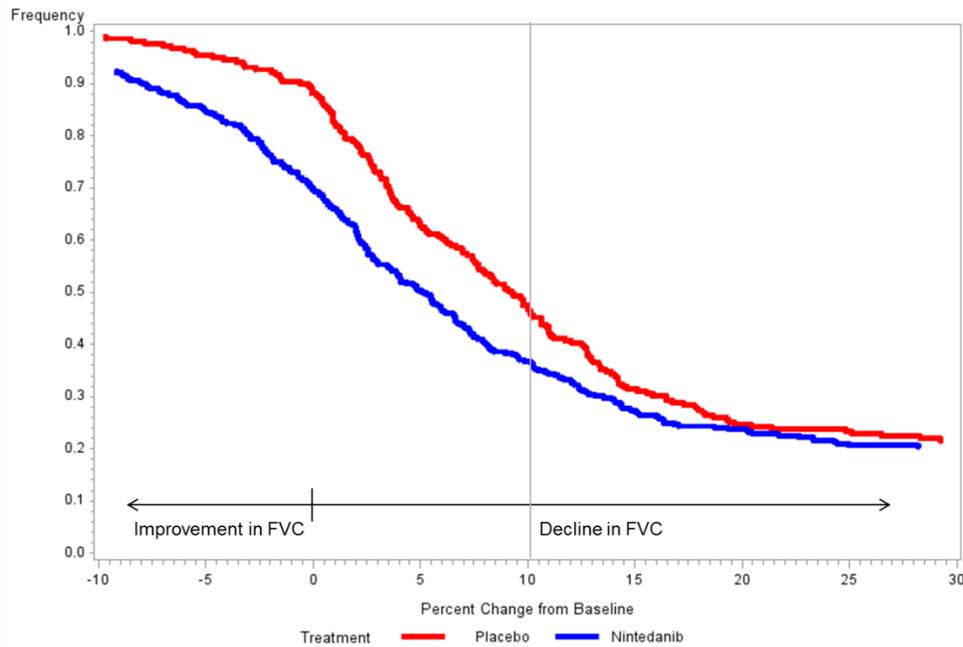
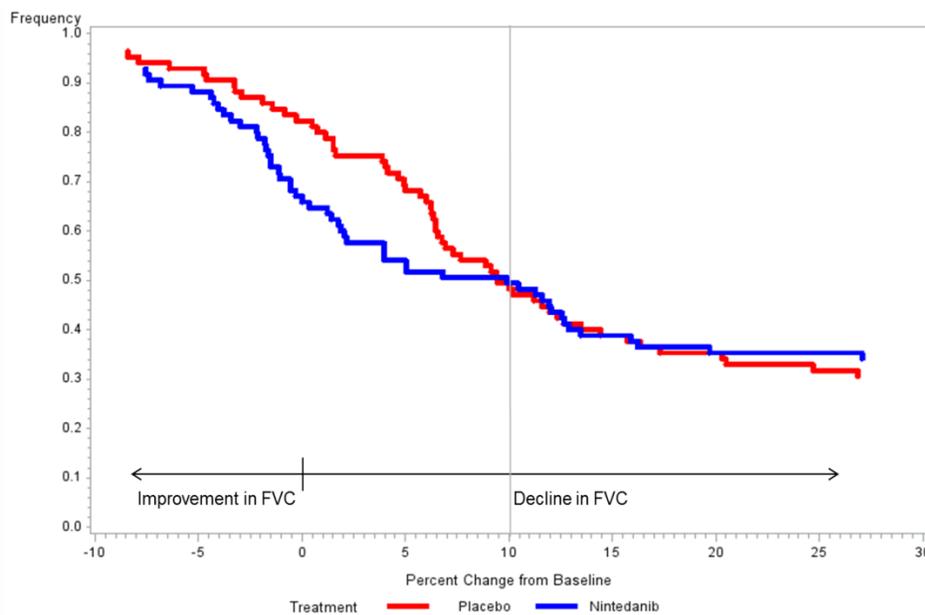


Figure 13. Cumulative distribution of relative change from baseline in FVC: Study 1199.30



Patient Reported Outcomes (PROs)

In Study 1199.32, no significant difference between nintedanib and placebo was observed for the SGRQ responders at 52 weeks, SGRQ components (symptoms, activity, and impact score), IPF

specific version of SGRQ, SOBQ, PGI-C responders, CASA-Q cough domains, or EQ-5D (descriptive statistics favored placebo). There was a small numerical trend favoring nintedanib compared to placebo for most of the PRO assessments.

In Study 1199.34, the proportion of SGRQ responders at 52 weeks, defined by a change from baseline of ≤ -4 points, was greater for nintedanib (25.2%) than placebo (16.9%). The odds ratio was 1.67 (95% CI: 1.08, 2.57) and was statistically significant. The adjusted mean change from baseline to Week 52 in the SGRQ activity, impact, and activity domain, the IPF specific version of SGRQ, were statistically significantly lower for nintedanib compared placebo. Numerically, the results were in favor of nintedanib for SOBQ total score, PGI-C responders, and CASA-Q cough domains, however, statistical significance was not achieved for these PROs.

Overall, the PRO secondary endpoint outcomes are consistent with the primary analysis that showed a statistically significant difference in SGRQ score at 52 weeks for Study 1199.34 and not Study 1199.32.

Risk of acute IPF exacerbation

For Study 1199.32, over the 52 weeks of the trial, the incidence rate of exacerbations (calculated as the number of patients with at least 1 acute IPF exacerbation divided by the total number of years at risk) was 6.6 per 100 patient-years in the nintedanib group compared with 5.6 per 100 patient years in the placebo group. This yielded a non-significant risk ratio of 1.17 (95% CI: 0.56, 2.46).

For Study 1199.34, the incidence rate of exacerbations was 3.9 per 100 patient-years in the nintedanib group compared with 10.2 per 100 patient years in the placebo group. The difference in the incidence rates of exacerbations between the treatment groups was statistically significant in favor of nintedanib with a risk ratio of 0.38 (95% CI: 0.19, 0.77).

These outcomes support the results obtained for the key secondary endpoint of the time to first acute IPF exacerbation (statistically significant difference only seen in Study 1199.34).

DLco and SpO₂

Absolute change from baseline in DLco over 52 weeks

For both studies, the change from baseline in DLCO over time was comparable between the treatment groups. The adjusted mean absolute change from baseline to Week 52 in DLCO (mmol/min/kPa) was -0.380 for nintedanib and -0.365 for placebo for Study 1199.32, and -0.286 for nintedanib and -0.400 for placebo for Study 1199.34.

Absolute change from baseline in SpO₂ over 52 weeks

For both studies the adjusted absolute mean change from baseline to Week 52 in SpO₂ (%) numerically favored nintedanib (Study 1199.32: -0.24% for nintedanib vs. -0.53% for placebo; Study 1199.34: -0.39% for nintedanib vs. -0.66% for placebo).

6.1.7 Subpopulations

A subgroup analysis was performed by the sponsor post-hoc by the HRCT diagnosis of UIP. Patients with no honeycombing on HRCT and no available lung biopsy were compared with patients with honeycombing on HRCT or a diagnosis confirmed by lung biopsy. For all 3 efficacy endpoints analyzed, i.e. the annual rate of decline in FVC, the change from baseline in SGRQ total score, and the time to first acute IPF exacerbation, the treatment effect of nintedanib was comparable across the 2 subgroup categories. Furthermore, the non-significant treatment-by-subgroup interaction p-values suggested that the criteria for diagnosis of UIP had no influence on the treatment effect for FVC, SQRQ total score, and IPF exacerbations.

The statistical reviewer performed subgroup analyses by demographics, region, and baseline disease characteristics in terms of FVC change from baseline at Week 52. The subgroup analyses were consistent with the results from the overall population in terms of FVC change.

For further details regarding the statistical analysis, See Dr. Yongman Kim’s statistical review.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

Dose reductions/increases

Study 1199.32 and 1199.34

Dose reductions were allowed by protocol for the phase 3 studies (1199.32, 34) from 150 mg BID to 100 mg BID (both temporary and permanent) for intolerance (AEs). If the reduced dose was well tolerated, re-escalation was possible within 4 weeks. If the AE was considered non-treatment related (e.g., IPF exacerbation), re-escalation could occur after 8 weeks.

Study 1199.30

For Study 1199.30, subjects could be treated with a reduced dose (reduction by 50 mg QD for those patients in the 50 mg QD or BID group, and by 50 mg BID for those patients in the 100 mg or 150 mg BID group) due to an AE. Once a patient had undergone a nintedanib dose reduction, there was no provision for re-escalation or re-challenge with a higher dose. Dose reduction had to occur in a blinded fashion, so any reduced dose took the form of one fewer capsule in the morning and one fewer capsule in the evening.

In all 3 studies dose reductions occurred more frequently in the nintedanib group compared to placebo. Dose reductions and increases are summarized in for all 3 studies in Table 18.

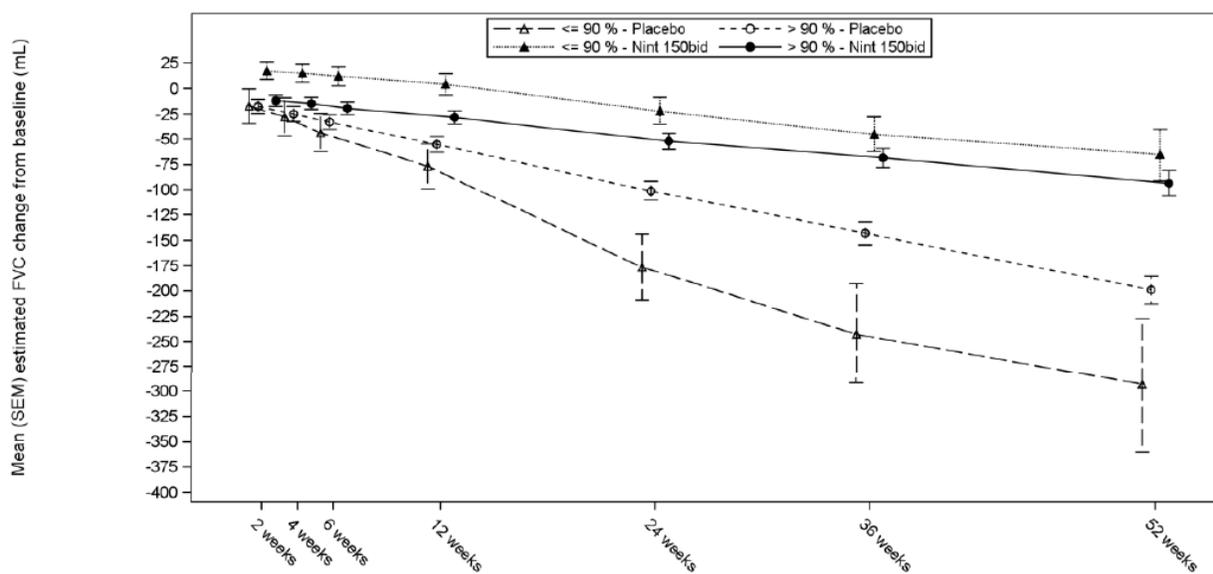
Table 18. Dose reductions/increases (Studies 1199.32, and 1199.34; Treated population. Study 1199.30; Randomized Population)						
	Study 1199.32		Study 1199.34		Study 1199.30	
	Placebo	Nintedanib 150 mg BID	Placebo	Nintedanib 150 mg BID	Placebo	Nintedanib 150 mg BID
	N=204 n (%)	N=309 n (%)	N=219 n (%)	N=329 n (%)	N=87 n (%)	N=85 n (%)
Patients with at least 1 dose reduction	10 (4)	82 (27)	6 (3)	96 (29)	7 (8)	20 (23)
Patients with at least 1 dose increase to 150 mg BID	5 (3)	20 (7)	2 (1)	20 (6)	-	-

“ - ” = data not provided
 Source: Module 2.7.3 SCE, Table 4.1:1, p 113; Study 1199.30, Table 10.1:1, p 120

Subgroup analysis of the primary endpoint (FVC decline over time) by dose intensity suggests that the dose reductions and temporary reductions did not have a major impact on efficacy. Dose intensity was defined as the total sum of trial medication administered over the duration of the trial (taking dose reductions into account and subtracting treatment interruptions, if applicable)

divided by the amount of trial medication that would have been received had the 150 mg BID dose been administered over the entire duration of the planned treatment period (372 days) or until discontinuation of trial medication (whichever occurred earliest). Subgroup analysis by dose intensity was similar for patients with >90% dose intensity compared to those patients with ≤ 90% dose intensity (Figure 14).

Figure 14. Mean (SEM) observed FVC change from baseline (mL) over time by dose intensity (>90%, ≤ 90%) - Pooled 1199.32 and 1199.34



Number of Patients		2 weeks	4 weeks	6 weeks	12 weeks	24 weeks	36 weeks	52 weeks
≤ 90 % - Placebo		17	16	16	15	15	14	7
> 90 % - Placebo		400	391	387	383	366	351	315
≤ 90 % - Nint 150bid		153	150	147	143	125	110	94
> 90 % - Nint 150bid		471	462	458	442	425	406	364

Source: Module 2.7.3 SCE, Figure 4.1:1, p 114

Reviewer comment: Although pooled efficacy was not evaluated in this review, the dose intensity subgroup analysis was not provided for individual studies, and is therefore presented here as supportive data.

Dose finding Study 1199.30

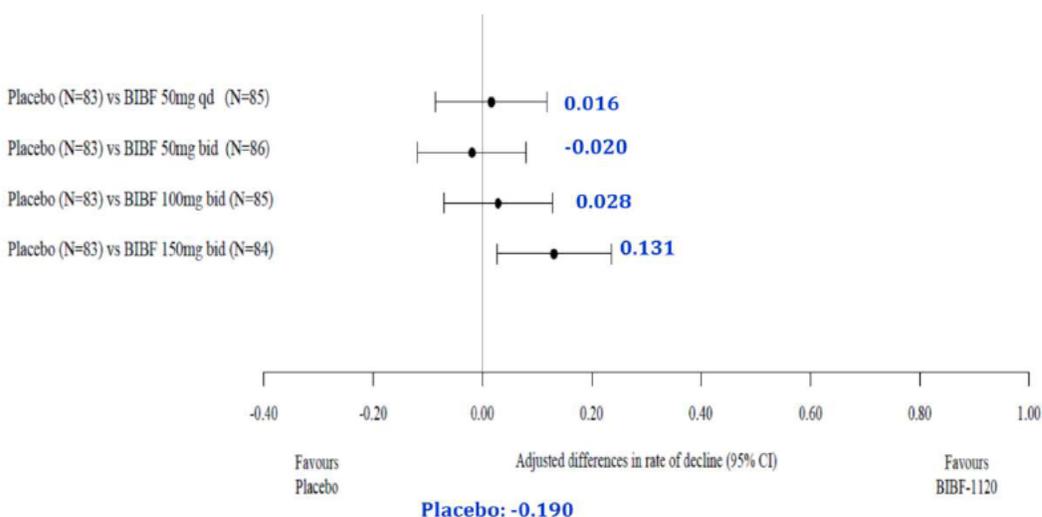
The 150 mg BID was chosen as the treatment dose for the phase 3 studies, based on Study 1199.30. Four doses of nintedanib (50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID) were compared with placebo for the annual rate of decline in FVC over 52 weeks, as seen in Table 19.

Table 19. Primary Efficacy Results for All Doses: Study 1199.30 (Randomized Population)					
	Placebo	Nintedanib			
	N=87 n (%)	50 mg daily N=87 n (%)	50 mg BID N=86 n (%)	100 mg BID N=86 n (%)	150 mg BID N=86 n (%)
Rate of decline in FVC (mL) over 52 weeks					
Adjusted rate ¹ (SE)	-190 (36)	-174 (37)	-210 (35)	-162 (35)	-60 (40)
95% CI	(-262,-119)	(-247,-102)	(-279,-141)	(-231,-93)	(-135,-16)
Comparison vs. Placebo					
Adjusted rate (SE)		16 (52)	20 (51)	28 (51)	131 (53)
95% CI		(-86,118)	(-119,80)	(-71,128)	(27, 235)

¹Based on a random coefficient regression with terms for treatment-by-time, gender-by-height, gender-by-age, patient effect, patient-by-time (patient effect and patient-by-time random, all other effects fixed) and a variance component variance-covariance matrix
 Source: Module 2.7.3 SCE, Table 4.2:1, p 115

The same data is also shown visually in Figure 15.

Figure 15. Rate of decline in FVC (L/year) at 52 weeks



Source: Module 5.3.1, Study 1199.30 CSR, Figure 11.4.1.1.1

The primary endpoint of annual rate of decline in FVC treatment difference between nintedanib 150 mg BID and placebo reached statistical significance. The differences between the lower nintedanib doses and placebo were not significant. In addition, the 150 mg BID group was also the only treatment group with statistically significant differences compared to placebo for the

key secondary endpoints of SGRQ total score at 52 weeks [treatment difference: -6.12, 95% CI: -11, -2], and time to first acute IPF exacerbation [HR: 0.16; 95% CI: 35, 71].

In summary, the proposed treatment dose of 150 mg BID is well supported.

Further discussion of dose rationale can be found in the clinical pharmacology review.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

Persistence of efficacy after the blinded 1 year treatment period is supported by the dose-blinded active-treatment extension period of Study 1199.30 (period 2) up to 7 months and the open-label long-term extension study of studies 1199.32 and 1199.34 (Study 1199.33) up to 6 months. Study 1199.35 (the open-label long-term extension study of Study 1199.30) provides supportive evidence, but is less interpretable as a mean FVC change from baseline analysis was not performed due to the variability of treatment duration for individual subjects.

Study 1199.30 (period 2)

Subjects enrolled in the placebo-controlled, double-blind, 52-week period of Study 1199.30 (period 1) had the option to enroll in a dose-blinded active treatment extension period (period 2). Subjects continued in the treatment arm they were randomized to during period 1. Placebo subjects were rolled over to the nintedanib 50 mg daily arm (lowest dose). The primary efficacy results for the entirety of the Study 1199.30 (period 1 +period 2) are shown in Table 19.

Table 20. Rate of Decline in FVC (mL) for All Doses: Study 1199. 30 Period 1 + Period 2 (~ 80 weeks, Randomized Population)					
	Placebo	Nintedanib			
	N=87 n (%)	50 mg daily N=87 n (%)	50 mg BID N=86 n (%)	100 mg BID N=86 n (%)	150 mg BID N=86 n (%)
Number analyzed	84	86	86	85	85
Rate of decline in FVC (mL)					
Adjusted rate ¹ (SE)	-211 (30)	-177 (31)	-202 (29)	-196 (29)	-104 (32)
95% CI	(-270,-152)	(-237,-116)	(-259, -146)	(-253,-139)	(-166,-42)
Comparison vs. Placebo					
Adjusted rate (SE)		34 (43)	9 (42)	15 (42)	107 (44)
95% CI		(-50, 119)	(-73, 90)	(-67, 97)	(21, 192)

¹Based on a random coefficient regression with terms for treatment-by-time, gender-by-height, gender-by-age, patient effect, patient-by-time (patient effect and patient-by-time random, all other effects fixed) and a variance component variance-covariance matrix
 Source: Module 5.3.1, Study 1199.30 CSR, Table 15.2.1.1.2.2:5, p 578

The mean exposure past 52 weeks was 7 months for all groups (placebo = 7 months, nintedanib 150 mg BID = 7 months). The adjusted rate of decline in FVC (mL) was slightly higher than at

52 weeks (-60 mL/year at week 52 compared to -104 mL/year over ~ 80 weeks (52 weeks + 29 weeks for median duration of period 2)).

The treatment difference remained statistically significant for the 150 mg BID group versus placebo after the entire period of treatment (from baseline to cut off date) including post 52 weeks data, even though patients of the placebo group were actually receiving 50 mg QD of active treatment during period 2. For the nintedanib 150 mg BID group, the rate of decline in FVC is slightly lower than at ~ 1.5 years compared to 1 year (131 ml/year at 52 weeks vs. 107 ml/year with mean exposure of 80 weeks), but remained lower in the nintedanib group compared to placebo.

Study 1199.33

Subjects enrolled in studies 1199.32 and 1199.34 had the option to roll-over into an open-label long term safety study (1199.33). Subjects were treated with 150 mg BID, unless they had reduced their dose to 100 mg BID in the parent trial, in which case they could receive either 100 mg or 150 mg BID. Spirometry data was captured. At the time of data lock (Sept 17, 2013), 680 subjects were enrolled in the study. A total of 679 subjects received treatment (Study 1199.32, N=332; Study 1199.34, N=345), with a mean exposure of 6.4 months. Efficacy data was provided up to 48 weeks. Notably, after 6 months, the number of subjects analyzed was low. The change from baseline in FVC (mL) for Study 1199.33 is summarized in Table 21.

Table 21. Change from baseline in FVC (mL): Study 1199.33 (Treated population)		
Week	N	FVC (mL) Mean (SD)
2	644	11 (141)
4	625	2 (152)
6	616	-0.5 (173)
12	563	-14 (179)
24	367	-46 (187)
36	175	-58 (222)
48	48	-118 (215)

Source: Module 5.3.5.1, Study 1199.33, Table 11.4.1.2:1, p 68, Table 15.2.1:1, p 300

The change from baseline in FVC (mL) is similar to what was seen the blinded study period at matched time points (Figure 5 and Figure 6).

Study 1199.35

Subjects enrolled in studies 1199.30 had the option to roll-over into an open-label long term safety study (1199.35). Subjects were treated with the same range of doses at Study 1199.30. Subjects on placebo were treated with 50 mg daily. A total of 227 subjects completed Study 1199.30 period 1 and continued through period 2. Of those, 199 subjects were enrolled in the study (at the time of data lock (July 2, 2013)). The mean treatment duration was 22 months. The analysis of mean FVC data over time was not performed given the variable duration of nintedanib exposure. As a result of the limitations associated with assessing mean change in

FVC for this trial, individual patient data were assessed. The FVC value from week 52 of trial 1199.30 was used as the baseline, as this value was a fixed timepoint for all patients. Individual patients randomized to nintedanib 150 mg bid at the start of trial 1199.30 who continued into trial 1199.35 generally experienced a gradual decrease in FVC change from Visit 9 of trial 1199.30.

6.1.10 Additional Efficacy Issues/Analyses

None.

7 Review of Safety

Safety Summary

The safety evaluation of nintedanib similarly relies on data from Studies 1199.30 (Phase 2), 1199.32, and 1199.34. Pooling of data across trials to examine the emergence of safety signals was deemed acceptable as these trials were similar (1199.32 and 1199.34 were identical) in design/duration and the patient population was comparable in terms of demographics, baseline characteristics, and dose of nintedanib received. Safety assessments in these 3 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing. Each of these studies had associated long-term safety studies (1199.30 period 2, 1199.33, and 1199.35) that did not reveal any additional safety signals.

There were a total of 723 patients treated with nintedanib 150 mg BID and 508 patients treated with placebo. The mean treatment duration was similar between the treatment groups (10-11 months). Subjects could dose reduce from 150 mg BID to 100 mg BID or dose interrupt for adverse events. In the phase 3 studies, the majority of dose reductions occurred due to an adverse event and were more common in the nintedanib treated patients (28%) compared to placebo (4%). A total of 98% of placebo and 76% of nintedanib treated patients finished the study at the full dose, resulting in a dose intensity (actual amount of drug received over the study divided by the amount of drug planned) of 99% in the placebo treated subjects and 94% of nintedanib treated subjects. Similar dose reduction results were seen in Study 1199.30.

Overall, there were numerically fewer deaths in the nintedanib treated patients (5.3%) vs. placebo- treated patients (8.5%). The most common AE leading to death was IPF (4.1% placebo vs. 2.5% nintedanib), followed by pneumonia (0.6% placebo vs. 0.7% nintedanib). Deaths are discussed in further detail in the efficacy summary above.

The overall occurrence of serious adverse events (SAEs) was equally distributed across treatment groups (~30%). The 3 SAEs that were reported more frequently in the nintedanib group as compared with placebo were myocardial infarction (1.1% nintedanib, 0.4% placebo), diarrhea (0.7% nintedanib, 0.2% placebo), and transient ischemic attack (0.4% nintedanib, 0% placebo).

AEs leading to discontinuation were slightly more frequent in the nintedanib-treated patients (20.6%) compared to placebo (15.0%). Diarrhea was the most common reason for discontinuation (5.3% nintedanib vs. 0.2% placebo). The next most frequent adverse events leading to discontinuation more frequently in the nintedanib-treated patients compared to placebo-treated patients were nausea, decreased appetite, and weight decreased.

The overall rates of patients with AEs leading to permanent dose reduction were higher in the nintedanib group (16.3%) than in the placebo group (1.4%). The rates were highest in patients with adverse events in the system organ class (SOC) of GI Disorders (13.3% nintedanib vs. 0% placebo). The common AEs (>2 patients) that led to dose reduction that were reported more frequently by patients treated with nintedanib than placebo included diarrhea, nausea, abdominal pain, decreased appetite, hepatic function abnormal, weight decreased, and transaminase increased.

Before unblinding, the Applicant identified a number of clinically important adverse events of special interest (AESI). These AESI were identified based upon relevant non-clinical findings, human experience in previously conducted nintedanib IPF clinical trials, and potential class effects of tyrosine kinase inhibitors including the effects on the platelet derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR). Abdominal pain (15.2% nintedanib vs. 6.1% placebo) and liver enzyme elevation (14.4% nintedanib vs. 2.6% placebo) were the most common AESIs. Arterial thromboembolic events, major adverse cardiovascular events (MACE), thromboembolic events, and venous thromboembolism were overlapping AESI's and were all more frequent in the nintedanib group. Myocardial infarction was the most common AE within these groups occurring in 1.5% of nintedanib-treated patients vs. 0.4% of patients in the placebo group. In the case of hepatic laboratory abnormalities, there were no Hy's law cases. Liver enzyme elevations were more frequent (14% nintedanib vs. 2.6% placebo), led to more frequent early discontinuations (2.1% nintedanib vs. 0.4% placebo), and permanent dose reductions (1.5% nintedanib vs. 0.2% placebo) in nintedanib treated patients compared to placebo treated patients. The majority of elevated liver enzymes and bilirubin events were $\leq 3x$ ULN and $\leq 1.5x$ ULN, respectively. Most patients returned to within the normal range by the end of treatment.

Common adverse reactions that occurred at a frequency of $\geq 5\%$ and more commonly than placebo include: diarrhea, nausea, abdominal pain, vomiting, liver enzyme elevation, decreased appetite, headache, and weight decreased.

The safety database is adequate to assess the safety of nintedanib. The safety findings should be factored into the risk-benefit assessment of nintedanib treatment in patients with IPF.

7.1 Methods

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

The clinical review of safety is based primarily on the pooled results of Studies 1199.32, 1199.34, and 1199.30 (150 mg BID and placebo treatment arms only). Long-term extension studies for each of the blinded studies (1199.33, 35, 30 (period 2)) are presented separately, as supportive safety in Section 7.7.2 Long-term safety.

All analyses were based on the safety population, unless otherwise specified.

7.1.2 Categorization of Adverse Events

The version of MedDRA differs amongst the studies as their start dates were separated by 4 years. The phase 3 studies used version 16.1 and Study 1199.30 used version 13.0.

The analysis of AEs was based on the concept of treatment-emergent AEs. In general, AEs with an onset date (or worsening) between the first intake of study medication and 28 days after the discontinuation of study medication were designated as treatment-emergent.

Double-counting of AEs occurred in a limited number of patients in the IPF program. In trial 1199.30, the last dose of study medication in period 1 was administered on the same day as the first dose of study medication in period 2. By definition, AEs with an onset (or worsening) on the day of first study drug intake in period 2 were counted towards both periods 1 and 2. The same applied for patients who continued from trial 1199.30 period 2 into trial 1199.35 and the analysis of AEs in such patients.

The assessment of AEs was based on frequencies of patients with AEs rather than exposure adjusted incidence rates, especially for Studies 1199.32, and 34, because exposure to study medication was similar in the 2 treatment groups (i.e. treatment durations were similar, and there was no major difference in the premature discontinuation rates).

Missing or incomplete AE dates were imputed according to the Applicant's standards; missing values with respect to other safety evaluations were not imputed. The analyses of AEs focused on the following: all AEs; serious AEs (SAEs); AEs leading to death; AEs leading to discontinuation of study medication; AEs leading to dose reduction; other significant AEs (as per ICH E3); drug-related AEs (as assessed by the investigator); pre-defined AEs of particular note; and AESIs. Subgroup analyses were performed for AEs for intrinsic factors (gender, age, race, renal impairment at baseline, and body weight) and extrinsic factors (smoking history). Other significant AEs (as per ICH E3) were analyzed as non-serious adverse events that led to discontinuation of the study treatment or to dose reduction.

Reviewer comment: Drug-related AEs as assessed by the sponsor or investigator will not be further discussed during this review.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

The Sponsor established multiple safety groupings for the safety analyses of this clinical development program. The patient population for these safety groupings were the same as the treated population used for efficacy analyses. The sponsor established a primary safety analysis grouping comprised of the phase 3 studies (1199.32 and 1199.34) and labeled them safety grouping (SG) 1.1. A supportive SG comprised of Study 1199.30, period 2, placebo and 150 mg BID treatment arms was labeled SG 1.2. Due to similar design and conduct, the safety data from Study 1199.30 was considered to be important as well. As a result, an additional safety grouping including Studies 1199.32, 1199.34, and 1199.30 (placebo and 150 mg BID treatment arms only) was requested from the Sponsor. Analysis of the safety data based upon the newly requested safety grouping (SG 1= 1.1 + 1.2) is the focus of the safety review.

Additional supportive safety is presented for the long-term extension studies (1199.30 period 2, 1199.33, and 1199.35: SG 2.2) in Section 7.7.2 Long-term safety. The safety database is presented in Table 22.

Table 22. Safety Groupings		
Study	Placebo	Nintedanib 150 mg BID
SG 1 (Randomized Blinded)		
1199.32 ¹	204	309
1199.34 ¹	219	329
1199.30 ²	85	85
TOTAL	508	723
SG 2.2 (Open-label extensions)		
1199.30 Period 2	54	184
1199.33 ³	282	397
1199.35 ³	37	35
TOTAL	373	480
¹ SG 1.1 ² SG 1.2 ³ At time of data lock Source: Module 2.7.4, SCS, Table 1.2.1:1, p 45		

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

The extent of exposure for the pooled phase 3 studies (1199.32 and 1199.34) and the phase 2 dose-finding study (1199.30) is described in Table 23.

Table 23. Overall duration of exposure to nintedanib for SG-1: Studies 1199.32, 1199.34, and 1199.30

	Placebo N=508	Nintedanib 150 mg BID N=723
Duration of exposure (months)		
mean (SD)	11(3)	10 (3)
sum (patient-years) ¹	458	616
Duration of exposure categories, n (%)		
≤ 3 months	28 (6)	68 (10)
> 3 months - ≤ 6 months	19 (4)	44 (6)
> 6 months - ≤ 12 months	365 (72)	466 (65)
> 13 months	1 (<1)	0

¹ The sum of duration of exposure [patient-years] is defined as the sum of duration of exposure of all patients [days]/365.25
 Source: Module 1.11.3, Response to information request 6.20.14, Table 18.2.1.1, p 266

Demographics

For all 3 studies the patient population was representative of the IPF population. For the phase 3 studies, the median age of the patient population was 67 years. A larger proportion of the randomized population was male and Caucasian. The demographic parameters were fairly evenly split between the two treatment groups. The distribution of patients by age category showed some imbalances, with a higher proportion of younger (< 65 years) and elderly (>75 years) patients in the nintedanib group compared to placebo. The mean age was similar between the groups in both studies. Most patients were ex-smokers, while approximately one quarter of patients never smoked.

The demographics for the phase 2 study were similar. Demographic information for the treated population for all 3 studies is summarized in Table 9 and Table 10.

7.2.2 Explorations for Dose Response

Explorations for dose response are conducted in two ways in this review. As there was a protocol-defined scheme for dose reduction secondary to adverse events, dose response for adverse events can be examined in the setting of dose reduction. In addition, Study 1199.30 included multiple dose groups, and therefore dose response can also be examined with escalating doses. This is discussed further in in Section 7.5.1 Dose Dependency for Adverse Events.

Exploration of Dose Response with Dose Reduction

Due to differences in the schemes for management of adverse events (AEs) between the phase 2 and phase 3 studies, further analyses of exposure and dose modifications were not conducted on the pooled data. Data for the pooled phase 3 studies and the phase 2 study are described separately in Table 24 and Table 25, respectively.

Table 24. Exposure with Dose reductions: SG 1.1 - Studies 1199.32 and 34		
	Placebo N=423	Nintedanib 150 mg BID N=638
Patients with at least 1 dose reduction, n (%)	16 (4)	178 (28)
1 dose reduction	16 (4)	163 (26)
2 dose reductions	0	13 (2)
>2 dose reductions	0	2 (<1)
Time to first dose reduction categories, n (%)		
≤ 31 days	1 (<1)	22 (3)
> 31 and ≤ 61 days	4 (<1)	26 (4)
> 61 and ≤ 92 days	0	20 (3)
> 92 and ≤ 183 days	5 (1)	63 (10)
> 183 days	6 (1)	47 (7)
Patients with at least 1 dose re-escalation, n (%)	7 (1.7)	40 (6.3)
Patients finishing study on 150 mg BID, n (%)	414 (97.9)	487 (76.3)
Total dose (g) over 52 weeks, mean (SD) ¹	98 (26)	89 (32)
Dose intensity ² (%), mean (SD)	99 (5)	94 (11)
Dose intensity by category		
≤ 90%	18 (4)	154 (25)
> 90 to < 100%	28 (7)	66 (10)
≥ 100%	377 (89)	418 (66)
¹ Total dose calculated as duration of treatment (days) multiplied with the actual dose (g) taken		
² Dose intensity calculated as the actual amount of drug received over the study divided by the amount of drug that would have been administered had the protocol specified first dose (150 mg BID) been administered as planned for 52 weeks (or until study discontinuation).		
Source: Module 2.7.4, SCS, Table 1.2.3.2:2, p 52; Table 1 2 3 2:1, p 51.		

More patients underwent dose reduction in the nintedanib group compared to placebo. All placebo patients and the majority of nintedanib subjects had a single dose reduction. Dose reductions were distributed evenly over time. The majority of dose reductions were for related AEs.

Reviewer comment: The total exposure, while not strictly adherent to ICH guidelines is adequate. For orphan diseases with unmet medical need, we have historically accepted safety data from studies in other indications as well. Taken together with the clinical development program in oncology, the exposure is considered adequate to conduct a pre-marketing safety assessment.

Table 25. Dose reductions: SG 1.2 - Study 1199.30		
	Placebo N=87	Nintedanib 150 mg BID N=86
Patients with any dose reduction, n (%)	7 (8)	20 (23)
Intermittent dose reduction	2 (2)	2 (2)
Definitive dose reduction	5 (6)	18 (21)
¹ The sum of duration of exposure [patient-years] is defined as the sum of duration of exposure of all patients [days]/365.25		
Source: Module 5.3.1, Study 1199.30, Table 10.1:2, p120		

For the phase 3 studies most first dose reductions occurred before 6 months. Similarly, a time to dose reduction analysis (not shown) for the phase 2 study showed that dose reduction was more likely to occur in the nintedanib group and during the first 6 months. Overall, the pattern and frequency of dose reduction was similar between the phase 3 and phase 2 studies.

When the doses were reduced, patients experienced an abatement in their symptoms, which supports a dose-response relationship with respect to adverse events, and supports the sponsor's recommendation for dose modification to 100 mg for adverse events. This dose effect was seen specifically for GI disorders (excluding abdominal pain) and investigations (driven by liver function abnormalities).

7.2.3 Special Animal and/or In Vitro Testing

No special animal and/or in vitro testing was conducted or required to further explore the safety profile of nintedanib

7.2.4 Routine Clinical Testing

The routine clinical testing in the development program for nintedanib included: clinical chemistry (including AST, ALT, bilirubin, gamma GT, hepatic AP, BNP, CK, TSH, LDH), hematology including CD4 and CD8 lymphocyte counts, coagulation parameters, urinalysis, pregnancy testing, and 12 lead ECGs. The routine clinical testing was adequate.

7.2.5 Metabolic, Clearance, and Interaction Workup

Refer to section 4.4 Clinical Pharmacology.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

While nintedanib is a new molecular entity, and first in class, there are other approved drugs that are similar. (See Section 2.4 Important Safety Issues with Consideration to Related Drugs).

7.3 Major Safety Results

Safety Results

7.3.1 Deaths

The sponsor analyzed deaths, in terms of AEs leading to deaths. Deaths are summarized in Table 26.

Table 26. AEs leading to death: SG 1- Studies 1199.32, 1199.34, and 1199.30		
SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patient with any AE leading to death	43 (8.5)	38 (5.3)
Infections and infestations	8 (1.6)	7 (1.0)
Pneumonia	3 (0.6)	5 (0.7)
Respiratory tract infection	3 (0.6)	1 (0.1)
Septic shock	1 (0.2)	1 (0.1)
Bacteremia	1 (0.2)	0
Pathogen resistance	1 (0.2)	0
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.2)	6 (0.8)
Lung neoplasm malignant	0	2 (0.3)
B-cell lymphoma	0	1 (0.1)
Chloroma	0	1 (0.1)
Lung adenocarcinoma metastatic	0	1 (0.1)
Metastatic neoplasm	0	1 (0.1)
Non-small cell lung cancer	1 (0.2)	1 (0.1)
Cardiac disorders	9 (0.8)	3 (0.4)
MI	1 (0.2)	2 (0.3)
Atrial fibrillation	0	1 (0.1)
Atrial flutter	0	1 (0.1)
Angina pectoris	1 (0.2)	0
Cardiac arrest	3 (0.6)	0
Cardiac failure	1 (0.2)	0
Cardio-respiratory arrest	1 (0.2)	0
Cardiopulmonary failure	1 (0.2)	0
Cor pulmonale	1 (0.2)	0
Respiratory, thoracic, and mediastinal	30 (5.9)	23 (3.2)
IPF	21 (4.1)	18 (2.5)
Respiratory Failure	2 (0.4)	2 (0.3)
Acute respiratory failure	1 (0.2)	1 (0.1)
Dyspnea	2 (0.4)	1 (0.1)
Pulmonary embolism	0	1 (0.1)
Hypoxia	2 (0.4)	0
Pneumothorax	1 (0.2)	0
Pulmonary fibrosis	1 (0.2)	0

Table 26. AEs leading to death: SG 1- Studies 1199.32, 1199.34, and 1199.30		
SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Gastrointestinal disorders	0	1 (0.1)
Duodenal ulcer	0	1 (0.1)
Gastrointestinal hemorrhage	0	1 (0.1)
Hematemesis	0	1 (0.1)
General disorders and administration site conditions	0	1 (0.1)
Sudden death	0	1 (0.1)

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.1.0, p 330-1

Overall, there were more deaths in the placebo group compared to nintedanib. With the exception of Neoplasms, benign, malignant, and unspecified, all adverse event SOC/PTs were greater in the placebo group compared to nintedanib.

Reviewer comment: Although malignancy is more common in IPF patients, a higher proportion of patients with neoplasms, benign, and malignant would not be expected compared to placebo. This was further analyzed in Section 7.3.5 Submission Specific Primary Safety Concerns.

7.3.2 Nonfatal Serious Adverse Events

An overview of SAEs for SG 1 is provided in Table 27.

Table 27. SAEs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)		
SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patients with SAEs	153 (30.1)	217 (30.0)
Infections and infestations	47 (9.3)	60 (8.3)
Bronchitis	4 (0.8)	9 (1.2)
Lung infection	1 (0.2)	4 (0.6)
Appendicitis	1 (0.2)	3 (0.4)
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	16 (3.1)	20 (2.8)
Lung neoplasm malignant	2 (0.4)	4 (0.6)
Nervous system disorders	12 (2.4)	12 (1.7)
Transient ischemic attack	0	3 (0.4)
Cardiac disorders	30 (5.9)	33 (4.6)
Myocardial Infarction	2 (0.4)	8 (1.1)
Atrial fibrillation	2 (0.4)	4 (0.6)
Acute myocardial infarction	0	3 (0.4)

Table 27. SAEs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Respiratory, thoracic, and mediastinal	75 (14.8)	84 (11.6)
Acute respiratory failure	2 (0.4)	6 (0.8)
Pulmonary embolism	3 (0.6)	6 (0.8)
Pneumomediastinum	1 (0.2)	3 (0.4)
Gastrointestinal disorders	7 (1.4)	23 (3.2)
Diarrhea	1 (0.2)	5 (0.7)
Musculoskeletal and connective tissue disorders	6 (1.2)	10 (1.4)
Intervertebral disc protrusion	1 (0.2)	4 (0.6)
Renal and urinary disorders	5 (1.0)	7 (1.0)
Renal failure acute	1 (0.2)	3 (0.4)
General disorders and administration site conditions	9 (1.8)	14 (1.9)
Chest pain	4 (0.8)	7 (1.0)
Investigations	3 (0.6)	10 (1.4)
Hepatic enzyme increased	0	3 (0.4)

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.1.4, p 300-309

The overall occurrence of SAEs was equally distributed across treatment groups (30.0%-30.1%). In general, the numbers of patients experiencing individual SAEs were small, without striking imbalances noted. Bronchitis was the most common SAE (N=4 (0.8%) placebo vs. N=9 (1.2%) nintedanib). The largest differences were seen for myocardial infarction (2 (0.4%) vs 8 (1.1%)), and diarrhea (1 (0.2%) vs 5 (0.7%)).

Reviewer comment: If the preferred terms of myocardial infarction and acute myocardial infarction are taken together, the difference between placebo and nintedanib increases to 2 (0.4%) vs. 11 (1.5%).

7.3.3 Dropouts and/or Discontinuations

AE's leading to premature treatment discontinuation for all 3 studies are summarized in Table 28.

Table 28. AEs leading to premature treatment discontinuation reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patients with AEs leading to permanent treatment discontinuation	76 (15.0)	149 (20.6)
Metabolism and nutrition disorders	2 (0.4)	12 (1.7)
Decreased appetite	1 (0.2)	11 (1.5)
Cardiac disorders	13 (2.6)	7 (1.0)
MI	0	3 (0.4)
Acute myocardial infarction ¹	0	2 (0.3)
Gastrointestinal disorders	7 (1.4)	61 (8.4)
Diarrhea	1 (0.2)	38 (5.3)
Nausea	0	17(2.4)
Abdominal pain	1 (0.2)	7 (1.0)
Vomiting	1 (0.2)	7 (1.0)
Abdominal pain upper ¹	3 (0.6)	4 (0.6)
General disorders and administration site conditions	5 (1.0)	11 (1.5)
Asthenia	0	5 (0.7)
Investigations	3 (0.6)	23 (3.2)
Weight decreased	1 (0.2)	8 (1.1)
Alanine aminotransferase increased	0	4 (0.6)
Hepatic enzyme increased	0	4 (0.6)
Aspartate aminotransferase increased	0	3 (0.4)
Blood bilirubin increased	1 (0.2)	3 (0.4)

¹Listed due to similar PT with ≥ 2 patients
 Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.1.7, p 316-321

More subjects discontinued treatment due to an AE in the nintedanib group (N=149 (21%)) compared to placebo (N=76 (15%)). The most common AE leading to discontinuation was diarrhea, followed by nausea, decreased appetite, and weight decreased.

7.3.4 Significant Adverse Events

If patients experienced intolerable AEs to the 150 mg BID dose, the dose could be reduced, temporarily or permanently (see Dose-reduction for Studies 1199.32 and 34, and Dose-reduction for Study 1199.30).

AE's leading to permanent dose reduction are listed in Table 29.

Table 29. AEs leading to permanent dose reduction reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patients with AEs leading to permanent dose reduction	7 (1.4)	118 (16.3)
Metabolism and nutrition disorders	0	7 (1.0)
Decreased appetite	0	6 (0.8)
Gastrointestinal disorders	0	96 (13.3)
Diarrhea	0	79 (10.9)
Nausea	0	15 (2.1)
Abdominal pain	0	6 (0.8)
Abdominal pain upper	0	6 (0.8)
Hepatobiliary disorders	0	7 (1.0)
Hepatic function abnormal	0	5 (0.7)
Investigations	2 (0.4)	15 (2.1)
Weight decreased	1 (0.2)	4 (0.6)
Transaminase increased	0	3 (0.4)

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.1.4, p 300-309

More patients underwent permanent dose reduction to an AE in the nintedanib group (N=118 (16%)) compared to placebo (N=7 (1%)). Similar to AEs leading to treatment discontinuation, the most common AE leading to permanent dose reduction was diarrhea, followed by nausea, and decreased appetite.

7.3.5 Submission Specific Primary Safety Concerns

AESIs

Before unblinding, the Applicant identified a number of clinically important adverse events of special interest (AESI). These AESI were identified based upon relevant non-clinical findings, human experience in previously conducted nintedanib IPF clinical trials, and potential class effects of tyrosine kinase inhibitors including effects on the platelet derived growth factor receptor (PDGFR) α and β , fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR).

Major adverse cardiovascular events (MACEs) were included as an AESI. This category comprised of the following:

- AEs leading to death in the primary SOCs of cardiac disorders and vascular disorders
- any AEs of the sub- SMQ myocardial infarction within the SMQ of ischemic heart disease

- any stroke (based on a BI-internal definition)
- the preferred terms sudden death, cardiac death, and sudden cardiac death

A patient with a preferred term falling into at least one of these categories was counted as having a MACE. Of note, this AESI category was partly overlapping with other AESI categories, i.e. cardiac arrhythmias and thromboembolic events.

Certain other AESI definitions were overlapping. For example, bilirubin increase was defined as an AESI but was also analyzed as component of the SMQ of liver-related investigation. Furthermore, thromboembolic events (SMQ) include 3 sub-SMQs, i.e. arterial thromboembolism, venous thromboembolism, and embolic and thrombotic events of unspecified vessel type, and mixed arterial and venous thromboembolic events. Of these, thromboembolic events and the first 2 sub-SMQs were analyzed as AESIs. AESIs and serious AESIs (SAESIs) are summarized (>2 patients reporting in the nintedanib group and greater than placebo) in Table 30.

Table 30. AESIs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group and associated AESIs : SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

AESI/Preferred Term	All AESI		SAESIs		AE leading to Death	
	n (%)					
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)	Placebo (N=508)	Nintedanib 150 mg BID (N=723)	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patients with AESIs	215 (42.3)	299 (55.2)	57 (11.2)	78 (10.8)	12 (2.4)	11 (1.5)
Abdominal pain	31 (6.1)	110 (15.2)	1 (0.2)	0	0	0
Abdominal pain	13 (2.6)	62 (8.6)	1 (0.2)	0	0	0
Abdominal pain upper	18 (3.5)	51 (7.1)	0	0	0	0
Arterial thromboembolism	4 (0.8)	18 (2.5)	3 (0.6)	15 (2.1)	1 (0.2)	2 (0.3)
Myocardial infarction	2 (0.4)	8 (1.1)	2 (0.4)	8 (1.1)	1 (0.2)	2 (0.3)
Acute myocardial infarction	0	3 (0.4)	0	3 (0.4)	0	0
Transient ischemic attack	1 (0.2)	3 (0.4)	0	3 (0.4)	0	0
Bilirubin increased	1 (0.2)	8 (1.1)	0	0	0	0
Bleeding¹	37 (7.3)	69 (9.5)	6 (1.2)	9 (1.2)	0	1 (0.1) ²
Epistaxis	15 (3.0)	27 (3.7)	1 (0.2)	1 (0.1)	0	0
Contusion	4 (0.8)	10 (1.4)	0	1 (0.1)	0	0
Rectal hemorrhage	5 (1.0)	8 (1.1)	0	0	0	0
Hypertension³	20 (3.9)	25 (4.8)	2 (0.4)	5 (0.7)	0	0
Hypertension	15 (3.0)	25 (3.5)	0	2 (0.3)	0	0
Blood pressure increased	3 (0.6)	6 (0.8)	0	0	0	0
Hypertensive crisis	2 (0.4)	5 (0.7)	2 (0.4)	3 (0.4)	0	0
Gastrointestinal Perforation	0	2 (0.3)	0	2 (0.3)	0	0
Duodenal ulcer perforation	0	1 (0.1)	0	1 (0.1)	0	0
Peritoneal abscess	0	1 (0.1)	0	1 (0.1)	0	0

Table 30. AESIs reported in >2 patients in the nintedanib group and at a greater incidence than in the placebo group and associated AESIs : SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

AESI/Preferred Term	All AESI		SAESIs		AE leading to Death	
	n (%)					
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)	Placebo (N=508)	Nintedanib 150 mg BID (N=723)	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Peritonitis	0	1 (0.1)	0	1 (0.1)	0	0
Hypothyroidism	3 (0.6)	8 (1.1)	0	1 (0.1)	0	0
Liver enzyme elevation	13 (2.6)	104 (14.4)	1 (0.2)	5 (0.7)	0	0
Gamma-glutamyltransferase increased	6 (1.2)	29 (4.0)	0	0	0	0
Hepatic enzyme increased	3 (0.6)	25 (3.5)	0	3 (0.4)	0	0
Alanine aminotransferase increased	2 (0.4)	24 (3.3)	0	0	0	0
Hepatic function abnormal	1 (0.2)	20 (2.8)	0	0	0	0
Aspartate aminotransferase increased	1 (0.2)	18 (2.5)	0	0	0	0
Liver function test abnormal	2 (0.4)	9 (1.2)	0	0	0	0
Transaminases increased	1 (0.2)	9 (1.2)	1 (0.2)	2 (0.3)	0	0
Blood alkaline phosphatase increased	0	7 (1.0)	0	0	0	0
MACE	18 (3.5)	26 (3.6)	13 (2.6)	18 (2.5)	9 (1.8)	4 (0.6) ⁴
Myocardial infarction	2 (0.4)	8 (1.1)	2 (0.4)	8 (1.1)	1 (0.2)	2 (0.3)
Blood creatinine phosphokinase	3 (0.6)	6 (0.8)	0	0	0	0
Acute myocardial infarction	0	3 (0.4)	0	3 (0.4)	0	0
Transient ischemic attack	1 (0.2)	3 (0.4)	0	3 (0.4)	0	0
Thromboembolic events	13 (2.6)	27 (3.7)	12 (2.4)	23 (3.2)	1 (0.2)	3 (0.4)
Myocardial infarction	2 (0.4)	8 (1.1)	2 (0.4)	8 (1.1)	1 (0.2)	2 (0.3)
Pulmonary embolism	3 (0.6)	6 (0.8)	3 (0.6)	6 (0.8)	0	1 (0.1)
Acute myocardial infarction	0	3 (0.4)	0	3 (0.4)	0	0
Transient ischemic attack	1 (0.2)	3 (0.4)	0	3 (0.4)	0	0
Venous thromboembolism	5 (1.0)	8 (1.1)	5 (1.0)	7 (1.0)	0	1 (0.1)
Pulmonary embolism	3 (0.6)	6 (0.8)	3 (0.6)	6 (0.8)	0	1 (0.1)

¹ Patients with known bleeding risk were excluded

² Gastrointestinal hemorrhage and hematemesis in the same patient

³ Hypertension was most common baseline condition, see Section 6.1.2 Demographics

⁴ Other deaths under MACE for nintedanib were due to atrial fibrillation (2), atrial flutter, and sudden death.

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.2.1, p 343-350; Table 18.3.1.2.2, p 351-354; Table 18.3.1.2.3, p 359-360

The following AESI are not included in Table 30, with the reason listed below:

1. **Cardiac arrhythmias, cutaneous serious skin reactions, fatigue, pneumonic infection, rash, and renal failure** were more frequent in the placebo group compared to nintedanib for both AESIs and SAESIs (except renal failure SAESIs which were the same for both groups). There were 6 deaths due to cardiac arrhythmias (4 (0.8%) placebo, 2 (0.3%) nintedanib) and 2 due to cardiac failure (both in placebo group). Pneumonia was responsible for 8 deaths (3 (0.6%) placebo vs 5 (0.7%) nintedanib).
2. For **cardiac failure** the difference favoring placebo was only 0.1% and none of the preferred terms were greater in the nintedanib group. The SAESIs favored nintedanib.
3. **Liver related investigation** was very similar to the liver enzyme elevation analyses for both AESIs and SAESIs.

Abdominal pain and liver enzyme elevation were the most common AESIs occurring in 15% and 14% of nintedanib subjects, respectively. Arterial thromboembolic events, MACE, and thromboembolic events and venous thromboembolism were overlapping AESI's and were all more frequent in the nintedanib group. Myocardial infarction was the most common AE within these groups occurring in 1.1% of patients treated with nintedanib. Acute myocardial infarction was captured as a separate AE, however represents the same clinical endpoint. When combining these two AEs, the occurrence in nintedanib-treated patients increases to 1.5%. Notably, cardiac arrhythmias and cardiac failure were more frequent in the placebo group. Patients were excluded for a history of myocardial infarction within 6 months of unstable angina within 1 month.

Although hypertension was numerically higher in nintedanib treated patients compared to placebo, the mean differences in blood pressure were negligible. For further details, see 7.4.3 Vital Signs.

Reviewer comment: The proposed package insert lists the AESIs of arterial thromboembolic events, risk of bleeding, and gastrointestinal perforation in the Warnings and Precautions.

Lung Transplants

The safety of patients treated with nintedanib and receiving lung transplants was of special interest, as nintedanib may impair wound healing and might be associated with an increased risk of bleeding. Exclusion criteria and withdrawal criteria were specified in all clinical trial protocols to exclude patients who required lung transplants. In some trial protocols (i.e. 1199.30, 1199.32, 1199.34, and 1199.35) it was specifically highlighted that being on a transplantation list was not a reason to exclude patients from participation.

A total of 7 patients in the phase 3 studies received lung transplants. Of these, 4 were treated with nintedanib. In 3 of 4 patients in the nintedanib arm who received a lung transplant, the procedure was performed several months after the permanent discontinuation of nintedanib treatment.

In Study 1199.30, 1 patient treated with nintedanib 50 mg BID underwent transplant. The patient was on treatment at the time of transplant.

No abnormal bleeding or impaired wound healing was reported for any of the lung transplants.

Malignancy

A malignancy analysis was performed as an evaluation of AEs leading to death showed an imbalance favoring placebo for the neoplasm SOC (Table 26). Malignancy was not a condition for exclusion and was reported as a baseline condition in 52 (10%) placebo and 69 (9.5%) nintedanib subjects. Additionally, carcinogenicity studies showed no evidence for a carcinogenic potential for nintedanib.

A malignancy SMQ analysis run by this reviewer showed more events (54 nintedanib vs. 24 placebo) and a higher frequency of patients with PTs within the malignancy SMQ in the nintedanib group (44 (4.5%)) compared to placebo (20 (3.9%)) (Table 31).

Table 31. Malignancies SMQ: SG 1 - Studies 1199.32, 1199.34, and 1199.30 (Randomized Population)				
	Placebo N=511		Nintedanib¹ N=983	
	Events	n (%)	Events	n
Study 30	2	2 (3.8)	25	21 (6.1)
N	87		345	
Study 32	11	9 (4.4)	18	14 (4.5)
N	205 ²		309	
Study 34	11	9 (4.1)	11	9 (2.7)
N	219		329	
TOTAL for all studies	24	20 (3.9)	54	44 (4.5)

¹ Any treatment dose
² Missing one patient from randomized set
 Source: Module 5.3.5.1, Data tabulation dataset legacy from each study. Malignancy SMQ analysis using MAED

The malignancy SMQ (last change version 14.0) includes the 4 sub-SMQs listed below:

1. Malignant or unspecified tumors
2. Malignancy related conditions
3. Malignancy related therapeutic and diagnostic procedures
 - a. Some of these procedures are also used for the treatment of non-malignancy conditions
4. Tumor markers

Cyst, nevus, and benign tumor terms are excluded from this SMQ.

The malignancy SMQ analysis was driven by Study 1199.30 which showed a higher number of patients with a PT within the neoplasm SOC (neoplasms, benign, malignant, and unspecified) in the nintedanib group (2 (2.4%)) compared to placebo (1 (1.2%)), although the numbers were very small. This difference is increased when including the lower dose arms (13 (2.8%)), showing that no dose effect is demonstrated, although the number of patients in the high dose arm are low (n=85). After removing the benign PTs from the SOC (seborrhic keratosis from the nintedanib all doses group; 12 (3.5%), the difference was still seen (Table 32).

Table 32. Frequency of patients with Neoplasms benign, malignant and unspecified (incl cysts and polyps) and Malignancy AEs¹ for Study 1199.30 (Treated population)			
SOC/Preferred Term (number of events)	Placebo N=85 n (%)	Nintedanib 150 mg BID N=85 n (%)	Nintedanib All doses N=344 n (%)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (1.2)	2 (2.4)	13² (3.8)
Basal cell carcinoma ²	0	0	1
Colon Cancer ²	0	0	2
Gastric cancer	0	0	1
Lung adenocarcinoma metastatic	0	1	1
Lung neoplasm	0	0	1
Lung neoplasm malignant	0	0	1
Lung squamous cell carcinoma stage unspecified	0	0	1
Malignant melanoma	0	0	1
Myelodysplastic syndrome	0	1	1
Non-small cell cancer	1	0	0
Prostate cancer	0	0	1
Seborrhic keratosis	0	0	1
Small cell lung cancer stage unspecified	0	0	1
Squamous cell carcinoma of skin ²	0	0	1
Thyroid neoplasm	0	0	1
Total malignancy AEs¹	1 (1.2)	2 (2.4)	12² (3.5)

¹ Malignancy adverse events are based on the Neoplasms benign, malignancy, and unspecified (incl cysts and polyps) MedDRA system organ class, with seborrhic keratosis PT excluded
² Patient 3199 (nintedanib 100 mg BID) had basal cell, squamous cell, and colon cancer.
 Source: Module 5.3.1, Study 1199.30 CSR, p 1089; AE listing, Table 7.3, p 122

The phase 3 studies (1199.32 and 1199.34) did not show this imbalance.

Overall, the malignancy imbalance is small, inconsistent across studies, and not likely to be clinically relevant. Moreover, the analysis is confounded by the existence of baseline

malignancies, since this was not a condition of exclusion, and the carcinogenicity studies showed no evidence for a carcinogenic potential for nintedanib.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Table 33. Common AEs reported in $\geq 5\%$ patients in the nintedanib group and $> 1\%$ greater than the placebo group: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)		
SOC/PTs	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Patients with AEs	456 (89.8)	689 (95.3)
Gastrointestinal disorders	196 (28.6)	551 (76.2)
Diarrhea	91 (17.6)	445 (61.5)
Nausea	36 (7.1)	176 (24.3)
Vomiting	15 (3.0)	85 (11.8)
Abdominal pain	13 (2.6)	62 (8.6)
Abdominal pain upper	18 (3.5)	51 (7.1)
Constipation	20 (2.9)	39 (5.4)
Metabolism and nutrition disorders	62 (12.2)	132 (18.3)
Decreased appetite	24 (4.7)	81 (11.2)
Nervous system disorders	82 (16.1)	129 (17.8)
Headache	24 (4.7)	54 (7.5)
Investigations	3 (0.6)	10 (1.4)
Weight decreased	15 (3.0)	69 (9.5)

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.1.2, p 271-272

There were slightly more patients with AEs in the nintedanib group (N=456 (90%)) compared to placebo (N=689 (95%)). This difference was mainly driven by gastrointestinal disorders, specifically diarrhea, nausea, vomiting, abdominal pain, and constipation. Other similar AEs such as decreased appetite and weight decreased were also more frequent in the nintedanib group. Headache stood alone without similarity to the other frequent AEs, and was more frequent in the nintedanib group compared to placebo.

Reviewer's comment: The Applicant recommends that emphasis be placed on taking nintedanib with food and following close monitoring and immediate symptomatic treatment of GI symptoms.

Diarrhea

Diarrhea was the most common AE, the most common AE leading to discontinuation, and the most common AE leading to dose reduction. A summary of characteristics for the AE of diarrhea is listed in Table 34.

Table 34. Diarrhea AEs: intensity, clinical consequences and outcome: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

	Placebo N (%)	Nint 150bid N (%)
Number of patients with at least one diarrhoea AE	91 (100.0)	445 (100.0)
Intensity of diarrhoea AE		
Mild	72 (79.1)	247 (55.5)
Moderate	17 (18.7)	172 (38.7)
Severe	2 (2.2)	25 (5.6)
Missing	0 (0.0)	1 (0.2)
Drug relationship of diarrhoea AE		
Yes	50 (54.9)	377 (84.7)
No	41 (45.1)	67 (15.1)
Missing	0 (0.0)	1 (0.2)
Outcome of diarrhoea AE		
Recovered	85 (93.4)	388 (87.2)
Not yet recovered [1]	6 (6.6)	52 (11.7)
Sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	5 (1.1)
Clinical consequences		
Neither discontinued nor reduced [2]	90 (98.9)	343 (77.1)
Permanent dose reduction of trial drug	0 (0.0)	64 (14.4)
Permanent discontinuation of trial drug	1 (1.1)	38 (8.5)
Patients with serious diarrhoea AEs	1 (1.1)	5 (1.1)
Fatal	0 (0.0)	0 (0.0)
Immediate life-threatening	0 (0.0)	0 (0.0)
Persistent or significant disability/incapacity	0 (0.0)	0 (0.0)
Requires hospitalisation	1 (1.1)	5 (1.1)
Prolongs hospitalisation	0 (0.0)	0 (0.0)
Congenital anomaly/birth defect	0 (0.0)	0 (0.0)
Other comparable medical criteria	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
 Percentages are calculated using number of patients with at least one event per treatment as the denominator.
 MedDRA version used for reporting: 16.1
 For patients with several episodes, worst intensity, relationship and outcome and last clinical consequence during on-treatment period are displayed
 [1] The patient has not yet returned to his/her previous health status, continues to be followed for the adverse event, but is expected to recover without sequelae
 [2] Includes temporary interruptions and temporary dose reductions

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.3.1.1, p 363

For those patients on nintedanib, the majority of patients had mild (55%) or moderate (39%) diarrhea. The majority of patients recovered (87%). No fatal or diarrhea sequelae cases were reported. Most patients had no clinical consequences due to the AE of diarrhea (77%). Permanent dose reduction was seen in 14% of the cases and permanent discontinuation was seen in 9%. A total of 5 (1%) patients required hospitalization (compared to 1 (<1%) in placebo).

Diarrhea time to onset, number, and duration of episodes is listed in Table 35.

Table 35. Diarrhea AE: time to onset, number, and duration of episodes: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

	Placebo	Nint 150bid
Number of patients [N (%)]	508 (100.0)	723 (100.0)
Time to first onset of diarrhoea AE [1] [days]		
P25	NC	28.0
Median	NC	154.0
P75	NC	NC
Time (days) to first onset of diarrhoea AE in categories [N (%)]		
<= 31 days	48 (9.4)	191 (26.4)
> 31 - <= 61 days	12 (2.4)	54 (7.5)
> 61 - <= 92 days	5 (1.0)	48 (6.6)
> 92 - <= 183 days	13 (2.6)	81 (11.2)
> 183 days	13 (2.6)	71 (9.8)
No diarrhoea	417 (82.1)	278 (38.5)
Number of diarrhoea episodes in categories [N (%)]		
0	417 (82.1)	278 (38.5)
1	70 (13.8)	273 (37.8)
2	15 (3.0)	111 (15.4)
3	3 (0.6)	33 (4.6)
>=4	3 (0.6)	28 (3.9)
Duration of diarrhoea episodes [Days] [2]		
N	91	445
Mean	52.6	153.9
SD	110.5	129.2
Min	1	1
Median	7.0	127.0
Max	453	505

[1] Median, 25th and 75th percentiles are calculated from the Kaplan-Meier curve for each treatment arm
 [2] For patients with several episodes, total duration during on-treatment period
 NC=Not Calculable

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.3.1.2, p 364

The median time to onset was 154 days. Out of the 445 subjects (Table 34) who reported diarrhea, 191 or 43% reported diarrhea within the first month. Only 71 or 16% reported the first episode of diarrhea after 6 months on treatment. The majority of subjects reported one episode of diarrhea (N=273, 61%), compared to 28 subjects (6%) who reported 4 or more episodes. In subjects on nintedanib, diarrhea lasted a mean of 154 days, with a range of 1 to 505 days.

Nausea

Nausea was the 2nd most common AE, the 2nd most common AE leading to discontinuation, and the 2nd most common AE leading to dose reduction. A summary of characteristics for the AE of diarrhea is listed in Table 36.

Table 36. Nausea AEs: intensity, clinical consequences and outcome: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)

	Placebo N (%)	Nint 150bid N (%)
Number of patients with at least one nausea AE	36 (100.0)	176 (100.0)
Intensity of nausea AE		
Mild	34 (94.4)	131 (74.4)
Moderate	2 (5.6)	42 (23.9)
Severe	0 (0.0)	3 (1.7)
Drug relationship of nausea AE		
Yes	22 (61.1)	139 (79.0)
No	14 (38.9)	37 (21.0)
Outcome of nausea AE		
Recovered	30 (83.3)	160 (90.9)
Not yet recovered [1]	6 (16.7)	15 (8.5)
Sequelae	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Unknown	0 (0.0)	1 (0.6)
Clinical consequences		
Neither discontinued nor reduced [2]	36 (100.0)	148 (84.1)
Permanent dose reduction of trial drug	0 (0.0)	11 (6.3)
Permanent discontinuation of trial drug	0 (0.0)	17 (9.7)
Patients with serious nausea AEs	0 (0.0)	0 (0.0)
Fatal	0 (0.0)	0 (0.0)
Immediate life-threatening	0 (0.0)	0 (0.0)
Persistent or significant disability/incapacity	0 (0.0)	0 (0.0)
Requires hospitalisation	0 (0.0)	0 (0.0)
Prolongs hospitalisation	0 (0.0)	0 (0.0)
Congenital anomaly/birth defect	0 (0.0)	0 (0.0)
Other comparable medical criteria	0 (0.0)	0 (0.0)

A patient may be counted in more than one seriousness criterion.
 Percentages are calculated using number of patients with at least one event per treatment as the denominator.
 MedDRA version used for reporting: 16.1
 For patients with several episodes, worst intensity, relationship and outcome and last clinical consequence during on-treatment period are displayed
 [1] The patient has not yet returned to his/her previous health status, continues to be followed for the adverse event, but is expected to recover without sequelae
 [2] Includes temporary interruptions and temporary dose reductions

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.3.2.1, p 367

For those patients on nintedanib, the majority of patients had mild (74%) nausea and recovered (91%) without clinical sequelae. No fatal cases or hospitalizations due to nausea were reported. Permanent dose reduction was seen in 6% of the cases and permanent discontinuation was seen in 10%.

Nausea time to onset, number, and duration of episodes is listed in Table 37.

Table 37. Nausea AE: time to onset, number, and duration of episodes: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population,)

	Placebo	Nint 150bid
Number of patients [N (%)]	508 (100.0)	723 (100.0)
Time to first onset of nausea AE [1] [days]		
P25	NC	356.0
Median	NC	NC
P75	NC	NC
Time (days) to first onset of nausea AE in categories [N (%)]		
<= 31 days	23 (4.5)	110 (15.2)
> 31 - <= 61 days	5 (1.0)	24 (3.3)
> 61 - <= 92 days	1 (0.2)	10 (1.4)
> 92 - <= 183 days	2 (0.4)	20 (2.8)
> 183 days	5 (1.0)	12 (1.7)
No nausea	472 (92.9)	547 (75.7)
Number of nausea episodes in categories [N (%)]		
0	472 (92.9)	547 (75.7)
1	35 (6.9)	132 (18.3)
2	1 (0.2)	32 (4.4)
3	0 (0.0)	10 (1.4)
>=4	0 (0.0)	2 (0.3)
Duration of nausea episodes [Days] [2]		
N	36	176
Mean	105.1	121.3
SD	150.0	135.4
Min	1	1
Median	17.0	44.0
Max	443	400

[1] Median, 25th and 75th percentiles are calculated from the Kaplan-Meier curve for each treatment arm
 [2] For patients with several episodes, total duration during on-treatment period
 NC=Not Calculable

Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.3.2.2, p 368

For the patients treated with nintedanib, the median time to onset was not estimable by time-to-event analysis. Nausea started in the first month of treatment in 110 out of 176 patients (63%). Only 12 patients (7%) reported the first episode of nausea after 6 months on treatment. The majority of subjects reported one episode of nausea (N=132 (75%)), compared to 2 subjects (1%) who reported 4 or more episodes. In subjects on nintedanib, nausea lasted a mean of 121 days, with a range of 1 to 400 days.

Vomiting

Vomiting was the 3rd most common AE (N=85, 12% nintedanib vs N=85, 3% placebo) and a common reason for treatment discontinuation (1% nintedanib vs 0.2% placebo). For those patients on nintedanib, the majority of patients had mild (64%) or moderate (32%) vomiting. The majority of patients recovered (94%). No fatal or nausea sequelae cases were reported. Permanent dose reduction and treatment discontinuation was seen in 8% of the cases. One patient required hospitalization. For the patients treated with nintedanib, the median time to onset was not estimable by time-to-event analysis. Vomiting started in the first month of treatment in

40 (47%) patients. A total of 15 or 15% reported the first episode of vomiting after 6 months on treatment. The majority of subjects reported one episode of vomiting (N=63, 74%), compared to 3 subjects (4%) who reported 4 or more episodes. Vomiting lasted a mean of 46 days, with a range of 1 to 390 days.

Weight decreased

The AE of weight decreased was a common AE (N=69, 9.5% nintedanib vs N=15, 3% placebo), a common reason for treatment discontinuation (1.1% nintedanib vs 0.2% placebo) and permanent dose reduction (0.6% nintedanib vs 0.2% placebo). For those patients on nintedanib, the majority of patients had mild (62%) or moderate (36%) weight decrease. The majority of patients recovered (70%). No fatal cases were reported. Permanent dose reduction occurred in 4% and treatment discontinuation was seen in 12% of the cases. One patient required hospitalization. Notably, one patient on placebo reported weight decrease that was persistent and resulted in significant disability/incapacity. For the patients treated with nintedanib, the median time to onset was not estimable by time-to-event analysis. Weight decrease was reported most commonly after 6 months of treatment (n=25, 36%). The majority of subjects reported one episode of weight decrease (N=67, 97%). Weight decrease lasted a mean of 181 days, with a range of 3-430 days.

Decreased appetite

Decreased appetite was a common AE (N=81, 11% nintedanib vs N=24, 5% placebo), a common reason for treatment discontinuation (1.5% nintedanib vs 0.2% placebo) and permanent dose reduction (0.8% nintedanib vs 0% placebo). For those patients on nintedanib, the majority of patients had mild (65%) or moderate (33%) decreased appetite. The majority of patients recovered (88%). No fatal cases were reported. Permanent dose reduction occurred in 7% and treatment discontinuation was seen in 14% of the cases. One patient required hospitalization (one placebo patient was also hospitalized). For the patients treated with nintedanib, the median time to onset was not estimable by time-to-event analysis. Decreased appetite started in the first month of treatment in 29 (%) patients. A total of 17 or % reported the first episode of decreased appetite after 6 months on treatment. The majority of subjects reported one episode of decreased appetite (N=75, 10%). Decreased appetite lasted a mean of 140 days, with a range of 2 to 494 days.

Association between multiple AEs

It was noticeable that the proportions of patients with weight decrease (9.5%) and with concurrent weight decrease and diarrhea (6.6%) were not very different, suggesting a possible association between diarrhea and weight loss. This was also seen for dehydration (0.7%) and dehydration and diarrhea (0.6%). The proportion of patients with weight decrease and concurrently decreased appetite in the nintedanib group was 3.2% (compared to 9.5% and 11.2% for each AE alone, respectively).

7.4.2 Laboratory Findings

Liver enzymes and bilirubin

Patients with impaired hepatic function were excluded from participation in the IPF trials (aspartate aminotransferase (AST) and alanine aminotransferase (ALT) > 1.5x upper limit of normal (ULN)). A summary of individual liver enzymes and bilirubin worse values on treatment are summarized in Table 38.

Table 38. Summary of individual patients liver enzyme and bilirubin worse value on treatment: SG 1 - Studies 1199.32, 34, and 1199.30 (Treated population)		
	n (%)	
	Placebo (N=508)	Nintedanib 150 mg BID (N=723)
Maximum ALT		
≥ 3x ULN	3 (0.6)	30 (4.1)
≥ 5x ULN	0	10 (1.4)
≥ 8x ULN	0	4 (0.6)
Maximum AST		
≥ 3x ULN	1 (0.2)	23 (3.2)
≥ 5x ULN	1 (0.2)	8 (1.1)
≥ 8x ULN	1 (0.2)	4 (0.6)
AST and/or ALT		
≥ 3x ULN	3 (0.6)	36 (5.0)
≥ 5x ULN	1 (0.2)	14 (1.9)
≥ 8x ULN	1 (0.2)	5 (0.7)
Maximum total bilirubin		
≥ 1.5x ULN	4 (0.8)	15 (2.1)
≥ 2x ULN	2 (0.4)	3 (0.4)
Maximum ALKP		
≥ 1.5x ULN	6 (1.2)	41 (5.7)
≥ 2x ULN	1 (0.2)	17 (2.4)

ALKP = alkaline phosphatase
 Values from central laboratory
 Source: Module 1.11.3, Response to information request 6.20.14, Table 18.3.1.2.2, p 451

The majority of elevated liver enzymes and bilirubin events were ≤ 3x ULN and ≤ 1.5x ULN, respectively. Most patients returned to within the normal range by the end of treatment. Liver enzyme elevations appeared to occur with an even distribution over time, without an accumulation at a certain time relative to the start of treatment.

Although no patient fulfilled the laboratory criteria for potential Hy's law cases, one patient in Study 1199.32 had elevated total bilirubin measured at a local lab (not a central lab and therefore

is not presented in Table 38) in conjunction with transaminases elevations which led to the identification of the patient as a potential Hy's law case.

Reviewer's comment: Hy's Law describes severe liver injury defined as instances of transaminase elevation accompanied by elevated bilirubin (even if obvious jaundice was not present). These cases have been associated with, and have often predicted, post-marketing serious liver injuries (fatal or requiring transplant). The estimated mortality of such cases is 10%. The rationale here is that hepatocellular injury great enough to interfere with bilirubin excretion) involves a large fraction of the liver cell mass (7). Per the Guidance for Industry: Drug Induced Liver Injury: Premarketing Clinical Evaluation, July 2009, the criteria for Hy's Law are: 1) ALT or AST >3 x ULN in concert with a serum bilirubin >2 x ULN, without initial findings of cholestasis (i.e. elevated alkaline phosphatase) and, 2) no other reason for these elevations, such as viral hepatitis, pre-existing or acute liver disease, or another drug.

The patient had relevant AEs reported, i.e. liver injury due to underlying pancreas head tumor and common bile duct obstruction. Thus, the patient does not represent a Hy's law case (other explanation for AST, ALT and bilirubin elevation). The narrative is provided below.

Patient 44002, Study 1199.32

A 78 year-old male patient was randomized to receive nintedanib 150 mg BID on Mar 5, 2012. On [REDACTED] (b)(6) (9 months later) the patient had non-serious elevated bilirubin. The temperature was 36.0°C, **ALT 650 (19x ULN)**, **AST 588 (17x ULN)** and bilirubin 65 (4x ULN). Additionally it was stated that there **was jaundice** as well as fatigue, diarrhea, and dark urine (consistent with abnormal liver function) but no abdominal discomfort. Study medication was stopped the previous day [REDACTED] (b)(6). The following day the patient was admitted to the hospital for fever, abdominal pain, and continued jaundice. Endoscopic retrograde cholangiopancreatography (ERCP) on [REDACTED] (b)(6) showed **malignant obstruction of the common bile duct** and confirmed **adenocarcinoma at the head of the pancreas**. The patient had a history of prostate carcinoma with metastases to bone. He also required a pancreatic stent in 2010.

In the ovarian cancer clinical development program for nintedanib (discussed also in Section 7.7.3 Other indications) 4 patients treated with nintedanib had laboratory values for liver enzymes and bilirubin matching the criteria for potential Hy's law cases. The sponsor also states that a fifth case was reported based on an AE, presumably without laboratory evidence. Alternative causes for the alterations were suggested for 3 of the patients, chemotherapy with paclitaxel was also considered as potential cause for 4th patient. In the fifth patient who had onset of liver value elevations 20 months after oral therapy and in 2 of the other cases, the time course of liver value elevations was not suggestive of a nintedanib effect. In this and 3 of the 4 other patients, nintedanib was continued at reduced dose for many months afterwards, and also in the fifth case nintedanib had been reintroduced for a more limited duration without recurrence of a potential Hy's law constellation.

This reviewer notes the following:

- There were no cases of Hy’s law in the nintedanib IPF program.
- The 5 potential Hy’s law cases in the ovarian cancer program, although initially concerning, were in the setting of confounders such as hepatotoxic chemotherapy and 3 of the 5 had had alternative causes.

It is reassuring that all of the potential cases were continued at reduced doses of nintedanib without recurrence of a potential Hy’s law constellation.

The primary review division (DPARP: Division of Pulmonary, Allergy, and Rheumatology Products) has requested internal liver experts to review the cases and their evaluation is pending. The outcome of their review will be noted in the Cross-Discipline Team Leader Review.

Other laboratory findings

Overall, the mean changes in hematology, coagulation, chemistry, and thyroid parameters did not demonstrate any clinically significant change and were similar across treatment groups.

Reviewer comment: Thyroid parameters were monitored as hypothyroidism has been seen in other tyrosine kinase inhibitors with similar pathways (VEGFR, PDGFR, FGFR, and Lck).

7.4.3 Vital Signs

There were no clinically relevant mean changes from baseline in blood pressure (BP) or pulse from baseline to week 52 in all 3 studies. For the phase 3 studies, blood pressure was analyzed for marked increases (systolic BP (sBP) > 150 mmHg and increase ≥ 25 mmHg above baseline, diastolic (BP) DBP >90 mmHg and increase >10 mmHg above baseline). The marked changes in blood pressure for all 3 studies are summarized in Table 39.

Table 39. Marked changes in blood pressure: SG 1.1 - Study 1199.32 and 1199.34 (Treated population)

	Placebo N (%)	Nintedanib 150 mg bid N (%)
Patients	423 (100.0)	638 (100.0)
Systolic blood pressure		
Patients with measurements	421 (99.5)	635 (99.5)
Increase	27 (6.4)	61 (9.6)
Decrease	24 (5.7)	29 (4.5)
Diastolic blood pressure		
Patients with measurements	421 (99.5)	635 (99.5)
Increase	45 (10.6)	109 (17.1)
Decrease	38 (9.0)	37 (5.8)

Source: Module 2.7.4, SCS, Table 4.1:1, p 157

More patients in the nintedanib group had marked increases in blood pressure compared to placebo (27% vs. 17%). AEs under the hypertension AESI which included hypertension, blood

pressure increased, and hypertensive crisis were reported in slightly more patients receiving nintedanib (4.8%) than in the placebo group (3.9%) (Table 30). It is noteworthy that a high percentage of patients in these studies had a known medical history of hypertension (MedDRA preferred term). Of the patients with hypertension reported as an AE, some, but not all had a medical history of hypertension. The incidence of Serious AEs under the hypertension AESI was low and similar between groups (nintedanib group (5 (0.7%) nintedanib vs 2 (0.4%) placebo). The mean change from baseline after 52 weeks of treatment was low for both systolic (-2.0 mm Hg placebo; 0.1 mmHg nintedanib) and diastolic (-1.4 mmHg placebo; 0.2 mmHg nintedanib) blood pressure.

7.4.4 Electrocardiograms (ECGs)

ECG sub-studies were performed in Japanese patients participating in the randomized, 52-week phase 3 trials (N=19 placebo, N=31 nintedanib). 12-lead ECGs were to be recorded at the first drug administration visit, before administration of study drug, and at Week 4 and 24, at 3 hours after administration of study drug. The ECGs were centrally read by a cardiologist. ECG parameters and heart rate were analyzed using descriptive statistics. Changes from baseline were not calculated. Based on the limited data from these sub-studies, there was no discernable effect of nintedanib on the QT interval.

The effects of nintedanib have not been evaluated in a formal, placebo-controlled thorough QT/QTc study as described by ICH E14, because it was considered not ethical to expose healthy volunteers to nintedanib at the required exposure and for the required duration of time. In a dedicated phase 2 trial in patients with renal cell carcinoma, performed in the clinical development program for nintedanib in oncology indications, neither a single dose nor multiple doses of nintedanib 200mg BID prolonged the QTc interval in patients with renal cell carcinoma. See the review by Dr. Devi Kozeli with the QT interdisciplinary review team for further details.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Study 1199.30 included 4 doses of nintedanib. In general, a dose effect for adverse events was demonstrated, which supports the sponsor's recommendation for dose modification to 100 mg for adverse events. This dose effect was seen specifically for GI disorders (excluding abdominal pain) and investigations (driven by liver function abnormalities) as seen in Table 40.

Table 40. Adverse events occurring in $\geq 10\%$ of patients in any treatment group: Study 1199.30 (all doses, Treated population)

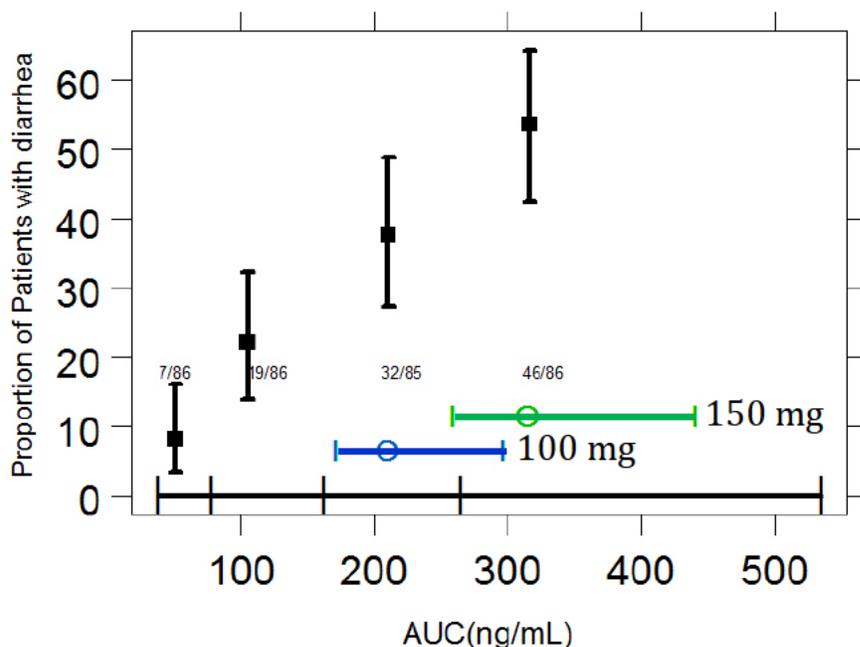
System organ class/ Preferred term	Placebo N (%)	Nintedanib			
		50 mg qd N (%)	50 mg bid N (%)	100 mg bid N (%)	150 mg bid N (%)
Patients	514 (100.0)	86 (100.0)	88 (100.0)	90 (100.0)	731 (100.0)
Patients with adverse events	458 (89.1)	78 (90.7)	77 (87.5)	85 (94.4)	694 (94.9)
Gastrointestinal disorders	197 (38.3)	33 (38.4)	32 (36.4)	50 (55.6)	554 (75.8)
Diarrhoea	91 (17.7)	8 (9.3)	17 (19.3)	32 (35.6)	447 (61.1)
Nausea	36 (7.0)	8 (9.3)	8 (9.1)	17 (18.9)	177 (24.2)
Vomiting	15 (2.9)	1 (1.2)	6 (6.8)	11 (12.2)	85 (11.6)
Abdominal pain upper	18 (3.5)	6 (7.0)	10 (11.4)	2 (2.2)	51 (7.0)
Infections and infestations	282 (54.9)	44 (51.2)	54 (61.4)	57 (63.3)	406 (55.5)
Nasopharyngitis	79 (15.4)	11 (12.8)	8 (9.1)	16 (17.8)	93 (12.7)
Bronchitis	57 (11.1)	11 (12.8)	16 (18.2)	7 (7.8)	76 (10.4)
Upper respiratory tract infection	55 (10.7)	7 (8.1)	10 (11.4)	13 (14.4)	65 (8.9)
Respiratory, thoracic and mediastinal disorders	220 (42.8)	34 (39.5)	35 (39.8)	38 (42.2)	281 (38.4)
Cough	75 (14.6)	11 (12.8)	17 (19.3)	20 (22.2)	93 (12.7)
Idiopathic pulmonary fibrosis	72 (14.0)	11 (12.8)	7 (8.0)	9 (10.0)	68 (9.3)
Dyspnoea	59 (11.5)	7 (8.1)	14 (15.9)	12 (13.3)	55 (7.5)
Investigations	79 (15.4)	7 (8.1)	7 (8.0)	12 (13.3)	209 (28.6)
General disorders and administration site conditions	123 (23.9)	16 (18.6)	15 (17.0)	19 (21.1)	173 (23.7)
Musculoskeletal and connective tissue disorders	115 (22.4)	12 (14.0)	16 (18.2)	26 (28.9)	138 (18.9)
Metabolism and nutrition disorders	62 (12.1)	5 (5.8)	11 (12.5)	11 (12.2)	132 (18.1)
Decreased appetite	24 (4.7)	3 (3.5)	4 (4.5)	4 (4.4)	81 (11.1)
Nervous system disorders	82 (16.0)	15 (17.4)	20 (22.7)	20 (22.2)	129 (17.6)
Skin and subcutaneous tissue disorders	75 (14.6)	10 (11.6)	14 (15.9)	13 (14.4)	100 (13.7)

MedDRA version used for reporting: 16.1

Source: Module 2.7.4, SCS, Table 2.1.2.3:1, p 91

Since diarrhea was the most common adverse event observed in the trials, an exposure-response analysis was conducted by the clinical pharmacology team for diarrhea. Consistent with dose response, the proportion of patients with diarrhea increased with increasing steady state AUC (Figure 16).

Figure 16. The relationship of proportions of patients with diarrhea with steady state AUC: Study 1199.30, all doses.



The black symbols represent the mean and 95% CI in each exposure quartile. The horizontal black line represents the exposure range in each quartile.

A similar pattern was seen for SAEs (not shown) and AEs leading to discontinuation (Table 41).

Table 41. AEs leading to discontinuation of study medication >2% of patients in any group: Study 1199.30 (Treated population)

System organ class/ Preferred term	Placebo N (%)	Nintedanib			
		50 mg qd N (%)	50 mg bid N (%)	100 mg bid N (%)	150 mg bid N (%)
Patients	514 (100.0)	86 (100.0)	88 (100.0)	90 (100.0)	731 (100.0)
Patients with AEs leading to permanent treatment discontinuation	76 (14.8)	20 (23.3)	14 (15.9)	13 (14.4)	151 (20.7)
Gastrointestinal disorders	7 (1.4)	2 (2.3)	2 (2.3)	2 (2.2)	61 (8.3)
Diarrhoea	1 (0.2)	1 (1.2)	1 (1.1)	0 (0.0)	38 (5.2)
Nausea	0 (0.0)	0 (0.0)	1 (1.1)	0 (0.0)	17 (2.3)
Investigations	3 (0.6)	0 (0.0)	1 (1.1)	0 (0.0)	25 (3.4)

Source: Module 2.7.4, SCS, Table 2.1.3.3:1, p 97

Overall the recommendation to dose reduce to 100 mg BID from 150 mg BID for adverse events is supported by the dose dependency for adverse events, specifically seen for GI disorders and liver enzyme elevations (under the SOC of investigations).

7.5.2 Time Dependency for Adverse Events

Time dependency for AEs are noted within the discussion for specific AEs under Section 7.4.1 Common Adverse Events.

7.5.3 Drug-Demographic Interactions

Subgroup analyses for the two phase 3 studies (1199.32 and 34) were performed for AEs for intrinsic factors (gender, age, race, and body weight) and extrinsic factors (smoking history).

Several subgroup categories were rather small, and their safety results should therefore be considered with some caution. In particular, these were female patients (21% of all patients in SG-1.1), patients ≥ 75 years (17%), and patients < 65 kg (19%).

Overall, premature treatment discontinuation was more frequent and mean treatment duration was shorter (without noticeable differences in dose intensity) in the following groups:

- Women compared to men
- Age ≥ 75 years
- Asians compared to white
- Body weight < 65 kg compared to ≥ 65 kg

AE differences between treatment groups were more pronounced for the following subgroups and AEs:

- Decreased appetite, nausea, vomiting, and abdominal pain in women compared to men.
- Weight decreased incidences increased with age
- Liver enzyme increased in Asians
- Vomiting, decreased appetite, weight decrease and liver enzymes in subjects < 65 kg

Details for each subgroup analysis are provided below by demographic.

Gender

In women, premature treatment discontinuation was twice as frequent in the nintedanib group (32.1%) than in the placebo group (15.7%) resulting in the mean treatment duration in female patients receiving nintedanib being shorter (9.4 months) than in those receiving placebo (11.1 months), or in male patients of either treatment group (10.8 vs. 10.5 months). Among nintedanib patients, dose reductions were twice as frequent in female patients (46.6%) as in male patients (23.1%). Consequently, the mean dose intensity was lowest in female patients in the nintedanib

group (88.7%) compared to female placebo patients (99.0%) and males (98.9% nintedanib vs. 95.0% placebo). AEs leading to discontinuation were more frequent in female patients receiving nintedanib (29.8%) than in those receiving placebo (11.2%) or in male patients (13.5% placebo, 16.6% nintedanib). Among nintedanib patients, AE incidences were consistently higher in female than in male patients. For several AEs by preferred term that were more frequent with nintedanib, the difference between treatment groups was more pronounced in female than in male patients. This was observed for decreased appetite (males: 6.9% placebo vs. 9.3% nintedanib; females: 1.1% placebo vs. 16.0% nintedanib), nausea (males: 6.0% placebo vs. 20.7% nintedanib; females: 9.0% placebo vs. 38.9% nintedanib), vomiting (males: 2.4% placebo vs. 7.1% nintedanib; females: 3.4% placebo vs. 29.0% nintedanib), and abdominal pain (males: 2.7% placebo vs. 7.3% nintedanib; females: 1.1% placebo vs. 14.5% nintedanib).

Age

Mean treatment duration was shorter in the nintedanib than the placebo arm in patients ≥ 75 years (placebo: 10.5 months, nintedanib: 9.0 months). With age, the discontinuation rates increased and the difference in discontinuation rates between treatment arms widened (< 65 years, placebo: 15.2%, nintedanib: 17.1%; 65-74 years: 19.9% placebo vs. 24.3% nintedanib; ≥ 75 years: 24.2% placebo vs. 41.0% nintedanib). In patients ≥ 75 years, the proportion of patients with dose reductions was 38.5% in the nintedanib arm and 9.7% in the placebo arm and thus higher than in the lower age categories (< 65 years: 2.1% placebo vs. 24.4% nintedanib; 65-74 years: 3.2% placebo vs. 26.6% nintedanib). The described differences did not lead to a noticeable difference in dose intensity between the age categories. The incidence of AEs leading to discontinuation in the nintedanib arm increased with age (< 65 years: 12.8%, 65-74 years: 19.8%, ≥ 75 years: 32.5%). With the exception of weight decreased (MedDRA preferred term), no age-related differences between treatment groups were seen for AEs. For weight decreased, the incidences increased with age in all age and treatment groups and the difference between treatment groups widened (< 65 years, placebo: 0.7%, nintedanib: 7.4%; 65-74 years: 4.6% vs. 9.1%; ≥ 75 years: 6.5% vs. 16.2%).

Race

In Asian patients, a somewhat higher discontinuation rate was observed (Asians: 21.1% placebo vs. 28.9% nintedanib vs. Whites: 19% placebo vs. 23% nintedanib) and the treatment duration was shorter in the nintedanib group (9.8 months) than in the placebo group (10.8 months). Dose reductions were slightly more frequent in White patients in either treatment group (5.2% placebo vs. 29.4% nintedanib), compared with Asians (2.3% placebo vs. 25.8% nintedanib). Despite these differences in some of the exposure parameters, there was no apparent difference in dose intensity between the races.

Body weight

Patients with a low body weight had higher discontinuation rates in both treatment groups and a greater discrepancy in discontinuation rates between the groups (26.3% placebo vs. 35.7% nintedanib) than patients of ≥ 65 kg weight (17.3% placebo vs. 21.7% nintedanib). The mean treatment duration was shorter in patients < 65 kg who received nintedanib (9.5 months) than in those receiving placebo (10.4 months). The rate of patients with dose reductions was low in placebo patients of either weight category (< 65 kg: 2.6%, ≥ 65 kg: 4.0%). Nintedanib patients with weight ≥ 65 kg had a dose reduction rate of 25.8%, while nintedanib patients of < 65 kg had a higher dose reduction rate of 36.5%. However, within each body weight category, mean dose intensity did not differ in a relevant way between the treatment groups.

For vomiting a greater discrepancy between treatment arms was seen in patients < 65 kg (3.9% placebo vs. 19.8% nintedanib) than in patients ≥ 65 kg (2.3% placebo vs. 9.6% nintedanib). No differences between the body weight categories were seen for any other gastrointestinal AE. A slightly more pronounced treatment difference in patients of lower body weight as compared to patients of higher weight was also seen for decreased appetite (< 65 kg: 3.9% placebo vs. 15.1% nintedanib; ≥ 65 kg: 6.1% placebo vs. 9.6% nintedanib) and weight decreased (< 65 kg: 5.3% placebo vs. 13.5% nintedanib; ≥ 65 kg: 3.2% placebo vs. 8.8% nintedanib).

Small differences between body weight categories were seen for increased liver enzymes reported as AE. These were more frequent with nintedanib than with placebo in patients of lower body weight, while the difference was small or not present at all in patients ≥ 65 kg. This was observed for the following preferred terms: hepatic function abnormal (< 65 kg: 1.3% placebo vs. 7.1% nintedanib ; ≥ 65 kg: 0.0% placebo vs. 1.6% nintedanib), ALT increased (< 65 kg: 1.3% placebo vs. 5.6% nintedanib; ≥ 65 kg: 0.0% placebo vs. 2.5% nintedanib), AST increased (< 65 kg: 1.3% placebo vs. 4.8% nintedanib; ≥ 65 kg: 0.0% placebo vs. 2.0% nintedanib), and hepatic enzyme increased (< 65 kg: 0.0% placebo vs. 5.6% nintedanib; ≥ 65 kg: 0.6% placebo vs. 2.7% nintedanib).

7.5.4 Drug-Disease Interactions

Renal impairment at baseline

Nintedanib is predominantly eliminated via metabolism and biliary/fecal excretion; renal excretion is a minor elimination pathway. To assess the safety of nintedanib by renal status in the phase 3 studies (1199.32 and 1199.34), patients with baseline creatinine clearance < 90 mL/min were classified as patients with renal impairment.

Overall, patients with renal impairment had higher discontinuations rates, shorter mean treatment durations, more dose reductions, and more AEs leading to discontinuation. Decreased appetite, weight decreased, and hypertension (expected) were slightly more frequent in patients with renal impairment compared to normal renal function.

Details of the subgroup analysis are provided below:

Patients with impaired renal function were more frequently of female gender (24.2%), Asian (38.6%), never-smokers (31.0%), had a higher mean age (70.4 years) and a lower body weight (71.9 kg) than was the case in patients with normal renal function (female: 16.7%, Asian: 20.5%, never-smoker: 24.4%, age: 62.4 years; weight: 87.5 kg). The confounding with age was as expected, as renal function is known to decrease with age.

In patients with renal impairment, discontinuation rates were higher and the difference between treatment groups was wider (placebo 23.0%, nintedanib 32.9%) than in patients with normal renal function (12.9% placebo vs. 15.4% nintedanib). Patients with impaired renal function and receiving nintedanib had a shorter mean treatment duration (9.7 months) than those receiving placebo (10.6 months) or patients with normal renal function (11.2 nintedanib vs. 10.9 months placebo). Dose reduction occurred in 22.5 % of subjects with normal renal function and 32.9% of the patients with renal impairment receiving nintedanib

AEs leading to discontinuation were more frequent in patients with renal impairment, and the discrepancy between treatment arms was more pronounced (16.8% placebo vs. 27.2% nintedanib) than in patients with normal kidney function (7.9% placebo vs. 10.8% nintedanib). SAEs were more frequent in patients with renal impairment than in those with normal renal function but were balanced between treatment groups in each of the 2 subgroups. Decreased appetite and weight decreased were slightly more frequent in patients with renal impairment than in patients with normal renal function, and the difference between treatment groups was somewhat larger in patients with renal impairment (decreased appetite, renal impairment: 7.0% placebo vs. 13.9% nintedanib, normal renal function: 3.9% placebo vs. 7.2% nintedanib; weight decreased, renal impairment: 4.5% placebo vs. 11.8% nintedanib, normal renal function: 2.2% placebo vs. 7.5% nintedanib). Hypertension was slightly more frequent in patients with renal impairment and treated with nintedanib (5.1%) than in those receiving placebo (2.9%) or patients with normal renal function (2.8% nintedanib vs. 2.3% placebo). Hypertension is known to be associated with impaired renal function independent of age.

7.5.5 Drug-Drug Interactions

An important drug-drug interaction to explore is nintedanib and pirfenidone, an IPF treatment approved outside the US. If nintedanib is approved for marketing and pirfenidone is approved for marketing in the US, they will likely be used in conjunction, as no other therapies are currently approved to treat IPF.

The sponsor explored this interaction in Study 1199.31. Study 1199.31 was a multicenter (8 study sites in Japan) double-blind, randomized, placebo-controlled (within a dose group) study to evaluate the safety and pharmacokinetics of multiple rising doses of nintedanib (50 mg BID, 100 mg BID, and 150 mg BID) on top of standard medical care with stratification according to pirfenidone use in Japanese patients with IPF. The mean duration of treatment was 14 days for

nintedanib 50 and 100 mg BID and 27 days for nintedanib 150 mg BID. A total of 21 patients were treated with pirfenidone and nintedanib at various doses, as described in Table 42.

Table 42. Treatment groups: Study 1199.31 (Randomized and Treated population)			
	Nintedanib 50 mg BID N=9	Nintedanib 100 mg BID N=9	Nintedanib 150 mg BID N=32
	n		
Placebo	2	1	4
Pirfenidone 1800 mg/day	1	0	4 ¹
Nintedanib	2	4	11
Pirfenidone 1800 mg/day + Nintedanib	4	4	13 ²
Mean exposure (days)	14	14	27

¹ 1 patient treated with 1200 or 600 mg/day of pirfenidone
² 4 patients treated with 1200 or 600 mg/day of pirfenidone
 Source: Module 5.3.5.1, Study 1199.31 CSR, Figures 10.1:1 p 88, 10.1:2, p 89, 10.1:3, p 91

The results for the gastrointestinal AEs as well as the liver enzyme AEs are listed in Table 43.

Table 43. Gastrointestinal and Investigations AEs for the nintedanib150 mg BID treatment group more common than placebo: Study 1199.31 (Randomized and treated population)				
	Placebo N=7¹	Pirfenidone N=5²	Nintedanib N=11	Pirfenidone + Nintedanib N=13
	N (%)			
Gastrointestinal disorders	1 (14.3)	1 (20.0)	4 (36.4)	7 (53.9)
Nausea	0	0	1 (9.1)	4 (30.8)
Vomiting	0	0	0	5 (38.5)
Diarrhea	0	0	2 (18.2)	2 (15.4)
Gastritis erosive	1 (14.3)	0	0	0
Abdominal discomfort	0	1 (20.0)	1 (9.1)	0
Abdominal pain upper	0	1 (20.0)	0	0
Periproctitis	0	1 (20.0)	0	0
Stomatitis	0	0	1 (7.7)	0
Investigations		0	2 (18.2)	1 (7.7)
Transaminases increased	0	0	0	1 (7.7)
ALT increased	0	0	2 (18.2)	0
AST increased	0	0	2 (18.2)	0
CPK increased	0	0	1 (9.1)	0
GGT increased	0	0	1 (9.1)	0

CPK = blood creatine phosphokinase, GGT = gamma-glutamyltransferase
¹ All placebo patients (Table 42: 2 + 1 + 4)
² All pirfenidone only patients (Table 42: 1 + 0 + 5)
 Source: Module 5.3.5.1, Study 1199.31 CSR, Table 12.2.2:1, p 145; Table 15.3.2:4, p 252; Table 15.3.2:4, p 255

Overall, patients with pirfenidone experienced nausea and vomiting more frequently than those without pirfenidone, whereas frequency and intensity of AEs in liver transaminases increases did not show any particular difference between with and without pirfenidone background. Analysis in the changes in clinical laboratory parameters also supports this finding. However, it should be noted that it is difficult to draw conclusions from the small number of patients.

Patients enrolled in Study 1199.31 who were on pirfenidone had the option of enrolling in an open-label roll over study (1199.40). A total of 20 patients from Study 1199.31 enrolled into Study 1199.40. As of the data cut off (Oct 17, 2013), 12 patients are being treated (6 patients withdrew for AEs and 2 for non-compliance). The mean exposure of nintedanib 150 mg BID was 11 months. Overall the safety profile for the 20 patients enrolled in the study was similar to the parent trial. No conclusions could be made regarding the effects of co-administration of pirfenidone and nintedanib as there was no comparator group.

The clinical pharmacology reviewed drug-drug interactions, as below.

Effect of coadministered drugs on nintedanib exposure

- Nintedanib is a substrate of P-gp. A minor extent of the biotransformation of nintedanib consisted of CYP pathways.
- Coadministration with the P-gp and CYP3A4 inhibitor ketoconazole increased exposure of nintedanib by 1.61-fold based on AUC and 1.83-fold based on C_{max}. Monitor patients closely for tolerability of nintedanib, and manage the adverse reactions by dose interruption, dose reduction, or discontinuation as necessary.
- Coadministration with the P-gp and CYP3A4 inducer rifampicin, decreased exposure of nintedanib to 50.3% based on AUC and to 60.3% based on C_{max}.
- Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH<3. However, based on population pharmacokinetic analysis, coadministration with proton pump inhibitors or histamine H₂ antagonists did not influence the exposure of nintedanib.
- Coadministration with pirfenidone, decreased exposure of nintedanib to 68.3% based on AUC and to 59.2% based on C_{max}. No dose adjustment recommended for nintedanib when coadministered with pirfenidone.

Effect of nintedanib on exposure of coadministered drugs

- Concomitant use with nintedanib had no effect on the exposure of pirfenidone, another drug for IPF.

Effect of nintedanib on pharmacodynamics interaction

- Nintedanib is a VEGFR inhibitor, and may increase the risk of bleeding. Nintedanib may increase the effect of anticoagulation treatment. Patients receiving a full dose of anticoagulant were excluded in the phase 3 trials. Monitor patients closely for bleeding potential and adjust anticoagulation treatment as necessary.

Further details regarding drug-drug interactions can be found in the clinical pharmacology review.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

See Section 7.3.4 Significant Adverse Events for a discussion of malignancies in the pivotal trials.

7.6.2 Human Reproduction and Pregnancy Data

Nintedanib is a potent teratogen and reproductive toxicant. It is embryocidal and teratogenic when pregnant animals are exposed to the drug. Nintedanib causes implantation loss, resorptions, and malformations at maternally non-toxic doses in rats and rabbits. It also causes sex ratio changes in rabbits and decreases female fertility in rats, as detailed below.

In animal reproduction toxicity studies, nintedanib caused embryofetal deaths and teratogenic effects in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Fetal malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, misshaped, or asymmetrically ossified), ribs (bifid or fused), and sternbrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ration was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on an AUC basis at a maternal oral dose of 60 mg/kg/day). The effects seen for nintedanib are similar to other tyrosine kinase inhibitors.

The recommended pregnancy category based on the review from the pharmacology-toxicology team is D to be consistent with the other tyrosine kinase inhibitors for life-threatening serious conditions (oncology products).

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

In Study 1199.34 one patient was inadvertently exposed to a dose of 600 mg daily for a total of 21 days. A non-serious adverse event (nasopharyngitis) occurred and resolved during the period of incorrect dosing, with no onset of other reported events. Overdose was also reported in two patients in oncology studies who were exposed to a maximum of 600 mg twice daily for up to 8 days. Adverse events reported were consistent with the existing safety profile of nintedanib. Both patients recovered.

7.7 Additional Submissions / Safety Issues

7.7.1 120-day Safety Update

The 4-month Safety Update included safety data from patients receiving long-term nintedanib treatment in ongoing open-label extension trials (Studies 1199.33, 1199.35 and 1199.40), with data assessed from all patients treated in these studies up to April 15, 2014 (date of database lock for 120-day safety update). This analysis included additional data from 55 patients who started treatment in trial 1199.33 after the original database lock (DBL) for the Summary of Clinical Safety (SCS).

The mean nintedanib treatment duration for trial 1199.33 increased from 6.4 months at the time of the SCS to 11.6 months for this analysis; the treatment duration increased from 21.9 months to 25.7 months for trial 1199.35 and from 18.0 months to 21.3 months for trial 1199.40. At the time of data snapshot for this 4-month Safety Update, 574 patients from trial 1199.33, 74 patients from trial 1199.35, and 9 patients from trial 1199.40 were still receiving study medication in their respective studies.

Overall, the type and frequencies of events reported in this 4-month Safety Update were consistent with those reported at the time of the original data base lock for the SCS, similar to the 52-week parent trials, and therefore confirmed a similar safety profile for long-term nintedanib dosing.

7.7.2 Long-term safety

The long-term safety evaluation of nintedanib relies on 3 open-label safety extension studies of Studies 1199.30, 1199.32, and 1199.34. The following open-label safety studies are detailed in this section:

- Study 1199.30 period 2 (blinded (to treatment dose) extension of Study 1199.30 period 1)
- Study 1199.35 (open-label extension of Study 1199.30 (period 2))
- Study 1199.33 (open-label extension of Studies 1199.32 and 1199.34)

The long-term safety database consists of 286 patients who were treated in Study 1199.30 period 2 and 227 of those patients who completed period 2 and were enrolled into Study 1199.35. In addition, 679 patients were enrolled in Study 1199.33 from the phase 3 studies (1199.32 and 1199.34). The mean treatment duration was the longest for Study 1199.35 at 22 months. Studies 1199.30 period 2 and 1199.33 had similar mean treatment durations (~6-7 months). Studies 1199.35 and 1199.33 are on-going. The 4-month safety update, detailed above, reported a similar safety profile with an additional 6 months of data, for all 3 studies (see Section 7.7.1 120-day Safety Update). Dose reductions were allowed, similar to the parent trials.

The most frequent causes for all safety analyses (deaths, SAEs, AEs leading to study discontinuation, and AEs leading to permanent dose reduction) by SOC were respiratory,

thoracic, and mediastinal disorders (driven by IPF), infections and infestations, neoplasms benign, malignant and unspecified, and cardiac disorders. This was similar to the parent trials.

The frequencies of deaths, SAEs, AEs leading to discontinuation, and AEs leading to permanent dose reduction in Studies 1199.30 period 2 and 1199.33 were similar to the parent trials (parent trials: 5% deaths, 30% SAEs, 21% AEs leading to discontinuation, and 16% AEs leading to permanent dose reduction) likely due to the 6-7 month mean treatment duration, as opposed to 22 months for Study 1199.35. Study 1199.33 also had the most subjects enrolled (almost 3 times more than either Study 1199.35 or Study 1199.30 period 2).

AESI's were not evaluated in the long-term extension studies.

Common adverse reactions were similar to the parent trials for all 3 long-term extension studies. The most common adverse reactions centered by SOC were gastrointestinal disorders, infections and infestations, respiratory, thoracic and mediastinal disorders, and investigations. Diarrhea was the most common adverse event in all 3 studies (Study 1199.30 period 2: 30%, Study 1199.33: 43%, Study 1199.35: 49%). Diarrhea was followed closely by nausea, abdominal pain, and vomiting in terms of frequency. In the parent trials, diarrhea occurred in 62% of nintedanib treated subjects.

There were no cases of Hy's law. Liver enzyme elevations showed a similar pattern in all 3 long-term extension studies as their parent trials, in that the maximum ALT and AST for the majority of patients was < 5x ULN. Liver enzyme elevations lead to early study discontinuation in one study (Study 1199.35; n=3 (1.5%)) compared to 2.1% for the parent trials. Liver enzyme elevations were also an uncommon cause for permanent dose reduction (Study 1199.30 period 2: 0.3%, Study 1199.33: 0.4%, Study 1199.35: 2%) as it was for the parent trials (1%).

Overall, there were no new safety signals in the long-term extension studies.

Methods

The protocols and subject disposition will be discussed separately for each study. Safety results will be discussed together for all 3 studies. Efficacy results for these extension studies are detailed in Section 6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects.

Safety assessments in these 3 studies included adverse events (AEs), physical examinations, vital signs, ECGs, and clinical laboratory testing.

Study 1199.30 Period 2

This section contains a brief discussion of the protocol as it pertains to period 2. The protocol was generally the same as period 1 (see Section 5.3.2 Study 1199.30).

Administrative Information

- **Study title:** Optional active treatment extension to Study 1199.30 until last patient out
- **Study dates:** September 14, 2007 to June 10, 2010 (Study 1199.30 period 1 + period 2)
- **Study sites:** 92 centers in 25 countries
- **Study report date:** February 25, 2011

Objectives/Rationale

Primary Objectives

- To assess the safety of oral nintedanib treatment in patients with IPF who had already completed the 1 year treatment period (1) of Study 1199.30.

Study Design and Conduct

Overview

Subjects who completed the placebo-controlled, double-blind, 1-year period (period 1) of Study 1199.30 had the option to enroll into an active-treatment extension study, blinded to dose treatment, until the last subject enrolled in Study 1199.30 completed the 52-week treatment period. Subjects randomized to placebo during period 1 were rolled over to nintedanib 50 mg daily (the lowest active-treatment dose used in period 1).

The schedule of assessments is summarized in Table 44.

Table 44. Schedule of Assessments: Study 1199.30 Period 2

	Optional treatment ³									Fup
Visit	10	11	12	12a	13	13a	X ⁴	Xa	EOT ⁵	Fup ⁶
Days										
Weeks of treatment from V9	V9+2	+4	+12	+18	+24	+30	+nx24	X+6		EOT+2
Time window allowed (days)	±3	±3	±3	±7	±7	±7	±14	±14		±3
Physical examination, vital signs	X	X	X		X		X		X	X
AE, concomitant medication, exacerbations	X	X	X		X		X		X	X
Laboratory tests	X	X	X	X*	X	X*	X	X*	X	
Urinary pregnancy test	X	X	X		X		X		X	
Resting 12-lead ECG	X	X	X		X		X		X	
FVC, FEV ₁ (spirometry)	X	X	X		X		X		X	
SpO ₂ (resting)	X	X	X		X		X		X	X
DL _{CO}					X		X		X	
Blood sampling for PK ²									X	
Study drug dispensation		X	X		X		X			
Compliance check	X	X	X		X		X		X	
Dispensation of laboratory kit if needed			X		X		X			

Visit 12a, 13a and Xa: only lab test for transaminases.

³ After visit 9, continuation of blinded active treatment was permitted with visits occurring at 2, 4, 12 and 24 weeks after visit 9 and then every 6 months.

⁴ A visit should have occurred at least every 6 months (until every evaluable entered patient had or would have had completed visit 9), and lab test for transaminases every 6 weeks.

⁵ The End Of Treatment (EOT) visit had to be completed by patients when they discontinued trial treatment. Then, the follow-up visit should have been performed (see #⁶), except if they entered the roll over trial.

⁶ Any patient who had discontinued treatment should have come to a follow-up visit 2 weeks after discontinuation.

Source: Module 5.3.5.1, Study 1199.30 CSR, Flow Chart, p 85

Population

The inclusion and exclusion criteria were unchanged from the parent trial.

Safety Endpoints

The safety analysis was based on the reported AEs, vital signs, physical exam, and review of laboratory data. The safety assessor was the Principal Investigator.

Subject Disposition

Subject disposition for Study 1199.30, period 2 is summarized in Table 45.

Table 45. Subject Disposition: Study 1199.30 Period 2					
	Placebo n (%)	Nintedanib 50 mg daily n (%)	Nintedanib 50 mg BID n (%)	Nintedanib 100 mg BID n (%)	Nintedanib 150 mg BID n (%)
Study 1199.30 Period 1					
Randomized	87 (100)	87 (100)	86 (100)	86 (100)	86 (100)
Treated	85 (98)	86 (99)	86 (100)	86 (100)	85 (99)
Completed	61 (70)	62 (71)	68 (79)	72 (84)	53 (62)
Study 1199.30 Period 2¹	Nintedanib 50 mg daily²				
Treated	111 (100)		64 (100)	63 (100)	48 (100)
Discontinued	12 (11)		7 (11)	7 (11)	8 (17)
AE	6 (11)		5 (9)	4 (6)	6 (10)
Patient withdrew	0		0	2 (3)	1 (2)
Other	1 (2)		0	1 (2)	0
Ongoing patients	89 (80)		51 (80)	49 (78)	38 (79)

¹% calculated from period 2 treated population
² Placebo patients were treated with the nintedanib 50 mg daily in period 2
 Source: Module 5.3.1, Study 1199.30 CSR, Table 15.2.1.1.2.2-5, p 578, Table 10.1:1, p 115

Study 1199.35

Administrative Information

- **Study title:** A phase 2 open-label, roll-over study of the long-term tolerability, safety and efficacy of oral nintedanib in patients with IPF.
- **Study dates:** August 5, 2010 to July 2, 2013 (date of interim data-lock)
- **Study sites:** 59 centers in 21 countries
- **Study report date:** March 21, 2014

Objectives/Rationale

Objectives

The primary objective of the trial was to establish the long-term tolerability and safety profile of nintedanib in patients with idiopathic pulmonary fibrosis (IPF) who had completed parent trial 1199.30. As a secondary objective, the effects of long-term treatment with nintedanib on selected efficacy parameters were to be investigated.

Study Design and Conduct

Overview

This was a prospective, open-label, roll-over clinical trial that offered nintedanib treatment to patients with IPF who had completed a prior clinical trial (trial 1199.30) with the same study drug. At the end of the 52-week treatment period (period 1) of parent trial 1199.30, patients who

were still on study treatment (placebo or nintedanib at doses of 50 mg once daily, 50 mg twice daily, 100 mg bid, or 150 mg bid) could enter an optional, active-blinded treatment period (period 2). At the start of period 2, patients randomized to placebo were switched in a blinded manner to nintedanib 50 mg daily; other patients continued to receive the dose used at the end of period 1 (either the randomized dose or a reduced dose). After the trial 1199.30 database was locked, patients could continue receiving open-label nintedanib in roll-over trial 1199.35. At the start of trial 1199.35, the study protocol specified that patients were to receive the same nintedanib dose as administered at the end of period 2 of trial 1199.30. During the trial, protocol amendment 1 was implemented (Sep 2010) and specified that patients were to be given the option to continue with their current nintedanib dose or receive nintedanib 150 mg bid.

The schedules of assessments are shown in Table 46.

Table 46. Schedule of Assessments: Study 1199.35

Visit	0	1 ¹	LT1	2	LT2	3	LT3	4	x ²	EOT	Fup
Week	≤Visit 1 ³	0	8	17	25	34	42	52			EOT+4
Time window (weeks)			±2	±2	±2	±2	±2	±2			+ 1 week
Informed consent	X										
Demographics		X									
In-/exclusion criteria		X									
Physical examination		X		X		X		X		X	X
Vital signs and weight		X		X		X		X		X	
Urine pregnancy test ⁴		X		X		X		X		X	
Liver function tests only			X ⁵		X ⁵		X ⁵				
Complete laboratory tests		X		X		X		X		X ⁶	
Medication compliance				X		X		X		X	
FVC		X		X		X		X		X	
DL _{co}		X		X		X		X		X	
First nintedanib intake		X									
Dispense nintedanib		X		X		X		X			
Drug accountability				X		X		X		X	
AEs and exacerbations		X		X		X		X		X	X
Concomitant medications		X		X		X		X		X	X
Termination of nintedanib										X	
End of patient participation in the trial											X

Fup=follow up, LT=laboratory tests

¹ Visit 1 was to be conducted on the same day as the last treatment visit of parent trial 1199.30. Baseline assessments (apart from concomitant medications and concomitant diseases) were obtained from the last visit of parent trial 1199.30 or from Visit 1 of trial 1199.35 if new values were recorded at this time.

² The same procedures were to be repeated as often as needed, comprising: 1 visit every 4 months including full laboratory assessment; 1 intermediate liver function test between visits.

³ Consent was to be obtained before or at Visit 1.

⁴ For all women of childbearing potential.

⁵ Transaminases (AST, ALT, GGT), AP and bilirubin.

⁶ Laboratory tests to be performed if previous tests were assessed more than 2 months earlier.

Source: Module 5.3.5.2, Study 1199.35 CSR, Table 9.5.8:1, p 53

Population

Key Inclusion Criteria (different from parent trials)

1. Treated in parent trial 1199.30 period 1 and period 2 and did not discontinue the parent trial.

Key Exclusion Criteria (different from parent trials)

1. Unlike the parent trials, specific lab and concomitant conditions and risks (e.g. myocardial infarction, bleeding and thrombotic risks) were not included in the exclusion criteria, although were considered before a patient was included in the trial.

Safety Endpoints

The safety analysis was based on the reported AEs, vital signs, physical exam, and review of laboratory data. The safety assessor was the Principal Investigator.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Efficacy Endpoints

Descriptive statistics of FVC and % predicted FVC values and absolute and relative change from baseline

Statistical Plan

All parameters were analyzed descriptively, with Kaplan-Meier estimates presented for time-to-event analysis.

Protocol Amendments

Protocol Amendment 1 (Sept 2, 2010)

- The option to be treated with 150 mg BID even if subjects were treated with lower doses in the parent trial
- The option to dose reduce from 150 mg BID to 100 mg BID (prior to this amendment subjects were withdrawn for intolerable AEs) with appropriate parameters.

Protocol Amendment 2 (Nov 29, 2012)

- Specified more detailed AE management

Subject Disposition

Subject disposition for Study 1199.35 is summarized in Table 45.

Table 47. Subject Disposition: Study 1199.35					
	Placebo n (%)	Nintedanib 50 mg daily n (%)	Nintedanib 50 mg BID n (%)	Nintedanib 100 mg BID n (%)	Nintedanib 150 mg BID n (%)
Study 1199.30 Period 1					
Randomized	87 (100)	87 (100)	86 (100)	86 (100)	86 (100)
Treated	85 (98)	86 (99)	86 (100)	86 (100)	85 (99)
Completed	61 (70)	62 (71)	68 (79)	72 (84)	53 (62)
Study 1199.30 Period 2¹	Nintedanib 50 mg daily²				
Treated	111 (100)		64 (100)	63 (100)	48 (100)
Discontinued	12 (11)		7 (11)	7 (11)	8 (17)
Completed	89 (80)		51 (80)	49 (78)	38 (79)
Study 1199.35³					
Treated	64 (100)		51 (100)	45 (100)	38 (100)
Discontinued	37 (58)		25 (49)	21 (47)	22 (58)
AE	31 (48)		19 (37)	17 (38)	16 (42)
Non-compliant	0		0	0	1 (3)
Lost to follow-up	3 (5)		1 (2)	0	0
Patient withdrew	3 (5)		3 (6)	2 (4)	3 (8)
Other	0		2 (4)	2 (4)	2 (5)
Discontinued but completed planned observation time	10 (16)		11 (22)	11 (24)	6 (16)
Completed on study medication	27 (42)		26 (51)	24 (53)	16 (42)
Completed with or without study medication	37 (58)		37 (73)	35 (78)	22 (58)
¹ % calculated from period 2 treated population ² Placebo patients were treated with the nintedanib 50 mg daily in period 2 and Study 1199.35 ³ % calculated from Study 1199.35 treated population Source: Module 5.3.1, Study 1199.30 CSR, Table 15.2.1.1.2.2:5, p 578, Study 1199.35 CSR, Table 10.1:1, p 69, Table 10.1:2, p 70, Table 15.1.1:1, p 129					

Study 1199.33

Administrative Information

- **Study title:** An open-label extension trial of the long-term safety of oral nintedanib in patients with IPF
- **Study dates:** July 2, 2012 to September 17, 2013 (date of interim data-lock)
- **Study sites:** 166 centers in 23 countries

- **Study report date:** April 3, 2014

Objectives/Rationale

Primary Objectives

- To access the long-term safety of oral nintedanib treatment in patients with IPF who had completed 1 year of treatment and the follow-up period of phase 3 parent trials 1199.32 and 1199.34

Study Design and Conduct

Overview

Study 1199.33 was an open-label extension (OLE) trial for patients with IPF that had completed 52 weeks of treatment and the 4 week follow-up period of parent trials 1199.32 and 1199.34. Subjects were treated with nintedanib 150 mg BID, with the option of starting on the lower 100 mg BID dose if they were dose reduced during the parent trials. The treatment allocation during the parent trials remained blinded at the time of enrollment into this OLE study. The protocol was similar as the parent trials in terms of dose reductions.

The schedules of assessments are shown in Table 48.

Table 48. Schedule of Assessments: Study 1199.33

Visit	1 ^{1,2}	2 ^{1,2}	3	4	5	6	6a	7	7a	8	8a	9	Xa ³	X ³	EOT ⁴	FU ⁵
Week	-6 to 0	0	2	4	6	12	18	24	30	36	42	48	56+ every 16 weeks	64+ every 16 weeks		
Day	-42 to 1	1	15	29	43	85	127	169	211	253	295	337				
Time window (days)			±3	±3	±3	±3	±7	±7	±7	±7	±7	±7	±14	±14		+ 7
Informed consent	X ⁶															
Demographics	X															
Baseline conditions	X															
Physical examination (including weight)	X ⁷	X	X	X	X	X		X		X		X		X	X	X
Vital signs	X ⁷	X	X	X	X	X		X		X		X		X	X	X
12-lead ECG		X						X				X				
Laboratory tests	X ⁷	X	X	X	X	X	X ⁸	X	X ⁸	X	X ⁸	X	X ⁸	X	X	
Pregnancy test ⁹		X	X	X	X	X		X		X		X		X	X	X
Pulmonary function tests (FVC)		X	X	X	X	X		X		X		X		X	X	X
In-/exclusion criteria		X														
TVRS/TWRS		X		X		X		X		X		X		X	X	
Dispense nintedanib ¹⁰		X		X		X		X		X		X		X		
First nintedanib intake		X														
Collect trial drug				X		X		X		X		X		X	X	
Drug accountability				X		X		X		X		X		X	X	
AEs and concomitant medications	X ¹¹	X ¹¹	X	X	X	X		X		X		X		X	X	X
Exacerbations	X	X	X	X	X	X		X		X		X		X	X	X
Termination of nintedanib															X	
End of patient participation in the trial																X

Visit 1 and Visit 2 could occur on the same date if the period between Visit 9 (end of treatment) of the parent trial (1199.32 or 1199.34) and the first visit for trial 1199.33 was ≤6 weeks. This rule did not apply to patients requiring bronchodilator washout, as they needed to sign informed consent at Visit 1 in order to perform washout for pulmonary function tests at Visit 2.

² Visit 1 was to occur at least 1 day after the follow-up visit of the parent trial and Visit 2 was to occur within 12 weeks of Visit 9 (end of treatment) of the parent trial (1199.32 or 1199.34).

³ The same scheme was to be repeated as often as needed; with 1 complete visit every 16 weeks and 1 intermediate visit for liver function monitoring.

⁴ The EOT visit was to be performed if a reason for withdrawal was met.

⁵ A follow-up (FU) visit was planned for 28 days after the last drug intake (+7 days).

⁶ The patient was required to sign informed consent prior to any study-related activities.

Source: Module 5.3.5.2, Study 1199.33 CSR, Table 9.5.8:1, p 46

Population

Key Inclusion Criteria (different from parent trials)

1. Treated in parent trial 1199.32 or 1199.34 and completed the 52-week treatment period and performed the 4 week follow-up visit.

Key Exclusion Criteria (different from parent trials)

1. AST and ALT >1.5x ULN. Patients could be included if they had transaminase values of >1.5x ULN but <3x ULN if these were also recorded on completing the parent trial.
2. A time period of >12 weeks between 52 week visit (Visit 9) of the parent trial and first dosing visit (Visit 2) of study 1199.33.

Safety Endpoints

The safety analysis was based on the reported AEs, vital signs, physical exam, and review of laboratory data. The safety assessor was the Principal Investigator.

Ethics

An institutional review board (IRB) reviewed and approved these studies. The study was performed in accordance with the Declaration of Helsinki and ICH GCP.

Subject disposition

Subject disposition for Study 1199.33 is displayed in Table 49.

Total from parent trials	1061
Study 1199.32	513
Study 1199.34	548
Study 1199.33	N (%)
Treated	679 (100)
Discontinued	77 (11)
AE	54 (8)
Non-compliant	1 (0.1)
Patient withdrew	10 (2)
Other	12 (2)
Discontinued but completed planned observation time	32 (5)
Ongoing on study medication	602 (89)
Ongoing with or without study medication	643 (95)

¹% calculated from period 2 treated population
² Placebo patients were treated with the nintedanib 50 mg daily in period 2
 Source: Module 5.3.1, Study 1199.33 CSR, Table 15.2.1.1.2.2-5, p 578, Table 10.1.1, p 59, Table 15.1.1.1, p 120

Safety

Exposure

Exposure for the all 3 open-label safety studies is summarized in Table 50.

Table 50. Overall duration of exposure to nintedanib for the long-term safety studies: Studies 1199.30 Period 2, 1199.35, and 1199.33 (Treated population)			
	Study 1199.30 Period 2¹	Study 1199.35¹	Study 1199.33
N	286	198	679
Duration of exposure (months)			
mean (SD)	7 (5)	22 (12)	6 (3)
Duration of exposure categories, n (%)			
≤ 3 months	65 (23)	11 (6)	105 (16)
> 3 - ≤ 6 months	78 (27)	15 (8)	223 (33)
> 6 - ≤ 12 months	27 (56)	28 (14)	322 (47)
> 12 - ≤ 18 months	-	25 (13)	29 (4) ²
> 18 - ≤ 24 months	-	13 (7)	-
> 24 months	-	106 (54)	-
Total dose (g), mean (SD) ¹	20 (19)	149 (100)	55 (28)
Duration 150 mg BID actually taken (months)	-	16 (12) ³	6 (3)
Duration 100 mg BID actually taken (months)	-	13 (11) ⁴	4 (3)
Duration off treatment (weeks)	-	0.8 (0.5)	0.7 (0.6)
Premature treatment discontinuation	-	105 (53)	77 (11)
Time to discontinuation, n (%)			
≤ 1 month	-	4 (2)	20 (3)
> 1 - ≤ 2 months	-	4 (2)	8 (1)
> 2 - ≤ 3 months	-	3 (2)	9 (1)
> 3 - ≤ 6 months	-	15 (8)	27 (4)
> 6 - ≤ 12 months	-	28 (14)	13 (2) ⁵
> 12 months	-	51 (26)	

¹ Data given for all nintedanib treatment groups (50 mg daily, 50 mg BID, 100 mg BID, and 150 mg BID)
² Data presented in sponsor's table as N= 13 (2%) for 12-13 months and N=16 (2%) for > 13 months
³ N=146 for 150 mg BID treatment group
⁴ N=80 for 100 mg BID treatment group
⁵ > 6 months
 -- " = data not provided
 Source: Module 5.3.1, Study 1199.30 CSR, Table 12.1.2:1, p 211, Table 15.3.6.1.2:1, p 1624-26, Table 15.1.7.1:1, p 519; Module 2.7.4 SCS appendix, Table 2.4.1, p 1184-6; Module 5.3.1, Study 1199-35 CSR, Table 15.3.1.1:1, p 227; Table 15.3.1.1:5, p 234

There were no apparent differences in duration of exposure and time off treatment between patients randomized to placebo or to nintedanib in the parent trials. Dose reductions were more frequent in patients who received placebo in the parent trials (20%) compared to nintedanib (10%). Treatment interruptions were also more frequent in patients randomized to placebo in the parent trial (18%) compared to nintedanib (11%); however, the mean duration of treatment interruptions was comparable (23 days, placebo vs. 22 days, nintedanib). More patients randomized to placebo (14%) than patients randomized to nintedanib (9%) in the parent trials permanently discontinued study treatment. The majority of patients in Study 1199.33 were treated for 3-12 months and received the full treatment dose (150 mg BID) for the entirety of the study. A total of 11% of subjects discontinued treatment (mostly due to an AE), with the majority being after 6 months.

Reviewer comment: The long-term safety studies provide safety data past the treatment time for the 1-year parent trials, as much as 22 months for Study 1199.35. Emphasis will be placed on Study 1199.33 given the larger number of patients. This study adds 6 months of treatment time.

Demographics were similar to the parent trials and will not be further detailed in this review.

There were no unexpected differences in baseline disease characterizations, baseline conditions, or concomitant therapies compare to the parent trials.

Lung Transplants

In Study 1199.33, 3 patients received lung transplants, and in Study 1199.35, 4 patients received lung transplants. Study treatment was discontinued upon transplant. No details were reported that indicated bleeding or impaired wound healing as complications of the lung transplantation.

Deaths

Study 1199.30 Period 2

Adverse events leading to death were reported in 7% (n=19) of patients. This was similar to period 1 which also had an incidence of 7% of subjects with AEs leading to death. The only fatal AE by SOC that was reported in more than 2 patients in any group were respiratory, thoracic and mediastinal disorders (5% overall). The most frequent preferred term was IPF (3%).

Study 1199.35

In trial 1199.35, the overall incidence of AEs leading to death was 21%. Adverse events reported in more than 2 patients overall were respiratory, thoracic and mediastinal disorders (n=29, 15%), followed by cardiac disorders (n=7, 4%) and infections and infestations (n=7, 4%) and general disorders and administration site conditions (n=3, 2%). The only preferred term reported in more than 2 patients was IPF (n=24, 12%).

Study 1199.33

In study 1199.33, incidence of AE leading to death was 4% (n=25). Of these, 3% (n=21) experienced respiratory, thoracic and mediastinal disorders with fatal outcome. The most frequent preferred terms were IPF (2%) and respiratory failure (0.6%). Other AEs leading to death that were reported in more than 2 patients were infections and infestations (0.6%) and cardiac disorders (0.4%). Patients who had been receiving placebo in the parent trials had a higher incidence of AEs leading to death (5%) compared with patients receiving nintedanib (3%).

SAEs

Study 1199.30 Period 2

The incidence of SAEs in study 1199.30 period 2 was 27%. The incidence of SAEs was higher in patients receiving nintedanib 150 mg BID in study 1199.30 period 1 (25%) than in those receiving placebo (19%). Incidences were between 22% and 42% in the other nintedanib dose groups of 50 mg QD to 100 mg BID. The most frequent SAE by SOC was respiratory, thoracic and mediastinal disorders (13%) driven by IPF (9%), infections and infestations (9%), neoplasms benign, malignant and unspecified (4%), and cardiac disorders (3%).

Study 1199.35

The frequency of patients with SAE in study 1199.35 was 54% overall. The most frequent SAEs by SOC were respiratory, thoracic and mediastinal disorders (29%); IPF (21%) was the most frequent preferred term in this SOC. Infections and infestations were the next most frequent SOC (15%), followed by cardiac disorders (10%).

Study 1199.33

In study 1199.33, 18% of patients experienced at least one SAE. The most frequent SAE by SOC were respiratory, thoracic and mediastinal disorders (8%) with IPF (3%) as most frequent preferred term. Infections and infestations were the second-most frequent SOC (5%), with pneumonia as most frequent preferred term (2%).

AEs leading to discontinuation

Study 1199.30 Period 2

Overall, 18% of patients experienced AEs that lead to treatment discontinuation in study 1199.30 period 2. The most frequent were respiratory, thoracic and mediastinal disorders, with IPF as the most frequent preferred term. This was similar to the frequency of 21% seen for the pooled parent trials.

Study 1199.35

In study 1199.35, 30% of patients experienced an AE leading to treatment discontinuation until the database lock for the interim analysis. The most frequent AEs leading to discontinuation by SOC were respiratory, thoracic and mediastinal disorders (12.6%), with IPF (11%) as the most frequent preferred term.

Study 1199.33

Until the time of the database lock for the interim analysis, 7% of patients experienced an AE leading to treatment discontinuation. The most frequent AE by SOC were respiratory, thoracic and mediastinal disorders (3%), with IPF (2%) as the most frequent preferred term. Respiratory, thoracic and mediastinal disorders were reported with a slightly higher frequency in patients who had received placebo in the parent trials (4%) than in those receiving nintedanib (2.8%). The difference was driven by respiratory failure (placebo 0.7%, nintedanib 0%). Also more frequent in the placebo group were gastrointestinal disorders (4% vs. 2%), driven by the preferred terms diarrhea (3% vs. 2%), nausea (1% vs. 0%), and vomiting (0.7% vs. 0%)

AEs leading to dose reduction

Study 1199.30 Period 2

Adverse events leading to dose reduction in study 1199.30 period 2 were reported in 3% (n=9) of patients overall. Diarrhea was the most common adverse event leading to dose reduction (2%), followed by nasopharyngitis (0.7%).

Study 1199.33

Adverse events leading to dose reduction in study 1199.33 were reported in 8% (n=56) of patients overall. The most frequently reported AE leading to permanent dose reduction by SOC were gastrointestinal disorders (7% overall). Also, this was the only SOC reported in >1% of patients overall. The most frequent preferred term in the SOC was diarrhea (5.6%). Other preferred terms were all reported in less than 1% of patients overall.

Study 1199.35

Adverse events leading to permanent dose reduction were reported for 19% of all patients in study 1199.35. Gastrointestinal disorders (16%) were most frequently reported as AE leading to permanent dose reduction. Within this SOC, diarrhea (12%) was the most frequent preferred term, followed by nausea (3%), abdominal pain (2%), and vomiting (2%); all reported in more than 1% of patients overall. The only other SOC reported in more than 1% of patients were investigations (5%); the most frequent preferred term within this SOC and the only preferred term with an incidence of more than 1% was weight decreased (3%).

Common AEs

Study 1199.30 Period 2

The 3 most frequent AEs by SOC overall were infections and infestations (47%), followed by respiratory, thoracic and mediastinal disorders (34%) driven by IPF (13%), and gastrointestinal disorders (30%) driven by diarrhea (14%), vomiting (4%), nausea (4%), and abdominal pain (2%).

Study 1199.35

Almost all patients (98%) in study 1199.35 experienced at least one AE. The 3 most frequent AEs by SOC were infections and infestations (71%), gastrointestinal disorders (62%), and respiratory, thoracic and mediastinal disorders (55.1%). The 3 most frequently reported AEs by preferred term were diarrhea (49.0%), IPF (27.8%), and bronchitis (20.7%).

Study 1199.33

The most frequent AE (occurring in >5% of patients) by SOC were gastrointestinal disorders (55.4%), with diarrhea as the most frequent preferred term (43.2%), followed by nausea (12%). Other common AEs by SOC were infections and infestations, and respiratory, thoracic, and mediastinal disorders. The most common AEs after diarrhea and nausea were cough (8%), nasopharyngitis, (7%), and bronchitis (6%).

Liver Enzymes and Bilirubin Elevations

The liver enzyme and bilirubin values for all 3 extension studies are given in Table 51.

Table 51. Patients with liver enzyme or bilirubin values analyzed as multiples of the ULN (Studies 1199.30 Period 2, 1199.35, and 1199.33)

	Nintedanib all doses N (%)		
	Study 1199.30 period 2	Study 1199.33	Study 1199.35
Patients	286 (100.0)	679 (100.0)	198 (100.0)
Maximum ALT			
≥ 3 ULN	3 (1.0)	12 (1.8)	12 (6.1)
≥ 5 ULN	2 (0.7)	2 (0.3)	3 (1.5)
≥ 8 ULN	2 (0.7)	0 (0.0)	0 (0.0)
Maximum AST			
≥ 3 ULN	2 (0.7)	7 (1.0)	6 (3.0)
≥ 5 ULN	1 (0.3)	2 (0.3)	0 (0.0)
≥ 8 ULN	1 (0.3)	0 (0.0)	0 (0.0)
Maximum AST and/or ALT			
≥ 3 ULN	3 (1.0)	15 (2.2)	14 (7.1)
≥ 5 ULN	2 (0.7)	2 (0.3)	3 (1.5)
≥ 8 ULN	2 (0.7)	0 (0.0)	0 (0.0)
Maximum total bilirubin ≥ 2 ULN	0 (0.0)	6 (0.9)	0 (0.0)
ALT and/or AST ≥ 3 ULN, bilirubin ≥ 2 ULN¹	0 (0.0)	0 (0.0)	0 (0.0)

¹ The elevation of total bilirubin had to occur within 30 days of the elevation of AST and/or ALT.

Source: Module 2.7.4, Table 3.1.4:1, p 147

There were no cases of Hy's law. Liver test elevations showed a similar pattern in all 3 long-term extension studies as their parent trials, in that the maximum ALT and AST for the majority of patients was $< 5x$ ULN. Liver test elevations lead to early study discontinuation in one study (Study 1199.35; n=3 (2%)) compared to 2% for the parent trials. Liver enzyme elevations were also an uncommon cause for permanent dose reduction (Study 1199.30 period 2: 0.3%, Study 1199.33: 0.4%, Study 1199.35: 2%) as it was for the parent trials (1%).

7.7.3 Other indications

BI ran two other clinical development programs for nintedanib for malignancy indications: non-small cell lung cancer (NSCLC) and ovarian cancer.

NSCLC

The NSCLC clinical development program includes 35 completed and ongoing trials. In the phase 3 studies (1199.13 and 1199.14), patients were treated with combination therapy with docetaxel plus nintedanib or placebo in repeated treatment courses for as long as they tolerated therapy, did not undergo disease progression, did not meet other treatment withdrawal criteria, and neither patient or investigator requested discontinuation. Patients who had completed at least 4 courses of combination therapy, and who were not eligible for further combination therapy, were permitted to continue with further courses of monotherapy with nintedanib/placebo. The

specific dosing regimen is not given, but for the overall program subjects were divided into above or below 200mg BID.

The most frequent AEs were gastrointestinal events (diarrhea and nausea), and liver-related investigation. These AESIs were more frequent in the nintedanib arm than in the placebo arm. Furthermore, relevantly more frequent in the nintedanib arm were the following AESIs: vomiting, mucositis, dehydration, hypertension, neutropenia grade ≥ 3 , febrile neutropenia, sepsis, venous thromboembolism; the following AEs: abscess, stomatitis, decreased appetite; and the following laboratory abnormalities: increased AST, increased ALT, blood ALKP increased, hyperbilirubinemia, electrolyte imbalances, WBC decreased and neutrophil count decreased. Most of the AEs were manageable with dose reduction or symptomatic treatment.

Ovarian Cancer

Nintedanib for the treatment of ovarian cancer was investigated in a multi-center, randomized, double-blind phase 3 trial (1199.15) in combination with carboplatin and paclitaxel compared to placebo plus carboplatin and paclitaxel in patients with advanced ovarian cancer. Oral treatment with nintedanib/placebo was to continue uninterruptedly as monotherapy after completion of six 3-week courses of combination chemotherapy, for a maximum duration of 120 weeks (~6 months) after randomization.

Safety in the trial was dominated by AEs representing GI disorders (diarrhea, nausea, vomiting, abdominal pain, and constipation), known side effects of cytotoxic chemotherapy (alopecia, neutropenia, anemia, thrombocytopenia, and peripheral neuropathy), fatigue, and increases of liver transaminases. Diarrhea was the most frequent AE in the nintedanib arm.

Overall the safety profile seen in the clinical programs for the oncology indications were consistent with the IPF program in conjunction with the known safety profile of the chemotherapeutic agents.

8 Postmarketing Experience

Nintedanib has never been marketed.

9 Appendices

9.1 Literature Review/References

1. Ley B, Collard H. Epidemiology of Idiopathic Fibrosis. *Clinical Epidemiology*, 2013; 5:483-492.
2. American Thoracic Society Idiopathic Pulmonary Fibrosis: Diagnosis and Treatment. *Am J. Respir Crit Care Med* 2013; 188: 733-48.

9.2 Labeling Recommendations

Trade Name:

The proposed trade name for nintedanib, Ofev, has been reviewed by the Office of Medication Error Prevention and Risk Management, under the Office of Surveillance and Epidemiology and was determined to be acceptable.

Suggested Revisions to Proposed Labeling

While the labeling has not been finalized at the time this review is being completed, we have proposed the following general recommendations as summarized in Table 52.

Table 52. Labeling recommendations	
Label Section	General Recommendations
General	<ul style="list-style-type: none"> All study names were replaced with simply study numbers (e.g. Study 1199.32 or INPULSIS-1 replaced with study 2).
Section 2 Dosage and Administration	<ul style="list-style-type: none"> Liver function tests prior to initiating treatment were added to Section 2 as prescribers need to know this information prior to administration. Dosage modifications for liver enzyme elevations are currently under review.
Section 4 Contraindications	<ul style="list-style-type: none"> change in pregnancy category from (b) (4) to D
Section 5 Warnings and Precautions	<ul style="list-style-type: none"> Edited arterial thromboembolism, risk of bleeding, gastrointestinal perforation to reflect events reported within the clinical program.
Section 6	<ul style="list-style-type: none"> Updated to include Study 1199.30 in the pooled safety data Removed
Section 14	<ul style="list-style-type: none"> This section was substantially reorganized to be presented by efficacy variable. Study 1199.30 was included among the pivotal studies, rather than being regarded as supportive, as it was similar in design/duration to the phase 3 studies. The figure from Study 1199.32 was chosen to be representative of the primary efficacy analysis for each study.

	<ul style="list-style-type: none">• A cumulative responder analysis was conducted by the statistical reviewer and included in this section. Figure 2 (Figure 11 from review) was added to show a cumulative responder distribution of change from baseline in percent predicted forced vital capacity, rather than to focus on a specific cut-point. Descriptions of the results at a cut-off of 10% FVC decline are included in the text.• Described key secondary endpoints in text (b) (4)• Removed (b) (4)• Survival results were given as rates for all-cause mortality per study (see memo placed in DARRTS).
--	--

9.3 Advisory Committee Meeting

IPF is a devastating disease with no approved medical therapies, and internal review of the data was convincing. No specific efficacy and safety concerns were identified for this application; therefore, early on in the review it was decided that an Advisory Committee would not be required for this application.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIYA O PATERNITI
09/02/2014

BANU A KARIMI SHAH
09/03/2014

1. Marketing History

Nintedanib is not currently marketed.

2. Items Required for Filing

The following items pertinent to a clinical review are included in the submission.

- Application form (FDA 356h): 1.1.2
- Index : eCTD
- Summary 2.7 (clinical summary)
- Clinical study reports
 - Study reports 5.3.5.1
 - Reports of analyses of data from more than one study: 5.3.5.3
 - Integrated summary of efficacy 2.7.3
 - Integrated summary of safety 2.7.4
 - Good Clinical Practice: within the body of each CSR
 - Debarment certification: 1.3.3
 - Pediatric use: Not applicable because of orphan drug status exemption
- Labeling: 1.14
- Case report forms: 5.3.5.1
- Financial disclosure 1.3.4

3. Pediatric Development

The PREA is not applicable to Nintedanib given the orphan status designation.

4. Review Timeline

Submission/Rec'd date: May 2, 2014
Filing date: July 1, 2014
60-Day Letter: July 1, 2014

File/Plan meeting: June 3, 2014
MCR meeting: August 4, 2014
Labeling meeting: September 11, 2014
WU meeting: November 20, 2014

Primary review: August 5, 2014
Secondary review: August 9, 2014
Labeling t-con: August 18, 2014
PeRC: Not applicable because of orphan drug status exemption

CDTL memo: August 12, 2014
DD memo: August 19, 2014
Action pkg to OD: August 12, 2014
OD memo: September 2, 2014

Division Action Goal Date: September 2, 2014

PDUFA date: January 2, 2014

5. Filing Checklist

On initial overview of the NDA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.	x			eCTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (e.g., are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (i.e., Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			Clinical overview, section 6, p 64
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?	x			505 (b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (i.e., appropriately designed dose-ranging studies)? Study Number: <u>1199.30</u>	x			

	Content Parameter	Yes	No	NA	Comment
	<p>Study Title: Phase 2, dose-ranging, randomized, double-blind, placebo-controlled trial evaluating the effects of Nintedanib on FVC decline during one year, in patients with IPF.</p> <p>Sample Size: 428 (85/arm)</p> <p>Arms: 50mg daily, 50mg BID, 100mg BID, 150mg BID, Placebo</p>				
EFFICACY					
14	<p>Do there appear to be the requisite number of adequate and well-controlled studies in the application?</p> <p>Pivotal Study #1: 1199.32</p> <p>Pivotal Study #2: 1199.34</p> <p>Supportive Study #3: 1199.30</p> <p>Indication: Treatment of IPF [REDACTED] (b) (4)</p>	x			
15	<p>Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?</p>	x			
16	<p>Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.</p>	x			
17	<p>Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?</p>	x			
SAFETY					
18	<p>Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?</p>	x			
19	<p>Has the applicant submitted adequate information to assess the arrhythmogenic potential of the</p>	x			Study 1199.26

	Content Parameter	Yes	No	NA	Comment
	product (e.g., QT interval studies, if needed)?				
20	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			
21	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure ¹) been exposed at the dose (or dose range) believed to be efficacious?	x			
22	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23	Has the applicant submitted the coding dictionary ² used for mapping investigator verbatim terms to preferred terms?	x			
24	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			
25	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			
OTHER STUDIES					
26	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?	x			
27	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (e.g., label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?			x	Exempt from PREA due to orphan drug status
ABUSE LIABILITY					
29	If relevant, has the applicant submitted			x	

¹ For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

² The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	information to assess the abuse liability of the product?				
FOREIGN STUDIES					
30	Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?			x	
DATASETS – per stats					
31	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34	Are all datasets to support the critical safety analyses available and complete?	x			
35	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?	x			
CASE REPORT FORMS					
36	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?			x	
FINANCIAL DISCLOSURE					
38	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? ____ Yes ____

6. Comments for the 74-day letter

None

7. Comments for the sponsor sent ahead of the 74-day letter

Your submission, dated May 2, 2014 to NDA 205832, is currently under review. We have the following information requests.

1. We note an increase in the number of malignancy adverse events in the nintedanib treatment group compared to placebo. Provide a descriptive analysis of all malignancy adverse events in your clinical development program, including ongoing, open-label, long-term extension studies. For each identified malignancy, include a narrative which includes the following information:
 - Trial
 - Patient number
 - Age/Gender
 - Treatment groups (all)(all treatment doses)
 - Treatment start (for each treatment group) (for each treatment dose)
 - Treatment end (for each treatment group) (for each treatment dose)
 - Total treatment duration (for each treatment group) (for each treatment dose)
 - First sign/symptoms date
 - Event onset date
 - Number of days from treatment start to first sign/symptom
 - Number of days from treatment start to event onset date
 - Outcome (e.g., fatal, early d/c)
 - Smoking status
 - Personal malignancy history
 - Weight decrease prior to event onset date (yes/no and quantitative data)
2. In addition to the requested narratives for malignancy adverse events, provide a brief summary of any additional information relevant to the malignancy imbalance, e.g., non-clinical information, biologic plausibility, interpretation of malignancy data from the clinical program, etc.
3. Provide safety analyses as included in the Summary of Clinical Safety for an additional safety grouping, which pools Studies 1199.32, 1199.34, and 1199.30 (treatment arms of nintedanib 150mg BID and Placebo).
4. Provide a pooled analysis on mortality from studies 1199.30, 1199.32, and 1199.34 with stratification for the studies, as previously provided for studies 1199.32 and 1199.34 (Table 3.2.1.5:1 in Summary of Clinical Efficacy). Provide a description of statistical models for the analyses requested and program codes used with appropriate documentation.
5. Clarify the location of the efficacy datasets in SAS transport format for the study 1199.30. Provide the data if not already included in the submission.
6. Clarify the location of the list of investigators who are sponsor employees (including both full-time and part-time). Provide the list if not already included in the submission.

8. Filing meeting slides

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

Summary

- **Recommendation: Fileable**
- 505(b)(1)
- Dose: 150mg twice daily
- Population: Adult patients with idiopathic pulmonary fibrosis
- Proposed Indications
 - Treatment of IPF to slow disease progression

 U.S. Food and Drug Administration
Protecting and Promoting Public Health
www.fda.gov

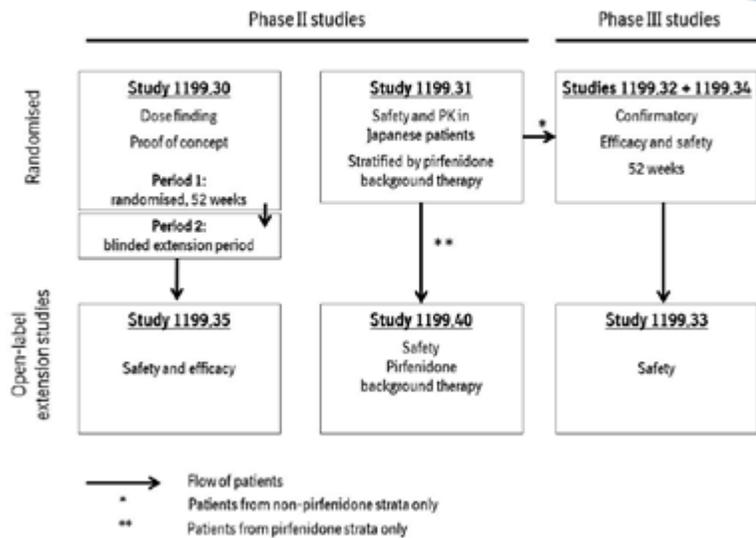
Introduction

- Small molecular receptor tyrosine kinase inhibitor
 - platelet-derived growth factor receptor (PDGFR) a and b
 - fibroblast growth factor receptor (FGFR) 1-3
 - vascular endothelial growth factor receptor (VEGFR) 1-3
- Blocks fibroblasts
 - Proliferation
 - Migration
 - Transformation
- Blocks Flt-3, Lck, Lyn and Src

Regulatory History

Date	Interaction	Notes
Aug 2006	Pre-IND meeting	-FVC cannot be used as a surrogate for survival -No tox support for dosing, went ex-US
Dec 1, 2010	EOP2	-Requested specification on addressing lung transplant -No literature supporting SGRQ in IPF
Apr 2011	IND 74,683 opened	-6/11: 2 international, replicate P3 trials begun
Jun 29, 2011	Orphan Designation	-Granted
May 29, 2013	Fast Track Designation	-Granted
Jul 18, 2013	Type C meeting	-Required modification to handle missing data -Emphasized importance of a mortality endpoint -Non-small cell cancer EU marketing application SCS is acceptable as supportive safety data
Nov 2013	Pre-NDA written responses	-Safety database acceptable -No plans to submit a REMS -Plans to submit Expanded Access Protocol in early 2014
April 2014	EAP opened	500 patients, 150mg BID (100mg option for intolerance)
May 2014	BTD Request	Ongoing

Flow of Studies



Phase 2

Trial	Design	Dose	Duration	N	Endpoints
P2-1199.30 (Completed)	DB, R, PC, PG, dose finding trial	50 mg QD 50 mg BID 100 mg BID 150 mg BID Placebo	52 weeks with option to continue in an active blinded treatment phase	428 (85/arm)	1-Annual rate of decline in FVC 2-Exacerbations, SGRQ
P2-1199.35 (Completed)	OL-rollover from 1199.30	50 mg QD 50 mg BID 100 mg BID 150 mg BID	Until all subjects completed study treatment	198	Long-term safety and efficacy
P2-1199.31 (Completed)	DB, R, PC Stratified by background pirfenidone	50 mg BIDx14 days 100 mgx14 days 150 mg BIDx28 days Placebo	14-28 days	50	Safety/PK
P2-1199.40 (Ongoing)	OL-rollover from 1199.31	150 mg BID as add on to pirfenidone	Until all subjects completed study treatment	20	Long-term safety and efficacy

Supportive safety

Additional supportive safety

Phase 3

Phase 3 Clinical Studies with Nintedanib					
Trial	Design	Dose	N	Duration	Endpoints
P3-1199.32 (Completed)	DB, R, PC, PG	150 mg BID Placebo	309 206	52 weeks with option to continue	1: Annual rate of decline in FVC 2: SGRQ, time to first exacerbation
P3-1199.34 (Completed)	DB, R, PC, PG	150 mg BID Placebo	220 331		
P3-1199.33 (Ongoing)	OL-rollover from 1199.32 and 1199.34	150 mg BID	485 (planned N=750)	Until all subjects completed study treatment	Long-term safety and efficacy

(b) (4)

Primary safety

Additional supportive safety

Sponsor's Efficacy Summary

Endpoint		Study 1199.32 (INPULSIS-1) (95% CI)	Study 1199.34 (INPULSIS-2) (95% CI)	Study 1199.30 (Phase 2 DR) (95% CI)
1 ^a	Annual rate of FVC decline (Treatment difference)	125.3 (77.7, 172.8) ✓	93.7 (44.8, 142.7) ✓	131 ^a (27, 235) ✓
2 ^a	5% FVC Responder analysis (Odds Ratio)	1.85 (1.28, 2.66) ✓	1.79 (1.26, 2.55) ✓	
2 ^a	10% FVC Responder analysis (Odds Ratio)	1.91 (1.32, 2.79) ✓	1.29 (0.89, 1.86)	
Key 2 ^a	Time to IPF Exacerbation (Hazard Ratio)	1.15 (0.54, 2.42)	0.38 (0.19, 0.77) ✓	0.16 ^a (0.04, 0.71) ✓
Key 2 ^a	SGRQ (Absolute change from baseline compared to placebo)	-0.05 -2.50, 2.40	-2.69 ^c -4.95, -0.43 ✓	-6.12 (-10.57, -1.67) ✓
	Pooled all-cause mortality (Hazard Ratio)	0.70 (0.43, 1.12)		0.73 ^d (0.27, 1.98)

^a Rate of decline in FVC (ml/year) at 12 weeks (phase 3 analysis is over 12 weeks)
^b Incidence of exacerbation
^c Does not meet MCID of 4
^d Overall survival

Primary Efficacy Endpoint

	Study 1199.32 INPULSIS-1		Study 1199.34 INPULSIS-2		Study 1199.30 Phase 2 DR	
	Nintedanib	Placebo	Nintedanib	Placebo	Nintedanib ^a	Placebo
N	309	204	329	219	84	83
Rate^a (SE) of decline in FVC (ml/year) over 52 weeks	-114.7 (15.33)	-239.9 (18.71)	-113.6 (15.73)	-207.3 (19.31)	60 ^b (40)	190 ^b (36)
Comparison vs. placebo						
Difference	125.3 ^c		93.7 ^c		131 ^d	
95% CI	(77.7, 172.8)		(44.8, 142.7)		(27, 235)	
p-value	<0.0001		0.0002		p=0.0136	

^a 150mg BID
^b Rate of decline in FVC (ml/year) at 12 weeks
^c Estimated based on a random coefficient regression model
^d Based on MMRM

Safety Groupings

- **Primary safety evaluation**
 - Phase 3 registration studies (1119.32 and 1199.34)
 - N=638 Nintedanib, N= 423 placebo
- **Supportive safety**
 - Phase 2 dose-ranging (1199.30)
 - N=85 Nintedanib 150mg and N=85 placebo
- **Additional supportive safety (irrespective of dose and duration)**
 - Phase 2 2-4 week safety study stratified by pirfenidone (1199.31)
 - Phase 2 OLE studies (1199.33, and 1199.35)
- **Non-IPF indication safety also included (non-pooled; 200mg BID)**
 - NSCLC, Multi-cancer, ovarian cancer, healthy volunteers (N=5390)

Exposure for Phase 3 studies

	Placebo (N=423)	Nintedanib (N=638)
Duration of exposure, mean (SD)	10.8 (2.8) months	10.3 (3.4) months
Total dose (g), mean (SD)	98 (26)	89 (31)
Duration on 150mg BID, mean (SD)	10.6 (3.0)	8.9 (4.1)
Duration on 100mg BID, mean (SD)	3.2 (3.9)	4.4 (3.3)

13-16% Subjects from US sites
 Median age: 67 years
 50-65% Caucasian
 20-40% Asian
 80% male
 70% ex-smokers
 FVC % predicted 80%
 DLCo 3.7 (Study 34) - 4.0 (Study 32) mm/min/kpa

Dose reduction

- Placebo 3.8% vs. 27.9% Nintedanib
- All placebo patients had a single dose reduction
- 25.5% of Nintedanib patients had a single dose reduction.
- Dose reductions were evenly distributed over time
- Majority (87.5% Placebo vs. 95.% Nintedanib) due to related Aes
- Finished treatment at starting dose (97.9% Placebo vs. 76.3% Nintedanib)

11

Summary of AEs

	Placebo N=423 N (%)	Nintedanib N=638 N (%)
Deaths	31 (7.3%)	37 (5.8%)
SAEs	127 (30%)	194 (30%)
AE leading to discontinuation	55 (13%)	123 (19%)
Any AE	379 (90%)	609 (96%)

12

AEs leading to death

SOC/PTs (≥ 2 patients)	Phase 3 (32 & 34)		Phase 2 DR Study (30)	
	Placebo (N=423)	Nintedanib (N=638)	Placebo (N=85)	Nintedanib 50-150mg (all doses) (N=428)
Patient with any AE leading to death	31 (7)	37 (6)	12 (14)	20 (5)
Respiratory, thoracic, and mediastinal	22 (5)	23 (4)	8 (9)	10 (2)
IPF	16 (4)	18 (3)	5 (6)	3 (<1)
Respiratory Failure	2 (<1)	2 (<1)	0	4 (<1)
Infections and infestations	6 (1)	7 (1)	2 (2)	3 (<1)
Pneumonia	2 (<1)	5 (<1)	1 (1)	3 (<1)
Respiratory tract infection	2 (<1)	1 (<1)	1 (1)	0
Neoplasms benign, malignant, and unspecified*	0	5 (<1)	1 (1)	3 (<1)
Lung neoplasms malignant	0	3 (<1)	1 (1)	3 (<1)
Cardiac disorders	6 (1)	3 (<1)	9 (2)	
MI	1 (<1)	2 (<1)	1 (<1)	
Cardiac arrest	1 (<1)	0	3 (<1)	

13

SAEs

SOC/PTs (≥ 1% and > placebo)	Placebo (N=423) N (%)	Nintedanib (N=638) N (%)
Patients with SAEs	127 (30)	194 (30)
Cardiac disorders	23 (5)	32 (5)
MI	2 (<1)	7 (1)
GI disorders	7 (2)	19 (3)
Diarrhea	1 (<1)	2 (<1)
Investigation	2 (<1)	8 (1)
Hepatic enzymes increased	0	2 (<1)
Musculoskeletal and CT disorders	4 (<1)	8 (1)
Hepatobiliary disorders	1 (<1)	7 (1)
Vascular Disorders	10 (2)	11 (2)
Hypertension	(0.5)	5 (0.8)

14

AEs leading to discontinuation

SOC/PTs (≥ 1%)	Placebo (N=423)	Nintedanib (N=638)
Patient with any AE leading to d/c	55 (13%)	123 (19%)
GI	5 (1%)	47 (7%)
Diarrhea	1 (<1%)	28 (4%)
Nausea	0	13 (2%)
Investigations¹	36 (5.7)	36 (5.7)
General Disorders and admin site²	4 (<1)	10 (2)
Metabolism and nutrition disorders	36 (5.7)	36 (5.7)
Decreased appetite	1 (<1)	9 (1)
Hepatobiliary disorders	1 (<1)	7 (1)

1: Driven by weight decreased, hepatic lab evaluations (AST, ALT, Bili, Alk Phos, GGT)

2: Fatigue, asthenia, malaise, general physical health deterioration greater in Nintedanib

AEs leading to permanent dose reduction

SOC/PTs (≥ 5%)	Placebo (N=423)	Nintedanib (N=638)
Patient with any AE leading to dose reduction	2 (<1)	101 (16%)
GI	0	82 (13)
Diarrhea	0	68 (11)
Nausea	0	11 (2)
Vomiting	0	7 (1)
Abdominal pain	0	6 (<1)
Investigation	2 (<1)	12 (2)
Weight decreased	1 (<1)	4 (<1)
Metabolism and nutrition disorders	0	5 (<1)
Decreased appetite	0	4 (<1)

SG 2.1: Dose effect in GI disorders, Investigations(excluding abdominal pain upper)

AESIs

PT (> placebo)	Placebo (N=423) N (%)	Nintedanib (N=638) N (%)	Placebo (N=423) N (%)	Nintedanib (N=638) N (%)
	All AEs		SAEs	
Abdominal pain	26 (6)	96 (15)	1 (<1)	0
Liver-enzyme elevation	11 (3)	87 (14)	1 (<1)	4 (<1)
Liver-related investigation	12 (3)	95 (15)	1 (<1)	4 (<1)
Arterial thromboembolism	3 (<1)	16 (3)	3 (<1)	13 (2)
Bleeding	33 (8)	66 (10)	6 (1)	8 (1)
Bilirubin increase	1 (<1)	8 (1)	0	0
Cardiac failure (tailored)	5 (1)	11 (2)	4 (<1)	8 (1)
GI perforation	0	2 (<1)	0	2 (<1)
Hypertension	17 (4)	33 (5)	2 (<1)	5 (<1)
Hypothyroidism	3 (<1)	7 (1)	0	0
MACE	11 (3)	23 (4)	8 (2)	16 (3)
Thromboembolic events	10 (2)	24 (4)	10 (2)	20 (3)
Myocardial Infarction	5 (1)	17 (3)	10 (2)	15 (2)

Common AEs

SOC/PTs (≥ 5%)	Placebo (N=423)	Nintedanib (N=638)
Patient with any AE	379 (90%)	609 (96%)
GI	168 (40%)	488 (77%)
Diarrhea	78 (18%)	398 (62%)
Nausea	28 (7%)	156 (25%)
Vomiting	11 (3%)	74 (12%)
Abdominal pain	10 (2%)	56 (9%)
Abdominal pain upper	15 (4%)	41 (6%)
Constipation	17 (4%)	38 (6%)
Investigation	227 (36%)	247 (39%)
Weight decreased	15 (4%)	62 (10%)
Metabolism and nutrition disorders	60 (14%)	115 (18%)
Decreased appetite	24 (6%)	68 (11%)
Nervous system disorders	147 (23.3)	134 (21.2)
Headache	19 (4.5%)	43 (6.7)
Vascular		
Hypertension	17 (4%)	33 (5%)

SG 2.1: Dose effect in GI disorders, Investigations(excluding abdominal pain upper)

Safety profile for NSCLC and Ovarian CA were similar

Diarrhea

	Nintedanib (N=398) %
Intensity	
Mild	57%
Moderate	38%
Severe	5%
Outcome	
Recovered	88%
Not yet recovered	11%
Clinical consequence	
Not d/c and no dose reduction	79%
Permanent dose reduction	14%
Permanent d/c	7%
SAEs	
Fatal	0
Hospitalized	0.5% (N=2)
Time of onset	
1 st month	44%
3 rd month	67%

- Mean duration 158 days (range 1-473)
- Nausea similar (except only 5% dose reduced and no SAEs)
- Dec appetite and Vomiting similar (except only 7% dose reduction and 1 SAE req hosp)
- Dec weight similar to vomiting. -1.4 kg on Pb vs. -3.1 kg on Nint

Liver Elevations (from label)

Adverse Reaction	Placebo n=423 %	Nintedanib, 150 mg n=638 %
GGT increased	1.4	3.8
ALT increased	0.2	3.1
AST increased	0.2	2.5
Bilirubin increased	0.2	1.3
Alkaline phosphatase increased	0.0	1.1

Liver Elevations

Table 3.1.1: 3 Patients with liver enzyme or bilirubin values analysed as multiples of the upper limit of normal in SG-1.1 / TS

	Placebo N (%)	Nintedanib 150 mg bid N (%)	
Patients	423 (100.0)	638 (100.0)	
Maximum ALT			
≥ 3 ULN	3 (0.7)	28 (4.4)	←
≥ 5 ULN	0 (0.0)	10 (1.6)	
≥ 8 ULN	0 (0.0)	4 (0.6)	
Maximum AST			
≥ 3 ULN	1 (0.2)	21 (3.3)	←
≥ 5 ULN	1 (0.2)	8 (1.3)	
≥ 8 ULN	1 (0.2)	4 (0.6)	
Maximum AST and/or ALT			
≥ 3 ULN	3 (0.7)	32 (5.0)	←
≥ 5 ULN	1 (0.2)	14 (2.2)	
≥ 8 ULN	1 (0.2)	5 (0.8)	
Maximum total bilirubin ≥ 2 ULN	2 (0.5)	3 (0.5)	
ALT and/or AST ≥ 3 ULN, bilirubin ≥ 2 ULN [†]	1 (0.2)	0 (0.0)	

[†] The elevation of total bilirubin had to occur within 30 days of the elevation of AST and/or ALT.

No cases of Hy's law

Subgroup Analysis

- Females and lower body weight patients
 - More frequent GI events and early discontinuations
- Older patients
 - More frequent early discontinuations
- No differences for race and smoker analysis

Cancer indications

- NSCLC and Ovarian CA
 - Consistent with the IPF program and known chemotherapy agents safety profile

Malignancies

SOC/PTs	N (%)			
	Phase 3 (32 & 34)		Phase 2 DR Study (30)	
	Placebo (N=423)	Nintedanib (N=638)	Placebo (N=85)	Nintedanib 50-150mg (N=343)
Neoplasms benign, malignant, and unspecified	5 (1.2)	12 (1.9)	1 (1.2)	13 (3.8)
Lung malignancy	2 (0.5)	4 (0.6)	1 (1.2)	5 (1.4)
Occurred > 6 months	2 (0.5)	5 (0.8)	0	8 (2.3)
	Lung adeno	NSCLC		Lung neoplasm
	Lung neoplasm	Pancreatic adeno		Small cell lung
		Gastric		Gastric
		Myeloid sarcoma		Colon (2)
		Colon		Lung squamous
				Myelodysplastic syndrome
				Prostate

Labeling

- Section 2: D & A
 - 150 mg twice daily, 12 hours apart
 - Dose reduction to 100mg or discontinue for AEs or liver function (b) (4)
- Section 5: W & P
 - **Embryofetal Toxicity:** MOA and animal studies
 - **Liver Enzyme and Bili elevations:** Phase 3 data, LFTs prior to TX, and periodically
 - **Arterial TE events:** Phase 3 data
 - **GI Disorders:** (diarrhea, N/V) Phase 3 data
 - **Risk of Bleeding:** MOA (Pb (b) (4)%, Tx 10%)
 - Venous Thromboembolism: MOA
 - **GI Perforation:** MOA (Pb 0%, Tx <0.3%)
 - Wound Healing Complication: MOA

Labeling

- Section 6: AEs
 - AE ≥ 5%
 - Liver elevations
- Section 14: Efficacy (pooled analysis included)
 - Study 32 and 34
 - Annual rate of decline in FVC (b) (4)
 - FVC Responder Analyses (b) (4)
 - Time to First Acute IPF Exacerbation
 - SGRQ
 - Survival Analysis
 - Supportive Phase 30
 - Annual rate of decline in FVC, Time to first exacerbation, SGRQ

Summary

- **Recommendation: Fileable**
- Safety
 - GI (**diarrhea** (generally mild-moderate), nausea, vomiting)
most common AEs
 - No Hy's law cases
 - Early discontinuations driven by diarrhea, and liver abnmls
 - Malignancy imbalance

27

Planning

- Consults
 - Labeling
- DSI - high level sponsor audit
- AC - TBD

28

Issues

- **Malignancy imbalance**
 - Relevance of signal
 - Relevance compared to pirfenidone
 - Consider IR for malignancy analysis including extension studies
 - AC?
- When will BI be ready to market Nintedanib?

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

MIYA O PATERNITI
06/16/2014

BANU A KARIMI SHAH
06/16/2014