CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	205832
Submission Date	5/2/2014
Brand Name	OFEV
Generic Name	Nintedanib
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OND Division	Division of Pulmonary, Allergy, and Rheumatology Products
Sponsor/Authorized Applicant	Boehringer Ingelheim, Inc.
Submission Type; Code	505(b)(1); priority review
Formulation; Strength(s)	Capsule; 150 mg and 100 mg
Indication	Idiopathic pulmonary fibrosis
Dosage Regimen	150 mg BID; with optional dose reduction to 100mg BID for management of adverse reaction

Note – In this review, early development names BIBF1120 is also used to refer to nintedanib

1. Executive Summary

Boehringer Ingelheim has submitted the NDA 205832 seeking the marketing approval for nintedanib, for the indication of "*the treatment of idiopathic pulmonary fibrosis (IPF)* (b)(4) [redacted]."

The Sponsor supports this NDA submission with 8 clinical pharmacology studies. The clinical pharmacology studies include a dose-ranging study (Phase 2), mass balance and dose-proportionality studies, drug-drug interaction studies, and assessment of food effect in healthy subjects.

The following are the major findings of the current review:

1) Based on the dose/exposure response relationship for efficacy, the 150 mg BID dosing regimen is reasonable as it is likely to maximize efficacy. The dose-response relationship for safety supports sponsor's dose reduction scheme of reducing the dose to 100 mg BID if adverse events are observed.

2) The dosing regimen of nintedanib has been adequately explored. Prior to the confirmatory trials, one dose ranging trial was conducted in patients with IPF. In this trial, 4 dosing regimens of nintedanib (50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID) were compared with placebo over 52 weeks of treatment. There was increased efficacy with respect to the annual rate of decline in FVC for the 150 mg BID compared to a dose of 100 mg BID or lower. Moreover, a dose/exposure-response relationship was observed for gastrointestinal disorders.

3) Absolute systemic bioavailability for nintedanib was ~5% under fed conditions. T_{max} was reached by 2-4 hours for nintedanib following oral administration. The systemic exposure increased in proportion to the dose in the dose range of 150 to 300 mg BID. 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.

4) Of the absorbed fraction, nintedanib is extensively metabolized, primarily through hydrolytic cleavage by esterases (resulting in BIBF1202) followed by glucuronidation by UGT enzymes (resulting in the BIBF1202 glucuronide). The major metabolites are not active at clinically relevant concentrations.

5) Based on in vitro studies, nintedanib is not an inhibitor or inducer of CYP pathways and has low potential for inhibition of OCT1, P-gp, BCRP. Nintedanib is a substrate

of P-gp. BIBF1202 is a substrate of OATP-1B1 and OATP-2B1. The BIBF1202 glucuronide is a substrate of MRP1 and BCRP.

6) In a study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

7) No adjustment of the starting dose is recommended for any intrinsic or extrinsic factors. The reviewer recommends to monitor individual patients for tolerability of nintedanib, and to manage the adverse reactions by dose interruption, dose reduction, or discontinuation as necessary.

8) 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 and/or bilirubin greater than 1.5 x ULN. 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 Office of Clinical Pharmacology recommends a Post Marketing Requirement for a hepatic impairment study.

1.1 Recommendations

The Office of Clinical Pharmacology has reviewed the clinical pharmacology information provided within NDA 205832 and recommends approval from a clinical pharmacology perspective.

1.2 Phase IV Commitments

The Office of Clinical Pharmacology recommends one Post Marketing Requirement (PMR) study.

Evaluate the impact of hepatic impairment on OFEV (nintedanib) pharmacokinetics; consequently, update the approved OFEV labeling with recommendations for appropriate use of OFEV in patients with hepatic impairment.

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Boehringer Ingelheim has submitted the NDA 205832 seeking the marketing approval for nintedanib, to be used as "*the treatment of idiopathic pulmonary fibrosis (IPF)* (b) (4) ."

Nintedanib is a small molecule tyrosine kinase inhibitor for 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. In addition, nintedanib inhibits Flt-3,

Lck, Lyn and Src kinases. Recommended dose is 150mg BID taken with food, with optional dose reduction to 100mg BID for management of adverse reaction.

Sponsor supported this NDA submission with 6 Phase 1 studies in healthy volunteers, 2 Phase 2 studies 2 Phase 3 studies in IPF patients, 1 QT/renal cell carcinoma study , and 6 meta-analysis and PopPK reports.

The efficacy of nintedanib at the 150 mg BID dose was established in 1 Phase 2 (1199.30) and 2 Phase 3 (1199.32 and .34) trials in IPF patients. In these trials, nintedanib reduced the annual rate of decline in FVC (primary endpoint) compared to placebo. The results were statistically significant in all trials. Additionally, overall mortality was numerically lower in the nintedanib group compared to the placebo. The hazard ratio (95% CI) was 0.7 (0.43, 1.12) in pooled data from phase 3 trials and 0.73(0.27, 1.98) in the phase 2 trial. The most common adverse events observed in the trials were gastrointestinal disorders (diarrhea, nausea, abdominal pain and vomiting) and liver enzyme elevations.

Rationale for the proposed 150mg BID dose

Dose/Exposure response

The dose for the phase III trials (150 mg BID) was selected based on the results from the phase II dose-finding trial 1199.30. In this trial, 4 doses of nintedanib (50 mg QD, 50 mg BID, 100 mg BID, and 150 mg BID) were compared with placebo over 52 weeks of treatment.

Efficacy: There was increased efficacy with respect to the annual rate of decline in FVC for the 150 mg BID compared to a dose of 100 mg BID or lower (Figure 1). Additionally, there was dose response relationship for change from baseline in SGRQ and time to first exacerbation. Consistent with the dose-response relationship, an exposure-response relationship was identified for the efficacy endpoints

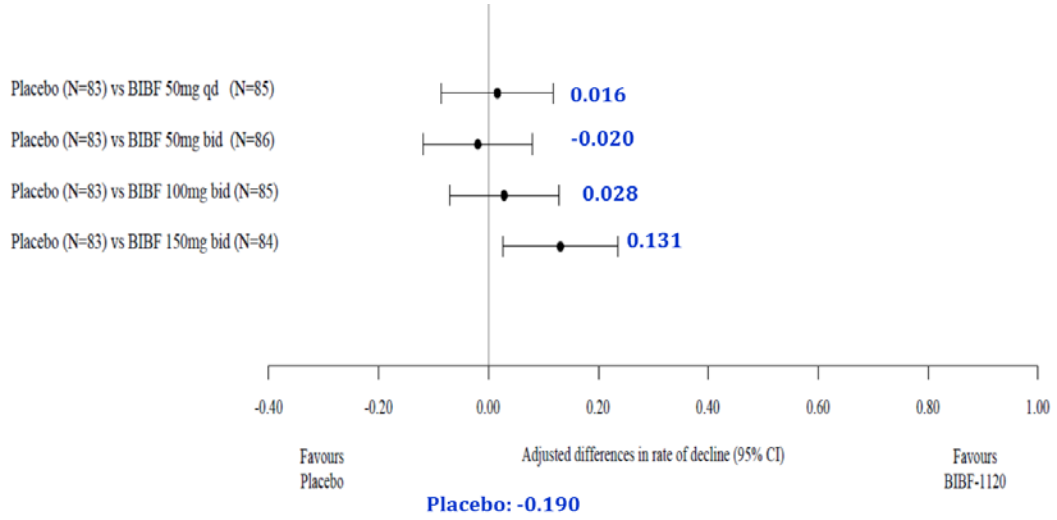

Figure 1. Rate of decline in FVC (L/yr) at 52 weeks

(Source: Fig 11.4.1.1.1, CSR 1199.30)

Safety: There was a dose-response relationship for gastrointestinal disorders (diarrhea, nausea, abdominal pain, decreased appetite). Additionally a higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group. The proportion of patients who discontinued trial medication was higher in the 150 mg BID group.

Based on the dose/exposure response relationship for efficacy 150 mg BID dose is reasonable as it is likely to maximize efficacy. The dose-response relationship for safety supports sponsor's dose reduction scheme of reducing the dose to 100 mg BID if AEs are observed. (See section 2.4).

Pharmacokinetics

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 enterohepatic 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 (Vss) 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, BCRP.

- Based on in vitro studies, nintedanib is a substrate of P-gP. 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 Population

- 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 Nnintedanib 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.

Drug-Drug Interaction (DDI)

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 Cmax. . 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 Cmax.
- Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH<3. However, in phase III studies, coadministration with proton pump inhibitors or histamine H2 antagonists did not influence the exposure (Ctrough) of nintedanib.
- Coadministration with pirfenidone, decreased exposure of nintedanib to 68.3% based on AUC and to 59.2% based on Cmax.. 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.

2. Question Based Review

2.1 List the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA

Fifteen in vitro studies using human biomaterials were conducted and are listed Table 1.

Table 1: Nintedanib (BIBF1120) and Its Major Metabolites BIBF1202 and BIBF1202-glucuronide In Vitro Studies Using Human Biomaterials

Drug	ADME	Objective	Study/Report name
Nintedanib (BIBF1120)	Distribution	Human plasma protein binding blood cell association	A075/02AR
	Metabolism	Metabolism of BIBF1120 in human liver microsomes and recombinant CYPs	A118_02LU
		Metabolism of BIBF1120 by hepatocytes of rat and human	A227_03TE
		Potential of BIBF1120 to inhibit UGT1A1	A249_06TE-b2883
		Potential of BIBF1120 to inhibit CYPs	A114_02LU VD
		Potential of BIBF1120 to induce CYPs	A020-08OS
		Transporters for BIBF1120 and BIBF1202	PK05008
BIBF1202	Distribution	Human plasma protein binding	PB 08-001
	Metabolism	Glucuronidation of BIBF1202	A217/02TE
		Glucuronidation of BIBF1202 by UGT1A1	A249_06TE-b2886
		Glucuronidation of BIBF1202	A267_07TE
		Potential of BIBF1202 to inhibit CYPs	A219-07LU
BIBF1202-glucuronide	Distribution	Human plasma protein binding	A090_08FU
	Metabolism	Potential of BIBF1202-Glucuronide to inhibit CYPs	A239/08LU
		Interaction of BIBF1202-Glucuronide and transporters	PKPR0801

(Source – reviewer summary)

Studies in Healthy Subjects

Four Phase 1 studies characterized the basic PK of nintedanib.

- 1199.20: Human [14C] ADME study
- 1199.75: Absolute bioavailability study
- 1199.21: Relative bioavailability study
- 1199.17: Food effect study

Two clinical studies evaluated drug-drug interactions with nintedanib

- 1199.161: Drug-drug interaction with ketoconazole in healthy volunteers
- 1199.162: Drug-drug interaction with rifampicin in healthy volunteers

Studies in Patients with cancer

Four Phase 1 studies characterized the single and/or multiple-dose PK of nintedanib.

- 1199.1: Phase I monotherapy
- 1199.2: Phase I monotherapy
- 1199.3: Phase I monotherapy
- 1199.19: Phase I monotherapy; Japan

A Phase II study evaluated the effect of nintedanib on QT interval.

- 1199.26: Phase II monotherapy in renal cell carcinoma patients, including QT evaluation.

Phase II studies with IPF

The dose ranging study 1130 evaluated more than one dose levels of nintedanib.

- 1199.30: Phase II in IPF
- 1199.31: Phase II combination with pirfenidone; Japan

Phase III Study

Two identical 52-week Phase III placebo-controlled trials to evaluate the efficacy and safety of Nintedanib 150 mg BID. Trough concentrations were collected at week 4 and 24 in the two Phase III studies 1199.32 and 1199.34, for a subpopulation in Japan, another sample at post dose 2-4h was collected.

Population Pharmacokinetic Studies

Population pharmacokinetic analysis used nintedanib plasma concentration-time data from study 1199.30, 1199.32 and 1199.34 in IPF patients.

2.1.1 What pertinent regulatory background or history contributes to the current assessment of the clinical pharmacology of this drug?

Nintedanib is a nonselective tyrosine kinase inhibitor discovered by Boehringer Ingelhem Pharmaceuticals Inc. Nintedanib was also referred as BIBF1120 during the development program and studied under IND 74,683 for the treatment of IPF (IND opened Apr 2011). There have been several interactions between Agency and Sponsor to discuss the clinical pharmacology program of the proposed product. The key Clinical Pharmacology and Biopharmaceutics agreements were summarized in Table 2. Nintedanib was granted orphan designation on Jun 29, 2011, and breakthrough designation in May 2014. The NDA is reviewed under priority review timelines.

Table 2. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Oct 2013)	• Agreed with delayed hepatic impairment study with proper labeling • Agreed on filing of renal impairment info based on IPF phase 3 Pop-PK analysis

EOP2 (Dec 2010)	• Agreed that 150 mg BID (with dose reduction option) is reasonable for Phase 3 evaluation. • Clarify that special population (hepatic impairment) assessment based on cancer phase 3 Pop-PK analysis is NOT acceptable • Ask for E-R analysis in phase III

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Nintedanib is a small molecule drug. Its structure is shown in Figure 2 and its physicochemical properties are listed in Table 3.

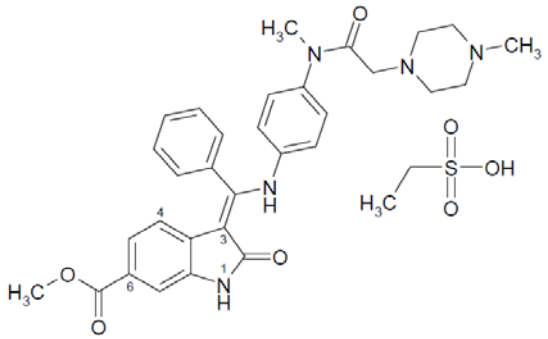

Figure 2. Molecular structure of nintedanib

Table 3: Nintedanib physical chemical properties

Molecular Formula	$C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$ ($C_{33}H_{39}N_5O_7S$)
Molecular Weight	649.76 g/mol (b) (4)
Physical State	BIBF 1120 ethanesulfonate is a bright yellow powder
Polymorphism	(b) (4)
Dissociation Constants	
Solubility	
Partition Coefficient	

For the drug product, BIBF 1120 capsules are soft gelatin capsules with a single-sided imprint, showing the BI company symbol and the strength. (b) (4) They appear as follows:

100 mg capsules are peach-colored, opaque, oblong and imprinted in black with the Boehringer Ingelheim company symbol and with "100",

□□150 mg capsules are brown-colored, opaque, oblong and imprinted in black with the Boehringer Ingelheim company symbol and with “150”.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

Nintedanib is proposed to act as 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 crucial for the proliferation, migration, and transformation of fibroblasts, representing essential mechanisms of the IPF pathology. In addition, nintedanib inhibits Flt-3, Lck, Lyn, and Src kinases.

The proposed indication is treatment of idiopathic pulmonary fibrosis (IPF) (b) (4) .

2.2.3 What are the proposed dosages and routes of administration?

The proposed dose is 150 mg BID to be given orally with food, with optional dose reduction to 100 mg BID for the management of adverse reactions.

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

Currently there are no drugs approved for IPF in the US. Pirfenidone is currently being reviewed for the same indication.

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

The clinical pharmacology and biopharmaceutics studies supporting this NDA and their design features are listed under section 2.1.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

The Sponsor used annual rate of decline in forced vital capacity (FVC) as the primary endpoint for all key efficacy studies (1199.30, 1199.32 and 1199.34). Key secondary endpoints include change from baseline in SGRQ total score and time to first acute IPF exacerbation. Other secondary endpoints for study 1199.32 and 1199.34 include survival, time to death, absolute change from baseline in FVC over 52 weeks, and relative change from base line in FVC over 52 weeks.

FVC is usually used as primary efficacy endpoint for IPF trials. The annual rate of decline in FVC, which is derived using a random coefficient regression model, is a new endpoint for IPF. For assessment of the primary endpoint, please see the medical and statistical reviews (Dr. Paterniti and Dr. Yongman Kim).

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately

identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Yes. In all relevant studies, nintedanib and its major metabolites, BIBF1202 and BEBF1202 glucuronide concentrations, were measured

2.4 Exposure-Response

2.4.1 Is there a dose/exposure-response relationship for effectiveness?

There was increased efficacy with respect to the annual rate of decline in FVC (primary endpoint) for the 150 mg BID compared to a dose of 100 mg BID or lower in phase 2 study 1190.30 (Table 4). A dose response relationship was observed for change from baseline in SGRQ and time to first exacerbation. Data from the phase 2 study 1199.30 was used for this analysis as this was a dose-ranging study in IPF patients and had a wide range of exposures. Patient characteristics and study design were similar between the phase 2 and the phase 3 studies (studies 1199.32 and 1199.34).

Consistent with the dose-response, increased efficacy with respect to annual rate of decline in FVC is observed in the highest exposure (steady state AUC) quartile compared to lower quartiles (Figure 3). The highest quartile corresponds to the exposures that are likely to be achieved with the 150 mg BID dose. Additionally, a trend for increase in efficacy with respect to change from baseline in SGRQ is observed with increasing exposure (Figure 3). For details see Pharmacometrics review.

Table 4: Dose-response for efficacy endpoints in Phase 2 study, 1190.30

Treatment	Randomized subject (N)	Annual rate of decline in FVC in L/year (SE)	Change from baseline in SGRQ Mean(SE)	Time to first exacerbation Hazard ratio* (95% CI)
Placebo	87	-0.190 (0.036)	5.19 (1.557)	-
50mg QD	87	-0.174 (0.037)	4.29 (1.713)	0.758 (0.326, 1.765)
50mg BID	86	-0.210 (0.035)	1.97 (1.717)	0.841 (0.362, 1.952)
100mg BID	86	-0.162 (0.035)	1.37 (1.655)	0.517 (0.193, 1.384)
150mg BID	86	-0.06 (0.039)	-0.42 (1.526)	0.158 (0.035,0.711)

*Treatment versus Placebo

(Source: Table 11.4.1.1.1:1, Table 11.4.1.2.7:1, Table 15.2.9.3.2:2 from CSR)

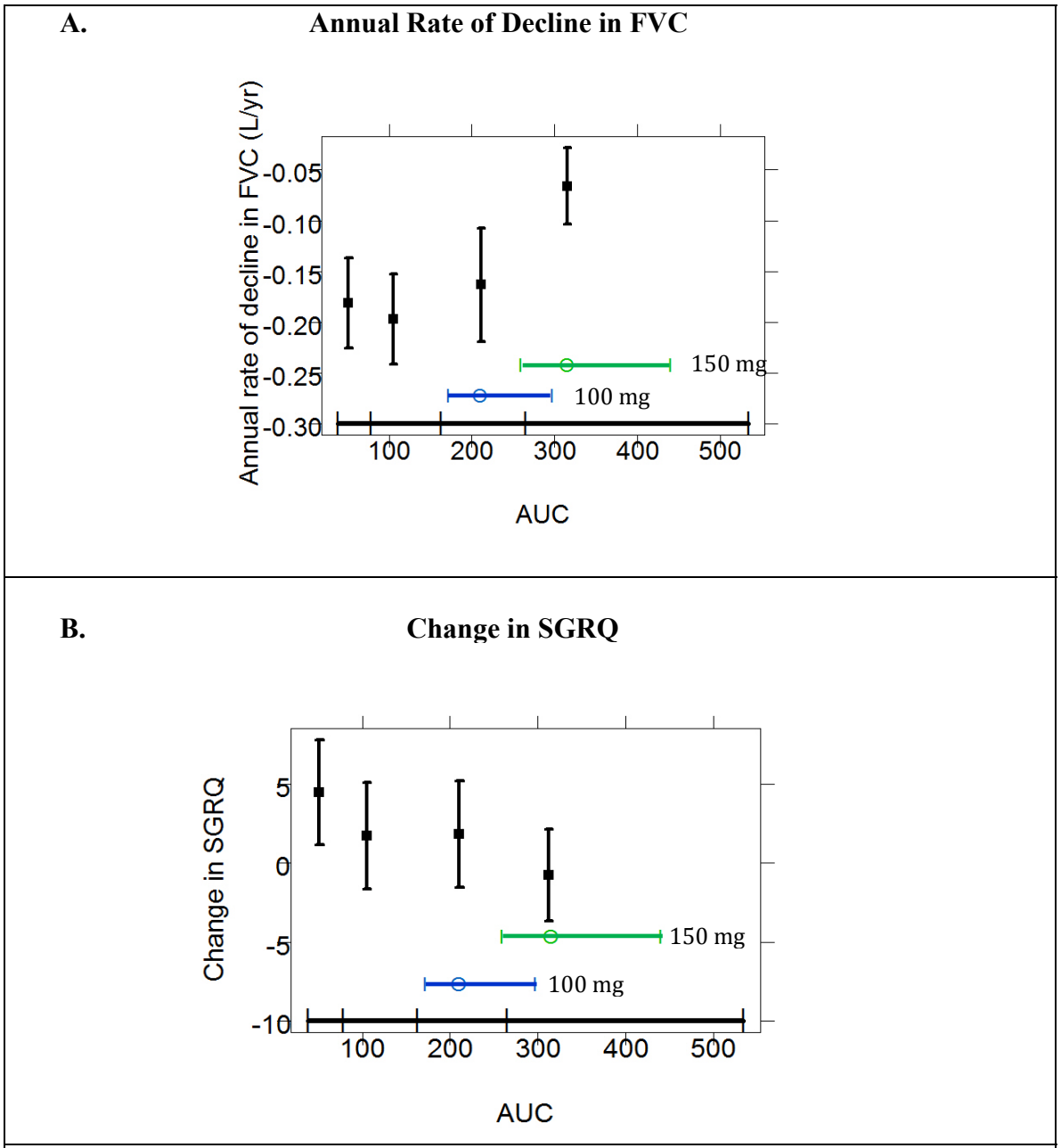

Figure 3: The relationship of A) annual rate of decline in FVC and B) change in SGRQ from baseline with steady state AUC. The black symbols represent the mean and 95% CI in each exposure quartile. The horizontal black line represents the exposure range in each quartile. The blue and green horizontal lines represent the exposure range achieved upon administration of 100 mg BID and 150 mg BID doses respectively.

2.4.3 Does this drug prolong QT/QTc Interval?

QT effect was evaluated in a phase 2 study in patients with renal cell cancer (1199.26). The trial was not a thorough QT trial and did not include a placebo or positive control or supra-therapeutic dose level (due to ethical reasons). Nintedanib was administered at a dose of 200 mg BID. Frequent ECG measurements were performed at baseline, after the first administration of nintedanib, and at steady state. The study demonstrated the lack of

effect of 200 mg nintedanib orally administered BID for 15 days on the QTcF interval as compared with baseline. The largest mean time-matched increase of QTcF at steady state was 3.1 ms (two-sided 90% CI: -0.2, 6.4). For further details refer to QT/IRT review of the study 1199.26 by Dr. Huifang Chen (DARRTS date 7/23/2014).

2.4.2 Is there a dose/exposure-response relationship for safety?

There is a dose-response relationship for gastrointestinal disorders (diarrhea, nausea, abdominal pain, decreased appetite) in phase 2, study 1190.30 (Table 5). Additionally a higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group (Table 6). Since diarrhea was the most common adverse event observed in the trials, an exposure-response analysis was conducted for diarrhea. Consistent with dose-response, the proportion of patients with diarrhea increased with increasing steady state AUC (Figure 4). For additional details see Pharmacometrics review.

Table 5: Dose-response for gastrointestinal adverse events

N = number of patients	Placebo N (%)	BIBF 50 mg qd N (%)	BIBF 50 mg bid N (%)	BIBF 100 mg bid N (%)	BIBF 150 mg bid N (%)	Total N (%)
Number of patients	85	86	86	86	85	428
Gastrointestinal disorders	27 (31.8)	33 (38.4)	31 (36.0)	49 (57.0)	63 (74.1)	203 (47.4)
Nausea	8 (9.4)	9 (10.5)	8 (9.3)	17 (19.8)	20 (23.5)	62 (14.5)
Vomiting	4 (4.7)	1 (1.2)	6 (7.0)	11 (12.8)	11 (12.9)	33 (7.7)
Abdominal discomfort	1 81.2)	2 (2.3)	3 (3.5)	3 (3.5)	5 (5.9)	14 (3.3)
Abdominal pain	3 (3.5)	3 (3.5)	5 (5.8)	4 (4.7)	6 (7.1)	21 (4.9)
Abdominal pain upper	3 (3.5)	6 (7.0)	10 (11.6)	2 (2.3)	10 (11.8)	31 (7.2)
Diarrhoea	13 (15.3)	9 (10.5)	17 (19.8)	32 (37.2)	47 (55.3)	118 (27.6)
Metabolism disorders	2 (2.4)	5 (5.8)	11 (12.8)	11 (12.8)	17 (20.0)	46 (10.7)
Decreased appetite	0	3 (3.5)	4 (4.7)	4 (4.7)	13 (15.3)	24 (5.6)
GI disorders leading to treatment discontinuation	2 (2.4)	2 (2.3)	2 (2.3)	2 (2.3)	14 (16.5)	22 (5.1)
Diarrhoea	0	1 (1.2)	1 (1.2)	0	10 (11.8)	12 (2.8)
Serious gastrointestinal disorders	0	2 (2.3)	2 (2.3)	1 (1.2)	4 (4.7)	9 (2.1)
Severe gastrointestinal disorders	0	2 (2.3)	2 (2.3)	3 (3.5)	5 (5.9)	12 (2.8)

(Source: Table 12.2.2.2:1 from CSR1199.30)

Table 6: Dose-response for liver enzyme elevation

	Placebo	50 mg qd	50 mg bid	100 mg bid	150 mg bid
Number of patients [N]	84	85	86	84	84
Frequency of patients [N (%)] with possible clinically significant* abnormalities					
AST	0 (0)	0 (0)	0 (0)	1 (1.2)	3 (3.6)
ALT	0 (0)	0 (0)	1 (1.2)	0 (0)	4 (4.8)
GGT	1 (1.2)	5 (5.9)	4 (4.7)	5 (5.9)	16 (19.0)
Bilirubin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*AST, ALT, GGT – increase by >3xULN. Bilirubin-increase by >34 umol/L

(Source: Table 12.2.2.2:1 from CSR1199.30)

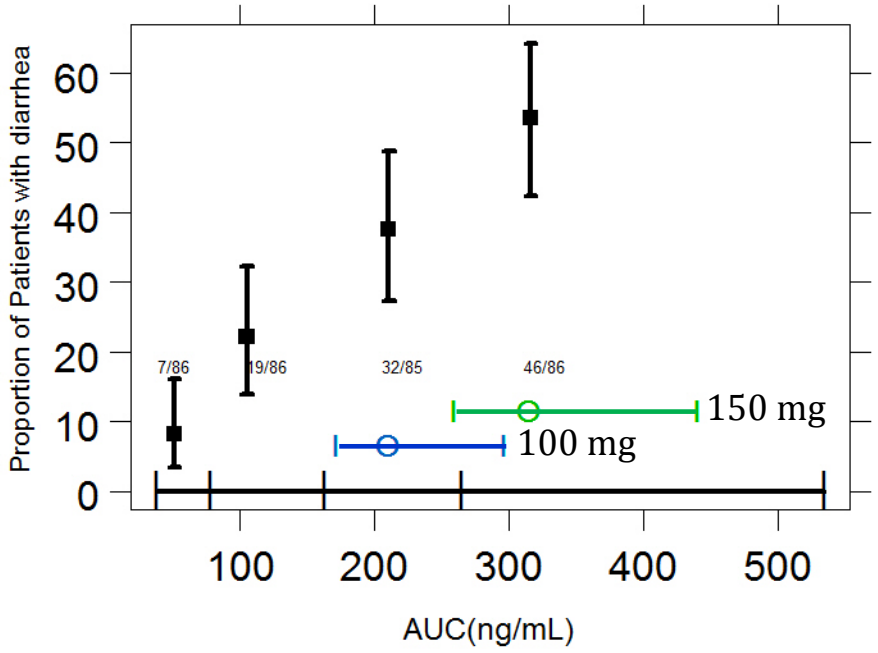

Figure 4: The relationship of proportions of patients with diarrhea with steady state AUC. The black symbols represent the mean and 95% CI in each exposure quartile. The horizontal black line represents the exposure range in each quartile.

2.4.4 Does the dose/exposure-response relationship for effectiveness and safety endpoints support the proposed dose and dose modification scheme?

The proposed starting dose of 150 mg BID is reasonable because of increased efficacy with respect to the annual rate of decline in FVC for the 150 mg BID compared to a dose of 100 mg BID or lower in phase 2, study 1190.30. Additionally a dose-response relationship was observed for change from baseline in SGRQ and time to first exacerbation. Since there are no currently approved therapy for IPF patients and the 5 year survival is low ranging from 20%-40%, it is reasonable to have a dose that maximizes efficacy. Increased GI disorders with increasing dose supports sponsor's dose reduction scheme, of reducing the dose to 100 mg BID if AEs are observed. Additionally, higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group. Thus sponsor's dose modification based on liver enzyme elevation is reasonable.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults and cancer patients?

Single dose PK in healthy adults

In a single dose study in healthy adults, nintedanib PK was characterized for 150 mg under fasting or fed conditions. The mean plasma concentration-time profile is shown in Figure 5. Following oral administration, maximum plasma concentration of BIBF1120

was reached at around 2 hours post dose under fasted and 4 hours under fed conditions. (Figure 5). In several other PK studies with nintedanib given by oral administration, a second peak in plasma was observed around 5-6 hours post-dose suggesting enterohepatic circulation (Figure 8). The terminal half-life after single dose was 13.6 h under fasted and 16.2 h under fed conditions. Nintedanib appears to follow bi-exponential disposition kinetics in healthy male volunteers. PK parameters after single dose of 150 mg nintedanib under fast and fed conditions are summarized in Table 7.

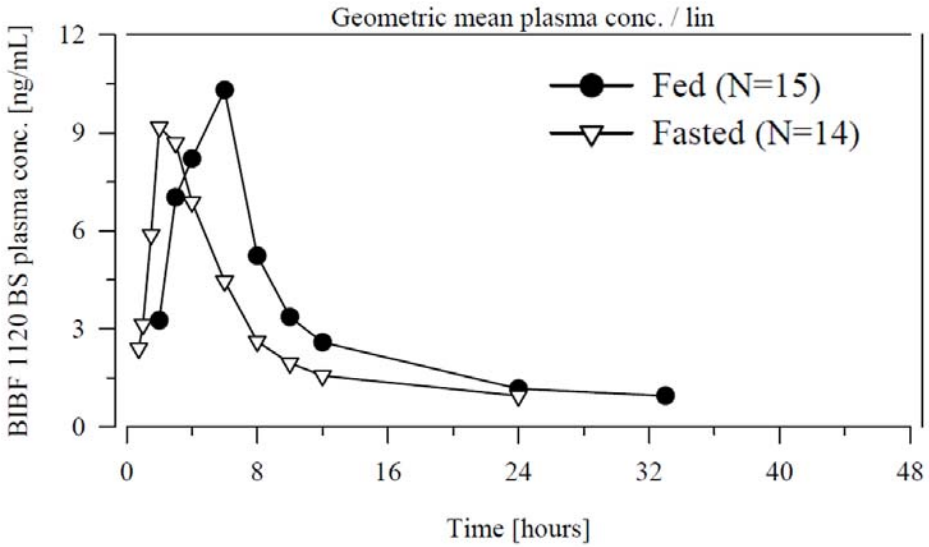

Figure 5: Mean Plasma BIBF1120 Concentrations vs Times Following Administration of a Single Oral Dose of 150mg nintedanib capsule to Fasted or Fed Healthy Subjects
(Source – Figure 11.5.2: 1, Study 1199-0017 report)

Table 7: Geometric mean (and gCV%) pharmacokinetic parameters of BIBF 1120 BS after single oral administration of 150 mg BIBF 1120 capsule in fed and fasted conditions to healthy male volunteers

BIBF 1120 capsule		Fasted	Fed
Parameter	**Unit**	**N=14**	**N=15**
t_{max}[1]	[h]	2.00 (1.48-3.98)	3.98 (1.50-6.05)
C_{max}	[ng/mL]	11.1 (60.3%)	13.2 (61.6%)
$AUC_{0-\infty}$	[ng·h/mL]	98.4 (33.0%)[2]	119 (53.9%)
AUC_{0-24}	[ng·h/mL]	79.0 (34.8%)[2]	90.2 (52.9%)
$t_{½}$	[h]	13.6 (15.2%)[1]	16.2 (40.3%)
CL/F	[mL/min]	25400 (33.0%)[1]	20900 (53.9%)
V_z/F	[L]	29900 (34.7%)[1]	29400 (47.0%)

(Source – Table 11.5.2: 1and Table 11.5.2: 3, Study 1199-0017 report)

Multiple dose PK in renal cell cancer patients

Multiple dose PK of nintedanib was characterized in previously untreated patients with renal cell cancer. Nintedanib PK after multiple doses was consistent with the single dose PK. The median T_{max} was about 3 hr and mean apparent terminal $t_{1/2}$ ranged from 9-15 hrs. After multiple dosing, there was a slight accumulation of BIBF 1120 compared to a single dose, leading to a geometric (g)mean accumulation ratio of 1.33 based on C_{max} (gCV 67.0%) and 1.66 based on AUC_{0-12} (gCV 52.5%), which was slightly lower than as expected based on the terminal half-life and BID dosing regimen. This indicated that the reported terminal half-life was slightly longer than the effective $t_{1/2}$ of nintedanib driving accumulation in plasma, which was estimated to be in the range of 9-10 h based on the observed accumulation ratios or the mean residence time. Mean plasma PK profiles are shown in Figure 6 and summary PK parameters are listed in Table 8. Based on visual inspection, steady state was reached on Day 15.

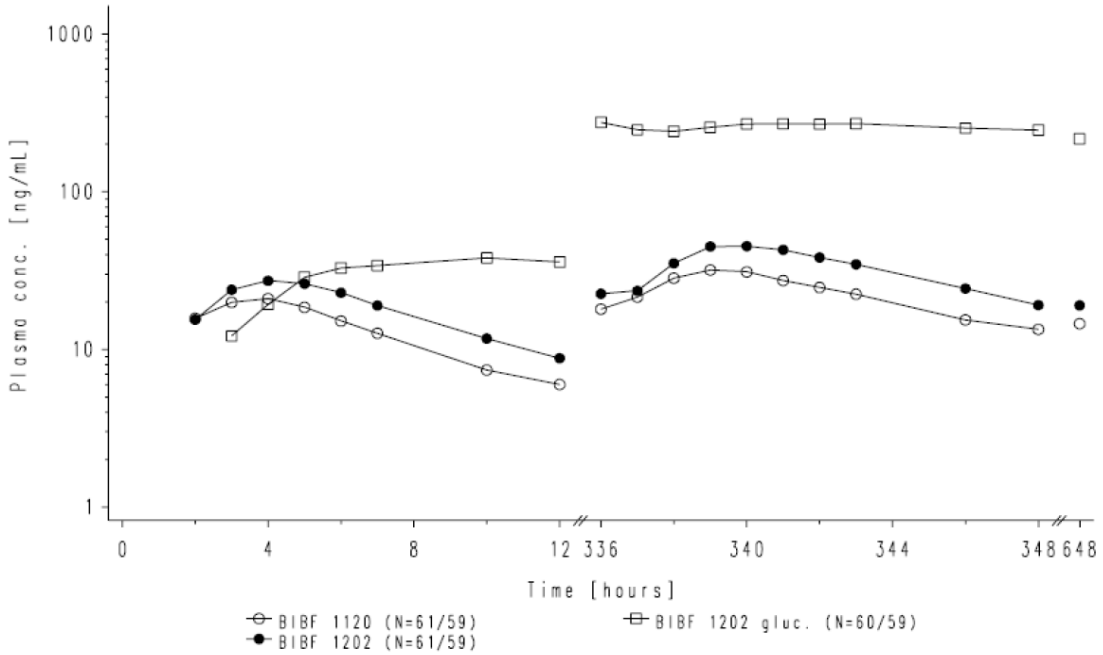

Figure 6: Geometric mean plasma concentration-time profiles of BIBF 1120, BIBF 1202, and BIBF 1202-glucuronide after single (Day 1) and multiple (Day 15) oral administration of 200 mg BIBF 1120 BID to patients with RCC

(Source – Figure 11.5.2.1:2, Study 1199.26 report)

Table 8: Geometric mean (and gCV%) standard pharmacokinetic parameters of nintedanib, BIBF 1202, and BIBF 1202 glucuronide in cancer patients after a single oral dose of nintedanib and at steady state following BID administration (1199.26; metaanalysis of studies 1199.1/2/3/19)

Study 1199.26 (if not indicated otherwise)			Nintedanib		BIBF 1202		BIBF 1202 glucuronide	
Single dose		N	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{0\text{-}12,norm}$	[(ng·h/mL)/mg]	59/59/49	0.819	67.8	1.08	95.4	1.64	99.2
$R_{AUC0\text{-}12,norm}$		--/59/49	NA	NA	1.35	88.4	1.64	113
$AUC_{0\text{-}\infty,norm}$ #	[(ng·h/mL)/mg]	65/47/--	1.33	78.5	2.47	186	NC	NC
$C_{max,norm}$	[(ng/mL)/mg]	61/61/60	0.159	71.4	0.174	117	0.210	104
$R_{Cmax,norm}$		-/61/55	NA	NA	1.12	97.0	1.01	127
t_{max}*	[h]	61/61/60	3.08	0.883 – 12.0	3.92	1.92 – 12.0	10.1	4.08 - 13.0
$t_{1/2}$ #	[h]	65/47/6	9.18	46.2	6.66	29.2	54.9	76.0
CL/F #	[mL/min]	65	12500	78.5	NA	NA	NA	NA
V_z/F #	[L]	65	9970	72.2	NA	NA	NA	NA
Steady state								
$AUC_{0\text{-}12,ss,norm}$	[(ng·h/mL)/mg]	58/59/55	1.35	67.5	2.03	131	14.7	170
$R_{AUC0\text{-}12,ss,norm}$		58/58/54	NA	NA	1.56	96.8	9.16	159
$R_{A,AUC0\text{-}12,norm}$		56/57/45	1.66	52.5	1.89	74.9	9.08	101
LI +		58/59/55; 65/47/--	1.02	NA	0.82	NA	NC	NC
$C_{max,ss,norm}$	[(ng/mL)/mg]	61/45/61	0.216	72.7	0.282	131	1.52	176
$R_{Cmax,ss,norm}$		61/61/61	NA	NA	1.34	106	5.40	161
$R_{A,Cmax,norm}$		59/59/61	1.33	67.0	1.60	85.4	7.12	102
$t_{max,ss}$*	[h]	61/61/61	2.92	0.00 – 6.83	3.08	0.00 – 9.93	4.05	0.00 - 12.00
$t_{1/2,ss}$ #	[h]	48/45/24	15.3	59.4	12.6	36.0	55.4	75.9
$CL/F_{,ss}$	[mL/min]	58	12400	67.5	NA	NA	NA	NA
$V_z/F_{,ss}$ #	[L]	48	18600	87.4	NA	NA	NA	NA

+ Calculated based on dose normalised gMean exposure estimates. gCV is therefore not applicable.
R_{Param} denotes metabolic ratios based on molar exposure, $R_{A,Param}$ denotes accumulation ratios.
* t_{max} is given as median and range.
\# Parameter estimate determined in metaanalysis of studies 1199.1/2/3/19 as last plasma sample in 1199.26 taken 12 h after administration and terminal phase thus not captured
LI Linearity index, defined as $AUC_{\tau,ss}/AUC_{0\text{-}\infty}$
NA Not applicable
NC Not calculated as terminal phase not captured in 1199.26 and bioanalytical assay for studies included in metaanalysis not fully quantitative

(Source – Table 3.2.1:1, summary of clinical pharmacology)

The metabolic ratios of BIBF 1202 to BIBF 1120 were slightly higher than 1 indicating a higher exposure to the ester-cleaved metabolite BIBF 1202 than to the parent compound BIBF 1120. The ratios increased by 15% to 20% at steady state compared to single dose conditions (Table 9).

The metabolic ratios of BIBF 1202-glucuronide to BIBF 1120 after single administration of BIBF 1120 were greater than 1 for AUC0-12 and equal to 1 for Cmax, suggesting a

slightly higher exposure of BIBF 1202-glucuronide than the parent compound BIBF 1120. At steady state conditions, the metabolic ratios of BIBF 1202-glucuronide to BIBF 1120 increased by about 6-fold for AUCτ,ss and Cmax,ss compared to single dose conditions indicating a higher exposure to BIBF 1202 glucuronide than BIBF 1120 at steady state.

The metabolic ratios of BIBF 1202-glucuronide to BIBF 1202 after single dose administration of BIBF 1120 were greater than 1 for AUC0-12 and smaller than 1 for Cmax. At steady state conditions, the metabolic ratios of BIBF 1202-glucuronide to BIBF 1202 increased by about 5-fold for AUCτ,ss and Cmax,ss compared to single dose conditions indicating a higher exposure to BIBF 1202 glucuronide than to BIBF 1120 at steady state.

Table 9. Ratios of metabolites and parent compound of Cmax(ss) and AUC0-12 (AUCτ,ss) after single and multiple oral administrations of 200 mg BIBF 1120

Ratios of metabolites and parent compound after single and multiple oral dosing of 200 mg BIBF 1120									
	BIBF 1202/BIBF 1120 [T/R]			BIBF 1202-glucuronide/ BIBF 1120 [Met]			BIBF 1202-glucuronide/ BIBF 1202 [MT/MR]		
	N	gMean	gCV%	N	gMean	gCV%	N	gMean	gCV%
$R_{AUC0-12}$	59	1.35	88.4	49	1.64	113	49	1.14	80.5
R_{Cmax}	61	1.12	97.0	60	1.01	127	60	0.858	81.0
$R_{AUC\tau,ss}$	58	1.56	96.8	54	9.16	159	55	5.70	101
$R_{Cmax,ss}$	61	1.34	106	61	5.40	161	61	4.02	89.6

(Source: Table 11.5.2.4:1, Study report 1199.26)

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

The pharmacokinetic characteristics of nintedanib were consistent across healthy volunteers, patients with IPF, and patients with advanced cancer. Observed nintedanib trough plasma concentrations in patients with IPF and advanced cancer patients are summarized in Table 10. The exposure of nintedanib in IPF patients was higher than in healthy subjects, possibly due to an elderly age group for IPF patients (Table 11). Inter-individual variability of PK parameters was generally higher in patients than in healthy volunteers, likely due to the more heterogeneous population, e.g. in terms of covariate distribution, comedication, and potential disease dependent changes in physiology.

Table 10. Geometric mean (and gCV%) dose normalized trough plasma concentrations of nintedanib and major metabolites after multiple oral administration of nintedanib twice daily as monotherapy in different populations

$C_{pre,ss,norm}$ [ng/mL/mg]	Study	Nintedanib		BIBF 1202		BIBF 1202 glucuronide	
		N	gMean (gCV%)	N	gMean (gCV%)	N	gMean (gCV%)
Patients with IPF, target population, after administration of 150 mg nintedanib bid	**1199.30**	70	0.0558 (76.0)	70	0.0645 (95.7)	40	0.484 (112)
	1199.32	250	0.0635 (72.4)	250	0.0665 (93.3)	251	0.670 (111)
	1199.34	274	0.0687 (71.3)	274	0.0784 (91.9)	275	0.779 (117)
Advanced cancer patients	**Metaanalysis (1199.1/2/3/19)***	263	0.0664 (106)	227	0.0895 (205)	---	---
	1199.26#	59	0.0918 (89.2)	59	0.115 (143)	59	1.36 (192)

* All bid dose levels combined
\# $C_{pre,ss,29,norm}$; after administration of 200 mg nintedanib bid
--- Semi-quantitative bioanalytical assay; estimate therefore not given.
(Source: Table 3.3:2, summary of clinical pharmacology)

Table 11. Comparison of Nintedanib Systemic Exposure in Healthy Subjects vs. Subjects with IPF following Oral Dosing with Nintedanib

Population	Study	Dose (mg)	N	Cmax (ng/mL/mg)	AUCτ,ss (ng*h/mL/mg)	$AUC_{0-\infty}$ (ng*h/mL/mg)
Healthy	1199.162	150 SD	26	0.147		1.22
	1199.75	100 SD	12	0.0843		0.562
	1199.17	150 SD	15	0.0878		0.796
IPF	1199.30, 32, and 34	150BID	981	0.12	1.014	

(Source: Table 11.2:1, Study report pop PK 1199.30, 32, 34; Study report 1199.162, 1199.75, 1199.17.)

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Based on population PK analysis of nintedanib in IPF patients, the IIV in F1 expressed as coefficient of variation was 41.8%, IIV in V2/F was 131%, IIV in KA 28.3%, and IOV in F1 was 33.3%.

2.5.4 What are the characteristics of drug absorption?

The absolute oral bioavailability of nintedanib following oral administration with food was ~4.67% in healthy volunteers. In single- and multiple-dose studies, maximum plasma concentrations were reached within 2-4 hrs. after oral administration. Absorption and bioavailability are decreased by transporter effects and first-pass metabolism. In-vitro studies using transfected MDCK cells, demonstrated that nintedanib is a P-gp substrate,

but not the BCRP efflux transporter (see sections 2.7.3 and 2.7.4). It also undergoes extensive intestinal and/or hepatic first-pass metabolism by esterases and UGT enzymes forming the metabolites BIBF 1202 and BIBF 1202 glucuronide. The effect of food intake on the bioavailability of nintedanib is described in section 2.8.3. Exposure increased by about 20% after administration under fed conditions.

2.5.5 What are the characteristics of drug distribution?

Following IV dosing, the apparent steady-state volume of distribution (V_{ss}) of nintedanib was estimated to be 1050 L, suggesting extensive distribution into tissues. The quantitative whole body autoradiography study in rats indicated a rapid and relatively homogenous tissue distribution with the exception of the CNS, possibly due to lack of partitioning through the blood-brain-barrier. Nintedanib related radioactivity was slowly transferred to milk of lactating rats without pronounced accumulation in the milk. A low percentage of the dose (0.18 - 0.5%) was secreted over 24 h.
In vitro studies determined high plasma protein binding for nintedanib with the bound fraction (f_B) in humans to be 97.8%. Nintedanib showed protein binding in a similar range to human serum albumin (HSA; fB = 97.5%). The binding to human alpha-1-acid glycoprotein (hAGP) was low at 0.14 g/L hAGP (f_B = 55.5%) and increased with hAGP concentration to 93.0% at 3.4 g/L hAGP. Based on these findings, HSA is considered to be the major binding protein in human plasma. Plasma protein binding of the metabolite BIBF 1202 was moderate (f_B = 77.8%), whereas it was high for BIBF 1202 glucuronide (f_B~97%). Nintedanib is distributed preferentially in plasma with a blood to plasma ratio of 0.869 and a blood cell to plasma ratio of 0.701.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Nintedanib is eliminated primarily by biliary/fecal excretion, and the hepatic metabolism and biliary excretion is the major route of elimination for nintedanib. The major route of excretion of total [^{14}C]-radioactivity was via feces, demonstrated by a fecal excretion of 93.4% of dose within 120 hours.

The urinary excretion of unchanged nintedanib within 48 h was about 1% of dose after intravenous administration and 0.05% after oral administration. In mass balance study, the urinary excretion of total [^{14}C]-radioactivity was 0.649% of dose, indicating that the contribution of renal clearance to the total clearance was low.

Table 12: Percentage of Parent (M0) and Metabolites (M1-BIBF1202, M2-BIBF1202 glucuronide) of nintedanib excreted by urine and feces in Male Subjects Following Oral Administration of a Single 100 mg Dose of [14C]nintedanib in solution

	metabolites (% of dose)				
	urine (0 - 24 h)		faeces (0 - 72 h)		urine + faeces
	mean	CV (%)	mean	CV (%)	
m1	0.2	17	58.4	22	58.6
m2[#]	0.07	40	0.1	283	0.17
m3	0.01	110	3.6	56	3.6
m4	0.01	85	2.6	84	2.6
m5	0.004	189	0.2	283	0.2
m7	0.03	33			0.03
m8	0.01	87			0.01
m9	0.02	117			0.02
m10	0.04	114			0.04
m0	0.14	24	19.9	48	20.0
sum	0.53		84.8		85.3
total excretion	0.53		87.6		88.1
not assigned	0		2.8		2.8

[#] combined data for the 1-*O*-acylglucuronide (m2) and its isomeric acylglucuronides (m2[*])

(Source – page 57, Study A248_05TE report, samples from study 1199.20)

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

BIBF 1202 (M1) and its acyl-glucuronide (M2) were the predominant circulating molecular entities besides the parent compound. In addition, two plasma sample pools (1 h and 2 h sampling time) showed the presence of another metabolite, designated M7, that was tentatively identified as a glucuronide conjugate of the parent compound (Table 13). The CYP3A4 metabolite M3 was not detected in plasma. At steady state, BIBF1202 glucuronide (M2) is the major metabolite in plasma (see section 2.5.2).

Table 13: Percentage of Circulating Parent (M0) and Metabolites (M1-BIBF1202, M2-BIBF1202 glucuronide)of nintedanib in Male Subjects Following Oral Administration of a Single 100 mg Dose of [14C]nintedanib in solution

mean data of pooled plasma samples, 1 h, 2 h, 6 h	
metabolite designation	**(% of sample radioactivity)**
m1	32
m2	30
m7	7
m0	24
sum	93

subjects / samples	metabolites (% of sample radioactivity)			
	pool 1 h	pool 2 h	pool 6 h	mean
metabolite designation				
m1	32.5	38.7	25.7	32.3
m2	28.3	15.3	47.1	30.2
m7	9.2	11.6	0.0	6.9
m0	9.8	34.5	27.1	23.8
sum	**79.8**	**100.0**	**100.0**	**93.3**

(Source – Table on page 56; Table 10.7 , Study A248_05TE report, samples from study 1199.20)

2.5.8 What are the characteristics of drug metabolism?

The proposed metabolic pathway for nintedanib is shown in Figure 7. Both in vitro and in vivo studies indicate that nintedanib is extensively metabolized. The metabolism of BIBF 1120 ES was predominantly characterized by the ester cleavage of the methyl ester moiety yielding BIBF 1202 (M1). Subsequently, BIBF 1202 was glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10, yielding the 1-*O*-acylglucuronide (M2) that underwent non-enzymatic isomerization resulting in isomeric acylglucuronides (designated as metabolite fractions M2*). In addition, oxidative N-demethylation, which is catalyzed by CYP3A4, yielded the secondary amine M3 (BIBF 1053). Finally, M4 was formed by a combination of ester cleavage and oxidative *N*-demethylation. A few other minor metabolites were observed, that were formed by phase I metabolic reactions and two phase II conjugation reactions (glucuronidation and formylation).

The biotransformation of nintedanib to BIBF 1202 (M1) was relatively fast for all routes of administration. Maximum plasma concentrations of BIBF 1202 were reached around the same time as for nintedanib. Exposure was in the same order of magnitude after oral administration and PK characteristics were similar.

Total exposure (AUC) to BIBF 1202 glucuronide (M2) was substantially higher than the one to nintedanib or BIBF 1202 after oral administration. Maximum plasma concentrations were reached later.

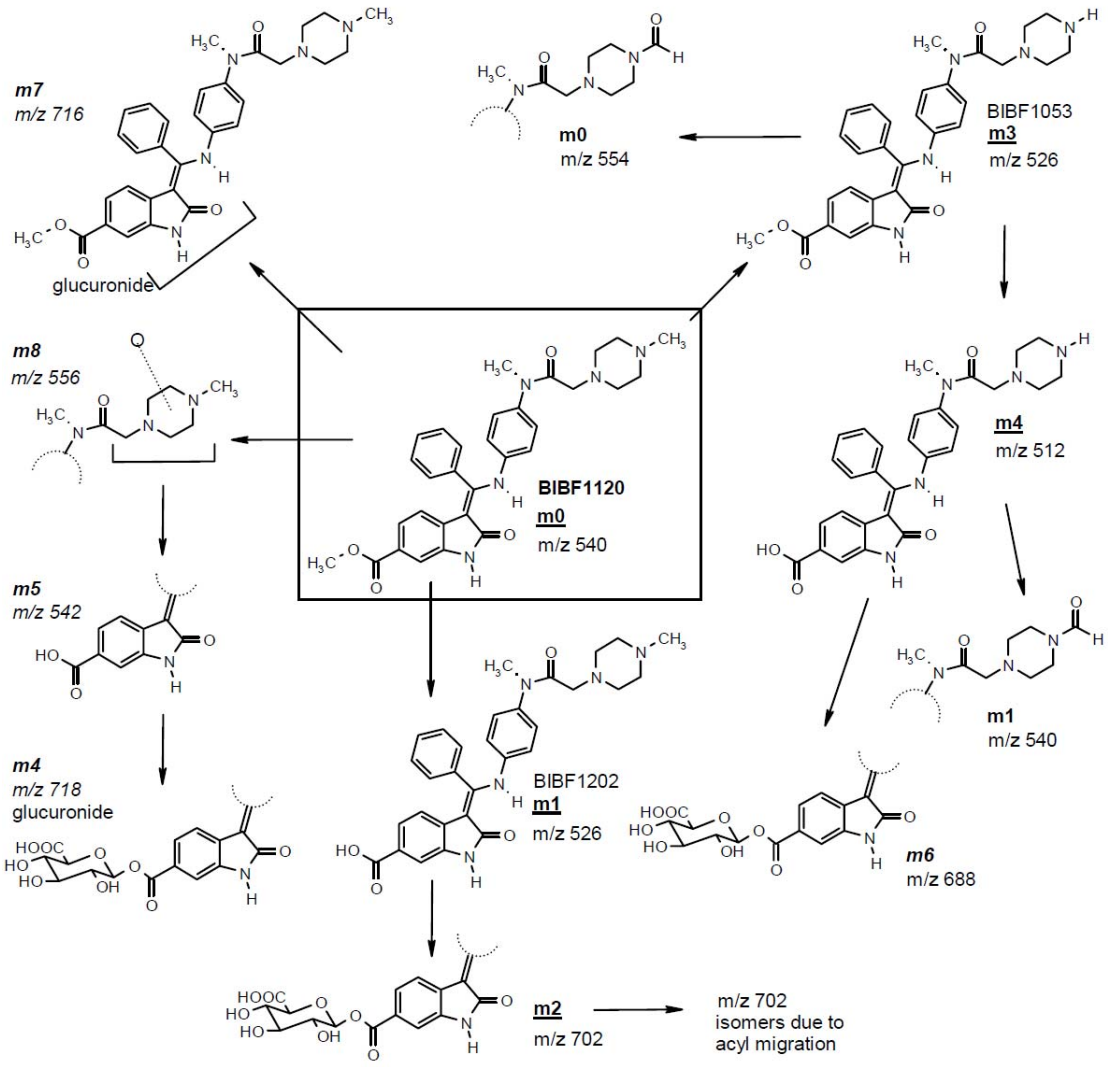

Figure 7: Proposed Metabolic Pathways for nintedanib (BIBF 1120) in Human Plasma
(Source – Figure 9:20, study report A248_05TE)

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

In vitro studies determined that nintedanib is not a substrate of BCRP. In the mass balance study, feces sample fractions that were collected 0 - 72 h after oral dosing and that were used for the assessment metabolite pattern comprised 88% of the administered dose, with 65-80% of the total dose excreted as metabolites (see section 2.5.6). This indicated that the drug related material was preferentially excreted via the bile, and majority of nintedanib was excreted in bile as metabolites.

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Biliary excretion is a major elimination pathway for nintedanib. The existence of the

enterohepatic recirculation for nintedanib was confirmed by the concentration-time profile (Figure 8). With a single oral dose of 100mg capsule, a second peak of ninedanib was observed in plasma at 5-6 hours post-dose, following the first peak at around 1-2 hours post-dose. Similar PK profile was observed in study 1199.161(single oral dose of 50 mg nintedanib with food) and 1199.162(single oral dose of 150 mg nintedanib with food). However, this phenomenon was not consistently observed in other PK studies (Figure 5). The available plasma concentration-time profile information does not suggest enterohepatic recirculation for BIBF1202 and BIBF1202 glucuronide.

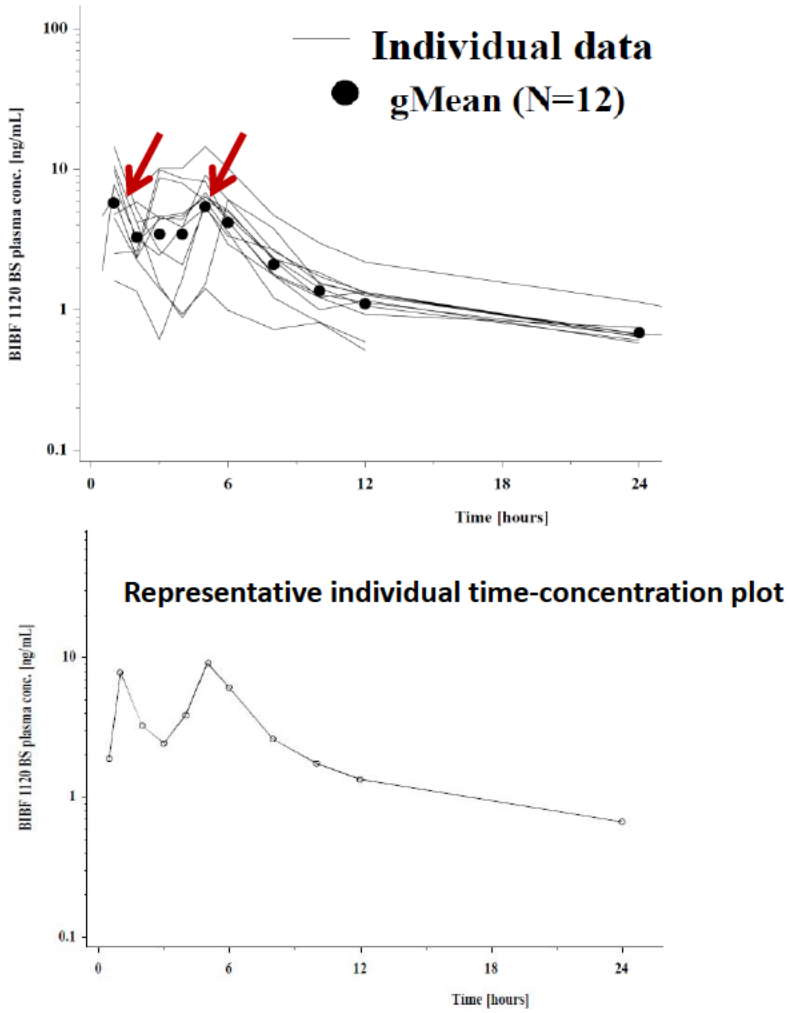

Figure 8. Plasma conc.-time profiles of BIBF 1120 BS after single oral administration of 100 mg BIBF 1120 capsule (semi-log scale)
(Source: Figure 15.6.5.2:28 and Figure 15.6.5.1:8 , study report 1199.75)

2.5.11 What are the characteristics of drug excretion in urine?

Mass balance study suggested that renal clearance constituted less than 1% of the total clearance of nintedanib. Estimates of renal clearance (CLr) of nintedanib were obtained in healthy subjects with intravenous administration. The estimate of renal clearance (CLr) was about 20 mL/min, which when adjusted for protein binding (fu of 2.2%), exceeds GFR, suggesting an additional contribution from active tubular secretion.

2.5.12 Based on PK parameters, what is the degree of the proportionality of the dose-concentration relationship?

Based on visual inspection, no relevant deviation from dose proportionality of exposure parameters, e.g. C_{max} or AUC, was observed across the dose range of 50-450 mg once daily and 150-300 mg twice daily in advanced stage cancer patients with various tumor types (Figure 9).

In the combined PopPK analysis of the Phase II/III studies 1199.10, 1199.13, 1199.14 in patients with NSCLC, and the Phase II IPF-study 1199.30, no considerable deviation from dose proportionality was found, either.

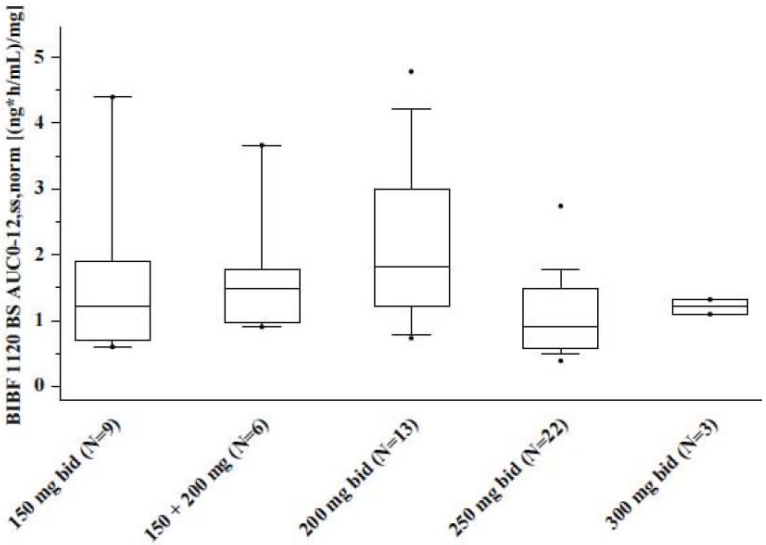

Figure 9. Comparison of dose normalized AUC0-12,ss values of BIBF 1120 at steady state after multiple twice daily administration of BIBF 1120
(Source: Figure 7.2.1.1:1, Report 1199_PK Metaanalysis Cancer Patients Monotherapy, U11-1639-01.)

2.5.13 How do the PK parameters change with time following chronic dosing?

$AUC_{0-\infty}$ for nintedanib after single dose is compared with $AUC_{\tau,ss\ (0-12h)}$ at steady state. CL/F(ss) of nintedanib did not change after multiple dosing compared to single dose administration. The linearity index, derived as $AUC_{\tau,ss}/AUC_{0-\infty}$ was 1.02 (Table 14). The pharmacokinetics of nintedanib can therefore be considered time-independent. PK information was collected in phase II and Phase III studies in IPF patients. Trough (pre-dose) concentrations are similar over a 12-month period, indicating no time-dependency in PK of nintedanib after the concentration reached steady state.

Table 14: Exposure of nintedanib after single or multiple doses

Study	**Treatment**	**N**	AUC* (ng.h/mL/mg) **gMean (CV%)**	CL/F (mL/min) **gMean (CV%)**
1199.26	Nintedanib SD	65	1.33 (78.5)	12500(78.5)
	Nintedanib BID Steady State	58	1.35 (67.5)	12400 (67.5)

N: Total subjects; SD: single dose; BID: twice daily dose
* $AUC_{0-\infty}$ for SD; $AUC_{\tau,ss}$ for BID
(Source – Table 3.2.1:1, Section 2.7.2, Summary of Clinical Pharmacology Studies)

2.5.14 Is there evidence for a circadian rhythm of the PK?

In clinical PK studies nintedanib given BID, it was observed that PK after single-dose was comparable with PK after multiple-dose, suggesting that circadian rhythm is not present for nintedanib PK.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, Cmax, Cmin) in patients with the target disease and how much of the variability is explained by the identified covariates?

Based on sponsor's population PK analysis of IPF patients (N=933), body weight, age, lactate dehydrogenase (LDH) levels and smoking history were identified as covariates influencing the PK of nintedanib. As shown in Table 15, exposure (steady state AUC) increased by 24% in a 55 kg patient (5th percentile) and decreased by 19% in 107 kg patient (95th percentile) compared to a 77 kg patient (median within the analyzed population). The magnitude of change for LDH and age were even lower. Exposure decreased by 21% in current smokers compared to ex-smokers or patients who have never smoked. Similarly, the magnitude of change in the exposure of BIBF 1202 due to body weight, age, LDH and smoking status were small (Table 16).

Table 15: Impact of individual covariates on the exposure of nintedanib

Covariate	Effect of covariate	Percentage change in $AUC_{\tau,ss}$*
Covariates included on CL/F		
WT	CL/F increased with increasing weight (and vice versa) as described using a power function (power of 0.634).	$AUC_{\tau,ss}$ increased by 24% in a 55 kg patient (5th percentile) and decreased by 19% in a 107 kg patient (95th percentile), as compared to a 77.1 kg patient (median within analyzed population).
LDH	CL/F changed linearly by 19.0% per 100 U/L difference to LDH of 205 U/L.	$AUC_{\tau,ss}$ was decreased by 10% for a patient with LDH of 146 U/L (5th percentile) and increased by 20% for a patient with LDH of 294 U/L (95th percentile) relative to a patient with the median LDH of 205 U/L (median within analyzed population).
Covariates included on F1		
AGE	F1 changed linearly by 0.976% per 1 year difference to age of 66 years.	$AUC_{\tau,ss}$ decreased by 14% in a 52 year old patient (5th percentile) and increased by 13% in a 79 year old patient (95th percentile), as compared to a patient with the median age of 66 years (median within analyzed population)
SMOK	F1 decreased by 21% in current smokers compared to ex- or never smoker (effect size fixed according to previous PopPK analysis [U13-1588]	$AUC_{\tau,ss}$ decreased by 21% in current smokers compared to ex- or never smoker
RACE+GEOR	F1 decreased by 16% for Korean patients as compared to Caucasians. F1 increased by 16% for Japanese patients and by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians	$AUC_{\tau,ss}$ decreased by 16% for Korean patients as compared to Caucasians. $AUC_{\tau,ss}$ increased by 16% for Japanese patients and by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians

* $AUC_{\tau,ss}$ (dose normalized) was calculated as F1 divided by CL/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

Source data: Appendix 16.1.4.1.2.1

(Source: Table 10.1.3.2:2 from combined population PK report for IPF patients)

Table 16: Impact of individual covariates on the exposure of the metabolite BIBF 1202

Covariate	Effect of covariate	Percentage change in $AUC_{\tau,ss}$*
Covariates identified for nintedanib affecting the BIBF 1202 exposure with the same effect size (due to interdependancy of F2 and F1)		
AGE	F1 changed linearly by 0.976% per 1 year difference to median age of 66 years in the analysed population.	$AUC_{\tau,ss}$ decreased by 14% in a 52 year old patient (5th percentile) and increased by 13% in a 79 year old patient (95th percentile), as compared to a patient with the median age of 66 years (median within analyzed population)
SMOK	F1 decreased by 21% in current smokers compared to ex- or never smoker (effect size fixed according to previous PopPK analysis [U13-1588].	$AUC_{\tau,ss}$ decreased by 21% in current smokers compared to ex- or never smoker
Covariates identified for both nintedanib and BIBF 1202 – different effect sizes for BIBF 1202 and nintedanib exposure		
WT	F2 decreased with increasing weight (and vice versa) as described using a power function (power of -0.782).	$AUC_{\tau,ss}$ increased by 26% for a 55 kg patient (5th percentile) and decrease by 19% for a 107 kg patient (95th percentile) relative to a patient weighing 77.1 kg (median within analyzed population).
RACE +GEOR	F1 decreased by 16% for Korean patients, increased by 16% for Japanese patients and increased by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians. F2/F1 ratio increased by 90% for Indian patients (fixed according to previous PopPK analysis [U13-1588]) and increased by 28 % for Asians except for Indians as compared to Caucasians.	$AUC_{\tau,ss}$ increased by 166% for patients with Indian origin, by 86% for Asians except for Indian, Korean or Japanese patients, by 5% for Korean patients and by 44% for Japanese patients as compared to Caucasians.
LDH	F2 decreased linearly by 10.8% per 100 U/L absolute difference to 688 U/L. For LDH levels higher than 688 U/L a constant F2 of 1 was assumed.	$AUC_{\tau,ss}$ was decreased by 11% for a patient with LDH of 146 U/L (5th percentile) and increased by 17% for a patient with LDH of 294 U/L (95th percentile) relative to a patient with the median LDH of 205 U/L (median within analyzed population).

* $AUC_{\tau,ss}$ (dose normalized) was calculated as (F2+ffM1*F1) divided by CL2/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

BIBF 1202 specific covariates		
SEX	CL2/F was decreased by 12% in female patients as compared to males.	$AUC_{\tau,ss}$ increased by 14 % in female patients as compared to males.
BBIL	CL2/F changed linearly by -1.31% per 1 µM difference to median BBIL of 9 µM in analysed population.	$AUC_{\tau,ss}$ was decreased by 5% for a patient with BBIL of 5 µM (5th percentile) and increased by 13% for a patient with BBIL of 18 µM U/L (95th percentile) relative to a patient with the median BBIL of 9 µM (median within analyzed population).

* $AUC_{\tau,ss}$ (dose normalized) was calculated as (F2+ffM1*F1) divided by CL2/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

(Source: Table 10.1.4.2:2 from combined population PK report for IPF patients)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

The differences in the exposure of nintedanib and BIBF 1202 are not sufficient to warrant a dose adjustment in any subgroups. Changes in exposure due to individual covariates were within the inter-patient variability range of nintedanib. Thus, changes in exposure are unlikely to explain any differences observed in the efficacy/safety of the drug.

2.6.2.1 Severity of Disease State

Not assessed.

2.6.2.2 Body Weight

See Pharmacometrics Review as stated in response 2.6.1.

2.6.2.3 Elderly

See Pharmacometrics Review as stated in response 2.6.1.

2.6.2.4 Pediatric Patients

As nintedanib in IPF has been granted Orphan Drug Status, there is no Pediatric Study Plan (PSP) included in this submission; per 21 CFR 314.55(d), Orphan Drugs are exempt from the requirements to assess pediatric use under PREA.

2.6.2.5 Race/Ethnicity

See Pharmacometrics Review as stated in response 2.6.1.
The sponsor's analysis divided patients into subgroups based on race and the country the study site was located as shown in Table 17. The model predicted estimates of exposures in Asians have higher exposures (as high as 50% increase in patients in Chinese, Taiwanese sites) compared to Caucasians. The Sponsor's rationale for grouping Asians and Caucasians together in Indian sites is unclear. It is also unclear why Asian patients in Korean sites have a 16% decrease in exposure compared to Caucasians. Due to the reasons mentioned above, sponsor's conclusion for impact of race on PK should be viewed with caution.

Table 17: Subgroups for Race and Study site in Population PK analysis

Category	RACE	Study site
Caucasian	Caucasian	Any site located not in India
Chinese	Asian	China
Korean	Asian	Korea
Taiwanese	Asian	Taiwan
Indian	Asian or Caucasian	India
Japanese	Asian	Japan
Other Asian	Asian	Country other than China, Korea,

		Taiwan, India or Japan
Black	Black	
American Indian/Alaska native	American Indian/Alaska native	

(Source :Reviewer's summary)

2.6.2.6 Renal Impairment

The contribution of renal excretion after oral administration of nintedanib both as unchanged drug (about 0.05% of dose; i.e., about 1% of the bioavailable fraction) and as drug related radioactivity was minor (about 0.6% of dose). Therefore, no dedicated study in renal impaired patients has been performed.

Creatinine clearance or GFR was investigated as a covariate in the Phase II/III PopPK analysis and in several supportive data sets (see Pharmacometrics Review, appendix 4.1). Overall, no significant effect of mild and moderate renal impairment as estimated by these parameters on the PK of nintedanib was found; data on severe renal impairment was too sparse to draw conclusions. The apparent trends for lower creatinine clearance or estimated GFR to be associated with higher exposure to nintedanib in univariate analyses could be explained reasonably well by patient age and/or body weight (estimation of creatinine clearance by the Cockcroft-Gault equation).

2.6.2.7 Hepatic 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.

(b) (4)

Reviewer's comment

Nintedanib was not evaluated in patients with Child Pugh B or C hepatic impairment. Therefore, nintedanib is not recommended in patients with moderate or severe hepatic impairment.

2.6.3 Does genetic variation impact exposure and/or response?

Datasets from three studies (studies 119.06, 119.10, and 119.75) were used to conduct a meta-analysis evaluating the impact on *UGT1A1*28* on the PK of nintedanib (BIBF 1120) and its metabolites (BIBF 1202 and BIBF 1202 glucuronide). According to the Sponsor's analysis, exposure to the active parent compound and the active metabolite BIBF 1202 is not affected by *UGT1A1*28* genotype. BIBF 1202 glucuronide exposure appears to be lower in *UGT1A1*28* homozygotes; however, since BIBF 1202 glucuronide does not have known biological activity, the consequences of this are unlikely to impact safety or efficacy of nintedanib.

(b) (4)

2.7 Extrinsic Factors

2.7.1 Is there an in vitro basis to suspect in vivo drug-drug interactions?

The potential for drug-drug interaction because of induction or inhibition of CYP enzymes or transporters by nintedanib is less likely at therapeutic concentrations. See sections 2.7.2 and 2.7.4 for further details.

2.7.2 Is the drug a substrate of CYP enzymes?

A minor extent of the biotransformation of nintedanib consisted of CYP pathways, predominantly CYP3A4. CYP3A4 pathway yielded a metabolite that could not be detected in plasma in the human [14C]-ADME study but only in excreta, predominantly feces (4% of dose). *In vitro*, CYP dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

The prevalent metabolic reaction was rapid hydrolytic cleavage by esterases resulting in the acid moiety BIBF 1202. BIBF 1202 was subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Nintedanib and its metabolites do not inhibit or induce CYP enzymes or UGT enzymes at clinically relevant concentrations. *In vitro* studies demonstrated little or no inhibition of 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4, 4A11, UGT1A1 or UGT2B7 activities for nintedanib, BIBF1202 or BIBF1202 glucuronide. Nintedanib weakly inhibited erythromycin N-demethylation via CYP 3A4 with an IC_{50} of 70.1 µM (one out of four substrates); BIBF 1202 glucuronide inhibited flurbiprofen 4'- hydroxylation via CYP 2C9 with an IC_{50} of 85.5 µM (one out of three substrates). All other IC_{50} values were above 100 µM (resp. 50 µM for CYP 2C8 inhibition by nintedanib, which was the highest concentration tested). The IC_{50} for UGT 1A1 dependent ß-estradiol metabolism was 24.5 µM for nintedanib and >200 µM for BIBF 1202. UGT 2B7 dependent ß-estradiol metabolism was inhibited by nintedanib with an IC_{50} of 77.6 µM and an IC_{50} >200 µM for BIBF 1202.

In vitro inhibition experiments of BIBF 1202 glucuronidation were performed with several compounds. Inhibition was competitive for the following compounds; the respective IC_{50} values are given in brackets: docetaxel (7.6 µM), paclitaxel (8.8 µM), simvastatin (84.5 µM), domperidone (25.0 µM), and diclofenac (78.6 µM). The IC_{50} for nintedanib inhibiting BIBF 1202 glucuronidation (competitive) was 1.7 µM; the K_i value was 12.6 µM.

The *in vitro* induction potential of nintedanib on human CYP enzymes was assessed in sandwich cultured primary human hepatocytes using a concentration range of 0.001 to 2 µM. Neither induction of enzyme activity nor mRNA levels was found for any of the P450 enzymes tested (CYP 1A2, 2B6, 2C8, 2C9, 2C19, and 3A4).

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

In *in vitro* studies, nintedanib was shown not to be a substrate of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, MRP-2, or BCRP. *In vitro* studies also showed that nintedanib was a substrate of OCT-1; these findings are considered to be of low clinical relevance.

Nintedanib inhibited OCT-1 mediated transport with an IC_{50} of 0.88 µM (Table 18); inhibition of P-gp was not clearly concentration-dependent. Maximum inhibition to 72.9% of the control value was observed at the intermediate concentration (3 µM), while transport increased back to nearly 100% at the highest concentration (30 µM). BIBF 1202 showed inhibition of four investigated uptake transporter with IC_{50} values of 14 µM and higher. BIBF 1202 glucuronide only weakly inhibited P-gp and MRP-2 at concentrations of 100 µM with 55% and 58 % of transport activity remaining, respectively.

Table 18. Transporter profiling of nintedanib, BIBF 1202, and BIBF 1202 glucuronide

	Nintedanib		BIBF 1202		BIBF 1202 glucuronide	
Transporter	**Substrate**	**Inhibitor/IC_{50}***	**Substrate**	**Inhibitor/IC_{50}***	**Substrate**	**Inhibitor/IC_{50}***
SLC-transporter						
OATP-1B1	No	No (10 µM)	Yes	14 µM	No	No (100 µM)
OATP-1B3	No	No (10 µM)	No	79 µM	No	No (100 µM)
OATP-2B1	No	No (10 µM)	Yes	50 µM	No	nd
OCT-1	Yes	0.88 µM	No	16 µM	No	nd
OCT-2	No	No (30 µM)	No	No (100 µM)	nd	No (100 µM)
OAT-1	nd	nd	nd	nd	nd	No (100 µM)
OAT-3	nd	nd	nd	nd	nd	No (100 µM)
ABC-transporter						
P-gp	Yes	Weak (30 µM)[#]	No	No (30 µM)	nd	Weak (100 µM)
MRP-2	No	No (30 µM)	No	No (30 µM)	Yes	Weak (100 µM)
BCRP	No	Weak (30 µM)[#]	No	Weak (30 µM)	Yes	No (100 µM)

nd not determined
IC_{50} not determined as inhibition was not clearly concentration dependent; expected to be >30 µM
* The highest concentration tested is given in brackets

(Source: Table 3.1.8:1, summary of clinical pharmacology)

2.7.5 Are there other metabolic/transporter pathways that may be important?

No other metabolic enzyme or transported pathway is known to be important for disposition of nintedanib in addition to those already discussed in sections 2.7.2 and 2.7.4

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

The effect of extrinsic factors on nintedanib exposure was summarized in Table 19.

Table 19. Extrinsic Factors

Co-administered drug	Rationale	Nintedanib		Dosing recommendation
		AUC_{inf}	C_{max}	
Ketoconazole	Inhibitor of P-gp, CYP3A4, and UGT 1A1	↑ 60%	↑ 83%	patients should be monitored closely for tolerability of nintedanib. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy.
Rifampicin	Inducer of P-gp and CYP3A4	↓ 50%	↓ 40%	No specific recommendation
Antacids (Phase 3, Ctrough)	pH dependent dissolution, Concomitant medicine	↔	↔	Not mentioned in label
Pirfenidone	Concomitant medicine	↓ 32%	↓ 40%	Not mentioned in label
Smoking (pop-PK)	Relevant patient population	↓ 21%		Not mentioned in label

(Source: Reviewer summary)

2.7.7 What are the drug-drug interactions?

-Effect of other drugs on Nintedanib

Effect of co-administration of ketoconazole, rifampicin, antacid, and pirfenidone on nintedanib exposure (AUC) and C_{max} was evaluated (Table 19).

Nintedanib is a substrate of P-gp. A minor extent of the biotransformation of nintedanib consisted of CYP pathways. Co-administration with ketoconazole (P-gp and CYP3A4 inhibitor) increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the P-gp and CYP3A4 inducer rifampicin, exposure to nintedanib decreased 50.3% based on AUC and 60.3% based on C_{max} upon co-administration with rifampicin compared to administration of nintedanib alone.

Based on a multiple-dose study in Japanese IPF patients, exposure to nintedanib decreased 68.3% based on AUC and 59.2% based on C_{max} upon co-administration with pirfenidone compared to administration of nintedanib alone.

Nintedanib displays a pH-dependent dissolution with increased solubility at acidic pH<3. However, based on steady state trough concentrations from Phase 3 PK data, co-administration with proton pump inhibitors or histamine H2 antagonists did not influence the exposure of nintedanib (Table 20). This data should be interpreted with caution as the co-medication information may not reflect the medication use on the day of PK sampling, and the Ctrough may not capture the action of antacid in absorption phase.

Table 20. Trough concentration in patients with or without co-medications of antacids

Study	Co-medication	N	Nintedanib Cpre,ss,norm gmean (ng/ml/mg)	gCV(%)	Ratio with co-med/without co-med
Study 1199.32	With PPI-H2RA	113	0.0608	63.1	0.93
	Without PPI-H2RA	144	0.0654	80.8	
Study 1199.34	With PPI-H2RA	97	0.0765	70.3	1.17
	Without PPI-H2RA	186	0.0654	70.3	

(Source: adapted from Table 11.5.2.3:1, CSR 1199.32 and Table 11.5.2.3:1, CSR 1199.34)

From population pharmacokinetic analysis, smoking status was found to significantly influence the exposure of nintedanib with a 21% lower bioavailability in current smokers compared to ex- and never-smokers.

-Effect of Nintedanib on other drugs

Effect of nintedanib co-administration on pirfenidone AUC and C_{max} was evaluated. Nintedanib did not have a relevant effect on the PK of pirfenidone.

In *in vitro* studies, nintedanib was shown not to be an inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2. *In vitro* studies also showed that nintedanib has weak inhibitory potential on OCT-1, BCRP, and P-gp. Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes *in vitro*.

Reviewer's comments

1. *Coadministration with ketoconazole significantly increased AUC and C_{max} of nintedanib by ~60% and 83%, respectively. Therefore, patients should be monitored closely for tolerability of nintedanib. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with nintedanib.*

   Ketoconazole is a potent inhibitor for CYP3A4 and also an inhibitor for P-gp. While the absolute bioavailability for nintedanib parent drug is only 4.67%, mass balance study indicated that 65-80% of the total oral dose was excreted as metabolites (see section 2.5.6) and only 20% of the total dose was excreted as parent drug. The data suggested that 65-80% of the oral dose was absorbed through GI tract and inhibition of P-gp is not likely to have a significant effect on the extent of oral absorption. Therefore, this reviewer concluded that P-gp inhibition cannot fully explain the increased exposure of nintedanib with ketoconazole, and CYP3A4 inhibition in GI tract and liver by ketoconazole may contribute to the increased nintedanib exposure.

2. *Coadministration with rifampicin significantly reduced AUC and C_{max} of nintedanib*

by ~50% and 40%, respectively. Rifampicin is an inducer for CYP3A4 and P-gp. These lower exposures may result in inefficacious concentrations; therefore, coadministration with rifampicin or other CYP3A and P-gp inducers is not recommended.

3. *No significant change in steady state trough concentrations of nintedanib was observed following co-administration with antacids. Since trough concentration is not a sensitive measure to evaluate the effect of antacids on drug absorption/exposure, a subgroup analysis for efficacy was also conducted utilizing data from phase 3 trials. Patients in the treatment arm taking proton pump inhibitor and H2-receptor antagonists showed slightly reduced efficacy with respect to annual rate of decline in FVC compared to patients without these co-medications (Table 21). However, a relatively larger effect was observed for patients in the placebo arm suggesting patients who needed these co-medications were likely to be poor responders due to other factors that are not related to drug exposure. Therefore, no dose adjustments are recommended.*

Table 21. Subgroup analysis for efficacy by patients with/without concomitant use of PPI and H2 receptor antagonists

Treatment arm	PPI + H2 receptor antagonists	N	Annual rate of decline in FVC (ml/yr)
Study 32			
Placebo	No	175	-221.49
Placebo	Yes	29	-315.62
Nint 150 mg	No	236	-108.07
Nint 150 mg	Yes	73	-137.58
Study 34			
Placebo	No	171	-204.46
Placebo	Yes	48	-244.99
Nint 150 mg	No	259	-111.43
Nint 150 mg	Yes	70	-113.92

(Source: reviewer analysis)

4. *Following co-administration with pirfenidone, nintedanib AUC decreased by ~32% and C_{max} reduced by ~40%, possibly due to CYP3A4 induction in liver and GI tract by pirfenidone. More AEs were observed when pirfenidone was co-administered with nintedanib. It is not clear whether the two drugs have additive or synergistic effect in efficacy. Given the limited data, no dose adjustments are recommended at this time.*

2.7.8 Does the label specify coadministration of another drug?

No, the nintedanib label does not mention specific coadministration with other drugs.

2.7.9 What other co-medications are likely to be administered to the target population?

All IPF patients are likely to take nintedanib in background of other drugs to treat IPF such as pirfenidone; supportive treatment to relieve symptoms of IPF, such as oxygen therapy, bronchodilators, and antibiotics; and drugs that manage GERD such as PPI.

IPF is more likely to occur in old age patients; therefore, there is a potential for other drugs such as anti-hypertensives, anti-diabetic, anti-hyperlipidemic etc. to be administered with nintedanib.

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

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.

2.8 General Biopharmaceutics

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

Sponsor proposed that nintedanib can be considered a BCS class 2 or 4 drug because of low aqueous solubility at neutral pH.

BIBF 1120 ethanesulfonate is classified as a drug substance with low solubility according to BCS (Biopharmaceutical Classification System). In terms of permeability, BIBF 1120 does not display straightforward pharmacokinetic and metabolic properties during the absorption phase, after oral application, that are solely governed by its physicochemical properties. *In vitro*, BIBF 1120 exhibits high passive permeability in the absence of active transport, however, in vivo absorption in the gastrointestinal tract is influenced by P-glycoprotein. BIBF 1120 is rapidly metabolized intracellularly by esterases to the resulting acid (BIBF 1202). Thus, BIBF 1120 can be classified as a BCS class II drug substance (low solubility – high permeability) or as BCS class IV (low solubility – low permeability).

Reviewer's comment: *Based on dissolution profile (Figure 10), there is potential for drug interaction with antacids.*

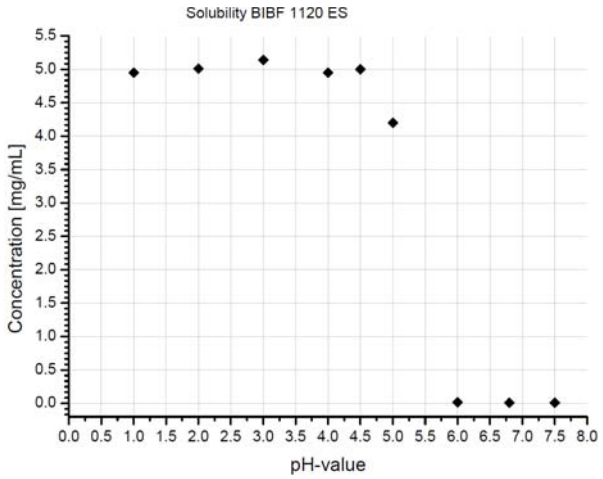

Figure 10. pH-dependent solubility profile of BIBF 1120 ethanesulfonate in aqueous media at 37°C
(Source: Figure 2, study 09/222-02, report U10-1363-02)

2.8.2 How is the proposed to-be-marketed formulation linked to the clinical service formulation?

Whereas initial clinical trials were performed with the dosage strengths 50 and 200 mg only, subsequent clinical trials were carried out with capsules of the dosage strengths 100 mg, 125 mg, and 150 mg. The capsule fill mix remained unchanged compared with the one used in capsules (50 and 200 mg) for initial clinical trials. No BA/BE studies were conducted as composition of the 100 mg and 150 mg soft gelatin capsules used in the phase III trials and the final commercial formulation are the same. Please refer to review by Office of New Drug Quality Assessment (ONDQA) for further details regarding formulation changes.

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

The effect of food was investigated in a dedicated study in healthy volunteers 1199.17. Nintedanib was administered at a dose of 150 mg consisting of three 50 mg capsules after an over-night fast of at least 10 hours or after a high-fat, high-caloric meal.

Exposure ($AUC_{0-\infty}$ and C_{max}) increased at mean by about 20% when nintedanib was administered under fed conditions. The absorption of nintedanib was delayed (median T_{max}; fasted: 2.00 h; fed: 3.98 h) and the inter-subject variability of total exposure increased under fed conditions (gCV of $AUC_{0-\infty}$: fasted: 33.0%, fed: 53.9%).

No relevant differences regarding food effect were seen with respect to the meal type in an across study comparison; exposure to nintedanib was comparable following administration as soft gelatin capsule after intake of a standard continental breakfast (1199.21) or a high caloric meal (1199.17; Table 22).

Table 22: Geometric mean pharmacokinetic parameters (%gCV) of nintedanib after single oral administration of 150 mg nintedanib as capsule in studies 1199.17 and 1199.21 after different meals

	Capsule, fed (standard breakfast) (Study 1199.21; N=36)	Capsule, fed (high fat, high caloric breakfast) (Study 1199.17; N=15)
$AUC_{0-\infty}$ (ng·h/mL)	128 (32.6%)	119 (53.9%)
AUC_{0-24} (ng·h/mL)	94.5 (31.2%)	90.2 (52.9%)
C_{max} (ng/mL)	13.7 (42.8%)	13.2 (61.6%)
t_{max} (h)*	2.00 (0.750-6.00)	3.98 (1.50-6.05)

(Source – Table 3.2.1:1, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were they bioequivalent or not?

There are two strengths of the to-be-marketed formulation, 100 mg and 150 mg soft gelatin capsule. No dedicated bioequivalence study was conducted to test the BE between the two strengths. The normalized exposure comparison was similar between the two strengths based on inter-individual comparison (Table 23).

In addition, the CL/F(ss) did not change with dose in studies which used soft gelatin capsules of 50mg and 200mg strength (section 2.5.12). This data suggested both linear kinetics and similar normalized exposure among capsules of different strengths. Overall, no considerable deviation from dose proportionality was found across different strength of capsules, and the formulation/strength used in phase 3 trials and the final commercial products are the same. Therefore, no additional BA/BE studies are necessary.

Table 23. Geometric mean (and gCV%) of pharmacokinetic parameters of nintedanib after oral administration of nintedanib as soft gelatin capsule to Japanese IPF patients

Study /population	Strength (mg/ capsule)	Dose, Fed (mg)	n	$AUC_{\tau,ss,norm}$ (h*ng/mL/mg)	$C_{max,ss,norm}$ (h*ng/mL/mg)
1199.31/ IPF	100	100 BID	4	1.15	0.200
	150	150 BID	9	1.45	0.264

(Source: Table 11.5.2.2.1:1, study report 1199.30)

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

The concentrations of the free base of nintedanib and its metabolites BIBF 1202 and BIBF 1202 glucuronide were quantified in human plasma and urine samples. Analytical methods used to measure the parent drug in different studies are listed in Table 24.

Several specific and highly sensitive HPLC-MS/MS methods (high-performance liquid chromatography coupled to tandem mass spectrometry) and UPLC-MS/MS methods (ultra-high performance liquid chromatography coupled to tandem mass spectrometry)

were developed and validated for human EDTA plasma and acidified urine. Single and multi-analyte assays for the simultaneous quantification of two or three analytes within one analytical run were developed and validated.

Different analytical methods were developed and validated throughout the development, and there are 17 analytical reports submitted in this NDA. Analytical methods used in different studies are listed in Table 24. The best lower limit of quantification (LLOQ) for nintedanib is 0.05 ng/mL for nintedanib, 0.1ng/mL for BIBF1202, and 0.1ng/mL for BIBF1202 glucuronide. At a single clinical dose of nintedanib (150 mg or 100 mg), plasma concentrations of nintedanib can be measure up to 48 h post dose.

Assays were developed and validated, and samples were analyzed in two sites: Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany (BI) and (b) (4) [redacted]. In this review, we summarized the most common method for the parent drug and metabolites in plasma, which were used to analyze samples in most of the pop-PK studies and DDI studies.

Analytical method for BIBF1120, BIBF1202 and BIBF1202 GLUC in plasma: report # U10-1387, U10-1149, and U13-1532

An assay for the simultaneous determination of BIBF 1120 BS, BIBF 1202 ZW, and BIBF 1202 GLUC in human plasma was developed and validated (U10-1149). The validated assay was then transferred (b) (4) [redacted], the assay was fully validated, and a cross-validation with the original assay was performed (U10-1387). U10-1149 and U10-1387 were validated over the concentration range of 0.500 to 500 ng/mL BIBF 1120 BS and 1.00 to 1000 ng/mL BIBF 1202 ZW and BIBF 1202 GLUC, respectively, using a sample volume of 50 µL.

In order to support clinical studies investigating a lower nintedanib dose, e.g. 1199.161, the assay was modified and revalidated with a lower concentration range of 0.0500 to 50.0 ng/mL BIBF 1120 BS and 0.100 to 100 ng/mL BIBF 1202 ZW and BIBF 1202 GLUC using a sample volume of 50 µL human plasma. The results of this validation study performed by (b) (4) [redacted] are reported in U13-1532.

Table 24: Summary of analytical methods for analysis of nintedanib in clinical

Study	Clinical study report reference	Analyte(s)	Matrix	Method reference	Remarks
1199.31	[U11-2158]	BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U10-1387]$	Analysed at (b) (4) [redacted]
1199.32		BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U10-1387]$	Analysed at [redacted]
1199.34		BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U10-1387]$	Analysed at [redacted]

1199.30	[U11-1225]	BIBF 1120 BS; BIBF 1202 ZW	plasma	[U08-1519]	
		BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U10-1149] $	
1199.161	[U13-1925]	BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U13-1532]$	Analysed at (b) (4)
1199.162	[U13-1478]	BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U13-1532]$	Analysed at
1199.75	[U10-1400]	BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	plasma	[U10-1149] $	
		BIBF 1120 BS; BIBF 1202 ZW; BIBF 1202 GLUC	urine	[U10-1666]	Analysed at

(Source – Table 1.4.1:2, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

2.9.2 Which metabolites have been selected for analysis and why?

Two major metabolites, BIBF1202 and BIBF1202 GLUC were analyzed in phase 2 and 3 studies.

2.9.3 For all moieties measured, is free, bound, or total measured?

Total (bound + unbound) concentrations were measured in plasma PK samples.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Table 24 presents a summary of analytical methods used for quantification of nintedanib and lists out the respective validation report numbers.

U10-1149 and U10-1387

50 µL human plasma was mixed with the solution of the deuterated internal standards [D8]BIBF 1120 BS, [D8]BIBF 1202 ZW and [D8]BIBF 1202 GLUC and samples were cleaned up by solid phase extraction (SPE) in the 96-well plate format. Chromatography was achieved on an analytical C18 (b) (4) column (b) (4) . The substances were detected by UPLC-MS/MS in the positive electrospray ionisation mode.

U13-1532

50 µL human plasma was mixed with the solution of the deuterated internal standards [D8]BIBF 1120 BS, [D8]BIBF 1202 ZW and [D8]BIBF 1202 GLUC and samples were cleaned up by solid phase extraction (SPE) in the 96-well plate format. Chromatography was achieved on an analytical C18 (b) (4) column (b) (4) The substances were detected by HPLC-MS/MS in the positive electrospray ionisation mode.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

U10-1149 and U10-1387

The standard curves were validated over the concentration range of 0.500 to 500 ng/mL for BIBF 1120 BS and 1.00 to 1000 ng/mL for BIBF 1202 ZW and BIBF 1202 GLUC, respectively. A linear regression model, with weighting factor of 1/concentration^2 was used for the curve fitting.

U13-1532

The standard curve were validated in plasma using method U13-1532 ranged from 0.05 to 50 ng/mL for BIBF 1120 BS and 0.1 to 100 ng/mL for BIBF 1202 ZW and BIBF 1202 GLUC, respectively.. A linear regression model, with weighting factor of 1/concentration^2 was used for the curve fitting.

2.9.5.1 What are the lower and upper limits of quantitation?

U10-1149 and U10-1387

LLOQ and ULOQ for U10-1149, U10-1387 analytical method were 0.500 and 500 ng/mL BIBF 1120 BS as well as 1.00 and 1000 ng/mL BIBF 1202 ZW and BIBF 1202 GLUC, respectively, using sample volumes of 50 µL human plasma. The acceptance criteria were not met for all analytes when using either of the automated dilution modes. However, the manual 1:9 (v/v) and 1:99 (v/v) dilution fulfilled the acceptance criteria for all three analytes.

U13-1532

LLOQ and ULOQ for U13-1532 analytical method were 0.05 ng/mL and 50 ng/mL BIBF for 1120 BS and 0.1 and 100 ng/mL for BIBF 1202 ZW and BIBF 1202 GLUC, respectively, using sample volumes of 50 µL human plasma. A 10-fold dilution factor was validated for 200/400/400 ng/mL concentration.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

The accuracy and precision of analytical methods U10-1149, U10-1387 and U13-1532 are listed in Table 25, Table 26 and Table 27, respectively.

Table 25: Accuracy and Precision of Nintedanib Analytical LC/MS/MS Assay in human plasma at a lower concentration range (Validation Report # U13-1532)

BIBF 1120 BS	LLOQ	QC_low	QC_mid	QC_high
Nominal concentration	0.0500 ng/mL	0.125 ng/mL	2.50 ng/mL	40.0 ng/mL
Accuracy (dev)	9.4%	3.7%	6.3%	2.5%
Precision (CV)	11.2%	7.8%	7.8%	9.0%
N	24	22	22	22
BIBF 1202 ZW				
Nominal concentration	0.100 ng/mL	0.250 ng/mL	5.00 ng/mL	80.0 ng/mL
Accuracy (dev)	7.5%	9.0%	5.4%	-3.4%
Precision (CV)	8.7%	8.8%	9.1%	9.6%
N	24	22	22	22
BIBF 1202 GLUC				
Nominal concentration	0.100 ng/mL	0.250 ng/mL	5.00 ng/mL	80.0 ng/mL
Accuracy (dev)	4.0%	6.5%	12.3%	-3.2%
Precision (CV)	16.2%	10.0%	7.5%	9.6%
N	24	22	22	22

(Source – Table 1.4.3.1:4, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Table 26: Accuracy and Precision of Nintedanib Analytical LC/MS/MS Assay (Validation Report # U10-1387)

BIBF 1120 BS	LLOQ	QC_low	QC_mid	QC_high
Nominal concentration	0.500 ng/mL	1.25 ng/mL	25.0 ng/mL	400 ng/mL
Accuracy (dev)	-2.8%	-1.4%	1.1%	-2.1%
Precision (CV)	11.5%	7.0%	3.2%	5.3%
N	24	27	28	28
BIBF 1202 ZW				
Nominal concentration	1.00 ng/mL	2.50 ng/mL	50.0 ng/mL	800 ng/mL
Accuracy (dev)	-3.1%	-0.3%	5.1%	-0.4%
Precision (CV)	13.3%	6.5%	2.5%	5.2%
N	24	27	28	28
BIBF 1202 GLUC				
Nominal concentration	1.00 ng/mL	2.50 ng/mL	50.0 ng/mL	800 ng/mL
Accuracy (dev)	9.7%	4.3%	8.1%	4.0%
Precision (CV)	8.3%	7.2%	3.4%	5.6%
N	24	27	28	28

(Source – Table 1.4.3.1: 3, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

Table 27: Accuracy and Precision of Nintedanib Analytical LC/MS/MS Assay (Validation Report # U10-1149)

BIBF 1120 BS	LLOQ	QC_low	QC_mid	QC_high
Original method core validation				
Nominal concentration	0.500 ng/mL	1.25 ng/mL	25.0 ng/mL	400 ng/mL
Accuracy (dev)	2.6%	2.1%	-7.6%	-2.8%
Precision (CV)	10.3%	5.2%	2.3%	3.7%
N	18	10	10	10
BIBF 1202 ZW				
Original method core validation				
Nominal concentration	1.00 ng/mL	2.50 ng/mL	50.0 ng/mL	800 ng/mL
Accuracy (dev)	1.4%	4.4%	-6.8%	0.6%
Precision (CV)	5.5%	4.8%	3.7%	2.4%
N	18	10	10	10
BIBF 1202 GLUC				
Original method core validation				
Nominal concentration	1.00 ng/mL	2.50 ng/mL	50.0 ng/mL	800 ng/mL
Accuracy (dev)	-9.2%	-2.2%	-8.6%	-4.4%
Precision (CV)	6.8%	5.7%	2.8%	2.5%
N	18	10	10	10

(Source – Table 1.4.3.1: 2, Section 2.7.1, Summary of Biopharmaceutic Studies and Associated Analytical Methods)

The selectivity of all the methods was evaluated by extracting and analyzing blank human plasma from 10 individual sources. All lots were free from significant interfering peaks in the drug and internal standard regions. Assessment of potential mutual interferences on the detection of the internal standards and the analytes was performed in neat solutions. No relevant interference between the analytes or the internal standards was observed.

2.9.5.3 What is the sample stability under conditions used in the study?

As nintedanib is a substrate of esterase, the stability of nintedanib and its major metabolites in plasma was investigated early in the drug development program. Table 28 summarizes the longest storage periods for which the stability of nintedanib in a given

biological matrix could be demonstrated. Generally, a deviation of less than 15% from the respective reference value or nominal concentration was considered acceptable.

The stability data suggested that there was no extensive hydrolytic degradation of nintedanib in blood. The stability of BIBF 1202 and BIBF1202 GLUC is similar to that of nintedanib.

Table 28. Stability of BIBF 1120 BS in biological matrices

Matrix	Condition	Longest verified storage period
Human whole-blood (EDTA)	Storage at room temperature	4 hours
	Storage in an ice/water bath	3 hours
Human plasma (EDTA), standard concentration range	Storage at room temperature	3 days
	Freeze/thaw cycles	3 cycles
	Storage at -20°C	615 days
Human plasma (EDTA), low concentration range	Storage at room temperature	24 hours
	Freeze/thaw cycles	3 cycles
	Storage at -20°C	371 days
Acidified[§] human urine	Storage at room temperature	48 hours
	Storage at 37°C	48 hours
	Freeze/thaw cycles	3 cycles
	Storage at -20°C	1498 days

§: containing 0.5 M citric acid

(Source: Table 1.4.5:1, Summary of biopharm)

For the bioanalytical methods stability was demonstrated under different conditions as discussed below:

<u>BIBF1120 BS, methods U10-1149, U10-1387 and U13-1532</u>

Stability of BIBF1120 BS was established under various conditions: Three freeze thaw cycles at -20°C; stability of processed samples (auto sampler reinjection and reproducibility) for 24 hours. Stock solution stability was also assessed for 250 days at room temperature and 369 days at 4°C.

<u>BIBF 1202, methods U10-1149, U10-1387 and U13-1532</u>

Stability of BIBF1202 was established under various conditions: Three freeze thaw cycles at -20°C; stability of processed samples (auto sampler reinjection and reproducibility) for 24 hours. Stock solution stability was also assessed for 250 days at room temperature and 369 days at 4°C.

<u>BIBF 1202 GLUC, methods U10-1149, U10-1387 and U13-1532</u>

Stability of BIBF1202 GLUC was established under various conditions: Three freeze thaw cycles at -20°C; stability of processed samples (auto sampler reinjection and reproducibility) for 24 hours. Stock solution stability was also assessed for 391 days at -20°C.

3. Detailed Labeling Recommendations

The revised labeling language based on the preliminary review is as below. Based on the clinical pharmacology review, most revisions were on drug-drug interactions and recommendations for hepatic impairment patients. In addition, we have the following comment to the sponsor:

"**a.** Update your clinical pharmacology section based on the draft guidance "Clinical Pharmacology Labeling for Human Prescription Drug and Biological Products—Considerations, Content and Format." (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM109739.pdf)

b. You stated that "Accumulation upon multiple administration was (b) (4) . Update the numbers, preferably with oral doses in IPF patients or healthy subjects. If different accumulations were observed in different studies, use the higher number in the label (e.g. accumulation is up to xx fold). Under the annotated label, provide the source study/data to support the claim in the label (not just general "see summary of clinical pharmacology").

c. Under elimination/excretion, you stated that (b) (4) . The half-life value reported should usually be the half-life based on the time to reach steady state (i.e., the effective half-life). Replace this statement with effective half-life in IPF or healthy subjects.

d. For renal impairment, update the information with results of your popPK report in IPF patients (pop PK 1199-0030-0032-0034)."

HIGHLIGHTS OF PRESCRIBING INFORMATION

----------DRUG INTERACTIONS----------

- Coadministration of (b) (4)-P-gp and CYP3A4 inhibitors may increase nintedanib exposure. Monitor patients closely for tolerability of TRADENAME. (7.1)

----------USE IN SPECIFIC POPULATIONS----------

- Nursing mothers: Discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. (8.3)
- Hepatic impairment: Monitor for adverse reactions and consider dose modification or discontinuation of TRADENAME as needed for patients with mild hepatic impairment. TRADENAME is not recommended for use in patients with moderate or severe hepatic impairment. (8.6, 12.3)
- Renal impairment: The safety and efficacy of TRADENAME have not been studied in patients with severe renal impairment and end stage renal disease.(8.7, 12.3)
- Smokers: Decreased exposure has been noted in smokers which may alter the efficacy profile of TRADENAME (8.8)

7 DRUG INTERACTIONS

7.1 P-glycoprotein (P-gp) Inhibitors and Inducers

Nintedanib is a substrate of P-gp and to a minor extent, CYP3A4*[see Clinical Pharmacology (12.3)]*. Coadministration with oral dose of a (b) (4)-P-gp and CYP3A4 inhibitor, ketoconazole, increased exposure to nintedanib by 60%. Concomitant use of potent P-gp and CYP3A4 inhibitors (e.g., erythromycin) with TRADENAME may increase exposure to nintedanib *[see Clinical Pharmacology (12.3)]*. In such cases, patients should be monitored closely for tolerability of TRADENAME. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy with TRADENAME *[see Dosage and Administration (2)]*.

Coadministration with oral dose of a [redacted] (b) (4) P-gp and CYP3A4 inducer, rifampicin, decreased exposure to nintedanib by 50%. Concomitant use of [redacted] (b) (4) P-gp and CYP3A4 inducers (e.g., carbamazepine, phenytoin, and St. John's wort) with TRADENAME should be avoided as these drugs may decrease exposure to nintedanib *[see Clinical Pharmacology (12.3)]*.

7.2 Anticoagulants

Nintedanib is a VEGFR inhibitor, and may increase the [redacted] (b) (4) and adjust anticoagulation treatment as necessary [*see Warnings and Precautions (5.5)*].

8 USE IN SPECIFIC POPULATIONS

8.6 Hepatic Impairment

Nintedanib is predominantly eliminated via biliary/fecal excretion (>90%) *[see Clinical Pharmacology (12.3)]*. No dedicated PK study was performed in patients with hepatic impairment. Monitor for adverse reactions and consider dose modification or discontinuation of TRADENAME as needed [redacted] (b) (4) for patients with mild hepatic impairment [redacted] (b) (4) (Child Pugh A). The safety and efficacy of nintedanib have not been investigated in patients with hepatic impairment classified as Child Pugh B or C. Therefore, treatment of patients with moderate (Child Pugh B) and severe (Child Pugh C) hepatic impairment with TRADENAME is not recommended *[see Warnings and Precautions (5.2)]*.

8.7 Renal Impairment

Based on a single dose study, ~~L~~less than 1% of [redacted] (b) (4) the total dose of nintedanib is excreted via the kidney *[see Clinical Pharmacology (12.3)]*. Adjustment of the starting dose in patients with mild to moderate renal impairment is not required. The safety, efficacy, and pharmacokinetics of nintedanib have not been studied in patients with severe renal impairment (<30 mL/min CrCl).

8.8 Smokers

Smoking was associated with decreased exposure to TRADENAME which may alter the efficacy profile of TRADENAME. Encourage patients to stop smoking prior to treatment with TRADENAME and to avoid smoking when using with TRADENAME [see Clinical Pharmacology (12.3)].

12 CLINICAL PHARMACOLOGY

12.2 Pharmacodynamics

Cardiac Electrophysiology

In a [redacted] (b) (4) study in renal cell cancer patients, QT/QTc measurements were recorded and showed that a single oral dose of 200 mg nintedanib as well as multiple oral doses of 200 mg nintedanib administered twice daily for 15 days did not prolong the QTcF interval.

12.3 Pharmacokinetics

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

The ~~pharmacokinetics (~~PK~~)~~ of nintedanib [redacted] (b) (4) -is linear- [redacted] (b) (4). Accumulation upon multiple administrations was [redacted] (b) (4). Nintedanib trough concentrations remained stable for more than one year.

Absorption

Nintedanib reached maximum plasma concentrations approximately 2 to 4 hours after oral administration as soft gelatin capsule under fed conditions [redacted] (b) (4) The absolute bioavailability of a 100 mg dose was 4.69% (90% CI: 3.615 to 6.078) in healthy volunteers. Absorption and bioavailability are decreased by transporter effects and substantial first-pass metabolism.

[redacted] (b) (4)

After food intake, nintedanib exposure increased by approximately 20% compared to administration under fasted conditions (CI: 95.3% to 152.5%) and absorption was delayed (median t_{max} fasted: 2.00 hours; fed: 3.98 hours).

Distribution

Nintedanib follows [redacted] (b) (4) bi-phasic disposition kinetics. After intravenous infusion, a high volume of distribution [redacted] (b) (4) (V_{ss}: 1050 L, [redacted] (b) (4)) was observed.

The *in vitro* protein binding of nintedanib in human plasma was high, with a bound fraction of 97.8%. Serum albumin is considered to be the major binding protein. Nintedanib is preferentially distributed in plasma with a blood to plasma ratio of 0.869.

Elimination

The effective half-life of nintedanib was between xx and xx hours.

Metabolism

The prevalent metabolic reaction for nintedanib is hydrolytic cleavage by esterases resulting in the free acid moiety BIBF 1202. BIBF 1202 is subsequently glucuronidated by UGT enzymes, namely UGT 1A1, UGT 1A7, UGT 1A8, and UGT 1A10 to BIBF 1202 glucuronide. Only a minor extent of the biotransformation of nintedanib consisted of CYP pathways, with CYP 3A4 being the predominant enzyme involved. The major CYP-dependent metabolite could not be detected in plasma in the human absorption, distribution, metabolism, and elimination study. *In vitro*, CYP-dependent metabolism accounted for about 5% compared to about 25% ester cleavage.

(b) (4) *Excretion*

(b) (4)

(b) (4) The major route of elimination of drug-related radioactivity after oral administration of [^{14}C] nintedanib was via fecal/biliary excretion (93.4% of (b) (4)), and the majority of TRADENAME was excreted as BIBF 1202. The contribution of renal excretion to the total clearance was low (0.649% of dose; (b) (4)). The overall recovery was considered complete (above 90%) within 4 days after dosing. (b) (4)

(b) (4)

Specific Populations

(b) (4)

Hepatic Impairment

No dedicated PK study was conducted in patients with hepatic impairment. As (b) (4) 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, monitor for adverse reactions and consider dose modification or discontinuation of TRADENAME as needed for patients with mild hepatic impairment. (b) (4)

(b) (4)

Renal Impairment

Based on a population pharmacokinetic analysis of data from (b) (4) patients with (b) (4) IPF, exposure to nintedanib was not influenced by mild (CrCl: 60 to 90 mL/min; N= (b) (4)) or moderate (CrCl: 30 to 60 mL/min; N= (b) (4)) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited (b) (4) .

Age, Body Weight, (b) (4) and Gender

Based on population pharmacokinetic analysis age, body weight, and gender were correlated with nintedanib exposure. However, their effects on exposure are not sufficient to warrant a dose adjustment.

(b) (4)

Drug Interactions

(b) (4) -*Potential for Nintedanib to affect other drugs*

Effect of nintedanib co-administration on pirfenidone AUC and C_{max} was evaluated in a multiple dose study. Nintedanib did not have an effect on the exposure of pirfenidone.

In *in vitro* studies, nintedanib was shown not to be an inhibitor of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, or MRP-2. *In vitro* studies also showed that nintedanib has weak inhibitory potential on OCT-1, BCRP, and P-gp; these findings are considered to be of low clinical relevance. Nintedanib and its metabolites, BIBF 1202 and BIBF 1202 glucuronide, did not inhibit or induce CYP enzymes *in vitro*.

Potential for Other Drugs to Affect Nintedanib

Nintedanib is a substrate of P-gp and, to a minor extent, CYP3A4. Coadministration with the (b) (4) -P-gp and CYP3A4 inhibitor ketoconazole increased exposure to nintedanib 1.61-fold based on AUC and 1.83-fold based on C_{max} in a dedicated drug-drug interaction study. In a drug-drug interaction study with the (b) (4) -P-gp and CYP3A4 inducer rifampicin, exposure to nintedanib decreased to 50.3% based on AUC and to 60.3% based on C_{max} upon coadministration with rifampicin compared to administration of nintedanib alone.

Based on a multiple-dose study in Japanese IPF patients, exposure to nintedanib decreased to 68.3% based on AUC and to 59.2% based on Cmax upon coadministration with pirfenidone compared to administration of nintedanib alone.

Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH<3. However, in the clinical trials, coadministration with proton pump inhibitors or histamine H2 antagonists did not influence the exposure (trough concentrations) of nintedanib.

(b) (4)

In *in vitro* studies, nintedanib was shown not to be a substrate (b) (4) of OATP-1B1, OATP-1B3, OATP-2B1, OCT-2, (b) (4) MRP-2, (b) (4) or BCRP. *In vitro* studies also showed that nintedanib (b) (4) -was (b) (4) a substrate of OCT-1; these findings are considered to be of low clinical relevance.

(b) (4)

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4. APPENDIX

4.1 PHARMACOMETRIC REVIEW

OFFICE OF CLINICAL PHARMACOLOGY: PHARMACOMETRIC REVIEW

Application Number	NDA 205832
Submission Date	May 2, 2014
Compound	Nintedanib
Dosing regimen (route of administration)	150 mg BID (oral administration)
Indication	Idiopathic Pulmonary Fibrosis
Clinical Division	DPARP
Primary PM Reviewer	Anshu Marathe, Ph.D., Jianmeng Chen, Ph.D.
Secondary PM Reviewer	Liang Zhao, Ph.D.

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1 SUMMARY OF FINDINGS

1.1 Key Review Questions

The purpose of this review is to address the following key questions.

1.1.1.1 Is there a dose/exposure-response relationship for effectiveness?

There was increased efficacy with respect to the annual rate of decline in FVC (primary endpoint) for the 150 mg BID compared to a dose of 100 mg BID or lower in phase 2 study 1190.30 (Table 29). There is dose response relationship for change from baseline in SGRQ and time to first exacerbation. Data from the phase 2 study 1199.30 was used for this analysis as this was a dose-ranging study in IPF patients and had a wide range of exposures. Patient characteristics and study design were similar between the phase 2 and the phase 3 studies (studies 1199.32 and 1199.34). See section 4 for a brief description of the phase 2 and phase 3 studies.

Consistent with the dose-response, increased efficacy with respect to annual rate of decline in FVC is observed in the highest exposure (steady state AUC) quartile compared to lower quartiles (Figure 11). The highest quartile corresponds to the exposures that are likely to be achieved with the 150 mg BID dose. Additionally, a trend for increase in efficacy with respect to change from baseline in SGRQ is observed with increasing exposure (Figure 11). A multivariate linear regression analysis for annual rate of decline in FVC and change from baseline in SGRQ identified exposure and gender as predictors of response(Table 29). Female patients showed better efficacy compared to male patients. The result of the multivariate analysis should be viewed with caution as gender is likely to be confounded with other factors such as body weight.

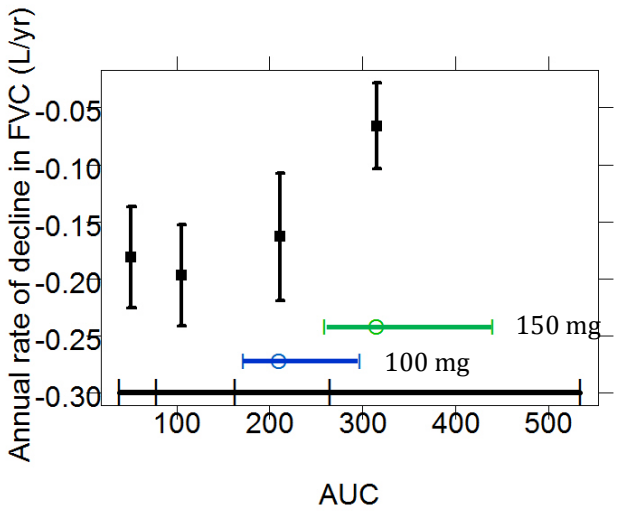
Table 29: Dose-response for efficacy endpoints in Phase 2, study 1190.30

Treatment	Randomized subject (N)	Annual rate of decline in FVC in L/year (SE)	Change from baseline in SGRQ Mean(SE)	Time to first exacerbation Hazard ratio* (95% CI)
Placebo	87	-0.190 (0.036)	5.19 (1.557)	-
50mgQD	87	-0.174 (0.037)	4.29 (1.713)	0.758 (0.326, 1.765)
50mgBID	86	-0.210 (0.035)	1.97 (1.717)	0.841 (0.362, 1.952)
100mgBID	86	-0.162 (0.035)	1.37 (1.655)	0.517 (0.193, 1.384)
150mgBID	86	-0.06 (0.039)	-0.42 (1.526)	0.158 (0.035,0.711)

*Treatment versus Placebo

(Source: Table 11.4.1.1.1:1, Table 11.4.1.2.7:1, Table 15.2.9.3.2:2 from CSR)

A. **Annual Rate of Decline in FVC**



B. **Change in SGRQ**

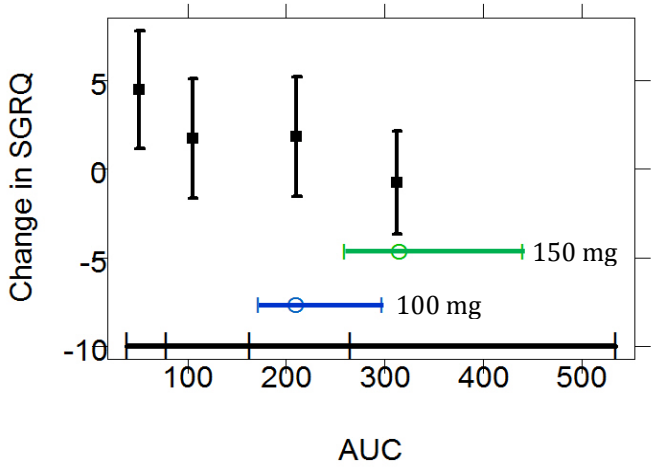


Figure 11: The relationship of A) annual rate of decline in FVC and B) change in SGRQ from baseline with steady state AUC. The black symbols represent the mean and 95% CI in each exposure quartile. The horizontal black line represents the exposure range in each quartile. The blue and green horizontal lines represent the exposure range achieved upon administration of 100 mg BID and 150 mg BID doses respectively.

Table 30: Linear regression analysis for A) Annual rate of decline in FVC and B) Change in SGRQ from baseline

A. Annual Rate of Decline in FVC

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	-0.22045	0.01700	7.80943	168.21	<.0001
AUC	0.00033541	0.00008642	0.69944	15.07	0.0001
gender	0.05660	0.02421	0.25366	5.46	0.0199

B. Change in SGRQ

Variable	Parameter Estimate	Standard Error	Type II SS	F Value	Pr > F
Intercept	6.08465	1.16718	5540.35561	27.18	<.0001
AUC	-0.01533	0.00608	1296.08798	6.36	0.0121
gender	-5.88518	1.65257	2585.48971	12.68	0.0004

The analysis included data from the placebo arm. Reference is male patients. Gender signifies female patients.

1.1.1.2 Is there a dose/exposure-response relationship for safety?

Yes, there is a dose-response relationship for gastrointestinal disorders (diarrhea, nausea, abdominal pain, decreased appetite) in phase 2, study 1190.30 (

Table 31). Additionally a higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group. Since diarrhea was the most common adverse event observed in the trials, an exposure-response analysis was conducted for diarrhea. Consistent with dose response, the proportion of patients with diarrhea increased with increasing steady state AUC (Figure 12). A multivariate logistic regression analysis identified exposure, smoking status and race a predictor (Table 33). The model predicted an increase in diarrhea with increasing steady state AUC, decreased diarrhea in Asians compared to Whites and decreased diarrhea in patients who never smoked or were ex-smokers compared to current smokers. The result of the multivariate analysis should be viewed with caution as the effect of local exposure (gastrointestinal tract) versus systemic exposure on incidence of diarrhea could not be distinguished. Additionally race is likely to be confounded with other factors such as body weight.

Table 31: Dose-response for gastrointestinal adverse events

N = number of patients	Placebo N (%)	BIBF 50 mg qd N (%)	BIBF 50 mg bid N (%)	BIBF 100 mg bid N (%)	BIBF 150 mg bid N (%)	Total N (%)
Number of patients	85	86	86	86	85	428
Gastrointestinal disorders	27 (31.8)	33 (38.4)	31 (36.0)	49 (57.0)	63 (74.1)	203 (47.4)
Nausea	8 (9.4)	9 (10.5)	8 (9.3)	17 (19.8)	20 (23.5)	62 (14.5)
Vomiting	4 (4.7)	1 (1.2)	6 (7.0)	11 (12.8)	11 (12.9)	33 (7.7)
Abdominal discomfort	1 81.2)	2 (2.3)	3 (3.5)	3 (3.5)	5 (5.9)	14 (3.3)
Abdominal pain	3 (3.5)	3 (3.5)	5 (5.8)	4 (4.7)	6 (7.1)	21 (4.9)
Abdominal pain upper	3 (3.5)	6 (7.0)	10 (11.6)	2 (2.3)	10 (11.8)	31 (7.2)
Diarrhoea	13 (15.3)	9 (10.5)	17 (19.8)	32 (37.2)	47 (55.3)	118 (27.6)
Metabolism disorders	2 (2.4)	5 (5.8)	11 (12.8)	11 (12.8)	17 (20.0)	46 (10.7)
Decreased appetite	0	3 (3.5)	4 (4.7)	4 (4.7)	13 (15.3)	24 (5.6)
GI disorders leading to treatment discontinuation	2 (2.4)	2 (2.3)	2 (2.3)	2 (2.3)	14 (16.5)	22 (5.1)
Diarrhoea	0	1 (1.2)	1 (1.2)	0	10 (11.8)	12 (2.8)
Serious gastrointestinal disorders	0	2 (2.3)	2 (2.3)	1 (1.2)	4 (4.7)	9 (2.1)
Severe gastrointestinal disorders	0	2 (2.3)	2 (2.3)	3 (3.5)	5 (5.9)	12 (2.8)

(Source: Table 12.2.2.2:1 from CSR1199.30)

Table 32: Dose-response for liver enzyme elevation

	Placebo	50 mg qd	50 mg bid	100 mg bid	150 mg bid
Number of patients [N]	84	85	86	84	84
Frequency of patients [N (%)] with possible clinically significant* abnormalities					
AST	0 (0)	0 (0)	0 (0)	1 (1.2)	3 (3.6)
ALT	0 (0)	0 (0)	1 (1.2)	0 (0)	4 (4.8)
GGT	1 (1.2)	5 (5.9)	4 (4.7)	5 (5.9)	16 (19.0)
Bilirubin	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*AST, ALT, GGT – increase by >3xULN. Bilirubin-increase by >34 umol/L
(Source: Table 12.2.2.2:1 from CSR1199.30)

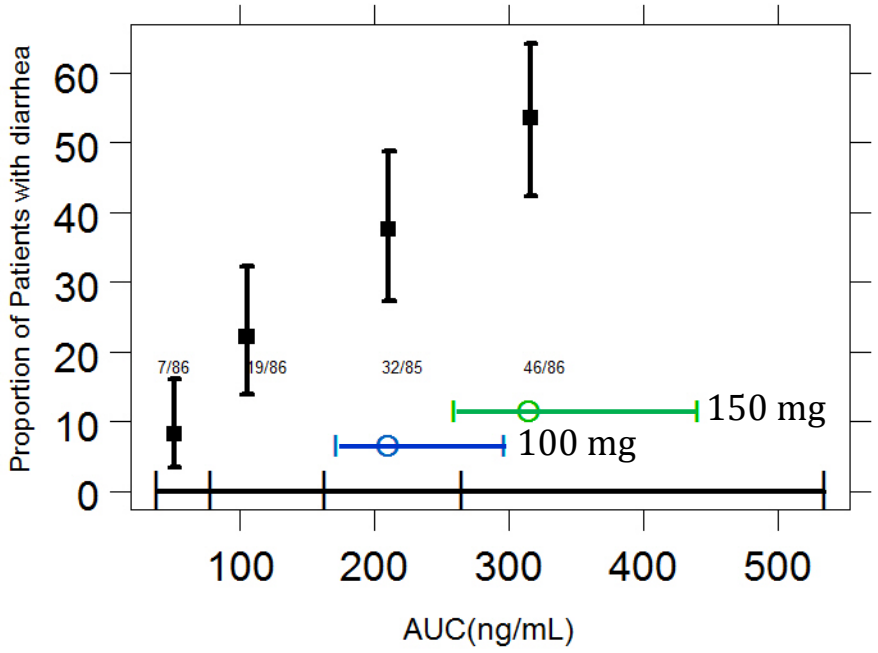


Figure 12: The relationship of proportions of patients with diarrhea with steady state AUC. The black symbols represent the mean and 95% CI in each exposure quartile. The horizontal black line represents the exposure range in each quartile.

Table 33: Parameters from logistic regression analysis for diarrhea

Analysis of Maximum Likelihood Estimates						
Parameter		DF	Estimate	Standard Error	Wald Chi-Square	Pr > ChiSq
Intercept		1	-2.2141	0.3477	40.5508	<.0001
AUC		1	0.00832	0.00125	44.1722	<.0001
smok	0	1	-0.6401	0.2760	5.3802	0.0204
smok	1	1	-0.5066	0.2579	3.8591	0.0495
racedc	Asian	1	-0.4404	0.1776	6.1481	0.0132

**White is the reference for race. Current smokers are the reference for smoking status. Smoking status 0 and 1 refer to patients who never smoked or ex-smokers respectively.*

1.1.1.3 Does the dose/exposure-response relationship for effectiveness and safety endpoints support the proposed dose and dose modification scheme?

Yes, the proposed starting dose of 150 mg BID is reasonable because of increased efficacy with respect to the annual rate of decline in FVC for the 150 mg BID compared to a dose of 100 mg BID or lower in phase 2, study 1190.30. Additionally dose-response relationship is observed for change from baseline in SGRQ and time to first exacerbation. Since there are no currently approved therapy for IPF patients and the 5 year survival is low ranging from 20%-40%, it is reasonable to have a dose that maximizes efficacy. Increased GI disorders with increasing dose supports sponsor's dose reduction scheme, of reducing the dose to 100 mg BID if AEs are observed. Additionally, higher proportion of subjects with greater than 3xULN increase in AST, ALT or GGT was observed in the 150 mg BID dose group compared to the 100 mg BID dose group. Thus sponsor's dose modification based on liver enzyme elevation is reasonable.

1.1.1.4 Are the effects of intrinsic factors on exposure significant from either efficacy or safety perspective?

Based on sponsor's population PK analysis of IPF patients (N=933) body weight, age, lactate dehydrogenase (LDH) levels and smoking history were identified as covariates influencing the PK of nintedanib. As shown in Table 34, exposure (steady state AUC) increased by 24% in a 55 kg patient (5th percentile) and decreased by 19% in 107 kg patient (95th percentile) compared to a 77 kg patient (median within the analyzed population). The magnitude of change for LDH and age were even lower. Exposure decreased by 21% in current smokers compared to ex-smokers or patients who have never smoked. Similarly, the magnitude of change in the exposure of BIBF 1202 (major metabolite) due to body weight, age, LDH and smoking status were small (Table 35). These effects on exposure of nintedanib and BIBF 1202 are not sufficient to warrant a dose adjustment. Changes in exposure due to individual covariates were within the inter-patient variability range of nintedanib. Thus these changes in exposure are unlikely to lead to significant difference in the efficacy/safety of the drug.

The sponsor's analysis divided patients into subgroups based on race and the country the study site was located as shown in Table 36. The model predicted Asians to have higher exposures (as high as 50% increase in patients in Chinese, Taiwanese sites) compared to Caucasians. Sponsor's rationale for grouping Asians and Caucasians together in Indian sites is unclear. It is also unclear why Asian patients in Koran sites have a 16% decrease in exposure compared to Caucasians. Due to the reasons mentioned above, sponsor's conclusion for impact of race on PK should be viewed with caution.

Table 34: Impact of individual covariates on the exposure of nintedanib

Covariate	Effect of covariate	Percentage change in $AUC_{\tau,ss}$*
Covariates included on CL/F		
WT	CL/F increased with increasing weight (and vice versa) as described using a power function (power of 0.634).	$AUC_{\tau,ss}$ increased by 24% in a 55 kg patient (5th percentile) and decreased by 19% in a 107 kg patient (95th percentile), as compared to a 77.1 kg patient (median within analyzed population).
LDH	CL/F changed linearly by 19.0% per 100 U/L difference to LDH of 205 U/L.	$AUC_{\tau,ss}$ was decreased by 10% for a patient with LDH of 146 U/L (5th percentile) and increased by 20% for a patient with LDH of 294 U/L (95th percentile) relative to a patient with the median LDH of 205 U/L (median within analyzed population).
Covariates included on F1		
AGE	F1 changed linearly by 0.976% per 1 year difference to age of 66 years.	$AUC_{\tau,ss}$ decreased by 14% in a 52 year old patient (5th percentile) and increased by 13% in a 79 year old patient (95th percentile), as compared to a patient with the median age of 66 years (median within analyzed population)
SMOK	F1 decreased by 21% in current smokers compared to ex- or never smoker (effect size fixed according to previous PopPK analysis [U13-1588]	$AUC_{\tau,ss}$ decreased by 21% in current smokers compared to ex- or never smoker
RACE+GEOR	F1 decreased by 16% for Korean patients as compared to Caucasians. F1 increased by 16% for Japanese patients and by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians	$AUC_{\tau,ss}$ decreased by 16% for Korean patients as compared to Caucasians. $AUC_{\tau,ss}$ increased by 16% for Japanese patients and by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians

* $AUC_{\tau,ss}$ (dose normalized) was calculated as F1 divided by CL/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

Source data: Appendix 16.1.4.1.2.1

(Source: Table 10.1.3.2:2 from combined population PK report for IPF patients)

Table 35: Impact of individual covariates on the exposure of the metabolite BIBF 1202

Covariate	Effect of covariate	Percentage change in AUCτ,ss*
Covariates identified for nintedanib affecting the BIBF 1202 exposure with the same effect size (due to interdependancy of F2 and F1)		
AGE	F1 changed linearly by 0.976% per 1 year difference to median age of 66 years in the analysed population.	$AUC_{\tau,ss}$ decreased by 14% in a 52 year old patient (5th percentile) and increased by 13% in a 79 year old patient (95th percentile), as compared to a patient with the median age of 66 years (median within analyzed population)
SMOK	F1 decreased by 21% in current smokers compared to ex- or never smoker (effect size fixed according to previous PopPK analysis [U13-1588].	$AUC_{\tau,ss}$ decreased by 21% in current smokers compared to ex- or never smoker
Covariates identified for both nintedanib and BIBF 1202 – different effect sizes for BIBF 1202 and nintedanib exposure		
WT	F2 decreased with increasing weight (and vice versa) as described using a power function (power of -0.782).	$AUC_{\tau\ ss}$ increased by 26% for a 55 kg patient (5th percentile) and decrease by 19% for a 107 kg patient (95th percentile) relative to a patient weighing 77.1 kg (median within analyzed population).
RACE +GEOR	F1 decreased by 16% for Korean patients, increased by 16% for Japanese patients and increased by 50% for Chinese, Taiwanese, Indian patients and other Asians as compared to Caucasians. F2/F1 ratio increased by 90% for Indian patients (fixed according to previous PopPK analysis [U13-1588]) and increased by 28 % for Asians except for Indians as compared to Caucasians.	$AUC_{\tau,ss}$ increased by 166% for patients with Indian origin, by 86% for Asians except for Indian, Korean or Japanese patients, by 5% for Korean patients and by 44% for Japanese patients as compared to Caucasians.
LDH	F2 decreased linearly by 10.8% per 100 U/L absolute difference to 688 U/L. For LDH levels higher than 688 U/L a constant F2 of 1 was assumed.	$AUC_{\tau,ss}$ was decreased by 11% for a patient with LDH of 146 U/L (5th percentile) and increased by 17% for a patient with LDH of 294 U/L (95th percentile) relative to a patient with the median LDH of 205 U/L (median within analyzed population).

* $AUC_{\tau,ss}$ (dose normalized) was calculated as (F2+ffM1*F1) divided by CL2/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

BIBF 1202 specific covariates		
SEX	CL2/F was decreased by 12% in female patients as compared to males.	$AUC_{\tau,ss}$ increased by 14 % in female patients as compared to males.
BBIL	CL2/F changed linearly by -1.31% per 1 µM difference to median BBIL of 9 µM in analysed population.	$AUC_{\tau,ss}$ was decreased by 5% for a patient with BBIL of 5 µM (5th percentile) and increased by 13% for a patient with BBIL of 18 µM U/L (95th percentile) relative to a patient with the median BBIL of 9 µM (median within analyzed population).

* $AUC_{\tau,ss}$ (dose normalized) was calculated as (F2+ffM1*F1) divided by CL2/F. The percentage change in $AUC_{\tau,ss}$ was determined by varying values of the covariate of interest while keeping all other covariates constant.

(Source: Table 10.1.4.2:2 from combined population PK report for IPF patients)

Table 36: Subgroups for Race and Study site in Population PK analysis

Category	RACE	Study site
Caucasian	Caucasian	Any site located not in India
Chinese	Asian	China
Korean	Asian	Korea
Taiwanese	Asian	Taiwan
Indian	Asian or Caucasian	India
Japanese	Asian	Japan
Other Asian	Asian	Country other than China, Korea, Taiwan, India or Japan
Black	Black	
American Indian/Alaska native	American Indian/Alaska native	

(source: reviewer summary)

1.2 Recommendations

Division of Pharmacometrics has reviewed NDA 205832 and finds the NDA acceptable provided an agreement regarding the label language can be reached between the sponsor and the Agency.

1.3 Label Statements

The following are the labeling recommendations relevant to clinical pharmacology for NDA 205832. The ~~red strikeout font~~ is used to show the proposed text to be deleted and

underline blue font to show text to be included or comments communicated to the sponsor.

12 CLINICAL PHARMACOLOGY

12.3 Pharmacokinetics

(b) (4)

Specific Populations

Renal Impairment
Based on a population pharmacokinetic analysis of data from 1191 patients with (b) (4) -IPF, exposure to nintedanib was not influenced by mild (CrCl: 60 to 90 mL/min; N= (b) (4) or moderate (CrCl: 30 to 60 mL/min; N= (b) (4) renal impairment. Data in severe renal impairment (CrCl below 30 mL/min) was limited (b) (4)

Age, Body Weight, (b) (4) and Gender
Based on population pharmacokinetic analysis age and body weight were correlated with nintedanib exposure. However, their effects on exposure are not sufficient to warrant a dose adjustment. There was no influence of sex on the exposure of nintedanib (b) (4)
(b) (4)

Reviewer's Comments:

(b) (4)

Comment to the sponsor: For renal impairment, update the information with results of your popPK report in IPF patients (pop PK 1199-0030-0032-0034).

2 RESULTS OF SPONSOR'S ANALYSIS

2.1 Population PK Analysis

Primary objective of sponsor's population PK analysis were:
1. Describing the PK of nintedanib and BIBF 1202 in IPF patients
2. Assessing the effect of various intrinsic and extrinsic factors on the PK of nintedanib and BIBF 1202

2.1.1 Methods

Data

The population PK analysis of nintedanib and BIBF 1202 in IPF patients was based on studies 1199.30, 1199.32 and 1199.34. The PK analysis dataset used for model development and covariate analysis included 933 IPF patients providing 3501 and 3264 PK observations for nintedanib and BIBF 1202, respectively. Patients had a median age of 66 years and a median body weight (WT) of 77.1 kg. 21.9 % of the patients were females. The Asian patients (including Indians) represented 26.3 % of all patients (Chinese: 9.2 %; Korean: 7.0 %; Taiwanese: 0.5%; Indian: 0.9%; Japanese: 7.4% and other Asian: 1.3 %), the Black patients 0.2% and the Caucasians 73.4 %. With respect to the renal and hepatic function, the median baseline creatinine clearance (CRCL) was 86.8 mL/min and the surrogate markers for liver function alanine and aspartate transaminase (ALT, AST) and total bilirubin (BIL) were all below the respective upper limit of the normal ranges for most of the patients (95.3 % at baseline).

The sampling scheme for the three studies is shown in

Table **37**.

Model Development

The final PK model from the previous Pop PK analysis of combined Phase II and III data in NSCLC and IPF patients was used as starting point for the model development. The model development was based on the PK analysis dataset and was separated into three steps: base model development, covariate model development and development of the final model. In accordance with the previous combined PopPK analysis, a sequential approach was used for the model development of nintedanib and its metabolite BIBF 1202. First, the base model was developed for nintedanib. Based on fixed PK parameter estimates from the nintedanib base model (i.e. typical values plus empirical Bayes estimates of individual η), the base model of BIBF 1202 was established. Subsequently, simultaneous parameter estimation for the combined nintedanib and BIBF 1202 base model was performed. The covariate analysis and the final model development were again performed for nintedanib alone, i.e. without consideration of BIBF 1202 plasma concentrations. After fixing the PK parameter estimates from the final nintedanib model and combining it with the structural and stochastic BIBF 1202 base model, the covariate and final model was established for BIBF 1202. Finally, simultaneous parameter estimation for the final combined nintedanib and BIBF 1202 model was performed.

Table 37: Sampling scheme for determination of plasma concentrations of nintedanib and BIBF 1202

Day of treatment	Planned time of blood sampling		
	1199.30	1199.32	1199.34
1	Visit 2: Pre-dose Post-dose: 2 h (1-3 h)		
29	Visit 4: Pre-dose Post dose: 2 h (1-3 h)	Visit 4 Pre-dose For Japan in addition (local amendment 1): Post dose: 2-4 h	Visit 4 Pre-dose For Japan in addition (local amendment 1): Post dose: 2-4 h
169	Visit 7: Pre-dose Post dose: 2 h (1-3 h) and 7 h (4-10 h)	Visit 7 Pre-dose For Japan in addition (local amendment 1): Post dose: 2-4 h	Visit 7 Pre-dose For Japan in addition (local amendment 1): Post dose: 2-4 h
365 (EOT for studies 1199.32 and 1199.34)	Visit 9: Pre-dose Post dose: 2 h (1-3 h) and 7 h (4-10 h)		
EOT (study 1199.30)	Pre-dose or at any time point post-dose		

(Source: Table 8.2.2.1 from combined population PK report for IPF patients)

2.1.2 Results

The plasma concentration-time profiles for nintedanib were adequately described by a one-compartment model with linear elimination, first order absorption and absorption lag time (ALAG). Inter-individual variability (IIV) terms could be implemented for the apparent volume of distribution (V2/F), relative bioavailability (F1) and absorption rate constant (KA). An inter-occasion variability (IOV) term was implemented for F1. The parameter estimates from the final model are shown in

Table 38. The goodness of fit plots for the model is shown in Figure 13.
"A one-compartment model with first order elimination was implemented for BIBF 1202. In order to account for the formation of BIBF 1202 in the intestine or via first pass effect, a first order absorption with lag time was implemented (in analogy to nintedanib absorption). The relative bioavailability (F2), the volume of distribution (V3/F) and the absorption rate constant (KA2) were implemented as functions of the individual parent F1, V2/F and KA, respectively. Additional formation of BIBF 1202 during nintedanib elimination was also considered by defining the rate of formation as a function of parent clearance (CL/V2*ffM1). As not all BIBF 1202 model parameters were identifiable, the parameters ALAG2 (absorption lag time for BIBF 1202), ffM1 and the ratio of V2/F to V3/F were fixed as already done for the previous Phase II/III PopPK analysis. The parameter estimates from the final model is shown in Table 39. The goodness of fit plots for the model is shown in Figure 14.

Effect of covariates on the exposure of nintedanib and BIBF 1202 are discussed in section 1.1.1.4.

Reviewer's comments:

- *Sponsor's population PK model adequately characterized the observed concentrations of nintedanib 2-hr post dose and slightly underestimated the Nintedanib trough concentration following QD dosing. This can be potentially attributed to using one-compartment model to describe PK profiles that have a second elimination phase marginally contributing to the overall exposure. However, the one compartment model reasonably captures the overall feature of patient PK profiles. The reviewer agrees with sponsor's assessment that no dose adjustment based on body weight, age or gender is warranted.*
- *The sponsor's analysis divided patients into subgroups based on race and the country that the study site was located as shown in Table 36. Sponsor's rationale for grouping Asians and Caucasians together in Indian sites is unclear. It is unclear why Asians in Korean sites had 16% decrease in exposure compared to Caucasians while Asian patients in China and Taiwan had an increase by 50% in exposure. Due to the reasons, sponsor's conclusion for impact of race on PK should be viewed with caution*

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Table 38: Parameter estimates of the final population PK model for nintedanib

Description of Run 775		
$KA = \theta_{KA} \cdot \theta_{PROJ} \cdot e^{\eta KA}$ $ALAG = \theta_{ALAG}$ $V2/F = \theta_{V2} \cdot e^{\eta V2}$ $CL/F = \theta_{CL} \cdot (WT/77.1)^{\theta WT} \cdot (1+\theta_{LDH} \cdot (LDH-205))$ $F1 = 1 \cdot (1+\theta_{AGE} \cdot (AGE-66)) \cdot \theta_{SMOK} \cdot \theta_{RACE+GEOR} \cdot \theta_{PROJ} \cdot e^{\eta F1+\kappa F1}$		
Residual random effect model: $LOG(Y) = LOG(\hat{Y}) + \varepsilon_1 \quad ; \ \varepsilon_1 \sim N(0, \sigma^2)$		
Run 775 (FOCE INTERACTION) Objective function = 471.68 [933 subjects, 3501 observations]	Parameter Estimate	Relative standard error of estimate (%)
Fixed effects		
CL/F [L/h]	994	3.23
V2/F [L]	265	9.89
KA [1/h]	0.0814	2.53
ALAG [h]	0.689	5.70
F1	1 FIXED[a]	NA
WT_CL/F:	0.634	17.5
RACE+GEOR_F1:		
Caucasian/Black	1 FIXED[a]	NA
Korean	0.844	7.42
Japanese	1.16	6.83
Indian/Chinese/Taiwanese/other Asian/ American Indian	1.50	5.92
SMOK_F1:		
Ex-or never-smoker	1 FIXED[a]	NA
Current smoker	0.794 FIXED[b]	NA
AGE_F1	0.00976	22.4

a Parameter was fixed to 1 as reference
b Parameter fixed to estimate from previous PopPK analysis [U13-1588]
* Estimate refers to relative standard error of variance estimate for IIV, IOV or residual variability
Source data: Appendix 16.1.4.1.2.1

Description of Run 775		
$KA = \theta_{KA} \cdot \theta_{PROJ} \cdot e^{\eta KA}$ $ALAG = \theta_{ALAG}$ $V2/F = \theta_{V2} \cdot e^{\eta V2}$ $CL/F = \theta_{CL} \cdot (WT/77.1)^{\theta WT} \cdot (1+\theta_{LDH} \cdot (LDH-205))$ $F1 = 1 \cdot (1+\theta_{AGE} \cdot (AGE-66)) \cdot \theta_{SMOK} \cdot \theta_{RACE+GEOR} \cdot \theta_{PROJ} \cdot e^{\eta F1+\kappa F1}$		
Residual random effect model: $LOG(Y) = LOG(\hat{Y}) + \varepsilon_1 \quad ; \ \varepsilon_1 \sim N(0, \sigma^2)$		
Run 775 (FOCE INTERACTION) Objective function = 471.68 [933 subjects, 3501 observations]	Parameter Estimate	Relative standard error of estimate (%)
Fixed effects		
LDH_CL/F	-0.00190	-11.8
PROJ_1199_30_KA	1 FIXED[a]	NA
PROJ_1199_32_34_KA	0.759	8.21
PROJ_1199_30_F1	1 FIXED[a]	NA
PROJ_1199_32_34_F1	1.16	5.41
Random effects		
IIV in V2/F [CV%]	131	16.3*
IIV in KA [CV%]	28.3	17.0*
IIV in F1 [CV%]	41.8	9.43*
IOV in F1 (occasion=visit) [CV%]	33.3	15.4*
σ of ADD residual variability	0.453	5.12*

a Parameter was fixed to 1 as reference
b Parameter fixed to estimate from previous PopPK analysis [U13-1588]
* Estimate refers to relative standard error of variance estimate for IIV, IOV or residual variability
Source data: Appendix 16.1.4.1.2.1

(Source: Table 10.1.3.2:1 from combined population PK report for IPF patients)

Table 39: Parameter estimates of the final population PK model for BIBF 1202

Description of Run 1614.1		
$CL2/F = \theta_{CL2} \cdot \theta_{SEX} \cdot (1+\theta_{BBIL} \cdot (BBIL-9))$		
$F2 = F1 \cdot \theta_{F2/F1} \cdot (WT/77.1)^{\theta WT} \cdot (1-\theta_{LDH} \cdot (\theta_{LDH\_Cutoff} - LDH)) \cdot \theta_{RACE+GEOR} \cdot e^{\eta F2}$		
$KA2 = \theta_{KA2/KA} \cdot KA \cdot \theta_{RACE+GEOR} \cdot \theta_{CT4}$		
$ALAG2 = \theta_{ALAG2/ALAG} \cdot ALAG$		
$V3/F = V2/F \cdot \theta_{V3/V2}$		
Residual random effect model:		
$LOG(Y) = LOG(\hat{Y}) + \varepsilon_1 \quad ; \ \varepsilon_1 \sim N(0, \sigma^2)$		
Run 1614.1 (FOCE INTERACTION) Objective function = -1284.44 [933 subjects, 3264 observations]	Parameter Estimate	Relative standard error of estimate (%)
Fixed effects		
CL2/F [L/h]	6.53	8.06
V3/V2	0.0185 FIXED[a]	NA
KA2/KA	1.08	3.24
ALAG2/ALAG	1 FIXED[b]	NA
F2/F1	11.8/1000	11.2
ffM1	0.931/1000 FIXED[b]	NA
WT_F2	-0.782	-11.9
RACE+GEOR_F2		
Caucasian/Black	1 FIXED[c]	NA
Indian	1.90 FIXED[b]	NA
Korean/Taiwanese/Japanese/other Asian/American Indian	1.28	4.22
LDH_F2	0.00108*	8.06
LDH_F2_Cutoff	688 FIXED[b]	NA
SEX_CL2		
Male	1 FIXED[c]	NA
Female	0.881	3.60

a Ratio of V3/V2 fixed according to rat data [U10-2525]
b Parameter fixed to estimate from the previous Phase II/III PopPK analysis [U13-1588]
c Parameter was fixed to 1 as reference
Formation rate of BIBF 1202 during elimination of nintedanib=CL/V2*ffM1.
* If LDH > LDH_Cutoff, then $\theta_{LDH\_F2} = 0$
** Estimate refers to relative standard error of variance estimate for IIV or residual variability
Source data: Appendix 16.1.4.1.2.2

Description of Run 1614.1		
$CL2/F = \theta_{CL2} \cdot \theta_{SEX} \cdot (1+\theta_{BBIL} \cdot (BBIL-9))$ $F2 = F1 \cdot \theta_{F2/F1} \cdot (WT/77.1)^{\theta WT} \cdot (1-\theta_{LDH} \cdot (\theta_{LDH\_Cutoff} - LDH)) \cdot \theta_{RACE+GEOR} \cdot e^{\eta F2}$ $KA2 = \theta_{KA2/KA} \cdot KA \cdot \theta_{RACE+GEOR} \cdot \theta_{CT4}$ $ALAG2 = \theta_{ALAG2/ALAG} \cdot ALAG$ $V3/F = V2/F \cdot \theta_{V3/V2}$		
Residual random effect model: $LOG(Y) = LOG(\hat{Y}) + \varepsilon_1 \quad ; \ \varepsilon_1 \sim N(0, \sigma^2)$		
Run 1614.1, (FOCE INTERACTION) Objective function = -1284.44 [933 subjects, 3264 observations]	Parameter Estimate	Relative standard error of estimate (%)
Fixed effects		
RACE+GEOR_KA2		
Not Japanese	1 FIXED[c]	NA
Japanese	1.46	5.39
BBIL_CL2	-0.0131	-22.1
CT4_KA2		
No Laxative intake	1 FIXED[c]	NA
Laxative intake	0.647	12.3
Random effects		
IIV in F2 [CV%]	39.3	10.1*
σ of ADD residual variability	0.429	4.09*

a Ratio of V3/V2 fixed according to rat data [U10-2525]
b Parameter fixed to estimate from the previous Phase II/III PopPK analysis [U13-1588]
c Parameter was fixed to 1 as reference
Formation rate of BIBF 1202 during elimination of nintedanib=CL/V2*ffM1.
* If LDH > LDH_Cutoff, then $\theta_{LDH\_F2} = 0$
** Estimate refers to relative standard error of variance estimate for IIV or residual variability
Source data: Appendix 16.1.4.1.2.2

(Source: Table 10.1.4.2:1 from combined population PK report for IPF patients)

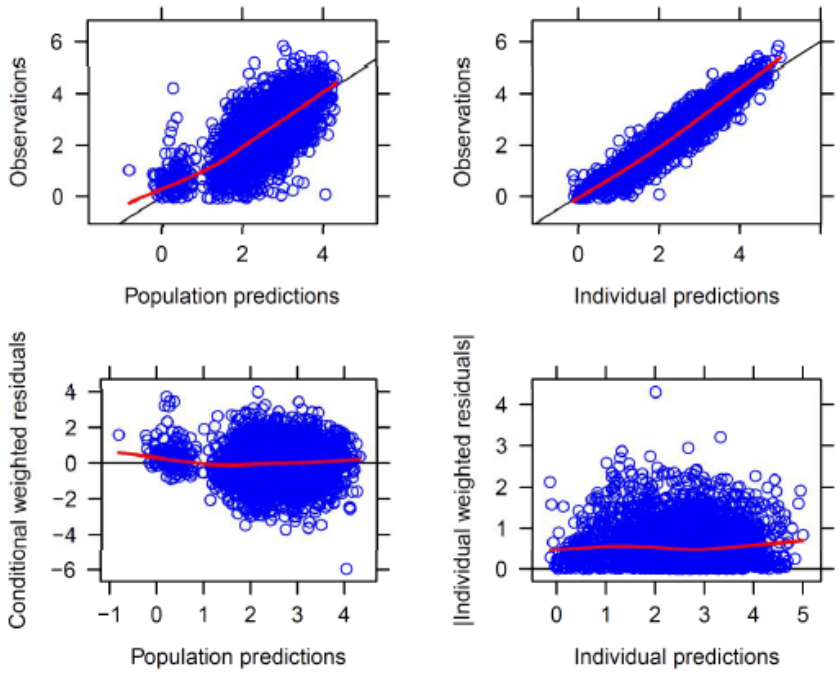

Figure 13: Goodness of fit plots for final model of nintedanib.
(Source: Figure 10.3.2.1:1 from combined population PK report for IPF patients)

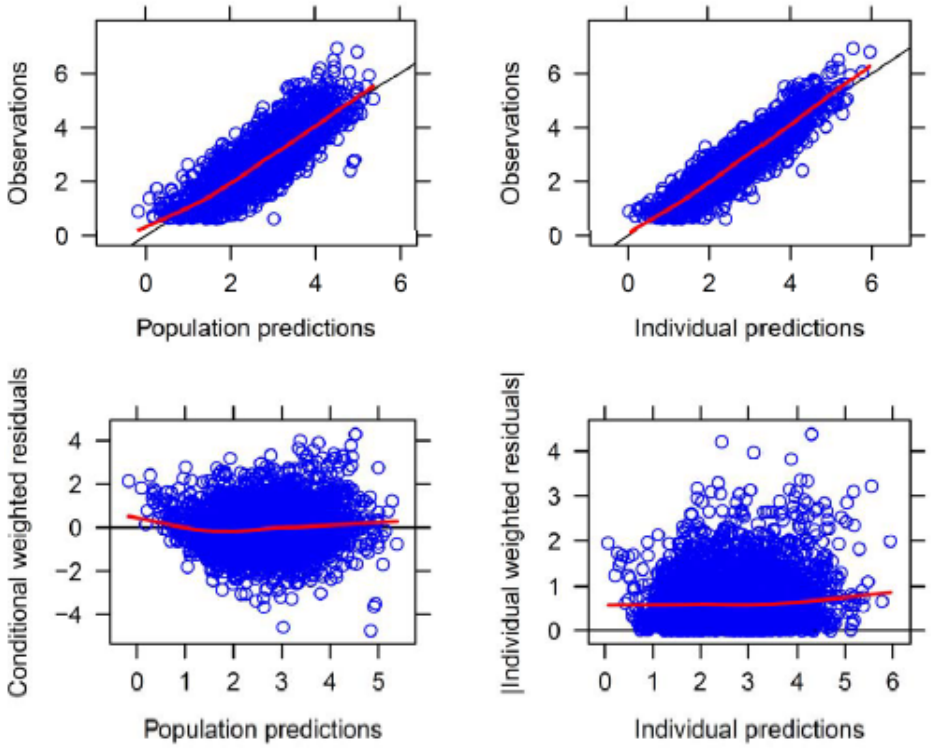

Figure 14: Goodness of fit plots for final model of BIBF 1202.
(Source: Figure 10.3.2.1:1 from combined population PK report for IPF patients.)

2.2 Exposure Response Analysis for Efficacy

The objectives of the exposure-response analyses described in this document were to investigate the association of the primary efficacy endpoint (i.e. the annual rate of decline in FVC) in the Phase II study for nintedanib in IPF (1199.30) and in the two Phase III studies 1199.32 and 1199.34 with exposure (PK) measurements as well as other intrinsic and extrinsic factors.

PK-Efficacy

As for the analysis of Phase III data, a linear disease progression modelling framework was used to explore the relationship between the time course of FVC and nintedanib trough concentrations (observed and model predicted). In addition, individual model predicted annual rates of FVC decline from primary statistical analysis were correlated with observed and model predicted nintedanib trough concentrations for comparison. As expected, adding Phase II data improved the description of the exposure-response relationship in particular for the lower concentration range and allowed establishing an exposure-FVC model.

Reviewer's comments:

- *Sponsor's ER analysis suggested that "inclusion of Phase 2 data improved the description of the exposure-response relationship and allowed establishing an exposure-FVC model". This is consistent with reviewer's finding of an exposure response relationship for annual rate of decline in FVC in Phase 2 study (see section 1.1.1.1)*

3 RESULTS OF REVIEWER'S ANALYSIS

3.1 Dose/Exposure Response Analysis

The primary objective of reviewer's dose/exposure response analysis was to ascertain that the sponsor's proposed starting dose of 150 mg BID and dose modification scheme (temporarily interrupt or reduce to 100 mg BID if patient experiences AEs) is appropriate.

3.1.1 Methods

Data sets used are summarized in Table 40. A linear regression analysis was conducted to link the predicted steady state AUC of nintedanib to the efficacy endpoints (i.e. annual rate of decline in FVC and change from baseline in SGRQ). A logistic regression analysis was conducted to link the predicted steady state AUC of nintedanib to the safety endpoint (i.e. proportion of patients with diarrhea. The analysis was conducted in S-PLUS. The covariates that were tested in the model were body weight, age, baseline creatinine clearance, baseline FVC, gender, race and smoking status. A stepwise selection procedure was implemented in SAS 9.3.

Table 40: Analysis Data Sets

Study Number	Name	Link to EDR
Study 1190.30	pkeffv2.xpt	\\cdsesub1\evsprod\nda205832\0016\m5\datasets\1199-30-32-34-er\analysis\pkeffv2.xpt
	pksafv2.xpt	\\cdsesub1\evsprod\nda205832\0016\m5\datasets\1199-30-32-34-er\analysis\pksafv2.xpt

3.1.2 Results

See section 1.1.1.1 for dose/exposure response results for efficacy.
See section 1.1.1.2 for dose/exposure response results for safety.

3.2 Effect of co-administration of proton pump inhibitors and H2 receptor antagonists on efficacy

Nintedanib displays a pH-dependent solubility profile with increased solubility at acidic pH<5. However, based on phase III pharmacokinetic analysis, coadministration with proton pump inhibitors or H2 receptor antagonists did not influence the steady state trough concentrations of nintedanib. Since trough concentration is not a sensitive measure to evaluate the effect of antacids on drug absorption/exposure, a subgroup analysis for efficacy was also conducted utilizing data from phase 3 trials. Patients in the treatment arm taking proton pump inhibitor and H2-receptor antagonists showed slightly reduced efficacy with respect to annual rate of decline in FVC compared to patients without these co-medications (Table 41). However, a relatively larger effect was observed for patients in the placebo arm suggesting patients who needed these co-medications were likely to be poor responders due to other factors that are not related to drug exposure.

Table 41: Subgroup analysis for efficacy by patients with/without concomitant use of PPI and H2 receptor antagonists

Treatment arm	PPI + H2 receptor antagonists	N	Annual rate of decline in FVC (ml/yr)
Study 32			
Placebo	No	175	-221.49
Placebo	Yes	29	-315.62
Nint 150 mg	No	236	-108.07
Nint 150 mg	Yes	73	-137.58
Study 34			
Placebo	No	171	-204.46
Placebo	Yes	48	-244.99
Nint 150 mg	No	259	-111.43
Nint 150 mg	Yes	70	-113.92

4 APPENDIX

Study 11990.30: This was a 52 week, double blind, randomized, placebo-controlled trial evaluating the effect of BIBF 1120 administered at oral doses of 50 mg qd, 50 mg BID, 100 mg BID and 150 mg BID on forced vital capacity decline during one year, in patients with idiopathic pulmonary fibrosis, with optional active treatment extension until last patient out. Figure 15 displays the FVC change from baseline overtime in the different treatment groups.

Study 1199.32: This was a 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF). Figure 16 displays the FVC change from baseline overtime in the placebo and the active treatment arm.

Study 1199.34: This was a 52 weeks, double blind, randomized, placebo-controlled trial evaluating the effect of oral BIBF 1120, 150 mg twice daily, on annual forced vital capacity decline, in patients with idiopathic pulmonary fibrosis (IPF). Figure 17 displays the FVC change from baseline overtime in the placebo and the active treatment arm.

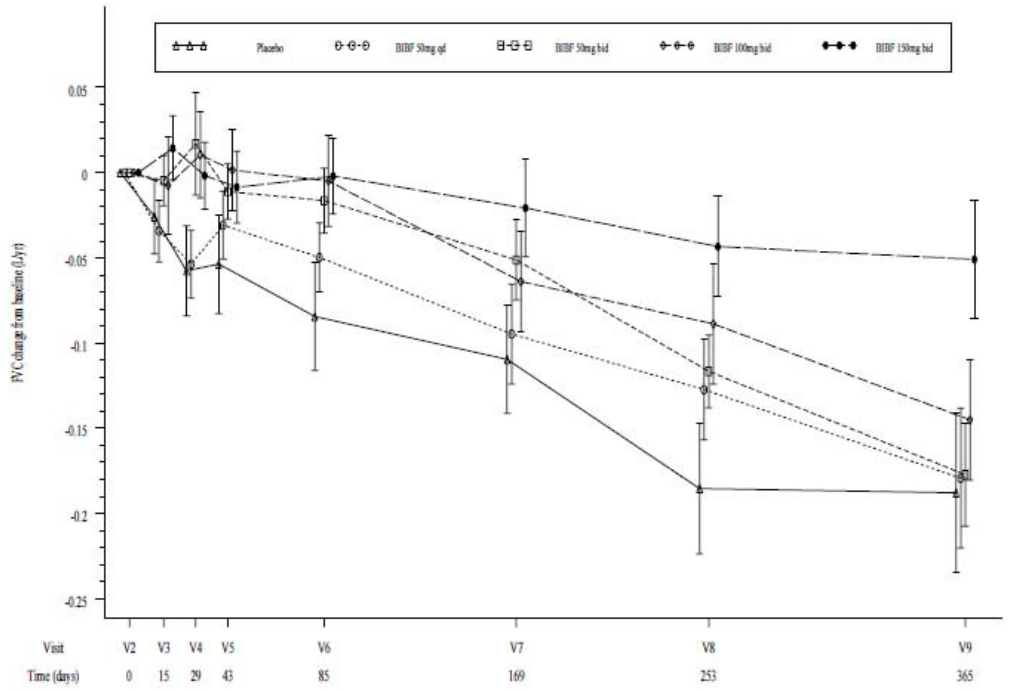

Figure 15: Observed FVC change from baseline (L) overtime by treatment group in phase 2 study 1190.30.
(Source: Figure 11.4.1.2.1: 1 of CSR1199.30)

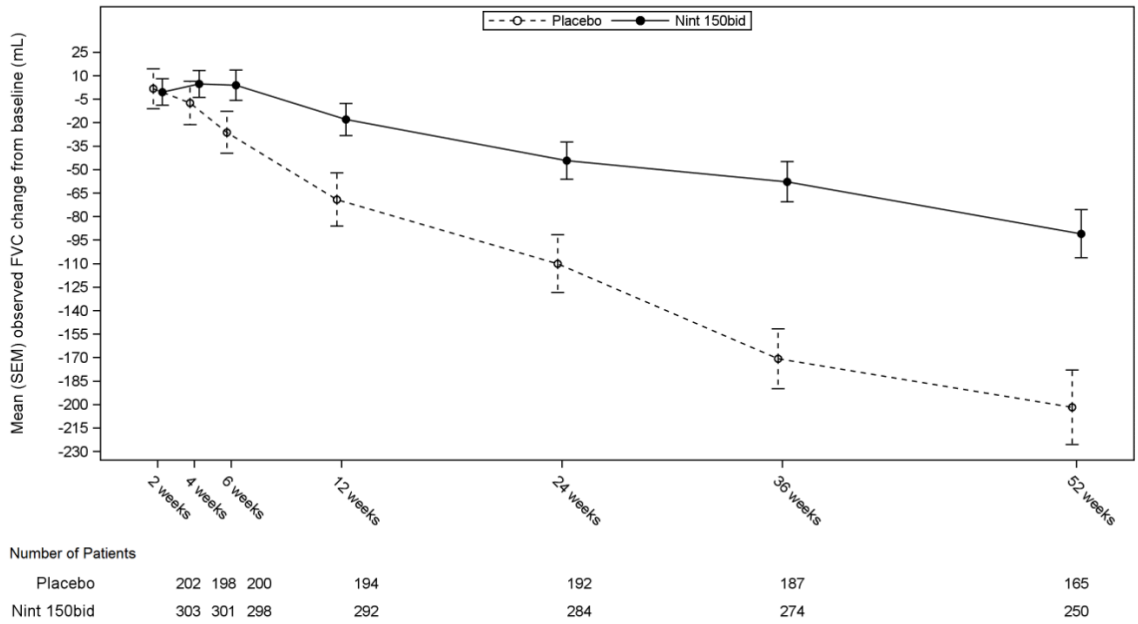

Figure 16: Observed FVC change from baseline (mL) overtime by treatment group in phase 3 study, 1190.32.
(Source: Figure 11.4.1.1:1 of CSR1199.32)

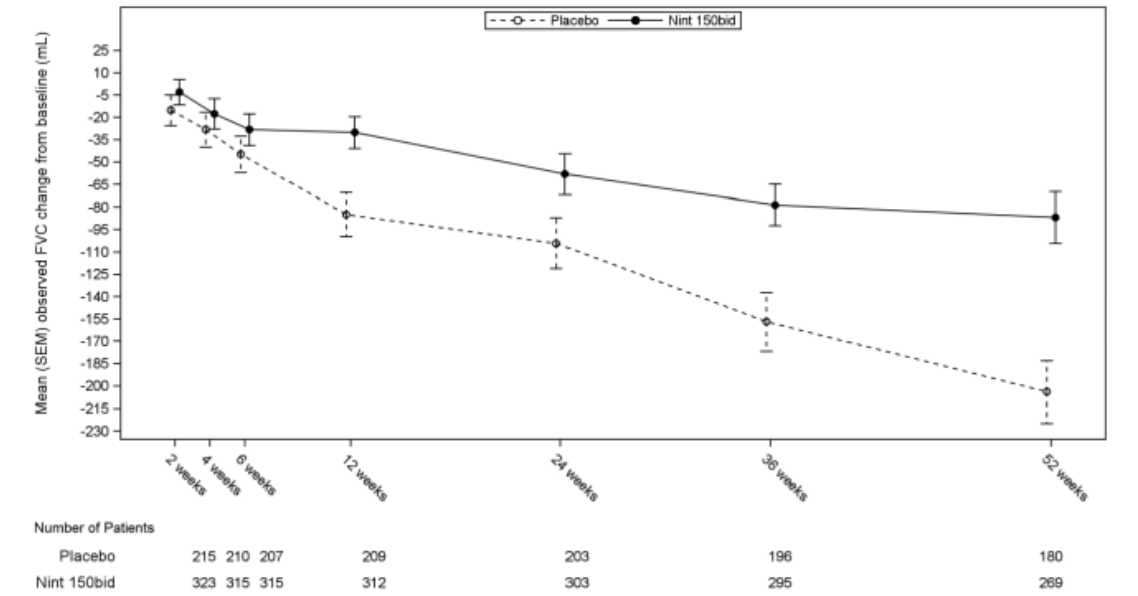

Figure 17: Observed FVC change from baseline (mL) overtime by treatment group in phase 3 study, 1190.34.
(Source: Figure 11.4.1.1:1 of CSR1199.34)

4.2 GENOMICS GROUP REVIEW

OFFICE OF CLINICAL PHARMACOLOGY
GENOMICS AND TARGETED THERAPY GROUP REVIEW

NDA/BLA Number	NDA 205832
Submission Date	5/2/2014
Applicant Name	Boehringer Ingelheim, Inc.
Generic Name	Nintedanib
Proposed Indication	The treatment of idiopathic pulmonary fibrosis (IPF) (b) (4).
Primary Reviewer	Robert Schuck, Pharm.D., Ph.D.
Secondary Reviewer	Christian Grimstein, Ph.D.

1 Background

Nintedanib (BIBF 1120) is a small molecule inhibitor of the receptor tyrosine kinases for 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. These growth factor receptors are key elements of the intracellular signaling cascade that drives proliferation, migration, and transformation of fibroblasts, which is critical to the pathology of idiopathic pulmonary fibrosis (IPF). Nintedanib also inhibits Flt-3, Lck, Lyn and Src kinases. In the current original NDA submission, Boehringer Ingelheim is seeking approval of nintedanib for the treatment of IPF (b) (4).

Nintedanib is metabolized predominately by esterases to form BIBF 1202, the major metabolite. BIBF 1202 is subsequently glucuronidated by UGT1A1, UGT1A7, UGT1A8, and UGT1A10 to BIBF 1202 glucuronide. The UGT1A enzyme family is highly polymorphic, and multiple variants exist in each isoform (PMID 19857043). According to the sponsor, BIBF 1202 maintains activity at some receptors, but is substantially less potent than the parent compound, and not a major contributor to the overall effect of nintedanib. BIBF 1202 glucuronide is not active at any of the nintedanib receptors.

Nintedanib is a substrate of P-glycoprotein (gene: *ABCB1*) and OCT-1. The BIBF1202 metabolite is a substrate of OATP-1B1 and OATP-2B1, and BIBF 1202 glucuronide is a MRP-2 and BCRP substrate. Functional polymorphisms have been identified in each of these transporters.

The purpose of this review is to evaluate the impact of *UGT1A1*28* and *ABCB1* genotypes on nintedanib pharmacokinetics (PK).

2 Submission Contents Related to Genomics

The Applicant submitted one dedicated pharmacogenomic report "pharmacokinetic meta-analysis across BIBF 1120 studies in patients and healthy volunteers with different *UGT1A1*28* genotypes" (U11-1903-01). In addition, the impact of *ABCB1* genotype on

nintedanib exposure was assessed in studies 1199.161 (study report: U13-1478-01) and 1199.162 (study report: U11-1925-01) and the clinical utility of the plasma biomarker Krebs von den Lungen (KL)-6 was evaluated in study 1199.30 (study report U13-1590-01).
The Invader® UGT1A1 Molecular Assay was used to genotype for the *UGT1A1*28* variant. The Analytical Report submitted by the sponsor indicates that allele frequencies are consistent with previous reports and no significant deviations from Hardy-Weinberg equilibrium were observed.

*Reviewer comment: UGT1A1*28 genotyping was performed using a commercially available assay and appears adequate. Genotyping methods for ABCB1 were not provided.*

3 Key Questions and Summary of Findings

3.1 Does *UGT1A1*28* genotype impact nintedanib pharmacokinetics?

Sponsor's analysis:

Three datasets were used to conduct a meta-analysis evaluating the effect of *UGT1A1*28* on the PK of nintedanib and its metabolites (BIBF 1202 and BIBF 1202 glucuronide, Table 42).

Table 42. Datasets and PK parameters included in meta-analysis.

Dataset	Study	PK parameter(s)	No. of UGT1A1 genotypes (rs8175347)			Total No. of patients
			*1/ *1	*1/ *28	*28/ *28	
1	1199.06	$AUC_{0\text{-}12,\ norm}$ $C_{max,\ norm}$	8	4	4	16
2	1199.06, 1199.10	$C_{pre,ss,norm,\ study,ind}$	36	38	15	89
3	1199.75	$AUC_{0\text{-}\infty,\ norm,\ i.v.}$, $C_{max,\ norm,\ i.v.}$, $AUC_{0\text{-}\infty,\ norm,\ p.o.}$, $C_{max,\ norm\ p.o.}$	11	13	0*	24**

* UGT1A1 *28/*28 homozygous subjects excluded (after screening, [U10-1400]), ** 12 patients (7 *1/*1 homoyzgotes and 5 *1/*28 heterozgotes) also received BIBF 1120 orally
Data source: Genotypes: [Appendix Table 10.1: 1] (1199.06), [Appendix Table 10.2: 1] (1199.10), [U10-1400] (1199.75)

(Source: U11-1903-01)

Dataset 1 was utilized to calculate dose-normalized $AUC_{0\text{-}12}$ and C_{max} for nintedanib, BIBF 1202, and BIBF 1202 glucuronide following oral administration in study 1199.06. $AUC_{0\text{-}12}$ and C_{max} were similar across genotypes for nintedanib. In contrast, BIBF 1202 $AUC_{0\text{-}12}$ and C_{max} were more than 2-fold higher in *UGT1A1*28* heterozygotes compared to wild-type individuals; however, in *UGT1A1*28* homozygotes BIBF 1202 $AUC_{0\text{-}12}$ and C_{max} were similar to wild-type individuals. BIBF 1202 glucuronide $AUC_{0\text{-}12}$ and C_{max} were lower in *UGT1A1*28* homozygotes than in wild-type or heterozygous individuals (Table 43).

Table 43. PK parameters by UGT1A1 genotype

Route	Analyte	PK parameter†	N	*1/*1	*1/*28	*28/*28
Dataset 1						
Oral	Nintedanib	$AUC_{0\text{-}12,\ norm}$ (ng*h/mL/mg)	8/4/4	1.33 (96.9)	1.37 (50.5)	1.67 (27.3)
Oral	Nintedanib	$C_{max,\ norm}$ (ng/mL/mg)	8/4/4	0.283 (79.5)	0.293 (38.8)	0.268 (27.7)
Oral	BIBF 1202	$AUC_{0\text{-}12,\ norm}$ (ng*h/mL/mg)	8/4/4	0.963 (74.8)	1.99 (146)	0.847 (70.7)
Oral	BIBF 1202	$C_{max,\ norm}$ (ng/mL/mg)	8/4/4	0.148 (115)	0.359 (162)	0.126 (110)
Oral	BIBF 1202 glucuronide	$AUC_{0\text{-}12,\ norm}$ (ng*h/mL/mg)	8/4/4	53.4 (101)	40.4 (379)	20.3 (65.9)
Oral	BIBF 1202 glucuronide	$C_{max,\ norm}$ (ng/mL/mg)	8/4/4	5.83 (103)	6.42 (243)	2.14 (78.0)
Dataset 2						
Oral	Nintedanib	$C_{pre,ss,norm,\ study,ind}$ (ng/mL/mg)	Not Specified	0.053 (103)	0.063 (51.3)	0.072 (69.6)
Oral	BIBF 1202	$C_{pre,ss,norm,\ study,ind}$ (ng/mL/mg)	33/34/15	0.061 (99.8)	0.083 (106)	0.077 (97.3)
Oral	BIBF 1202 glucuronide	$C_{pre,ss,norm,\ study,ind}$ (ng/mL/mg)	34/33/15	12.0 (138)	12.8 (176)	4.70 (299)
Dataset 3						
Oral	Nintedanib	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	7/5	0.613 (56.3)	0.497 (44.8)	N/A
Oral	Nintedanib	$C_{max,\ norm}$ (ng/mL/mg)	7/5	0.089 (38.2)	0.079 (39.0)	N/A
i.v.	Nintedanib	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	8/8	11.1 (35.4)	12.4 (17.9)	N/A
i.v.	Nintedanib	$C_{max,\ norm}$ (ng/mL/mg)	11/13	1.84 (30.5)	2.04 (16.0)	N/A
Oral	BIBF 1202	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	Not Specified	0.473 (38.8)	0.360 (45.4)	N/A
Oral	BIBF 1202	$C_{max,\ norm}$ (ng/mL/mg)	7/5	0.061 (60.9)	0.051 (67.0)	N/A
i.v.	BIBF 1202	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	3/1	3.47 (10.0)	3.30	N/A
i.v.	BIBF 1202	$C_{max,\ norm}$ (ng/mL/mg)	7/7	0.352 (34.5)	0.371 (15.9)	N/A
Oral	BIBF 1202 glucuronide	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	7/5	7.13 (75.7)	5.29 (126)	N/A
Oral	BIBF 1202 glucuronide	$C_{max,\ norm}$ (ng/mL/mg)	7/5	0.132 (50.1)	0.088 (78.6)	N/A
i.v.	BIBF 1202 glucuronide	$AUC_{0\text{-}\infty,\ norm}$ (ng*h/mL/mg)	4/3	36.2 (68.2)	25.3 (39.7)	N/A
i.v.	BIBF 1202 glucuronide	$C_{max,\ norm}$ (ng/mL/mg)	6/4	0.322 (60.3)	0.340 (50.6)	N/A

†Each study utilized multiple doses of nintedanib, therefore all PK parameters are presented as dose-normalized geometric mean (geometric CV%)
(Source: U11-1903-01)

Dataset 2 was utilized to calculate dose-normalized steady-state, pre-dose concentrations of nintedanib, BIBF 1202, and BIBF 1202 glucuronide ($C_{pre,ss,norm,study,ind}$) in studies 1199.06 and 1199.10. Consistent with the results from Dataset 1, nintedanib concentrations were similar across *UGT1A1*28* genotypes. In addition, BIBF1202 concentrations were similar across *UGT1A1*28* genotypes. However, BIBF 1202 glucuronide concentrations were 2-3 fold lower for *UGT1A1*28* homozygous individuals compared to wild-type and heterozygous individuals, which was consistent with the results obtained from Dataset 1.

In Dataset 3 dose-normalized $AUC_{0-\infty}$ was calculated following i.v. and oral administration of nintedanib. Only *UGT1A1*28* wild-type and heterozygous individuals were included as *UGT1A1*28* variant homozygotes were excluded from the study secondary to safety concerns. Consistent with the previous analyses, nintedanib $AUC_{0-\infty}$ and C_{max} were similar in *UGT1A1*28* wild-type and heterozygous individuals following i.v. and oral administration (Table 43), BIBF 1202 $AUC_{0-\infty}$ and C_{max} were also similar. *UGT1A1*28* heterozygotes had lower BIBF 1202 glucuronide $AUC_{0-\infty}$ following i.v. and oral administration. C_{max} was lower in *UGT1A1*28* heterozygotes following oral administration, but similar following i.v. administration.

*Reviewer comment: PK parameters for nintedanib and its main metabolite BIBF 1202 exhibit a high degree of variability both within and between UGT1A1*28 genotypes which may, at least in part, be attributed to small subject numbers in the studies. Exposure to the active parent compound and the main metabolite BIBF 1202 does not appear to differ by UGT1A1*28 genotype. BIBF 1202 glucuronide exposure appears to be lower in UGT1A1*28 homozygotes; however, since BIBF 1202 glucuronide does not confer any known biological activity, this is unlikely to affect safety or efficacy of nintedanib. Of note, the sponsor's rationale for excluding UGT1A1*28 homozygotes from the first-in-human study (1199.75) secondary to safety concerns is unclear.*

3.2 Does *ABCB1* (p-glycoprotein) genotype impact nintedanib pharmacokinetics?

<u>*Sponsor's analysis:*</u>

(b) (4)

(b) (4) (b) (4)

Reviewer comment: The sponsor conducted two pharmacogenetic analyses to evaluate the impact of ABCB1 polymorphisms on nintedanib PK parameters. Although no power calculation is presented, these small studies are likely under-powered to detect anything except for a very large genotype effect. Follow-up studies to further explore the potential impact of ABCB1 genotype on nintedanib PK are not indicated at this time.

3.3 Do changes in plasma concentrations of the biomarker Krebs von den Lungen (KL)-6 predict response to nintedanib?

Sponsor's analysis:

KL-6 is a fibroblast chemoattractant, and is hypothesized to be a prognostic biomarker for survival in IPF patients. Therefore, in study 1199.30, the sponsor conducted an exploratory analysis to evaluate the clinical utility of KL-6 as a biomarker in IPF patients. Control subjects consisted of samples obtained from KL-6 assay validation (see study report U13-1590-01, Appendix 9.2) which were pooled with additional samples from the sponsor's non-interventional study 352.2035 (healthy smokers and patients with mild chronic obstructive pulmonary disease).

Baseline KL-6 plasma levels were obtained in 427 of 428 (99.8%) of subjects treated in 1199.30. According to sponsor's analysis, median KL-6 plasma levels were significantly higher in the 427 IPF patients (1260 U/mL [IQR 853-1920]) compared to the 151 control subjects (294 U/mL [IQR 212-397], p<0.0001). Moreover, an empiric analysis in placebo-treated patients stratifying baseline KL-6 by <1000 U/mL and ≥1000 U/mL showed trend toward worse 12-month survival in patients with high KL-6 levels (log-rank test, p=0.0627). Among nintedanib treated patients with baseline KL-6 values ≥1000 U/mL, there were 4/52 (7.7%) deaths in the nintedanib 150 mg BID group compared to 9/62 deaths (14.5%) in the placebo group (p=0.272). However, among subjects with KL-6 <1000 U/mL, there were 3/33 (9.1%) deaths in the nintedanib 150 mg BID group compared to 0/23 deaths (0.0%) in the placebo group (p=0.159).

In patients treated with nintedanib, a decline in KL-6 levels was associated with a decrease in annual rate of decline in forced vital capacity (FVC) in the 50 mg BID (Spearman correlation coefficient -0.383, p=0.002) and 100 mg BID groups (Spearman correlation coefficient -0.532, p<0.001), but not 150 mg BID group for which the sponsor is seeking approval (Spearman correlation coefficient -0.009, p=0.951), the 50 mg QD group (Spearman correlation coefficient 0.070, p=0.602), or the placebo group (Spearman correlation coefficient -0.058, p=0.683).

No analysis of FVC stratified by baseline KL-6 plasma concentration was completed; therefore, it is unknown whether baseline KL-6 concentrations predict response as measured by rate of annual decline in FVC. In addition, the Report Summary states that exploratory analyses of KL-6 data are planned in studies 1199.32/34; however, these reports are not included in the submission.

Reviewer comment: The results of this exploratory analysis indicate that baseline plasma KL-6 concentrations appear higher in IPF patients compared to control subjects without IPF. However, clinical utility of KL-6 plasma levels remains to be elucidated.

4 Summary and Conclusions

The reviewer agrees with the sponsor's assessment that *UGT1A1*28* genotype may decrease BIBF 1202 glucuronide exposure, but does not affect the PK of nintedanib or the active BIBF 1202 metabolite. Since the parent drug and active metabolite concentrations are not impacted by *UGT1A1*28* genotype, the difference in exposure to the inactive metabolite BIBF 1202 glucuronide is not likely to impact the safety or efficacy of nintedanib. Moreover, based on the genetic analyses conducted in PK studies, *ABCB1* genotype does not appear to impact nintedanib PK.

5 Recommendations

The submission is acceptable from a Genomics and Targeted Therapy Group perspective. Additional gene-drug or drug-drug interaction studies do not appear to be indicated on the basis of these findings.

5.1 Post-marketing studies

None.

5.2 Label Recommendations

None.

4.3 INDIVIDUAL STUDY REVIEW

Note –
In this review, early development names BIBF1120 is also used to refer to nintedanib

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ADME In-Vitro STUDIES

1 Distribution

BIBF1120

Study # A075/02AR

Title: [^{14}C]BIBF 1120 ES: Species comparison of *in vitro* plasma protein binding and *in vitro* distribution into blood cells

- **Objective:**
  - To determine extent of binding of [^{14}C]BIBF 1120 ES to proteins in human, cynomolgus, rat and mouse plasma.
  - To determine the degree of protein binding of [^{14}C]BIBF 1120 ES in human serum albumin (HSA) and α1-acid glycoprotein (AAG)
  - To determine the blood to plasma concentration ratio of [^{14}C]BIBF 1120 ES at a concentration of 1 µM (equivalent to 0.312 µg/mL) in rat, monkey and human blood from pooled gender sources

- **Method:**
  - Plasma protein binding: Pooled plasma from mouse, rat, dog and monkey and human plasma segregated by individuals were used to determine the extent of protein binding by equilibrium dialysis. The samples were analyzed by liquid scintillation counting
  - Protein binding was determined using HSA at 4.5 g/L or AGP at 0.14, 0.7 and 3.4 g/L using equilibrium dialysis.
  - [^{14}C]BIBF 1120 ES was added to pooled whole blood samples from different species to the concentrations of 500 ng/ml. Aliquots were drawn at 2, 30, 60 and 180 minutes to analyze the radioactivity in blood cells and plasma (C_C/C_P).
- **Results:** [^{14}C]BIBF 1120 ES shows high plasma protein binding for human (98%), and the protein binding in human plasma is similar or higher compared to rat, mouse and monkey (Table 44) . The plasma protein binding was independent of the drug concentration in the investigated range from 50 to 2000 ng/ml.

Table 44: Summary of plasma protein binding in mouse, rat, dog, monkey and human

species	paraoxon [µM]	[^{14}C]BIBF 1120 BS [ng/ml]	N	mean (%)	SD (%)
human	0	50 - 2000	12	97.8	0.1
	10 - 100	200	6	97.9	0.2
cynomolgus	0	50 - 2000	9	93.2	0.7
	100	50 - 200	9	92.9	0.3
rat	10	50 - 2000	18	95.8	0.4
mouse	100	200	3	97.2	0.2

Mouse, Rat and Monkey data are based on pooled samples. Human data are reported as mean of 5 individuals
(source: Table 4.2:1, CSR A075-02ar)

The binding to HSA was 97.5 % and thus comparable to that measured in human plasma. The binding of BIBF 1120 BS depended on the AGP concentration. It was 55.5 %, 74.6 % and 93.0 % at AGP concentrations of 0.14 g/1, 0.7 g/1 and 3.4 g/1, respectively.

The in vitro distribution of BIBF 1120 BS related radioactivity in blood was time and species dependent. In human blood, C_b/Cp decreased from 0.869 at 5 minutes to 0.677 at 3 hours. This shift is likely caused by a degradation of BIBF 1120 BS to a metabolite with a different distribution behavior.

- **Conclusion:** Human plasma protein binding is 97.8% for nintedanib, and the free fraction in human plasma is similar or lower compared to animal plasma. HSA is the major binding protein in human plasma. The in vitro blood distribution (C_b/C_p) of drug related radioactivity changed with time.

BIBF1202

Study # PB08-001

Title: Determination of in vitro plasma protein binding of [^{14}C]BIBF 1202 ZW, a metabolite of BIBF 1120 BS, in plasma of rat, Rhesus monkey and human

- **Objective:** To determine the fractions of [^{14}C]BIBF 1202 ZW related radioactivity bound to plasma proteins in rat, Rhesus monkey and human in vitro

- **Method:** The plasma protein binding was determined by equilibrium dialysis using target concentrations of 5, 100 and 1000 ng/mL [14C]BIBF 1202 ZW. The radioactivity was quantified by means of liquid scintillation counting.

- **Results and Conclusion:** The fractions of [14C]BIBF 1202 ZW related radioactivity bound to plasma proteins in different species are shown in Table 45. [14C]BIBF 1202 ZW shows a moderate extent of protein binding in rat and human plasma and a low binding percentage in Rhesus monkey plasma.

Table 45: Summary of plasma protein binding in rat, monkey and human

Species	f_B [%] Mean
rat	77.2
Rhesus monkey	55.0
human	77.8

(source: Summary table, CSR PB08-001)

BIBF1202-glucuronide

Study # A090_08FU

Title: Determination of in vitro plasma protein binding of [14C]BIBF 1202 glucuronide, a metabolite of BIBF 1120 ES, in plasma of rat, Rhesus monkey and human

- **Objective:** To determine the fractions of [^{14}C]BIBF 1202 glucuronide related radioactivity bound to plasma proteins in rat, Rhesus monkey and human in vitro

- **Method:** The plasma protein binding was determined by equilibrium dialysis using target concentrations of 100, 1000 and 10000 nM (rat and Rhesus monkey) or 100, 1000, 10000 and 100000 nM (human) [14C]BIBF 1202 glucuronide in plasma pools. The radioactivity was quantified by means of liquid scintillation counting.

- **Results and Conclusion:** The fractions of [14C]BIBF 1202 glucuronide related radioactivity bound to plasma proteins in different species are shown in Table 46. The [14C]BIBF 1202 glucuronide plasma protein binding was moderate in Rhesus monkey (f_B ca. 84%) but high in rat and human plasma (f_B ca. 96% and 97%, respectively).

Table 46: Summary of plasma protein binding in rat, monkey and human

Species	Target conc. [nM]	mean f_B [%]
rat	100	96.0
	1000	96.2
	10000	94.9
Rhesus monkey	100	83.8
	1000	83.5
	10000	83.1
human	100	95.3
	1000	97.3
	10000	97.1
	100000	91.3

(source: Summary table, CSR A090_08FU)

2 In vitro Metabolism

BIBF1120

Study # A118_02LU

Title: Investigation of the human cytochrome P450 enzymes involved in the metabolism of [14C]BIBF 1120 ES

- **Objective:**
  - To investigate the contribution of human cytochrome P450 enzymes involved in the in vitro metabolism of [14C]BIBF 1120 ES.
  - To investigate was the contribution of microsomal and plasma esterases in the cleavage of [14C]BIBF 1120 ES
- **Method:** Radiolabeled BIBF 1120 ES was incubated with human liver microsomes and recombinant CYPs, human plasma and human blood. The quantitation of metabolites was carried out by measuring the radioactivity.
- **Results and Conclusion:**

  U1 was identified as di-demethylated BIBF 1120 ES, U2 as BIBF 1202, U3 as hydroxylated and U4 as N-demethylated BIBF 1120 ES, i.e. BIBF 1053.

  - [14C]BIBF 1120 ES underwent NADPH dependent metabolism by human liver microsomes under formation of BIBF 1053 (N-demethylated BIBF 1120 ES) and U3 (hydroxylated BIBF 1120 ES) and very low amounts of U1 (di-demethylated BIBF 1120 ES)
  - BIBF 1202 (O-demethylated BIBF 1120 ES) was formed by microsomal carboxyl esterases.
  - CYP 3A4 was identified as the major catalyst of [14C]BIBF 1120 ES in vitro metabolism with a Km of 60.7 µM for the formation of U4 and 142 µM for the formation of U3.
  - A minor contribution of CYP 2C8 in the metabolism of [14C]BIBF 1120 ES cannot be ruled out.

Table 47: Percentage of Metabolites of nintedanib in Human Liver Microsomes and Recombinant Human Cytochrome P-450 Isoforms

	turnover rate [% of total peak areas]					turnover rate [pmol/min/mg protein]				mean turnover rate [pmol/min/mg protein]			
	U1	U2	U3	U4	parent	U1	U2	U3	U4	U1	U2	U3	U4
parent	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
CYP control	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 1A1	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 1A2	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2A6	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2B6	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2C9-Arg	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2C9-Cys	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2C8	n.a.	n.a.	n.a.	1.22*	98.8	n.a.	n.a.	n.a.	20.3*	n.a.	n.a.	n.a.	19.0*
	n.a.	n.a.	n.a.	1.06*	98.9	n.a.	n.a.	n.a.	17.7*				
CYP 2C19	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	12.0*	n.a.	n.a.
	n.a.	0.72*	n.a.	n.a.	99.3	n.a.	12.0*	n.a.	n.a.				
CYP 2D6-Val	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 2E1	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				
CYP 3A4	n.a.	n.a.	1.15*	6.01	92.8	n.a.	n.a.	19.2*	100	n.a.	n.a.	17.7*	89.5
	n.a.	n.a.	0.97*	4.73	94.3	n.a.	n.a.	16.2*	78.8				
CYP 4A11	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.	n.a.
	n.a.	n.a.	n.a.	n.a.	100	n.a.	n.a.	n.a.	n.a.				

*: BLQ

(Source: Table 11:16 study report A118_02lu)

- **Conclusion:**

BIBF 1202 (O-demethylated BIBF 1120 ES) was formed by microsomal carboxyl esterases. CYP 3A4 was identified as the major catalyst of BIBF 1120 ES, and the role of CYP2C8 cannot be excluded.

Study # A227_03TE

Title: Metabolism of BIBF 1120 ES by hepatocytes of rat and human

- **Objective:**
  - to obtain information on the hepatic metabolism of BIBF 1120 ES in rats and human
  - to compare hepatic metabolism of BIBF 1120 ES in rats and humans
  - to assess the rate and extent of uptake of BIBF 1120 ES into hepatocytes

- **Method:** [^{14}C]BIBF 1120 ES was incubated with rat and human hepatocytes, and the quantitation of metabolites was carried out by measuring the radioactivity.

- **Results and conclusions:** BIBF 1120 ES was rapidly taken up into the hepatocytes and almost completely metabolized after 2 h of incubation for both human and rat hepatocytes. Ester hydrolysis was the most prevalent metabolic reaction followed by

oxidative N-demethylation. There is no unique metabolite identified in human hepatocyte, and the amounts of BIBF1202 were higher in human than in rat hepatocytes. BIBF1202

Study # A217/02TE

Title: In vitro glucuronidation of BIBF 1202 ZW by liver microsomes of rats, dogs, cynomolgus monkeys and human

- **Objective:** to obtain information on the relative extent of glucuronidation of BIBF 1202 ZW in human and 3 animal species.

- **Method:** BIBF 1202 was incubated with liver microsomes of rats, dogs, cynomolgus monkeys and human, and the quantitation of BIBF1202 and BIBF1202 glucuronide was carried out by HPLC with UV detection.

- **Results and Conclusion:** Glucuronidation was dependent on pH. The glucuronidation of BIBF 1202 ZW was most effectively at a pH of 6.5. There was a clear species difference in the extent of in vitro glucuronidation with the following rank order: r a t » cynomolgus = human > dog

Study # A249_06TE-b2886

Title: *In Vitro* glucuronidation of BIBF 1202, a metabolite of BIBF1120, by UDP-glucuronosyltransferase 1A1 (UGT1A1)

- **Objective:**
  • To assess the in vitro glucuronidation of BIBF 1202
  • To elucidate the enzymology of the UGT enzymes that catalyse the glucuronidation of BIBF 1202
- **Method:** The glucuronidation of BIBF 1202 was investigated by using human liver microsomes or expressed UDP-glucuronosyltransferases (UGT). BIBF1202 was incubated with human liver microsomes in the presence of the cosubstrate UDP-glucuronic acid. BIBF 1202 was also incubated with eight expressed human UGT enzymes. Several drugs or drug candidates were investigated for their potential as inhibitors of UGT1A1. The quantitation of BIBF1202 and BIBF1202 glucuronide was carried out by HPLC with UV detection.
  - **Results and Conclusion:** Of eight different human UGT enzymes only UGT1A1 was capable of catalyzing the formation of the acylglucuronide of BIBF 1202 (Table 48).

Table 48. Glucuronidation of BIBF1202 by expressed human UGT enzymes

UGT enzyme	rate [pmol/min/mg]
1A1	BLR#
1A1*	73.3
1A6	0
1A6*	0
1A9	0
1A9*	0
1A10*	0
2B7*	0
2B15*	0
1A3*	0
1A4*	0
mock	0

glucuronide peak was detectable, estimated to 3.7 pmol/min/mg
* UGT enzymes expressed in insect cells
BLR: below linear range
data source file: human_UGT.xls
(Source: Table 10:6, study report A249-06TE)

In order to assess whether the glucuronidation of BIBF 1202 by UGT1A1 could be inhibited by potential comedications, several drugs or drug candidates were investigated for their potential as inhibitors of UGT1A1 (Table 49). Inhibition that was greater than 30% at the highest tested concentration of 100 µM was not observed for ambroxol, etoposide, paracetamol and ciprofloxacin.

Table 49. Inhibition of Glucuronidation of BIBF1202 by drugs

Inhibitor	IC_{50} [µM]	K_i [µM]
BI 7325	2.0	1.5
docetaxel	7.6	
paclitaxel	8.8	
BI 2536	2.7	5.8
tipranavir	6.2	
BIBW 2992	11.1	10.9
BIBF 1120	1.7	12.6
simvastatin	84.5	
domperidon	25.0	
diclofenac	78.6	

(Source: Table in summary, study report A249-06TE)

Study # A267_07TE

Title: In Vitro glucuronidation of BIBF 1202, a metabolite of BIBF 1120, by intestinal microsomes of rat and human and expressed intestinal UDP-glucuronosyltransferases

- **Objective:**
  - To assess the in vitro intestinal glucuronidation of BIBF 1202

• To elucidate the enzymology of the UGT enzymes that catalyse the glucuronidation of BIBF 1202 in the intestine

- **Method:** The glucuronidation of BIBF 1202, the carboxylic acid metabolite of BIBF 1120, was investigated by using intestinal microsomes of rats and human. For this purpose microsome samples were used of pooled small intestine of rats as well as ileum and jejunum microsomes of individual human donors. In addition, expressed human intestinal UDP-glucuronosyltransferases (UGT) were investigated.

- **Results and Conclusion:** This study showed that BIBF 1202 is effectively glucuronidated in rat and human intestine. Human intestinal UGT1A7, UGT1A8 and UGT1A10 catalyzed BIBF 1202 glucuronidation with UGT1A8 exhibiting the highest intrinsic clearance (Table 50). In addition to the liver, the intestinal tract probably contributes to the glucuronidation of BIBF 1202 in human subjects.

Table 50. Glucuronidation of BIBF1202 by expressed human UGT enzymes

UGT enzyme	V_{max} [pmol/min/mg]	K_m [µM]
UGT1A7	22	31
UGT1A8	61	184
UGT1A10	112	88

(Source: Table in summary, study report A267-07TE)

3 In vitro Transporters

BIBF1120 and BIBF1202

Study # pk05008

Title: Hepatic and renal transporters involved in the hepatobiliary and urinary excretion of BIBF 1120 and BIBF 1202

- **Objective:** To evaluate the role of hepatic and renal uptake and efflux transporters in the hepatobiliary and urinary excretion of BIBF 1120 and BIBF 1202, and to identify the transporters involved.

- **Method:** Uptake of BIBF1120 and BIBF1202 were determined using Human Embryonic Kidney (HEK 293) cells expressing human OATP1B1, OATP1B3 or OATP2B1 and vector-transfected HEK293 cells; HEK293 cells transiently expressing human OCT1 or OCT2 and transiently vector transfected HEK293 cells.

  Bidirectional transport of BIBF1120 and BIBF1202 were determined using LLC-PK1 cells expressing human P-gp and parental LLC-PK1 cells; MDCKII cells expressing human MRP2 and BCRP and parental MDCKII cells.

  The effects of BIBF 1120 and BIBF 1202 (0.3, 3 and 30 µM) on the transcellular transport of [3H]digoxin, [3H]vinblastine and [3H]prazosin were also investigated.

- **Results and conclusions:**
  - Identification of transporters involved in hepatic and renal uptake of BIBF 1120 was not successful because of its high degree of binding to the cell surface and/or passive diffusion into the cells. BIBF 1120 inhibited OCT1 with an IC50 value of 0.88 µM, but no pronounced inhibition of other hepatic and renal uptake transporters was observed.
  - OATP1B1 and OATP2B1 are candidate transporters involved in the hepatic uptake of BIBF 1202. BIBF 1202 showed a broad inhibition spectrum toward hepatic uptake transporters with IC50 values in the range from 14 µM to 79 µM.
  - P-gp is a candidate transporter involved in the efflux of BIBF 1120. Vectorial transport activities of P-gp and BCRP were weakly inhibited by BIBF 1120.
  - The absence of efflux transport of BIBF 1202 in P-gp, MRP2 and BCRP transfectants and hCMV indicates that passive diffusion plays a key role in its biliary excretion.

BIBF1202-grucuronide

Study # PKPR0801

Title: In vitro evaluation of the interaction of BIBF 1202 glucuronide with human hepatobiliary transporters

- **Objective:** To investigate whether BIBF 1202 glucuronide is a substrate of P-gp, MRP2 and BCRP, and whether BIBF 1202 glucuronide is a substrate of OATP1B1, OATP1B3, OATP2B1 and OCT1
- **Method:** Uptake of BIBF 1202 glucuronide were determined using Human Embryonic Kidney (HEK 293) cells expressing human OATP1B1, OATP1B3, OATP2B1 or OCT1 and vector-transfected HEK293 cells (solute carrier uptake); MRP2- or BCRP-expressing MDCKII cells (membrane vesicle uptake).

  The membrane permeability of BIBF 1202 glucuronide was determined as 14-20 µL/90 min/cm2 using a monolayer of parental Madin Dorbin Canine Kidney (MDCK) II cells cultured on Transwell filters.

- **Results: T**he permeability of BIBF 1202 glucuronide was low (14-20 µL/90 min/cm^2), and almost comparable to the low permeability marker mannitol in the transcellular transport experiment .

  <u>OATP1B1, OATP1B3, OATP2B1, and OCT1</u>
  The uptake of BIBF 1202 glucuronide in transporter expressing cells was time-dependent but was not significantly higher than that in respective vector-transfected HEK293 cells. In addition, the effect of typical inhibitors specific to each transporter isoform at a concentration sufficient to achieve complete inhibition was not found to be significant between transporter isoform-expressing and vector-transfected cells. These results indicate that BIBF 1202 glucuronide is not a substrate of OATP1B1, OATP1B3, OATP2B1 and OCT1.

  <u>MRP2</u>

The uptake of BIBF 1202 glucuronide into inside-out MV from MRP2-expressing cells was time-dependent and higher than that in MV from parental MDCKII cells. The higher uptake was dramatically reduced in the absence of ATP as driving force of MRP2 and almost completely diminished in the presence of the MRP inhibitor MK-571. These results indicate that BIBF 1202 glucuronide is a substrate of MRP2.

BCRP
The uptake of BIBF 1202 glucuronide was higher in MV from BCRP-expressing MDCKII cells than that in the MV from parental MDCKII cells. The higher uptake was reduced to the level at AMP supplement instead of ATP and it was completely blocked by the BCRP inhibitor prazosin. These results indicate that BIBF 1202 glucuronide is a substrate of BCRP.

- **Conclusion:**
  - BIBF 1202 glucuronide is a substrate of BCRP and MRP2
  - BIBF 1202 glucuronide is not a substrate of OATP1B1, OATP1B3, OATP2B1 and OCT1
  - Transport by P-gp was not performed due to experimental limitations.

4 In vitro Enzyme Inhibition

BIBF1120

Study # A114_02LU VD

Title: BIBF 1120 ES: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

- **Objective:**
  - To obtain information on the affinity of BIBF 1120 ES to human cytochrome P450 enzymes.
  - To evaluate the potential of BIBF 1120 ES for metabolic drug-drug interactions based on inhibition of cytochrome P450 enzymes by BIBF 1120 ES.
- **Method:** Standard marker activity substrates for different enzymes were incubated with pooled human liver microsomes or human recombinant CYP3A4 Supersomes™ in the presence of NADPH, with BIBF1120 ES concentrations of 0 (control), 0.10, 1, 10 and 100 µM.
- **Results:** Results of in vitro experiments in the presence of BIBF 1120 ES up to 100 µM are listed in Table 51. BIBF 1120 ES demonstrated no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, or CYP4A11 activities. Weak inhibition of product formation was observed for CYP 3A4catalysed erythromycin N demethylation. For this reaction an IC50 value of 70.1 µM was found.

Table 51: Inhibition of test reactions by BIBF 1120 ES compared to model inhibitors

test reaction	CYP iso-enzyme	inhibitor	IC_{50} [µM]	literature data IC_{50}, K_i [µM]
coumarin 7-hydroxylation	2A6	BIBF 1120 ES	>100	-
coumarin 7-hydroxylation	2A6	tranylcypromine	0.22	K_i = 0.04*; [R02-0613]
bufuralol 1'-hydroxylation	2D6	BIBF 1120 ES	>100	-
bufuralol 1'-hydroxylation	2D6	quinidine	0.18	K_i = 0.78*; [R97-2013]
erythromycin N-demethylation	3A4	BIBF 1120 ES	70.1	-
erythromycin N-demethylation	3A4	ketoconazole	0.05	K_i = 0.5 [R00-0942]
lauric acid 11-hydroxylation	2E1	BIBF 1120 ES	>100	-
lauric acid 11-hydroxylation	2E1	diethyldithiocarbamate	>100	<100✠ [R99-0640]
lauric acid 12-hydroxylation	4A11	BIBF 1120 ES	>100	-
midazolam 1-hydroxylation	3A4	BIBF 1120 ES	>100	
midazolam 1-hydroxylation	3A4	ketoconazole	0.13	K_i = 0.11✧ [R02-0140]
nifedipine oxidation	3A4	BIBF 1120 ES	>100	-
nifedipine oxidation	3A4	ketoconazole	0.20	K_i = 0.015✝ [R01-1411]
paclitaxel 6α-hydroxylation	2C8	BIBF 1120 ES	>50	-
phenacetin O-deethylation	1A2	BIBF 1120 ES	>100	-
phenacetin O-deethylation	1A2	furafylline	4.24	K_i = 3* [R01-1411]
S-mephenytoin N-demethylation	2B6	BIBF 1120 ES	>100	-
S-mephenytoin N-demethylation	2B6	orphenadrine	>100	IC_{50} = 84 [R97-2010]
S-mephenytoin 4'-hydroxylation	2C19	BIBF 1120 ES	>100	-
testosterone 6ß-hydroxylation	3A4	BIBF 1120 ES	>100	-
testosterone 6ß-hydroxylation	3A4	ketoconazole	0.11	IC_{50} = 0.22 [R01-0602]
tolbutamide hydroxylation	2C9	BIBF 1120 ES	>100	-
tolbutamide hydroxylation	2C9	sulphaphenazole	0.69	K_i = 0.3* [R01-1411]

*: competitive inhibitor
✝: mixed inhibitor
✠: mechanism based inhibitor
✧: non competitive inhibitor
(Source: Table 11:25, CSR A114-02lu)

Conclusion: BIBF 1120 ES did not inhibit CYP enzymes at clinical relevant concentrations.

Study # A249_06TE-b2883

Title: In Vitro inhibition of UDP-glucuronosyltransferase 1A1 (UGT1A1) by various compounds

- **Objective:** To assess the potential of inhibition of UGT1A1 in human liver microsomes by different drugs and drug candidates

- **Method:** The glucuronidation of ß-estradiol was investigated by using human liver microsomes or expressed UDP-glucuronosyltransferase (UGT) 1A1 in the presence of different concentrations (0 - 200 µM) of potential inhibitors of UGT enzymes.

- **Results:** Inhibition of the 3- and 17-glucuronidation was observed for the following compounds (Table 52):

Table 52: Inhibition of test reactions by BIBF 1120 and other potential UGT inhibitors

Inhibitor	IC_{50} [µM] ß-estradiol 3-glucuronidation	ß-estradiol 17-glucuronidation
BI 7325	1.3	52.6
Docetaxel	13.6	32.5
Paclitaxel	18.7	32.4
BI 2536	21.7	72.5
Tipranavir	22.7	72
BIBW 2992	24.2	73.7
BIBF 1120	24.5	77.6
Simvastatin	60.2	43.8
Domperidone	74.9	48.2

(Source: Summary Table 1, CSR A249_06)

Conclusion: BIBF 1120 ES did not inhibit UGT enzymes at clinical relevant concentrations.

BIBF1202

Study # A219-07LU

Title: BIBF 1202: In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

- **Objective:**
  - To obtain information on the affinity of BIBF 1202 ZW to human cytochrome P450 enzymes.
  - To evaluate the potential of BIBF 1202 ZW for metabolic drug-drug interactions based on inhibition of cytochrome P450 enzymes by BIBF 1202 ZW.
- **Method:** Standard marker activity substrates for different enzymes were incubated with pooled human liver microsomes in the presence of NADPH, with BIBF1202 ZW concentrations of 0 (control), 0.1, 1, 10 and 100 µM.

- **Results:** Results of in vitro experiments in the presence of BIBF1202 up to 100 µM are listed in Table 53. BIBF1202 demonstrated no inhibition of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 or CYP4A11 activities.

Table 53: Inhibition of test reactions by BIBF 1202 compared to model inhibitors

Test reaction	CYP iso-enzyme	Inhibitor	IC_{50} [µM]	Literature data IC_{50}, K_i [µM]
amodiaquine *N*-deethylation	2C8	BIBF 1202 ZW	>100	-
amodiaquine *N*-deethylation	2C8	montelukast	0.22	K_i = 0.0092 to 0.15*; R06-0751
bupropion hydroxylation	2B6	BIBF 1202 ZW	>100	-
bupropion hydroxylation	2B6	ticlopidine	0.16	IC_{50} = 0.32 P04-09137
coumarin 7-hydroxylation	2A6	BIBF 1202 ZW	>100	-
coumarin 7-hydroxylation	2A6	tranylcypromine	0.45	K_i = 0.04*; R02-0613
diclofenac 4'-hydroxylation	2C9	BIBF 1202 ZW	>100	-
diclofenac 4'-hydroxylation		sulphaphenazole	0.23	K_i = 0.3 µM, R01-1411
dextromethorphan *O*-demethylation	2D6	BIBF 1202 ZW	>100	-
dextromethorphan *O*-demethylation	2D6	quinidine	0.06	K_i = 0.1 µM, P07-07229
lauric acid 11-hydroxylation	2E1	BIBF 1202 ZW	>100	-
lauric acid 11-hydroxylation	2E1	diethyldithiocarbamate	61.4	<100✠ R99-0640
lauric acid 12-hydroxylation	4A11	BIBF 1202 ZW	>100	-
midazolam 1'-hydroxylation	3A4	BIBF 1202 ZW	>100	-
midazolam 1'-hydroxylation	3A4	ketoconazole	0.09	K_i = 0.11✧ R02-0140
nifedipine oxidation	3A4	BIBF 1202 ZW	>100	-
nifedipine oxidation	3A4	ketoconazole	0.15	K_i = 0.015> R01-1411
phenacetin *O*-deethylation	1A2	BIBF 1202 ZW	>100	-
phenacetin *O*-deethylation	1A2	furafylline	2.75	K_i = 3* R01-1411
S-mephenytoin 4'-hydroxylation	2C19	BIBF 1202 ZW	>100	-
S-mephenytoin 4'-hydroxylation	2C19	ticlopidine	0.39	K_i = 1.2 P03-08796
testosterone 6ß-hydroxylation	3A4	BIBF 1202 ZW	>100	-
testosterone 6ß-hydroxylation	3A4	ketoconazole	0.09	IC_{50} = 0.22 R01-0602

*: competitive inhibitor
>: mixed inhibitor
✠: mechanism based inhibitor
✧: non competitive inhibitor

(Source: Table 10:25, CSR A219-07lu)

Conclusion: BIBF 1202 did not inhibit CYP enzymes at clinical relevant concentrations.

BIBF1202-Grucuronide

Study # A239/08LU

Title: BIBF 1202-Glucuronide (CD 6133): In vitro inhibition studies on cytochrome P450 dependent metabolic reactions

- **Objective:**
  - To obtain information on the affinity of BIBF 1202-Glucuronide (CD 6133)to human cytochrome P450 enzymes.
  - To evaluate the potential of BIBF 1202-Glucuronide (CD 6133)for metabolic drug-drug interactions based on inhibition of cytochrome P450 enzymes by BIBF 1202-Glucuronide.
- **Method:** Standard marker activity substrates for different enzymes were incubated with pooled human liver microsomes in the presence of NADPH, with BIBF1202-Glucuronide (CD 6133) concentrations of 0 (control), 0.1, 1, 10 and 100 µM.

- **Results:** Results of in vitro experiments in the presence of BIBF1202-Glucuronide up to 100 µM are listed in Table 54. BIBF1202-Glucuronide demonstrated no inhibition

of CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP2E1, CYP3A4 or CYP4A11 activities.

Table 54: Inhibition of test reactions by BIBF 1202-Glucuronide compared to model inhibitors

Test reaction	CYP iso-enzyme	Inhibitor	IC_{50} [µM]	Literature data IC_{50}, K_i [µM]
amodiaquine *N*-deethylation	2C8	BIBF 1202-glucuronide	>100	-
amodiaquine *N*-deethylation	2C8	montelukast	0.21	K_i = 0.0092 to 0.15*; R06-0751
bupropion hydroxylation	2B6	BIBF 1202-glucuronide	>100	-
bupropion hydroxylation	2B6	ticlopidine	0.12	IC_{50} = 0.32 P04-09137
coumarin 7-hydroxylation	2A6	BIBF 1202-glucuronide	>100	-
coumarin 7-hydroxylation	2A6	tranylcypromine	0.26	K_i = 0.04*; R02-0613
diclofenac 4'-hydroxylation	2C9	BIBF 1202-glucuronide	>100	-
diclofenac 4'-hydroxylation	2C9	sulphaphenazole	0.22	K_i = 0.3 µM, R01-1411
flurbiprofen 4'-hydroxylation	2C9	BIBF 1202-glucuronide	85.5	-
flurbiprofen 4'-hydroxylation	2C9	sulphaphenazole	0.23	
dextromethorphan *O*-demethylation	2D6	BIBF 1202-glucuronide	>100	-
dextromethorphan *O*-demethylation	2D6	quinidine	0.05	K_i = 0.1 µM, P07-07229
lauric acid 11-hydroxylation	2E1	BIBF 1202-glucuronide	>100	-
lauric acid 11-hydroxylation	2E1	diethyldithiocarbamate	63.7	<100✠ R99-0640
lauric acid 12-hydroxylation	4A11	BIBF 1202-glucuronide	>100	-
midazolam 1'-hydroxylation	3A4	BIBF 1202-glucuronide	>100	-
midazolam 1'-hydroxylation	3A4	ketoconazole	0.07	K_i = 0.11✧ R02-0140
nifedipine oxidation	3A4	BIBF 1202-glucuronide	>100	-
nifedipine oxidation	3A4	ketoconazole	0.08	K_i = 0.015> R01-1411
phenacetin *O*-deethylation	1A2	BIBF 1202-glucuronide	>100	-
phenacetin *O*-deethylation	1A2	furafylline	2.32	K_i = 3* R01-1411
S-mephenytoin 4'-hydroxylation	2C19	BIBF 1202-glucuronide	>100	-
S-mephenytoin 4'-hydroxylation	2C19	ticlopidine	0.29	K_i = 1.2 P03-08796
testosterone 6β-hydroxylation	3A4	BIBF 1202-glucuronide	>100	-
testosterone 6β-hydroxylation	3A4	ketoconazole	0.05	IC_{50} = 0.22 R01-0602

*: competitive inhibitor
>: mixed inhibitor
✠: mechanism based inhibitor
✧: non competitive inhibitor

(Source: Table 10:27, CSR A239-08lu)

Conclusion: BIBF 1202-glucuronide did not inhibit CYP enzymes at clinical relevant concentrations.

5 In vitro Enzyme Induction

BIBF1120

Study # A020-08OS

Title: BIBF 1120 ES: In vitro cytochrome P450 enzyme induction in primary human hepatocytes

- **Objective and Method:** To investigate in vitro induction potential of BIBF 1120 ES on cytochrome P450 enzymes in cultured primary human hepatocytes.
- **Results:**

No relevant induction of enzyme activity was observed neither for CYP1A2, 2B6, 2C8, 2C9, 2C19 nor 3A4 after treatment of sandwich cultured human hepatocytes from three donors with up to 2 µM BIBF 1120 ES for 48 h.
No relevant induction of gene expression was observed neither for CYP1A2, 2B6, 2C8, 2C9, 2C19 nor 3A4 after treatment of sandwich cultured human hepatocytes from three donors with up to 2 µM BIBF 1120 ES for 48 h.

- **Conclusion:**
  In summary, metabolic drug-drug interactions, based on induction of CYP enzymes by BIBF 1120 ES are unlikely to occur.

PHARMACOKINETICS

1 Mass Balance Study

Study # 1199.20

Title: Metabolism and pharmacokinetics of [^{14}C]-BIBF 1120 after administration of single doses of 100 mg [^{14}C]-BIBF 1120 oral solution in healthy male volunteers

- **Objective:**
  - To evaluate the metabolic profile
  - To determine the routes of excretion of [^{14}C] -BIBF 1120 in healthy male subjects.
  - To determine the protein binding of [14C]-radioactivity
  - To determine the pharmacokinetics of BIBF 1120, BIBF 1202 and total radioactivity after a single oral administration of [14C]-BIBF 1120 in healthy

- **Study design:** non-randomized, open-label, single-dose study.
- **Test drug and sample size:** 100 mg (free base) oral dose of [^{14}C] -BIBF 1120 ES containing a radiolabel dose of approximately 70 µCi. N=8.
- **Samples:**
  - Blood: sampling for PK pre-dose 0:15, 0:30, 0:45, 1, 1:30, 2, 3, 4, 6, 8, 10, 12, 24, 36, 48, 72 and 96 hours after study drug administration; blood sampling for metabolic profiling pre-dose, 1, 2 and 6 hours after study drug administration.
  - Urine sampling intervals day -1 (pre-dose sample / -32 to -1 hours), 0-4, 4-8, 8-24, 24-48, 48-72, 72-96 and 96-120 hours after study drug administration.
  - Feces sampling intervals day -1 (pre-dose sample / -32 to -1 hours), 0-24, 24-48, 48-72, 72-96 and 96-120 hours after administration.

- **Results**
  The overall recovery of the administered dose was approximately 92.4% by day 4. The main excretion route of BIBF 1120 and metabolites was found to be via the feces, urinary excretion plays only a minor role for the elimination of BIBF 1120 and

its metabolites. Cumulative total, urine, and fecal recovery of [14C] radioactivity following oral administration is shown in Figure 18.

Absorption:

BIBF 1120 was rapidly absorbed with maximum plasma concentrations after 1.3 hours after oral administration as a drinking solution.

Distribution:

There was no pronounced distribution of BIBF 1120 into red blood cells. The protein binding of [14C] radioactivity could not be determined within this trial due to low [14C] radioactivity concentrations in plasma.

Metabolism:

Peak plasma concentrations of BIBF 1202 and of [14C] radioactivity were reached around 1 hour later compared to BIBF 1120. Cmax and AUC_{0-12} of BIBF 1120 as well as of BIBF 1202 were equally ranged, however were significantly lower than the ones of [14C] radioactivity. The sum plasma concentrations of the parent compound (BIBF 1120) and of BIBF 1202 was significantly lower than the concentration of total [14C] radioactivity in plasma, as major metabolite BIBF1202-glucuronide was not measured in the study.

Elimination:

The total amount of [14C] radioactivity excreted in urine was about 0.649% of the dose. Most of the [14C] radioactivity excreted in feces was found in the time interval of 24 to 48 hours after dosing. The main excretion route of BIBF 1120 and metabolites was found to be via the feces, and urinary excretion plays only a minor role for the elimination of BIBF 1120 and its metabolites. The gMean t1/2 for BIBF 1120 was 13.7 h.

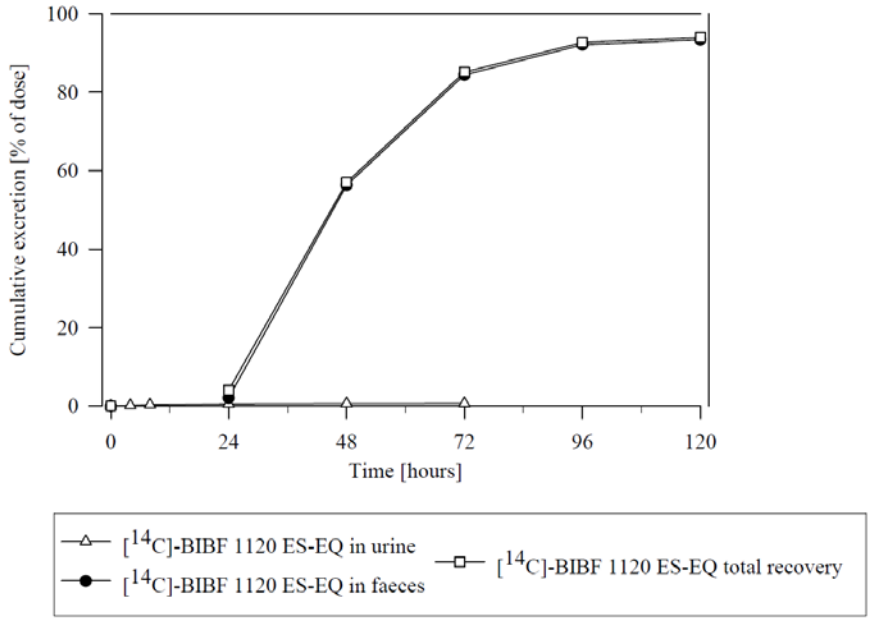


Figure 18: Geometric mean cumulative excretion of [14C]-BIBF 1120 ES-EQ in percent of dose in urine, feces and total recovery after single oral administration of 100 mg BIBF 1120 solution
(source: Figure 11.5.2:5, CSR 1199-020)

Table 55: Cumulative Percentage of Dose Excreted in Urine and Feces over 120 Hours by Male Subjects Following Oral Administration of a Single 100 mg Dose of [^{14}C]BIBF1120

100 mg	Total recovery of [^{14}C]-BIBF 1120 ES-EQ [% of dose] excreted in urine and faeces														
	Time intervals [h]														
	[% of dose] in urine					[% of dose] in faeces					Total recovery [% of dose]				
	0-24	0-48	0-72	0-96	0-120	0-24	0-48	0-72	0-96	0-120	0-24	0-48	0-72	0-96	0-120
gMean	0.526	0.614	0.649	---	---	2.04	56.3	84.4	92.1	93.4	3.97	57.0	85.1	92.7*	94.0*
Mean	0.542	0.633	0.668	---	---	14.2	59.4	84.9	92.1	93.5	14.7	60.0	85.5	92.8*	94.2*

(source: Table 15.5.1.2:17, CSR 1199-020)

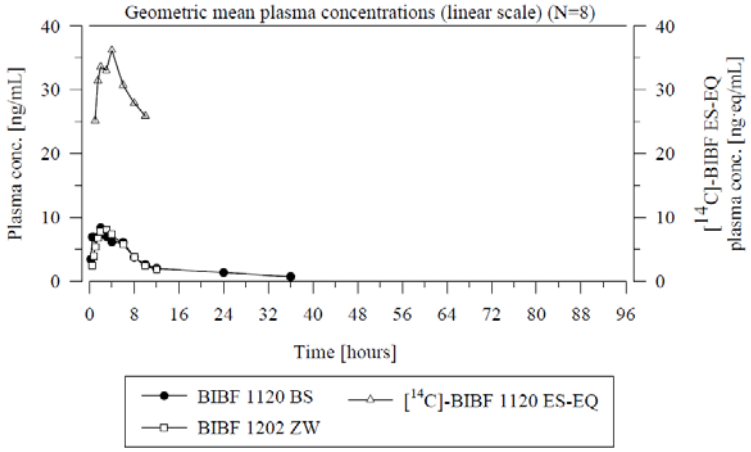


Figure 19. Geometric mean drug plasma concentration-time profiles of BIBF 1120 BS, BIBF 1202 ZW and [14C]-BIBF 1120 ES-EQ after single oral administration of 100 mg BIBF 1120 (2.60 MBq [14C]- BIBF 1120) solution
(source: Figure 11.5.2:4, CSR 1199-020)

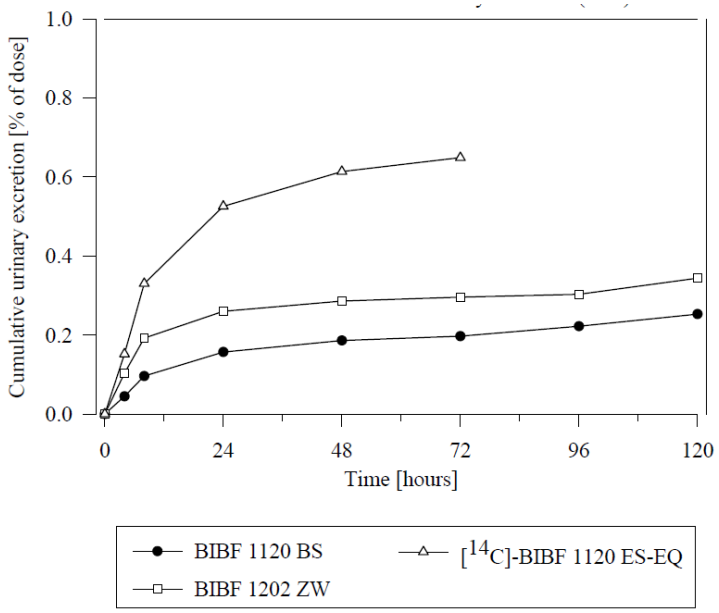


Figure 20. Geometric mean cumulative urinary excretion of BIBF 1120 BS, BIBF 1202 ZW and [14C]-BIBF 1120 ES-EQ in percent of dose after single oral administration of 100 mg BIBF 1120

solution
(source: Figure 11.5.2:5, CSR 1199-020)

Table 56: Percentage of Parent (M0) and Metabolites (M1-BIBF1202, M2-BIBF1202 glucuronide) of nintedanib excreted by urine and feces in Male Subjects Following Oral Administration of a Single 100 mg Dose of [14C]nintedanib in solution

	metabolites (% of dose)				
	urine (0 - 24 h)		faeces (0 - 72 h)		urine + faeces
	mean	CV (%)	mean	CV (%)	
m1	0.2	17	58.4	22	58.6
m2[#]	0.07	40	0.1	283	0.17
m3	0.01	110	3.6	56	3.6
m4	0.01	85	2.6	84	2.6
m5	0.004	189	0.2	283	0.2
m7	0.03	33			0.03
m8	0.01	87			0.01
m9	0.02	117			0.02
m10	0.04	114			0.04
m0	0.14	24	19.9	48	20.0
sum	0.53		84.8		85.3
total excretion	0.53		87.6		88.1
not assigned	0		2.8		2.8

[#] combined data for the 1-*O*-acylglucuronide (m2) and its isomeric acylglucuronides (m2*)

(Source – page 57, Study A248_05TE report, samples from study 1199.20)

Conclusion
The contribution of renal excretion to the total clearance was low, and the major route of elimination of total [14C] radioactivity was the liver, demonstrated by a fecal fraction excreted of 93.4% within 120 hours after dosing. The majority of the total dose was excreted as metabolites.

2 Multiple Rising Dose (4 weeks)

Trial # 1199.26

Title: A randomized, open-label, parallel-group Phase II study comparing the efficacy and tolerability of BIBF 1120 versus sunitinib in previously untreated patients with renal cell cancer

- **Objective:**
  - To compare the efficacy and safety of nintedanib versus sunitinib in patients with advanced renal cell cancer (RCC)
  - To investigate the effects of nintedanib on the heart rate corrected QT interval (QTcF).

Only results related to multiple dose PK are reviewed here. For QT results, please refer to QT-IRT review by Dr. Huifang Chen (DARRTS date 07/23/2014).

- **Study design:** A Phase II, open-label, 2:1 randomized, parallel-arm comparison of nintedanib versus sunitinib. Nintedanib was given continuously (courses of 4 weeks), while sunitinib was given in courses of 4 weeks followed by 2 weeks without treatment.

- **Test drug and sample size:** 200 mg BID (dose reduction to 150 mg BID or 100 mg BID in case of relevant AEs), n=96 (64 patients on nintedanib arm, and 32 patients on sunitinib arm)

- **Results:**

Nintedanib PK after multiple doses was consistent with the single dose PK. The median T_{max} was about 3 hr, mean apparent terminal $t_{1/2}$ ranged from 9-15 hrs. After multiple dosing, there was a slight accumulation of BIBF 1120 compared to a single dose, leading to a gMean accumulation ratio of 1.33 based on C_{max} (gCV 67.0%) and 1.66 based on AUC_{0-12} (gCV 52.5%), which was slightly lower than as expected based on the terminal half-life and BID dosing regimen. This indicated that the reported terminal half life was slightly longer than the effective t1/2 of nintedanib driving accumulation in plasma, which was estimated to be in the range of 9-10 h based on the observed accumulation ratios or the mean residence time. Mean plasma PK profiles are shown in Figure 21 and summary PK parameters are listed in Table 57. Based on visual inspection, steady state was reached on Day 15.

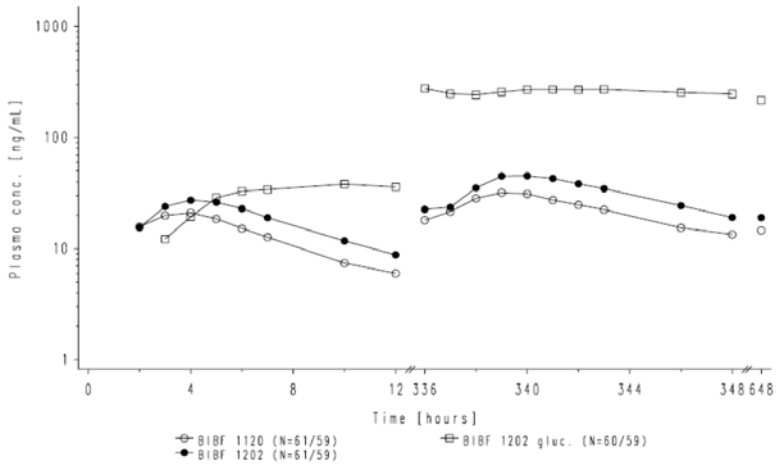


Figure 21: Geometric mean plasma concentration-time profiles of BIBF 1120, BIBF 1202, and BIBF 1202-glucuronide after single (Day 1) and multiple (Day 15) oral administration of 200 mg BIBF 1120 BID to patients with RCC
(Source – Figure 11.5.2.1:2, Study 1199.26 report)

Table 57: Geometric mean (and gCV%) standard pharmacokinetic parameters of nintedanib, BIBF 1202, and BIBF 1202 glucuronide in cancer patients after a single oral dose of nintedanib and at

steady state following BID administration (1199.26; metaanalysis of studies 1199.1/2/3/19)

Study 1199.26 (if not indicated otherwise)			Nintedanib		BIBF 1202		BIBF 1202 glucuronide	
Single dose		N	gMean	gCV [%]	gMean	gCV [%]	gMean	gCV [%]
$AUC_{0\text{-}12,norm}$	[(ng·h/mL)/mg]	59/59/49	0.819	67.8	1.08	95.4	1.64	99.2
$R_{AUC0\text{-}12,norm}$		--/59/49	NA	NA	1.35	88.4	1.64	113
$AUC_{0\text{-}\infty,norm}$ #	[(ng·h/mL)/mg]	65/47/--	1.33	78.5	2.47	186	NC	NC
$C_{max,norm}$	[(ng/mL)/mg]	61/61/60	0.159	71.4	0.174	117	0.210	104
$R_{Cmax,norm}$		-/61/55	NA	NA	1.12	97.0	1.01	127
t_{max}*	[h]	61/61/60	3.08	0.883 – 12.0	3.92	1.92 – 12.0	10.1	4.08 - 13.0
$t_{1/2}$ #	[h]	65/47/6	9.18	46.2	6.66	29.2	54.9	76.0
CL/F #	[mL/min]	65	12500	78.5	NA	NA	NA	NA
V_z/F #	[L]	65	9970	72.2	NA	NA	NA	NA
Steady state								
$AUC_{0\text{-}12,ss,norm}$	[(ng·h/mL)/mg]	58/59/55	1.35	67.5	2.03	131	14.7	170
$R_{AUC0\text{-}12,ss,norm}$		58/58/54	NA	NA	1.56	96.8	9.16	159
$R_{A,AUC0\text{-}12,norm}$		56/57/45	1.66	52.5	1.89	74.9	9.08	101
LI +		58/59/55; 65/47/--	1.02	NA	0.82	NA	NC	NC
$C_{max,ss,norm}$	[(ng/mL)/mg]	61/45/61	0.216	72.7	0.282	131	1.52	176
$R_{Cmax,ss,norm}$		61/61/61	NA	NA	1.34	106	5.40	161
$R_{A,Cmax,norm}$		59/59/61	1.33	67.0	1.60	85.4	7.12	102
$t_{max,ss}$*	[h]	61/61/61	2.92	0.00 – 6.83	3.08	0.00 – 9.93	4.05	0.00 - 12.00
$t_{1/2,ss}$ #	[h]	48/45/24	15.3	59.4	12.6	36.0	55.4	75.9
$CL/F_{,ss}$	[mL/min]	58	12400	67.5	NA	NA	NA	NA
$V_z/F_{,ss}$ #	[L]	48	18600	87.4	NA	NA	NA	NA

+ Calculated based on dose normalised gMean exposure estimates. gCV is therefore not applicable. R_{Param} denotes metabolic ratios based on molar exposure, $R_{A,Param}$ denotes accumulation ratios.
* t_{max} is given as median and range.
\# Parameter estimate determined in metaanalysis of studies 1199.1/2/3/19 as last plasma sample in 1199.26 taken 12 h after administration and terminal phase thus not captured
LI Linearity index, defined as $AUC_{\tau,ss}/AUC_{0\text{-}\infty}$
NA Not applicable
NC Not calculated as terminal phase not captured in 1199.26 and bioanalytical assay for studies included in metaanalysis not fully quantitative

(Source – Table 3.2.1:1, summary of clinical pharmacology)

The metabolic ratios of BIBF 1202 to BIBF 1120 were slightly higher than 1 indicating a higher exposure to the ester-cleaved metabolite BIBF 1202 than to the parent compound BIBF 1120. The ratios increased by 15% to 20% at steady state compared to single dose Conditions (Table 58).

The metabolic ratios of BIBF 1202-glucuronide to BIBF 1120 after single administration of BIBF 1120 were greater than 1 for AUC_{0-12} and equal to 1 for Cmax, giving a hint for higher exposure to the BIBF 1202-glucuronide than to the parent compound BIBF 1120. At steady state conditions, the metabolic ratios of BIBF 1202-glucuronide to BIBF 1120 increased by about 6-fold for AUCτ,ss and Cmax,ss compared to single dose conditions indicating a higher exposure to BIBF 1202 glucuronide than to BIBF 1120 at steady state. The metabolic ratios of BIBF 1202-glucuronide to BIBF 1202 after single administration of BIBF 1120 were greater than 1 for AUC_{0-12} and smaller than 1 for Cmax. At steady state conditions, the metabolic ratios of BIBF 1202-glucuronide to BIBF 1202 increased by about 5-fold for AUCτ,ss and Cmax,ss compared to single dose conditions indicating a higher exposure to BIBF 1202 glucuronide than to BIBF 1120 at steady state.

Table 58. Ratios of metabolites and parent compound of Cmax(,ss) and AUC0-12 (AUCτ,ss) after single and multiple oral administrations of 200 mg BIBF 1120

Ratios of metabolites and parent compound after single and multiple oral dosing of 200 mg BIBF 1120									
	BIBF 1202/BIBF 1120 [T/R]			BIBF 1202-glucuronide/ BIBF 1120 [Met]			BIBF 1202-glucuronide/ BIBF 1202 [MT/MR]		
	N	gMean	gCV%	N	gMean	gCV%	N	gMean	gCV%
$R_{AUC0-12}$	59	1.35	88.4	49	1.64	113	49	1.14	80.5
R_{Cmax}	61	1.12	97.0	60	1.01	127	60	0.858	81.0
$R_{AUCτ,ss}$	58	1.56	96.8	54	9.16	159	55	5.70	101
$R_{Cmax,ss}$	61	1.34	106	61	5.40	161	61	4.02	89.6

(Source: Table 11.5.2.4:1, Study report 1199.26)

DRUG-DRUG INTERACTIONS

3 DDI with Ketoconazole

Trial # 1199.161

Title: Relative bioavailability of nintedanib given alone and in combination with ketoconazole at steady state in healthy male volunteers (an open-label, randomized, two-way cross-over clinical Phase I study)

- **Objective:**

To investigate the relative bioavailability of a single dose of nintedanib when given alone and in combination with steady state ketoconazole in healthy male subjects.

- **Study design and treatment schedule:** randomized, open-label trial in healthy male subjects with a 2-way cross-over Pilot Part(N=8), followed by a 2-way cross-over Main Part(N=26)
- Pilot Part:
  - *Treatment A (Reference):* Nintedanib (50 mg) was given as a single dose on Day 1.
  - *Treatment B (Test):* Ketoconazole (400 mg) was given once daily for 3 days starting on Day -2 and nintedanib (50 mg) was given as a single dose 1 h after the ketoconazole administration on Day 1, with ketoconazole under steady-state conditions.

- Main Part:
    - *Treatment C (Reference):* Nintedanib (50 mg or 100 mg, depending on the results of the Pilot Part) was given as a single dose on Day 1.
    - *Treatment D (Test):* Ketoconazole (400 mg) was given once daily for 3 days starting on Day -2. In addition, depending on the results of the Pilot Part (see Section 7.4), 1 of the 3 following treatments was administered:
      • nintedanib (50 mg) was given as a single dose 1 h after the ketoconazole administration on Day 1,
      • nintedanib (100 mg) was given as a single dose 1 h after the ketoconazole administration on Day 1, or
      • nintedanib (50 mg) was given as a single dose 4 h before the ketoconazole administration on Day 1.
      In all 3 possible scenarios, nintedanib administration was done under steady state ketoconazole.

- **PK Sampling Schedule**

Blood –0, 0.5, 1, 2, 4, 6, 8, 12, 16, and 24 hrs in Periods 1 (Days 1) and 2 (Days 3 and 4)

- **Results:**

Many subjects showed double peaks within the first 6h after coadministration of nintedanib and ketoconazole, causing a double peak phenomenon in the gMean plasma concentration-time profile of the test treatment (Figure 22). Coadministration with ketoconazole increased C_{max} and AUC nintedanib AUC by ~61% and C_{max} increased by ~80% following coadministration with ketoconazole (Table 59).

Table 59: PK parameters and statistical summary for comparison of plasma nintedanib with and without ketoconazole

Pharmacokinetic parameter	Adjusted gMean		Adjusted gMean ratio of test to reference treatment [%]	90% CI of gMean ratio		Intra-individual gCV [%]
	Nintedanib+ ketoconazole (test) (N=29)	Nintedanib alone (reference) (N=31)		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	61.8	38.5	160.5	148.2	173.7	17.9
AUC_{0-tz} [ng·h/mL]	59.9	35.7	168.1	155.3	182.0	17.9
C_{max} [ng/mL]	7.5	4.2	179.6	157.6	204.8	29.9

(source: Table 11.5.2.4:1, CSR 1199-0161-01-15)

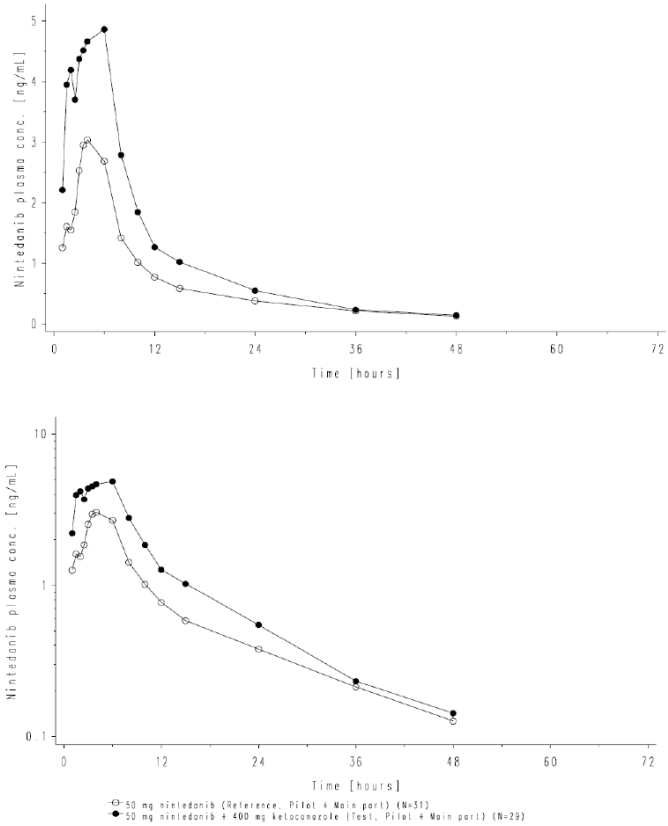


Figure 22: The gMean plasma concentration-time profiles of nintedanib after single oral administration of 50 mg nintedanib alone or following multiple oral administrations of 400 mg ketoconazole once daily over 3 days in the Pilot Part + Main Part (upper panel: linear scale; lower panel: semi-log scale)
(Source: Figure 11.5.2.1: 1 CSR1199.161)

The exposure to BIBF 1202 and BIBF 1202-glucuronide was also higher after coadministration of nintedanib and ketoconazole (test treatment) after administration of nintedanib alone (reference treatment).

The metabolic ratios of BIBF 1202 to nintedanib ($RAUC_{0-\infty,Met}$, $RAUC_{0-tz,Met}$, $RC_{max,Met}$) and of BIBF 1202-glucuronide to BIBF 1202 ($RAUC_{0-\infty,MT/MR}$, $RAUC_{0-tz,MT/MR}$, and $RC_{max,MT/MR}$) were comparable between both treatments.

Conclusions:
The strong P-gp inhibitor ketoconazole increased the exposure to nintedanib, BIBF 1202, and BIBF 1202-glucuronide when administered concomitantly. When coadministered with ketoconazole, nintedanib exposure increased by ~61%.

Reviewer's comment:

- The proposed label recommendation "*Monitor patients closely for tolerability of nintedanib, and manage the adverse reactions by dose interruption, dose reduction, or discontinuation as necessary.*" is reasonable.

- The enterohepatic recirculation was observed in this study.

- Ketoconazole is a potent inhibitor for CYP3A4 and also an inhibitor for P-gp. While the absolute bioavailability for nintedanib parent drug is only 4.67%, mass balance study indicated that 65-80% of the total oral dose was excreted as metabolites (see section 2.5.6) and only 20% of the total dose was excreted as parent drug. The data suggested that 65-80% of the oral dose was absorbed through GI tract and inhibition of P-gp is not likely to have a significant effect on the extent of oral absorption. Therefore, this reviewer concluded that P-gp inhibition cannot fully explain the increased exposure of nintedanib with ketoconazole, and CYP3A4 inhibition in GI tract and liver by ketoconazole may contribute to the increased nintedanib exposure.

4 DDI with Rifampicin

Trial # 1199.162

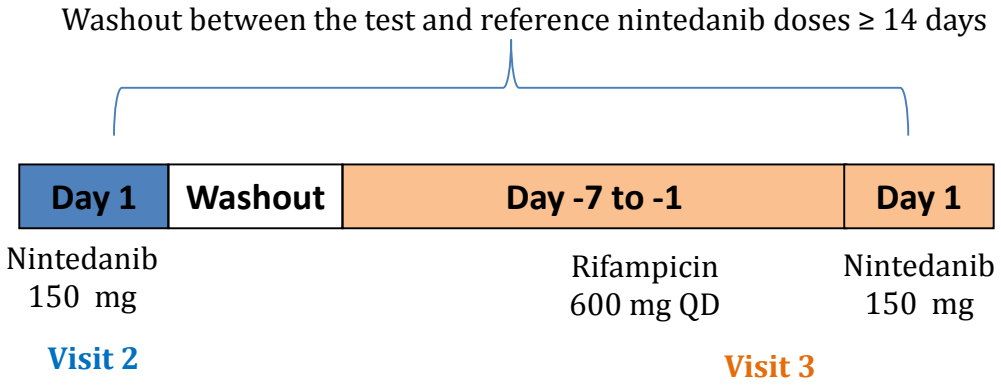
Title: Relative bioavailability of a single oral dose of nintedanib given alone and in combination with multiple oral doses of rifampicin in healthy male volunteers (an open-label, two-period, fixed sequence Phase I trial)

- **Objective:**

To investigate the effect of rifampicin (a P-glycoprotein inducer) on the pharmacokinetic parameters of nintedanib in healthy male subjects.

- **Study design and treatment schedule:**
  - Reference Treatment (R): A single dose of 150 mg nintedanib was administered on Day 1 of Visit 2.
  - Test Treatment (T): Rifampicin (600 mg) was administered once daily, in the evenings of Days -7 to -1 of Visit 3. A single oral dose of 150 mg nintedanib was then administered in the morning of Day 1 of Visit 3.

Administrations of nintedanib in treatment period 1 (R) and treatment period 2 (T) were to be separated by a wash-out period of at least 14 days.



Reviewer's comment:

Rifampicin dosing at 600 mg QD for seven days is considered adequate for P-gp induction and is preferred over use of lower doses. Inducers may take several days to exert their effects on P-gp and dosing for several days ascertains that P-gp induction is achieved before evaluating its effect on PK of nintedanib.

- **PK Sampling Schedule**

Plasma – 0, 0.5, 1, 2, 4, 6, 8, 12, 16 and 24 hours in Period 1 (Day 1) and Period 2 (Day 1)

- **Results and Conclusions:**

Coadministration with rifampicin significantly decreased nintedanib AUC by 50% and C_{max} by 40%. (Figure 23 and Table 60).

Reviewer's comment:

- The lower exposure may decrease the efficacy considering the steep exposure response relationship (section 2.4), therefore coadministration of rifampicin should be avoided. Rifampicin also decreased exposure to BIBF 1202 and BIBF 1202-glucuronide.
- The enterohepatic recirculation was observed in this study.

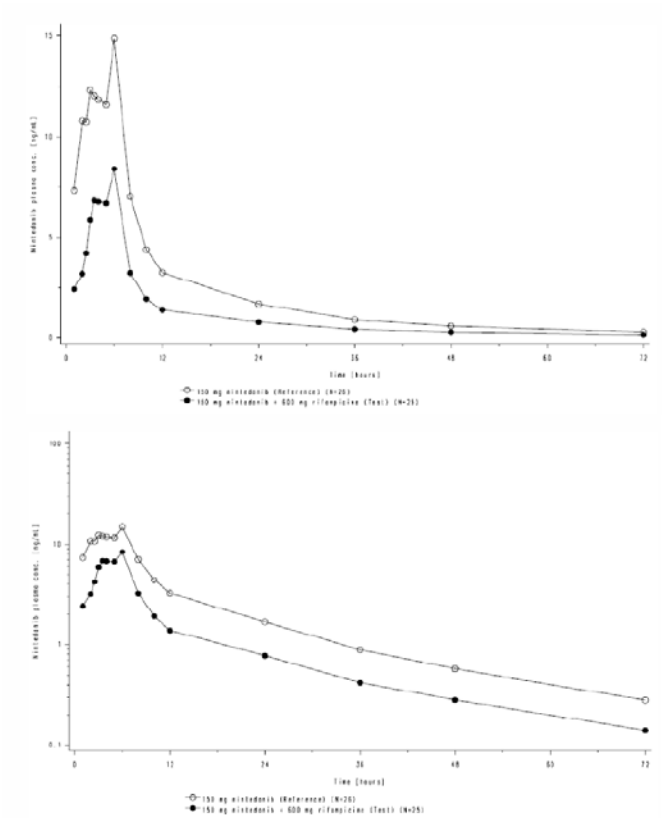


Figure 23: The gMean plasma concentration-time profiles of nintedanib after single oral administration of nintedanib 150 mg alone (reference) or following multiple oral administrations of rifampicin 600 mg once daily over 7 days (test) (upper panel: linear scale; lower panel: semi-log scale)

(Source: Figure 11.5.2.1: 1 CSR1199.162)

Table 60: Analysis of relative bioavailability of nintedanib after single oral administration of nintedanib 150 mg alone (reference) and following multiple oral administrations of rifampicin 600 mg once daily for 7 days (test)

Pharmacokinetic parameter	Adjusted gMean ratio of test to reference treatment (T/R)[1] [%]	2-sided 90% CI of gMean ratio		Intra-individual gCV [%]
		Lower limit [%]	Upper limit [%]	
$AUC_{0-\infty}$ [ng·h/mL]	50.12	47.16	53.28	12.7
AUC_{0-tz} [ng·h/mL]	49.98	46.89	53.29	13.3
C_{max} [ng/mL]	59.76	53.83	66.35	21.9

1 Reference: N=26, test: N=25
(Source: Table 2: 2, CSR 1199-0162)

5 DDI with Pirfenidone

Trial # 1199.31

Title: A double-blind, randomized, placebo-controlled (within a dose group) study to evaluate safety and pharmacokinetics of multiple rising doses of BIBF 1120 at 50 mg b.i.d. (14 days), 100 mg b.i.d. (14 days), and 150 mg b.i.d. (28 days) po, on top of standard medical care with stratification according to pirfenidone use, in Japanese patients with idiopathic pulmonary fibrosis

- **Objective:**
  • To investigate the safety of BIBF 1120 in Japanese patients with idiopathic pulmonary fibrosis (IPF), with and without pirfenidone background treatment
  • To assess the pharmacokinetics of BIBF 1120 in Japanese patients, with and without pirfenidone background treatment
  • To assess the pharmacokinetics of pirfenidone in Japanese patients, alone and in combination with BIBF 1120 treatment

  Only results related to PK are reviewed here. For efficacy and safety results, please refer to the clinical review by Dr. Miya Paterniti.

- **Study design –** double-blind, randomized, placebo-controlled (within a dose group), multi-center, dose-escalating trial for the assessment of the safety and pharmacokinetics of BIBF 1120 in Japanese patients with IPF. Dose transition was implemented sequentially from a lower dose group to a higher dose group (in the order of 50 mg BID X14day, 100 mg BID X14day, and 150 mg BID X28day, unit strength 50mg, 100 mg, 150 mg). PK interaction was assessed in the 150mg BID cohort (cohort 3).

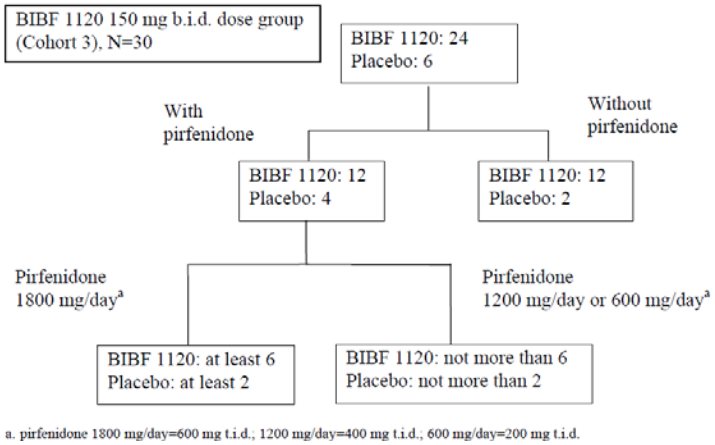


Figure 24. Study design for cohort 3
(Source: Figure 9.1:2, CSR1199.31)

- **PK Sampling Schedule for cohort 3 (Nintedanib 150mg BID, Pirfenidone 600mg TID)**

For Nintedanib - Plasma – day 1 and day 28 – predose, 0.5, 1, 2, 3, 4, 6, 8, 12 hrs; additional sample after day 28 dose– 24, 48, and 72 hrs; day 2, day 7, day 14 and day 21– predose.
For Pirfenidone - Plasma – day -1(without nintedanib) and day 28 (with nintedanib) – 0 (pre morning dose), 0.5, 1, 2, 3, 4(pre-lunch dose), 4.5, 5, 6, 7, 8, 10, 12 (pre-dinner dose) hrs

- **Results**

In the BIBF 1120 150 mg b.i.d. group, the mean plasma concentrations with pirfenidone co-administration tended to be lower than those without pirfenidone co-administration, but high variability was observed. (
Figure 25). On the other hand, coadministration with nintedanib had no significant effect on plasma concentration – time profile of pirfenidone (Figure 26). Geometric mean ratios and 90% CI for plasma PK parameters (AUC, Cmax) as well as amount of unchanged drug excreted in urine (Ae_{12}) and renal clearance (CL_R) were all within 0.8 to 1.25 for comparison of pirfenidone given with or without nintedanib (Table 61).

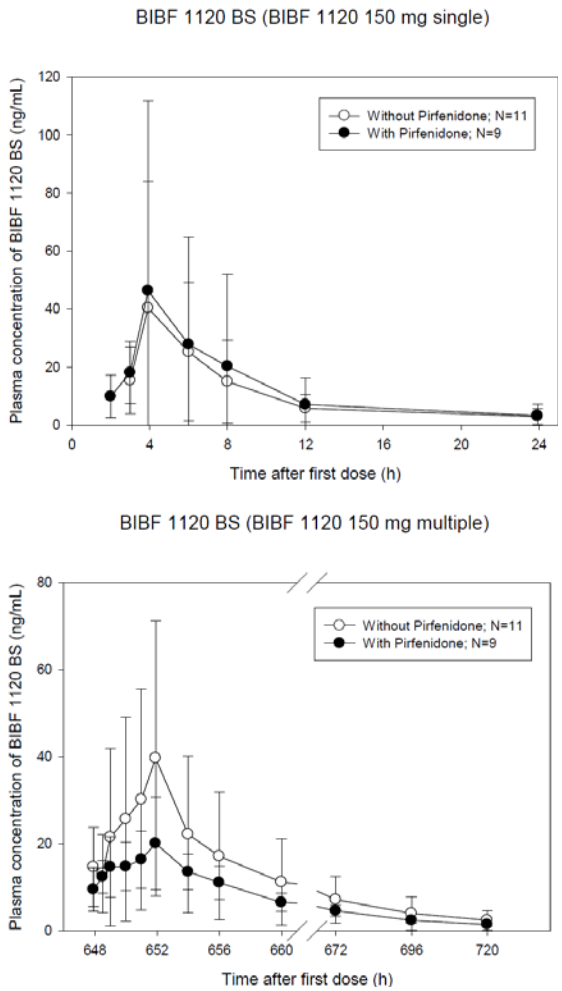


Figure 25: Arithmetic mean (±SD) plasma concentration-time profiles of BIBF 1120 BS after oral administration of 150 mg b i.d. BIBF 1120 with and without co-administration of 600 mg t i.d. pirfenidone
(Source: Figure 11.5.2.1.1:3, CSR1199.31)

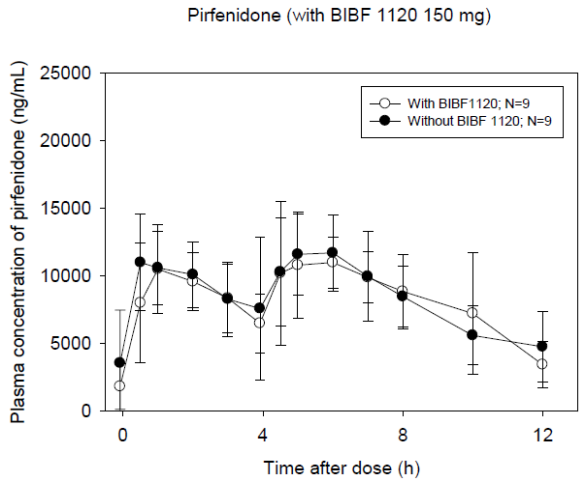


Figure 26. Arithmetic mean (±SD) plasma concentration-time profiles of pirfenidone after multiple

oral administrations of pirfenidone with and without co-administration of 150 mg b i.d. BIBF 1120
(Source: Figure 11.5.2.1.2:1, CSR1199.31)

- **Conclusions:**

Following coadministration with pirfenidone, nintedanib AUC decreased by ~32% and C_{max} reduced by ~40%, possibly due to CYP3A4 induction in liver and GI tract by pirfenidone. More AEs were observed when pirfenidone is coadministered with nintedanib. It is not clear whether the two drugs have additive or synergistic effect in efficacy. Therefore, no dose adjustments are recommended when nintedanib is coadministered with pirfenidone.

Table 61: Comparison of pharmacokinetic parameters of BIBF 1120 BS with and without co-administration of 600 mg t.i.d. pirfenidone

BIBF 1120 dose	50 mg			100 mg			150 mg		
	N	−	+	N	−	+	N	−	+
AUC_{0-12} (h*ng/mL)	-/3	NC	30.0 (8.86)	4/4	59.0 (67.2)	72.2 (87.1)	11/8	152 (60.6)	131 (154)
$AUC_{0-12,norm}$ (h*ng/mL/mg)	-/3	NC	0.601 (8.86)	4/4	0.590 (67.2)	0.722 (87.1)	11/8	1.01 (60.6)	0.871 (154)
C_{max} (ng/mL)	2/4	3.90 (264)	5.67 (30.2)	4/4	13.2 (66.9)	13.3 (117)	11/8	34.9 (62.8)	26.5 (160)
$C_{max,norm}$ (ng/mL/mg)	2/4	0.0780 (264)	0.113 (30.2)	4/4	0.132 (66.9)	0.133 (117)	11/8	0.232 (62.8)	0.177 (160)
t_{max}[a] (h)	2/4	2.98 (2.00-3.97)	3.88 (3.00-6.00)	4/4	4.48 (1.97-12.0)	4.97 (2.00-8.00)	11/8	3.90 (1.00-6.00)	3.90 (3.00-6.00)
$t_{1/2}$ (h)	-/-	NC	NC	3/3	8.27 (13.9)	6.95 (16.1)	11/7	8.48 (43.1)	7.03 (16.0)
$AUC_{\tau,ss}$ (h*ng/mL)	2/4	33.7 (165)	67.9 (16.7)	4/3	115 (32.4)	86.0 (62.7)	9/7	218 (58.3)	149 (18.0)
$AUC_{\tau,ss,norm}$ (h*ng/mL/mg)	2/4	0.674 (165)	1.36 (16.7)	4/3	1.15 (32.4)	0.860 (62.7)	9/7	1.45 (58.3)	0.993 (18.0)
$C_{max,ss}$ (ng/mL)	2/4	9.09 (173)	10.9 (50.3)	4/3	20.0 (64.5)	13.8 (113)	9/7	39.7 (68.1)	23.5 (27.2)
$C_{max,ss,norm}$ (ng/mL/mg)	2/4	0.182 (173)	0.219 (50.3)	4/3	0.200 (64.5)	0.138 (113)	9/7	0.264 (68.1)	0.157 (27.2)
$t_{max,ss}$[a] (h)	2/4	2.43 (1.00-3.87)	3.92 (1.00-6.00)	4/3	3.42 (2.00-4.07)	2.00 (2.00-6.00)	9/7	3.87 (1.00-3.97)	3.88 (1.00-3.95)
$t_{1/2,ss}$ (h)	-/4	NC	25.4 (25.5)	4/3	23.4 (22.4)	30.5 (20.1)	9/7	27.5 (20.1)	28.4 (22.7)
$CL/F_{,ss}$ (mL/min)	2/4	24700 (165)	12300 (16.7)	4/3	14500 (32.4)	19400 (62.7)	9/7	11500 (58.3)	16800 (18.0)

Note: Data are shown in gMean (gCV%). NC=not calculated
a. median (minimum-maximum)
N: number of patients (without/with pirfenidone).
−: without pirfenidone co-administration; +: with pirfenidone co-administration
(Source: Table 11.5.2.2.1:1, CSR1199.31)

Table 62: Comparison of pharmacokinetic parameters of pirfenidone after oral administration of 600 mg t.i.d. pirfenidone with and without coadministration of BIBF 1120

BIBF 1120 dose	50 mg			100 mg			150 mg		
	N	−	+	N	−	+	N	−	+
Post dose after breakfast									
$AUC_{0\text{-}4,ss}$ (h*ng/mL)	4/4	34400 (36.3)	34300 (39.9)	3/3	45800 (26.6)	35000 (32.2)	9/7	32500 (21.2)	35900 (21.8)
$C_{max,ss}$ (ng/mL)	4/4	11900 (28.9)	12800 (44.3)	4/3	14600 (41.5)	15300 (51.1)	9/8	11200 (26.6)	12600 (27.2)
$t_{max,ss}$[a] (h)	4/4	1.58 (1.00-3.00)	0.709 (0.500-2.00)	4/3	1.50 (0.500-3.03)	2.00 (0.500-2.00)	9/8	1.08 (0.500-2.98)	0.834 (0.467-3.92)
$RAUC_{0\text{-}4,ss,T/R}$	-/4	NA	0.995 (32.2)	-/2	NA	0.737 (51.8)	-/7	NA	1.08 (13.1)
$RC_{max,ss,T/R}$	-/4	NA	1.08 (45.1)	-/3	NA	0.973 (38.6)	-/8	NA	1.09 (12.4)
Post dose after lunch									
$AUC_{0\text{-}8,ss}$ (h*ng/mL)	4/4	72800 (40.7)	71000 (40.8)	3/3	84100 (11.4)	71500 (19.1)	8/6	60900 (22.9)	63600 (27.7)
$C_{max,ss}$ (ng/mL)	4/4	14600 (20.9)	12000 (37.3)	4/3	15100 (19.5)	12100 (10.7)	9/8	12900 (30.2)	12500 (23.0)
$t_{max,ss}$[a] (h)	4/4	1.00 (0.500-3.08)	2.50 (1.00-3.92)	4/3	2.00 (1.00-3.00)	4.00 (2.00-4.00)	9/8	1.00 (0.417-6.00)	2.00 (0.500-4.42)
$t_{1/2,ss}$ (h)	4/3	3.35 (50.5)	3.99 (31.7)	4/-	3.52 (49.0)	NC	8/5	3.10 (40.6)	3.24 (39.1)

Abbreviation: NA=not applicable; NC=not calculated
Data are shown in gMean (gCV%).
a. median (minimum-maximum)
b. $AUC_{0\text{-}12,ss}$ = $AUC_{0\text{-}4,ss}$ (post dose after breakfast) + $AUC_{0\text{-}8,ss}$ (post dose after lunch)
N: number of patients (without/with BIBF 1120 co-medication)
−: without BIBF 1120 co-administration
+: with BIBF 1120 co-administration

(Source: Table 11.5.2.2.3:1, CSR1199.31)

BIOPHARMACEUTICS

6 Absolute Bioavailability

Trial # 1199.75

Title: Safety and tolerability of single rising doses of 1 mg, 3 mg, 10 mg, and 20 mg of BIBF 1120 as intravenous infusion (single-blind, placebo controlled at each dose group) and absolute bioavailability of 100 mg BIBF 1120 as soft gelatin capsule (intra-individual comparison)

- **Objective:**
  - To assess the safety and tolerability of BIBF 1120 administered as intravenous (iv) infusions of 1, 3, 10, and 20 mg, and to assess the absolute bioavailability of orally administered 100 mg BIBF 1120 as soft gelatin capsules.
- **Study design and treatment schedule:**

  Randomized, single-dose, open-label study. To reduce possible gastrointestinal side effects, BIBF 1120 (iv and oral) was administered after a light breakfast in this trial.

  A total of 30 healthy male subjects, 25 to 46 years of age, were entered and 30 were treated (6 subjects placebo iv, 6 subjects BIBF 1120 1 mg iv, 6 subjects BIBF 1120 3 mg iv, and 12 subjects BIBF 1120 6 mg iv followed by BIBF 1120 100 mg orally).

The unit strength for soft gelatin capsule is 100 mg, and it is the to-be-marketed formulation.

Reviewer's comment:

This is a fixed sequence study, and the absolute bioavailability was calculated based on intra-individual comparison. As nintedanib and its major metabolites have little potential as perpetrators in DDI, and the washout period (5 days) is considered adequate, the fixed sequence study design is acceptable in assessing absolute availability.

- **PK Sampling Schedule**
  - After iv administration, PK samples were drawn at 0, 0.5, 1, 2, 3, 4, 4.25, 4.5, 4.75, 5, 6, 7, 8, 10, 12, 24, 34, and 48 hours after dosing
  - After oral administration, PK samples were drawn at 0, 0.5, 1, 2, 3, 4, 5, 6, 8, 10, 12, 24, 34, and 48 hours after dosing

- **Results**

As per the predefined conditions in the clinical trial protocol, dose escalation for iv administration was stopped at 6 mg based on interim PK analysis.

Pharmacokinetic results

The metabolites (BIBF1202 and BIBF1202 glucuronide) to parent drug (BIBF1120) ratio was higher after 100 mg oral administration compared to 6 mg iv administration, likely due to first pass metabolism.

The total fraction absorbed was calculated based on the sum of AUC0-tz for parent and metabolites, comparing oral administration with iv administration. The total percentage absorbed was estimated to be 23% compared with a bioavailability of the parent alone of 4.69% (Table 63), thereby confirming the large amount of metabolite formed by intestinal and/or hepatic first pass metabolism.

Table 63: Absolute bioavailability of BIBF 1120 after oral administration of BIBF 1120 100 mg relative to intravenous administration of BIBF 1120 6 mg (dose-normalized values)

Parameter	gMean ratio capsule/iv [%]	90% CI for gMean ratio	
		Lower limit [%]	Upper limit [%]
$AUC_{0-\infty}$	4.69	3.615	6.078
AUC_{0-tz}	4.88	3.826	6.223

(Source – Table 12.2.2:1, Study 1199-0075 report)

Reviewer's comment:

Based on the plasma concentration of parent drug and major metabolites, the sponsor suggested that the total absorbed percentage with oral administration was 23% compared to iv administration. The mass balance suggested that 65-80% of the total oral dose was excreted as metabolites (see study 1199.20), indicating that 65-80% of the oral dose was absorbed through GI tract and was subjected to substantial first pass metabolism.

The concentration-time profile suggested the existence of enterohepatic recirculation with oral dosing. With a single oral dose of 100mg capsule, a second peak of ninedanib was observed in plasma at 5-6 hours post-dose, following the first peak at around 1-2 hours post-dose (Figure 27). The second peak of nintedanib was not observed with iv infusion (four hour infusion period, Figure 28). The available plasma concentration-time profile information does not suggest enterohepatic recirculation for BIBF1202 and BIBF1202 glucuronide with either oral dosing or iv dosing.

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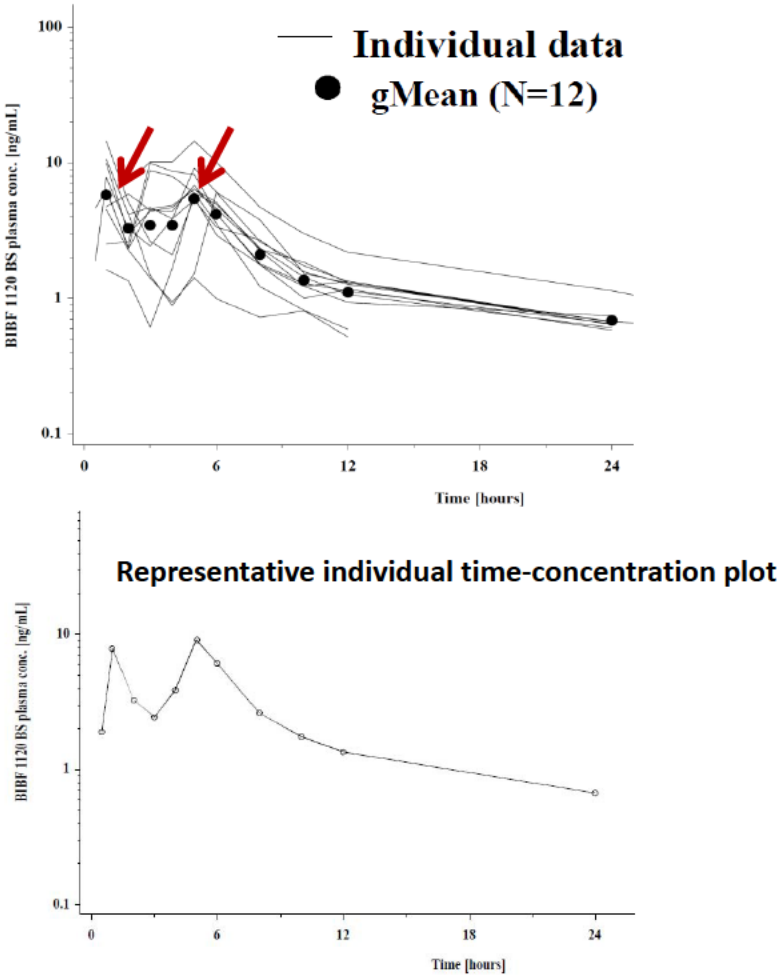

Figure 27. Plasma conc.-time profiles of BIBF 1120 BS after single oral administration of 100 mg BIBF 1120 capsule (semi-log scale)
(Source: Figure 15.6.5.2:28 and Figure 15.6.5.1:8 , study report 1199.75)

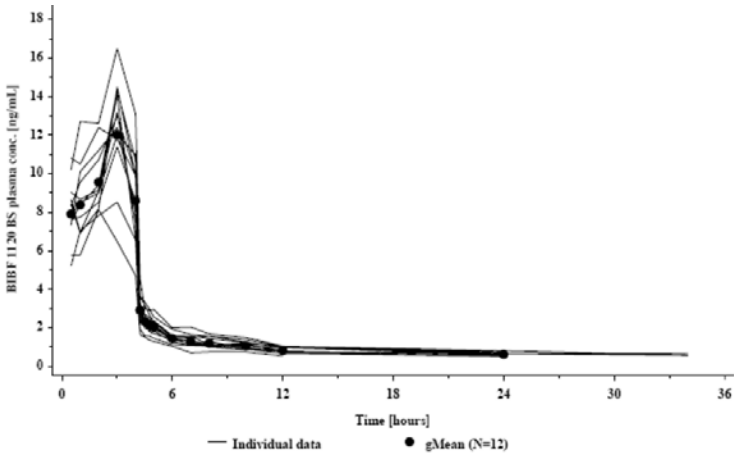

Figure 28. Plasma conc.-time profiles of BIBF 1120 BS after single intravenous infusion (4 hours) of 6 mg BIBF 1120 (linear scale)
(Source: Figure 11.5.2.1:3, study report 1199.75)

Safety Results:

No AEs occurred in the BIBF 1120 1 mg or BIBF 1120 3 mg iv dose groups, and some AEs were observed with the 6 mg iv dose group. Only 1 subject in the BIBF 1120 100 mg capsule group experienced diarrhea. No subject in the iv group experienced diarrhea.

SOC / PT	Placebo		BIBF 1120 1 mg iv		BIBF 1120 3 mg iv		BIBF 1120 6 mg iv		BIBF 1120 100 mg cap	
Number of subjects - N (%)	6	(100.0)	6	(100.0)	6	(100.0)	12	(100.0)	12	(100.0)
Total with AE	0	-	0	-	0	-	6	(50.0)	1	(8.3)
Eye disorders	0	-	0	-	0	-	1	(8.3)	0	-
Eye pain	0	-	0	-	0	-	1	(8.3)	0	-
Gastrointestinal disorders	0	-	0	-	0	-	0	-	1	(8.3)
Diarrhoea	0	-	0	-	0	-	0	-	1	(8.3)
Musculoskeletal and connective tissue disorders	0	-	0	-	0	-	1	(8.3)	0	-
Back pain	0	-	0	-	0	-	1	(8.3)	0	-
Nervous system disorders	0	-	0	-	0	-	4	(33.3)	0	-
Headache	0	-	0	-	0	-	4	(33.3)	0	-
Vascular disorders	0	-	0	-	0	-	1	(8.3)	0	-
Haematoma	0	-	0	-	0	-	1	(8.3)	0	-

(Source – Table 12.2.2:1, Study 1199-0075 report)

- **Conclusions**

There absolute bioavailability of BIBF1120 following oral administration with light breakfast was 4.7%. The low bioavailability was due to extensive first pass metabolism. Enterohepatic recirculation cannot be ruled out for nintedanib based on concentration-time profile.

7 Relative Bioavailability

Trial # 1199.21

Title: Safety and relative bioavailability of a single dose of 150 mg BIBF 1120

administered as soft gelatin capsules charge 1 compared to BIBF 1120 soft gelatin capsules charge 2 compared to BIBF 1120 administered as drinking solution following oral administration to healthy male volunteers in an open, randomized, intra-individual, crossover comparison design

- **Objectives**
  - To assess pharmacokinetics and the relative bioavailability of a single dose of BIBF 1120 soft gelatin capsule charge 1(unit strength 50mg) vs. BIBF 1120 soft gelatin capsule charge 2 (unit strength 50mg) vs BIBF 1120 drinking solution in healthy male subjects respectively
  - To establish an in-vitro-in-vivo correlation (IVIVC) for oral soft gelatin capsules with 150 mg BIBF 1120 in healthy male volunteers.

- **Study design and treatment schedule:**

Phase I, open label, randomized, single dose, two or three way crossover study with BIBF 1120 in 36 healthy male subjects. The treatments were three 50 mg BIBF 1120 soft gelatin capsules charge 1 and charge 2 and a drinking solution immediately after breakfast.

- **PK Sampling Schedule**

In each period PK samples were drawn at predose, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 33 and 48 hours after dosing

- **Results and Conclusions**

The total exposure after administration of the drinking solution was lower (84.2 ng·h/mL) compared to the capsule formulations. The relative bioavailability (based on AUC0-∞) means of capsule (fast) compared to the drinking solution was 152.37 %, the relative bioavailability of capsule (slow) was 144.74 %. The exposure in healthy subjects is similar between the two capsule formulations (Table 64, Figure 29). Pharmacokinetic parameter ratios of BIBF 1202-glucuronide to either BIBF 1120 BS or BIBF 1202 ZW were similar for all three formulations.

Table 64. Geometric mean pharmacokinetic parameters (%gCV) of BIBF 1120 BS after single oral administration of 150 mg BIBF 1120 as capsule (fast or slow) or as drinking solution (N=18)

	Capsule (fast - charge 1) [Test]	Capsule (slow - charge 2) [Reference]	Drinking solution
$AUC_{0-\infty}$ (ng·h/mL)	128 (35.1%)	122 (32.4%)	84.2 (48.6%)
AUC_{0-24} (ng·h/mL)	92.2 (31.2%)	89.4 (29.8%)	61.2 (43.6%)
C_{max} (ng/mL)	14.5 (53.3%)	13.0 (36.4%)	7.17 (46.7%)
t_{max} (h)*	2.00 (0.750-6.00)	2.00 (0.750-6.00)	4.00 (0.250-6.00)
$t_{1/2}$ (h)	17.1 (33.6%)	15.8 (25.1%)	14.7 (36.3%)
CL/F (mL/min)	19500 (35.1%)	20500 (32.4%)	29700 (48.6%)
V_z/F (L)	28800 (33.1%)	28000 (32.4%)	37700 (35.0%)

(Source: Table 11.5.2.3:1, CSR1199.21)

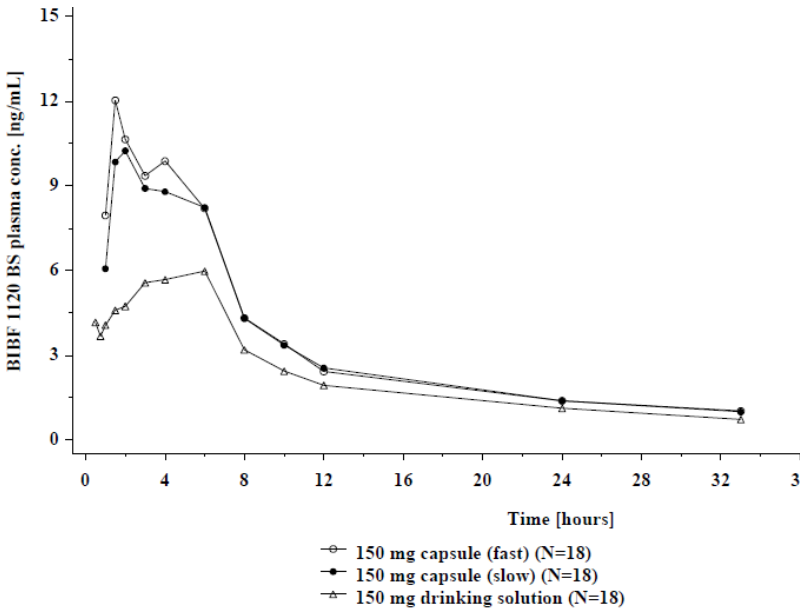

Figure 29. Geometric mean BIBF 1120 BS plasma concentration-time profiles after single oral administration of 150 mg BIBF 1120 as capsule (fast or slow) or as drinking solution
(source: Figure 15.5.5.3: 3, CSR1199.21)

Reviewer's comment:

In the individual plasma concentration-time profiles, a second peak of ninedanib was observed in all three formulations (Figure 30). This might be explained by enterohepatic recirculation.

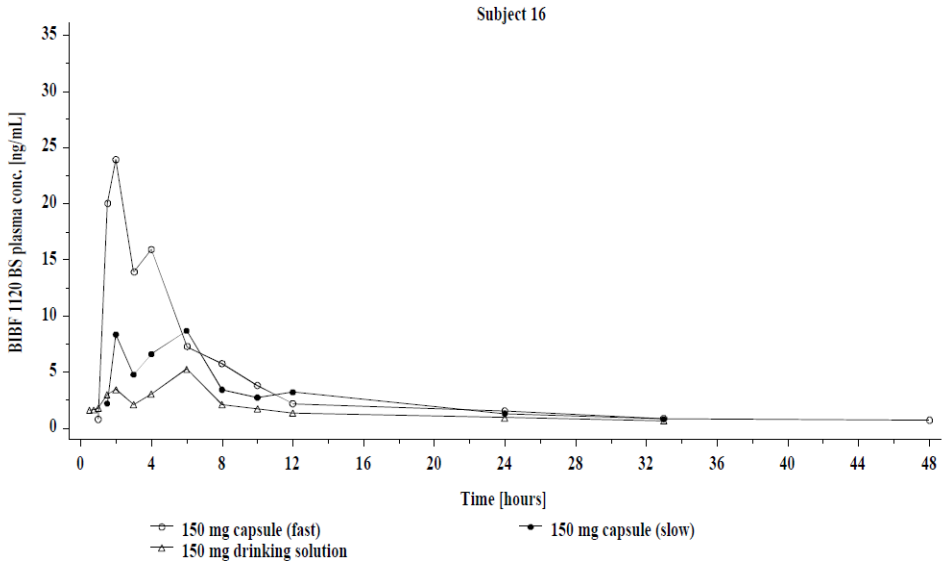

Figure 30. Typical individual BIBF 1120 BS plasma concentration-time profile after single oral administration of 150 mg BIBF 1120 as capsule (fast or slow) or as drinking solution
(source: Figure 15.5.5.1: 1, CSR1199.21)

8 Food Effect, Single Dose Study in Healthy Volunteers

Trial # 1199.17

Title: Safety and pharmacokinetics/bioavailability of a single dose of 150 mg BIBF 1120 administered as soft gelatin capsules with and without food to healthy male volunteers in an open, randomized, intraindividual crossover comparison design

- **Objective**
  - To evaluate the effect of food on the PK of single 150 mg BIBF 1120 soft gelatin capsule in healthy subjects.

- **Study design and treatment schedule:**

Randomized, open-label, single-dose, 2-way crossover study with 16 healthy male subjects. The unit strength for soft gelatin capsule is 50 mg.

- **PK Sampling Schedule**

In each period PK samples were drawn at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, 8, 10, 12, 24, 33, and 48 hours after dosing

- **Results and Conclusions**

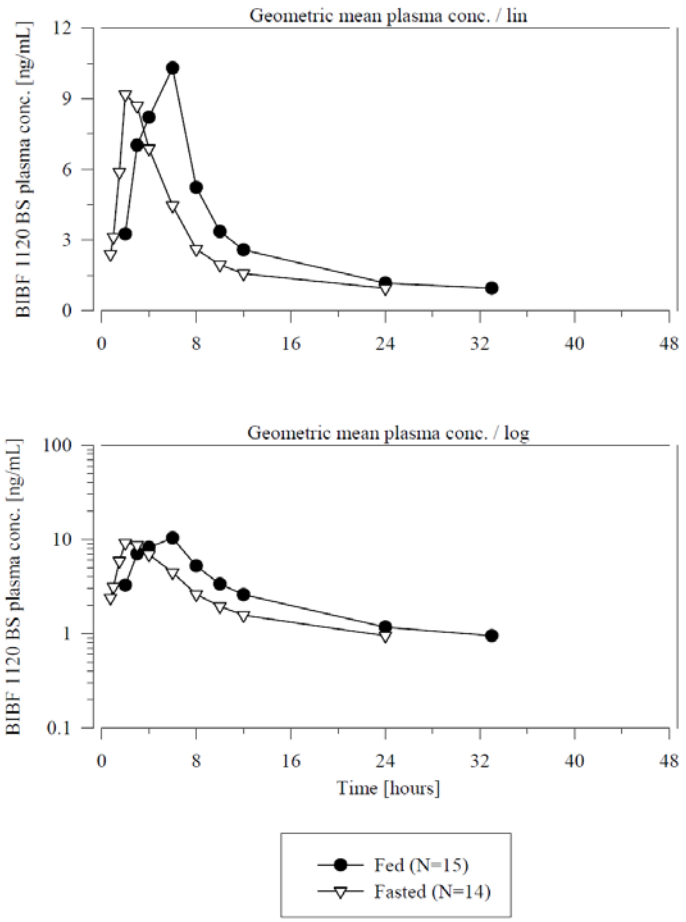

Figure 31. BIBF 1120 / 150 mg single oral administration in fed and fasted conditions.
(Source – Figure 15.5.5.3:2, Study 1199-0017 report)

Under fed conditions the rate of absorption of BIBF 1120 was decreased resulting in increased median tmax values of 4 hours (fed) compared to 2 hours (fasted), as shown in Figure 31. BIBF 1120 gMean Cmax and $AUC_{0-\infty}$ values increased around 20% under fed compared to fasted conditions. (Table 65 and Table 66).

Table 65: Summary of plasma BIBF1120 PK parameter values following single oral doses

BIBF 1120 capsule		Fasted	Fed
Parameter	**Unit**	**N=14**	**N=15**
t_{max}[1]	[h]	2.00 (1.48-3.98)	3.98 (1.50-6.05)
C_{max}	[ng/mL]	11.1 (60.3%)	13.2 (61.6%)
$AUC_{0-\infty}$	[ng·h/mL]	98.4 (33.0%)[2]	119 (53.9%)
AUC_{0-24}	[ng·h/mL]	79.0 (34.8%)[2]	90.2 (52.9%)
$t_{½}$	[h]	13.6 (15.2%)[1]	16.2 (40.3%)
CL/F	[mL/min]	25400 (33.0%)[1]	20900 (53.9%)
V_z/F	[L]	29900 (34.7%)[1]	29400 (47.0%)

(Source – Table 11.5.2: 1and Table 11.5.2: 3, Study 1199-0017 report)

Table 66: Statistical summary of treatment comparison under fed and fasted conditions

	Adjusted gMean ratio	Two-sided 90 % CI		intra-indiv. gCV	p-value for ratio outside interval 0.8-1.25
Parameter	**(Fed/Fasted) [%]**	**Lower limit [%]**	**Upper limit [%]**	**[%]**	
C_{max}	115.3	84.630	157.002	48.6	0.3244
$AUC_{0-\infty}$	120.6	95.349	152.474	31.6	0.33923

(Source: Table 11.5.2:2, CSR1199.17)

- **Conclusions**

Under fed conditions the exposure of BIBF 1120 increased around 20% compared to fasted conditions. Nintedanib is recommended to be taken with food for higher bioavailability and better tolerability. Enterohepatic recirculation was not observed in this study.

4.4 FILING MEMO

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**205832**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Nintedanib**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Tyrosine kinase inhibitor**
OCP Reviewer	**Jianmeng Chen, M.D., Ph.D.**	**Indication(s)**	**idiopathic pulmonary fibrosis (IPF)**
OCP Team Leader	**Satjit Brar, Pharm. D, Ph.D.**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer	**Anshu Marathe, Ph.D.**	**Dosing Regimen**	**150 mg BID**
Pharmacometrics Team Leader	**Liang Zhao, Ph.D.**		
Pharmacogenomics Reviewer	**Robert Schuck, Pharm. D, Ph.D.**	**Route of Administration**	**Oral**
Date of Submission	**5/2/2014**	**Sponsor**	**Boehringer Ingelheim, Inc.**
Estimated Due Date of OCP Review	**8/5/2014**	**Priority Classification**	**Priority**
PDUFA Due Date	**1/2/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**17**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		1199.20
Isozyme characterization:	**X**	**5**		A118-02LU A227_03TE A217/02TE A267_07TE A249_06TE-b2886
Blood/plasma ratio:	**X**	**1**		A075-02ar
Plasma protein binding:	**X**	**3**		A075-02ar A090-08fu Pb-08-001
Transporter specificity:	**X**	**2**		U12-2279-01 U05-3076-02
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		1199.75, SAD, IV
multiple dose:				
Patients-				Phase 1PK studies were done in cancer patients
single dose:	**X**			

multiple dose:	X			
Dose proportionality -		1		Metaanalysis in cancer patients U11-1639-01
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		1199.161-ketoconazole 1199.162-rifampicin
In-vivo effects of primary drug:	X	1		1199.31, no effect on pirfenidone
In-vitro:	X	5		A114_02LU VD A249_06TE-b2883 A020-08OS U08-1256-02 U09-1164-02
Subpopulation studies -				
ethnicity:				Population PK
gender:				Population PK
pediatrics:				Orphan designation
geriatrics:				Population PK
renal impairment:				Population PK
hepatic impairment:				Population PK
PD -				
Phase 2:	X	2		1199.30; 1199.31
Phase 3:	X	2		1199.32; 1199.34
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		1199.30; 1199.31
Phase 3 clinical trial:	X	2		1199.32; 1199.34
Population Analyses -		6		
Data rich:	X			
Data sparse:	X			Population PK and PK-PD analysis with data from Phase 2 trials
II. Biopharmaceutics				
Absolute bioavailability	X	1		1199.75
Relative bioavailability -				
solution as reference:	X	1		1199.21
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		1199.17
Bio-waiver request based on BCS				
BCS class	X			Applicant reports that the drugs substance is either a BCS Class 2 or 4 compound
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies		1		1199.26, QT information collected in RCC phase II study
Genotype/phenotype studies				Population PK
Chronopharmacokinetics				
Pediatric development plan				Orphan designation
Literature References				
Total Number of Studies		11		Clinical studies

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/s/

JIANMENG CHEN
09/03/2014

ANSHU MARATHE
09/03/2014

ROBERT N SCHUCK
09/03/2014

CHRISTIAN GRIMSTEIN
09/03/2014

LIANG ZHAO
09/03/2014

SATJIT S BRAR
09/03/2014

CHANDRAHAS G SAHAJWALLA
09/03/2014

BIOPHARMACEUTICS REVIEW Office of New Drug Quality Assessment			
Application No.:	NDA 205-832	**Reviewer:** Kareen Riviere, Ph.D.	
Submission Date:	5/2/2014; 8/6/2014		
Division:	DPARP	**Team Leader:** Tapash Ghosh, Ph.D.	
Applicant:	Boehringer Ingelheim	**Acting Supervisor:** Paul Seo, Ph.D.	
Trade Name:	Ofev	**Date Assigned:**	5/7/2014
Generic Name:	Nintedanib capsules	**Date of Review:**	8/14/2014
Indication:	treatment of idiopathic pulmonary fibrosis (IPF)	**Type of Submission:** 505(b)(1) Original	
Formulation/strengths:	IR capsules; 100 mg and 150 mg		
Route of Administration:	Oral		

SUMMARY:

This submission is a 505(b)(1) New Drug Application for 100 mg and 150 mg of Ofev (nintedanib) immediate release soft gelatin capsules. The proposed indication is for the treatment of idiopathic pulmonary fibrosis.

The focus of this Biopharmaceutics review is on the evaluation and acceptability of the proposed dissolution method and dissolution acceptance criterion.

A. Dissolution Method

The proposed dissolution method is:

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 ml	37 °C	0.1 M HCl

The proposed dissolution method is acceptable.

B. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is:

Acceptance Criterion
Q = (b) (4) at 60 min

Based on the mean in-vitro dissolution profile data for all strengths, the following dissolution acceptance criterion was recommended to the Applicant: **Q =** (b) (4). In a submission dated August 6, 2014, the Applicant accepted to revise the acceptance criterion.

RECOMMENDATION:

1. Ofev (nintedanib) 100 mg and 150 mg strength immediate release soft gelatin capsules are recommended for approval from a Biopharmaceutics standpoint with the following dissolution method and acceptance criteria for both strengths.
    i. Dissolution Method: Apparatus 2, 100 rpm agitation rate, 900 mL media volume, 37 °C, 0.1 M HCl buffer.
    ii. Dissolution Acceptance Criterion: Q = (b) (4).

Kareen Riviere, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

Tapash Ghosh, Ph.D.
Biopharmaceutics Team Leader
Office of New Drug Quality Assessment

cc: Dr. Paul Seo

ASSESSMENT OF BIOPHARMACEUTICS INFORMATION

1. Background

Drug Substance

The Applicant states that the drug substance is either BCS class II or IV. The structure of nintedanib is shown in Figure 1.

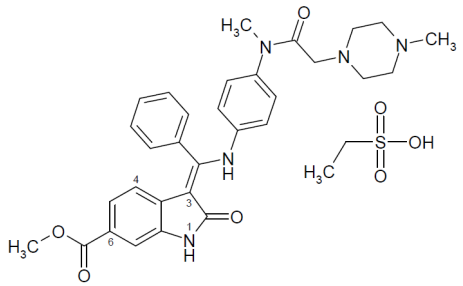

Figure 1. Chemical structure of nintedanib

The solubility profile of nintedanib is shown in Table 1. The Applicant states that the solubility of nintedanib is strongly pH dependent with an increased solubility at acidic pH, particularly for pH < 3. The solubility decreases by at least three orders of magnitude after pH 6 due to the non-protonated free base which has a low solubility in water.

Table 1. Solubility of Nintedanib at Different pH Values in Aqueous Buffer Systems

Dissolution media	**Solubility [mg/mL] at 37°C in 2 h**
0.1 M HCl (pH 1.0)	> 5
0.01 M HCl (pH 2.0)	> 5
Sodium formate buffer pH 3.0	> 5
Sodium acetate buffer pH 4.0	> 5
Sodium acetate buffer pH 4.5	> 5
Sodium acetate buffer pH 5.0	4.2
0.05 M Potassium phosphate buffer pH 6.0	0.018
0.05 M Potassium phosphate buffer pH 6.8	0.011
0.05 M Potassium phosphate buffer pH 7.5	0.011

Drug Product

The composition of nintedanib capsules of 100 mg and 150 mg strength are shown in Table 2. Both strengths were used for the pivotal phase 3 study 1199.13.

Table 2. Quantitative and Qualitative Composition of 100 mg and 150 mg Nindetanib Capsules

Part of capsule	Dosage strength	100 mg		150 mg	
	Ingredient	mg per capsule	[%]	mg per capsule	[%]
Fill material	BIBF 1120 ethanesulfonate	120.40 [1]	(b) (4)	180.60 [1]	(b) (4)
	Triglycerides, medium-chain	(b) (4)		(b) (4)	
	Hard fat				
	Lecithin				
	Subtotal (Fill)		100.00		100.00
Capsule shell	Gelatin	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	Glycerol (b) (4)				
	Titanium dioxide				
	Iron oxide red [2]				
	Iron oxide yellow [3]				
	Water, purified				
	Printing ink [5]	Black	-	Black	-
	Subtotal (Shell)	(b) (4)	100.00	(b) (4)	100.00
	Total				

Reviewer's Assessment:
Both strengths are proportionally similar in composition.

2. Dissolution Method

The proposed dissolution method is shown below.

USP Apparatus	Rotation Speed	Media Volume	Temp	Medium
2	100 rpm	900 ml	37 °C	0.1 M HCl

(b) (4)

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(b) (4)

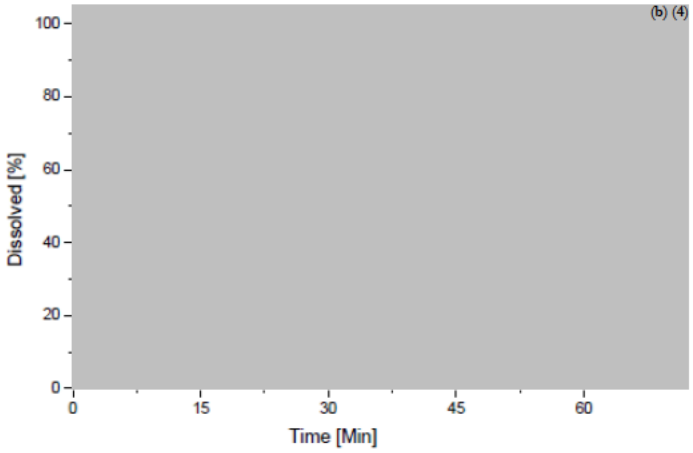
3. Dissolution Acceptance Criterion

The proposed dissolution acceptance criterion is shown below.

Acceptance Criterion
Q = (b) (4) at 60 min

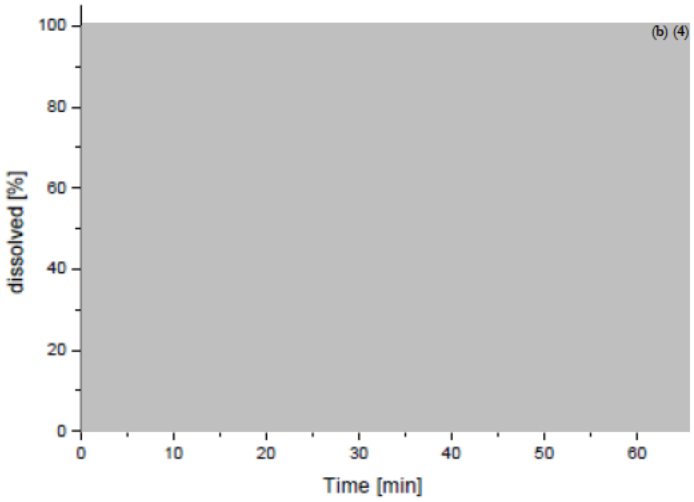
The dissolution profiles of representative 100 mg and 150 mg nintedanib capsules are depicted in Figure 10.

Figure 10. Dissolution Profiles of 100 mg and 150 mg Nintedanib Capsules, Phase III Clinical Trial Supply / Primary Stability Studies



The dissolution profiles of 150 mg nintedanib capsules stored under different conditions are depicted in Figure 11.

Figure 11. Dissolution Profiles of 150 mg Nintedanib capsules from Clinical Trial Batch 1451260001



<u>Reviewer's Assessment</u>:
The data in Figures 10 and 11 show that the proposed dissolution acceptance criterion is too permissive. Therefore, the following comment was conveyed to the Applicant on July 29, 2014.

> The following dissolution acceptance criterion is recommended: **Q** = (b) (4). This recommendation is based on the mean in-vitro dissolution profile data from the clinical and primary stability batches. Revise the dissolution acceptance criterion accordingly and submit an updated sheet of specifications for the drug product.

In a submission dated August 6, 2014, the Applicant accepted to revise the acceptance criterion.

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

/s/

KAREEN RIVIERE
08/14/2014

TAPASH K GHOSH
08/14/2014

Office of Clinical Pharmacology

New Drug Application Filing and Review Form

General Information about the Submission

	Information		Information
NDA/BLA Number	**205832**	**Brand Name**	**TBD**
OCP Division (I, II, III, IV, V)	**II**	**Generic Name**	**Nintedanib**
Medical Division	**Pulmonary, Allergy, and Rheumatology Products**	**Drug Class**	**Tyrosine kinase inhibitor**
OCP Reviewer	**Jianmeng Chen, M.D., Ph.D.**	**Indication(s)**	**idiopathic pulmonary fibrosis (IPF)**
OCP Team Leader	**Satjit Brar, Pharm. D, Ph.D.**	**Dosage Form**	**Capsules**
Pharmacometrics Reviewer	**Anshu Marathe, Ph.D.**	**Dosing Regimen**	**150 mg BID**
Pharmacometrics Team Leader	**Liang Zhao, Ph.D.**		
Pharmacogenomics Reviewer	**Robert Schuck, Pharm. D, Ph.D.**	**Route of Administration**	**Oral**
Date of Submission	**5/2/2014**	**Sponsor**	**Boehringer Ingelheim, Inc.**
Estimated Due Date of OCP Review	**8/5/2014**	**Priority Classification**	**Priority**
PDUFA Due Date	**1/2/2014**		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	**X**			
Tabular Listing of All Human Studies	**X**			
HPK Summary	**X**			
Labeling	**X**			
Reference Bioanalytical and Analytical Methods	**X**	**17**		
I. Clinical Pharmacology				
Mass balance:	**X**	**1**		1199.20
Isozyme characterization:	**X**	**5**		A118-02LU A227_03TE A217/02TE A267_07TE A249_06TE-b2886
Blood/plasma ratio:	**X**	**1**		A075-02ar
Plasma protein binding:	**X**	**3**		A075-02ar A090-08fu Pb-08-001
Transporter specificity:	**X**	**2**		U12-2279-01 U05-3076-02
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:	**X**	**1**		1199.75, SAD, IV
multiple dose:				
Patients-				Phase 1PK studies were done in cancer patients
single dose:	**X**			
multiple dose:	**X**			

Dose proportionality -		1		Metaanalysis in cancer patients U11-1639-01
fasting / non-fasting single dose:	X			
fasting / non-fasting multiple dose:	X			
Drug-drug interaction studies -				
In-vivo effects on primary drug:	X	2		1199.161-ketoconazole 1199.162-rifampicin
In-vivo effects of primary drug:	X	1		1199.31, no effect on pirfenidone
In-vitro:	X	5		A114_02LU VD A249_06TE-b2883 A020-08OS U08-1256-02 U09-1164-02
Subpopulation studies -				
ethnicity:				Population PK
gender:				Population PK
pediatrics:				Orphan designation
geriatrics:				Population PK
renal impairment:				Population PK
hepatic impairment:				Population PK
PD -				
Phase 2:	X	2		1199.30; 1199.31
Phase 3:	X	2		1199.32; 1199.34
PK/PD -				
Phase 1 and/or 2, proof of concept:	X	2		1199.30; 1199.31
Phase 3 clinical trial:	X	2		1199.32; 1199.34
Population Analyses -		6		
Data rich:	X			
Data sparse:	X			Population PK and PK-PD analysis with data from Phase 2 trials
II. Biopharmaceutics				
Absolute bioavailability	X	1		1199.75
Relative bioavailability -				
solution as reference:	X	1		1199.21
alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies	X	1		1199.17
Bio-waiver request based on BCS				
BCS class	X			Applicant reports that the drugs substance is either a BCS Class 2 or 4 compound
Dissolution study to evaluate alcohol induced dose-dumping				
III. Other CPB Studies		1		1199.26, QT information collected in RCC phase II study
Genotype/phenotype studies				Population PK
Chronopharmacokinetics				
Pediatric development plan				Orphan designation
Literature References				
Total Number of Studies		11		Clinical studies

On **initial** review of the NDA/BLA application for filing:

Criteria for Refusal to File (RTF): This OCP checklist applies to NDA, BLA submissions and their supplements					
No	**Content Parameter**	**Yes**	**No**	**N/A**	**Comment**
1	Did the applicant submit bioequivalence data comparing to-be-marketed product(s) and those used in the pivotal clinical trials?			X	The to-be-marketed formulation is the same formulation used in the pivotal clinical trials

2	Did the applicant provide metabolism and drug-drug interaction information? (Note: RTF only if there is complete lack of information)	X			
3	Did the applicant submit pharmacokinetic studies to characterize the drug product, or submit a waiver request?	X			
4	Did the applicant submit comparative bioavailability data between proposed drug product and reference product for a 505(b)(2) application?			X	
5	Did the applicant submit data to allow the evaluation of the validity of the analytical assay for the moieties of interest?	X			
6	Did the applicant submit study reports/rationale to support dose/dosing interval and dose adjustment?	X			
7	Does the submission contain PK and PD analysis datasets and PK and PD parameter datasets for each primary study that supports items 1 to 6 above (in .xpt format if data are submitted electronically)?	X			PK information is collected in all Phase 2 and 3 studies (study 1199.30, 32, 34). PopPK analysis and dataset were not submitted for Phase 3 studies. An IR was sent.
8	Did the applicant submit the module 2 summaries (e.g. summary-clin-pharm, summary-biopharm, pharmkin-written-summary)?	X			
9	Is the clinical pharmacology and biopharmaceutics section of the submission legible, organized, indexed and paginated in a manner to allow substantive review to begin? If provided as an electronic submission, is the electronic submission searchable, does it have appropriate hyperlinks and do the hyperlinks work leading to appropriate sections, reports, and appendices?	X			
Complete Application					
10	Did the applicant submit studies including study reports, analysis datasets, source code, input files and key analysis output, or justification for not conducting studies, as agreed to at the pre-NDA or pre-BLA meeting? If the answer is 'No', has the sponsor submitted a justification that was previously agreed to before the NDA submission?	X			PopPK analysis for phase 2 study was submitted. PopPK analysis and dataset were not submitted for Phase 3 studies. An IR was sent.
Criteria for Assessing Quality of an NDA (Preliminary Assessment of Quality)					
Data					
11	Are the data sets, as requested during pre-submission discussions, submitted in the appropriate format (e.g., CDISC)?	X			
12	If applicable, are the pharmacogenomic data sets submitted in the appropriate format?	X			
Studies and Analyses					

13	Is the appropriate pharmacokinetic information submitted?	X			
14	Has the applicant made an appropriate attempt to determine reasonable dose individualization strategies for this product (i.e., appropriately designed and analyzed dose-ranging or pivotal studies)?	X			This is a rare disease. The sponsor provided option for dose reduction in patients intolerant of standard doses.
15	Are the appropriate exposure-response (for desired and undesired effects) analyses conducted and submitted as described in the Exposure-Response guidance?	X			
16	Is there an adequate attempt by the applicant to use exposure-response relationships in order to assess the need for dose adjustments for intrinsic/extrinsic factors that might affect the pharmacokinetic or pharmacodynamics?	X			
17	Are the pediatric exclusivity studies adequately designed to demonstrate effectiveness, if the drug is indeed effective?			X	
18	Did the applicant submit all the pediatric exclusivity data, as described in the WR?			X	
19	Is there adequate information on the pharmacokinetics and exposure-response in the clinical pharmacology section of the label?	X			
General					
20	Are the clinical pharmacology and biopharmaceutics studies of appropriate design and breadth of investigation to meet basic requirements for approvability of this product?	X			
21	Was the translation (of study reports or other study information) from another language needed and provided in this submission?		X		

IS THE CLINICAL PHARMACOLOGY SECTION OF THE APPLICATION FILEABLE? _____Yes__

If the NDA/BLA is not fileable from the clinical pharmacology perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.
- None

Submission in brief:

Indication and mechanism of action
Boehringer Ingelheim has submitted the NDA 205832 seeking the marketing approval for Nintedanib, to be used as "*the treatment of idiopathic pulmonary fibrosis (IPF)* (b) (4) "

Nintedanib is a small molecule tyrosine kinase inhibitor for 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. In addition, nintedanib inhibits Flt-3, Lck, Lyn and Src kinases. Recommended dose is 150mg BID taken with food, with optional dose reduction to 100mg BID for management of adverse reaction.

There have been several interactions between Agency and Sponsor to discuss clinical pharm program for the proposed product as listed in Table 1.

Table 1. Summary of Regulatory history relevant to clinical pharmacology

PNDA (Oct 2013)	• Agreed with delayed hepatic impairment study with proper labeling • Agreed on filing of renal impairment info based on IPF phase 3 Pop-PK analysis
EOP2 (Dec 2010)	• Agreed that 150 mg BID (with dose reduction option) is reasonable for Phase 3 evaluation. • Clarify that special population (hepatic impairment) assessment based on cancer phase 3 Pop-PK analysis is NOT acceptable • Ask for E-R analysis in phase III

Summary of information submitted

NDA 205832 consists of 15 in vitro studies (Table 2) with human materials, 6 Phase 1 studies in healthy volunteers (including 2 drug-drug interaction trials), 2 Phase 2 studies (1199.30 and .31), 2 Phase 3 studies (1199.32 and .34) in IPF patients, 1 QT/renal cell carcinoma study (1199.26), and 6 metaanalysis and PopPK reports. The clinical pharmacology information for nintedanib is mainly derived from Phase 1 studies as well as in vitro studies evaluating permeability, plasma protein binding, role of transporters, and potential for CYP 450 metabolic enzymes inhibition and induction. Population based modeling analyses including population pharmacokinetics analysis were performed to assess the effect of covariates and to understand the PK in special populations such as renal impairment patients. In addition, 17 bioanalytical reports have been submitted to measure the levels of parent compound and main metabolites.

Table 2. In Vitro Studies for Nintedanib and Major Metabolites Using Human Biomaterials

Drug	ADME	Objective	Study/Report name
Nintedanib (BIBF1120)	Distribution	Human plasma protein binding blood cell association	A075/02AR
	Metabolism	Metabolism of BIBF1120 in human liver microsomes and recombinant CYPs	A118_02LU
		Metabolism of BIBF1120 by hepatocytes of rat and human	A227_03TE
		Potential of BIBF1120 to inhibit UGT1A1	A249_06TE-b2883
		Potential of BIBF1120 to inhibit CYPs	A114_02LU VD
		Potential of BIBF1120 to induce CYPs	A020-08OS
		Transporters for BIBF1120 and BIBF1202	U05-3076-02
BIBF1202	Distribution	Human plasma protein binding	PB 08-001
	Metabolism	Glucuronidation of BIBF1202	A217/02TE
		Glucuronidation of BIBF1202 by UGT1A1	A249_06TE-b2886
		Glucuronidation of BIBF1202	A267_07TE
		Potential of BIBF1202 to inhibit CYPs	U08-1256-02
BIBF1202-glucuronide	Distribution	Human plasma protein binding	A090_08FU
	Metabolism	Potential of BIBF1202-Glucuronide to inhibit CYPs	U09-1164-02

		Interaction of BIBF1202-Glucuronide and transporters	U12-2279-01

Rational for 150 mg bid dose selection

The dose for the phase III trials (150 mg bid) was selected based on the results from the phase II dose-finding trial 1199.30. In this trial, 4 doses of nintedanib (50 mg qd, 50 mg bid, 100 mg bid, and 150 mg bid) were compared with placebo over 52 weeks of treatment.

Efficacy: For the primary endpoint annual rate of decline in FVC, the difference between the nintedanib 150 mg bid dose and placebo reached nominal statistical significance (Figure 1). The differences between the lower nintedanib doses and placebo were not significant. Also, statistically significant differences in regard to the change from baseline in SGRQ total score and the time to first exacerbation were only shown for the nintedanib 150 mg bid dose.

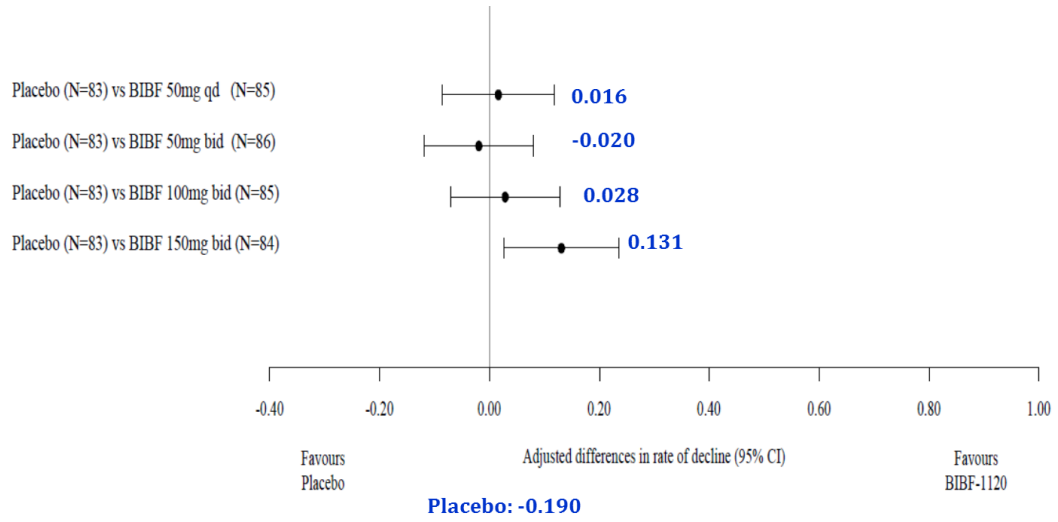


Figure 1. Rate of decline in FVC (L/yr) at 52 weeks
(Source: CSR 1199.30, Fig 11.4.1.1.1)

Table 3. Proportional hazard model for overall survival at 52 weeks

	Placebo	BIBF 50mg qd	BIBF 50mg bid	BIBF 100mg bid	BIBF 150mg bid
Number of patients in ~ Randomized set	87	87	86	86	86
Failure [N (%)]	9 (10.3)	11 (12.6)	3 (3.5)	4 (4.7)	7 (8.1)
Censored [N (%)]	78 (89.7)	76 (87.4)	83 (96.5)	82 (95.3)	79 (91.9)
Comparison vs Placebo					
Hazard ratio**		1.278	0.290	0.350	0.732
95% Confidence interval		(0.526, 3.102)	(0.078, 1.081)	(0.106, 1.154)	(0.271, 1.977)
p-value		0.5882	0.0653	0.0847	0.5383

(Source: CSR 1199.30, Table 11.4.1.2.2)

Safety: The incidence of several adverse events increased with increasing nintedanib dose, such as GI disorders and liver enzyme elevation. The proportion of patients who discontinued trial medication was higher in the 150 mg bid group.

Overall survival: In the randomized set, during the 52-week period, 9, 11, 3, 4 and 7 patients died in the placebo, 50 mg qd, 50 mg bid, 100 mg bid and 150 mg bid dose groups. (Table 3)

The benefit-risk-ratio was considered most favorable for the 150 mg bid dose, hence it was selected for testing in phase III.

Efficacy in Phase 3 trials

There are two Phase 3 studies supporting the efficacy and safety of nintedanib in IPF patients (1199.32 abd 1199.34). Both studies are randomized, double-blind, placebo controlled, 52 week studies. There is no major difference in study design, patient population, and the background therapy in the two Phase 3 studies. PK information is collected in both studies.
The submission of phase 3 efficacy results is summarized in the medical (Dr. Miya Paterniti) and biostatistics (Dr. Yongman Kim) reviews.

Effect of intrinsic/extrinsic factors

As per sponsor's proposal, nintedanib is recommended to be administered with food. No dose adjustments have been proposed based on studied intrinsic(Table 4) and extrinsic factors (Table 5). For hepatic impairment, no adjustment of the starting dose is recommended for mild cases. Nintedanib has not been investigated in patients with moderate or severe hepatic impairment, therefore nintedanib is not recommended in these patients. For renal impairment, no dose adjustments are recommended for mild or moderate cases, and it has not been studied in patients with severe renal impairment. Co-administration with ketoconazole (P-gP inhibitor) increases nintedanib exposure by about less than 2 fold, and the sponsor proposes close monitoring for AE although no adjustment of the starting dose is recommended. Following co-administration with rifampicin, exposure decreases by about 2 fold, and sponsor does not propose specific dose adjustment.

Table 4. Intrinsic Factors

	Impact		
Factor	**PK**	**AE***	**Dosing recommendation**
Gender	↑ AUC in female	More in female patients	No dose adjustment, mention about higher risk of liver enzyme elevation in females
Weight	↑ AUC in lower weight	More in patients <65kg	No dose adjustment,
Race	~ 20-80% higher exposure in Asian subjects	More in Asian	No dose adjustment
Age	↑ AUC in elderly	More in elderly	No dose adjustment
P-gP polymorphism	--	--	No dose adjustment
UGT1A1 polymorphism	--	--	No dose adjustment,

Table 5. Extrinsic Factors

Co-administered drug	Rationale	Nintedanib		Dosing recommendation
		AUC_{inf}	C_{max}	
Ketoconazole	Inhibitor of P-gp and UGT 1A1	↑ 60%	↑ 83%	patients should be monitored closely for tolerability of nintedanib. Management of adverse reactions may require interruption, dose reduction, or discontinuation of therapy.
Rifampicin	Inducer of P-gp	↓ 50%	↓ 40%	No specific recommendation
Anti-acid (pop-PK)	pH dependent dissolution	--	--	Not mentioned in label
Pirfenidone	Concomitant medicine	↓ 38%	↓ 30%	Not mentioned in label
Smoking (pop-PK)	Relevant patient population	↓ 21%		Not mentioned in label

Summary of drug-interaction studies

-Effect of other drugs on Nintedanib

Effect of co-administration of ketoconazole, rifampicin, anti-acid, and pirfenidone on nintedanib exposure (AUC) and C_{max} was evaluated (Table 5).

-Effect of Nintedanib on other drugs

Effect of nintedanib co-administration on pirfenidone AUC and C_{max} was evaluated. Nintedanib did not have a relevant effect on the PK of pirfenidone.

Effect on QT interval

As per sponsor's report, QT/QTc measurements were collected in a phase 2 study in renal cell cancer patients (1199.26). The study demonstrated the lack of effect of 200 mg nintedanib orally administered bid for 15 days on the QTcF interval as compared with baseline. The largest mean time-matched increase of QTcF at steady state was 3.1 ms (two-sided 90% CI: -0.2, 6.4). A thorough TQT study in healthy volunteers is not feasible for ethical reasons.

Pediatrics development plan

As nintedanib in IPF has been granted Orphan Drug Status, there is no Pediatric Study Plan (PSP) included in this submission; per 21 CFR 314.55(d), Orphan Drugs are exempt from the requirements to assess pediatric use under PREA.

Summary of Nintedanib PK

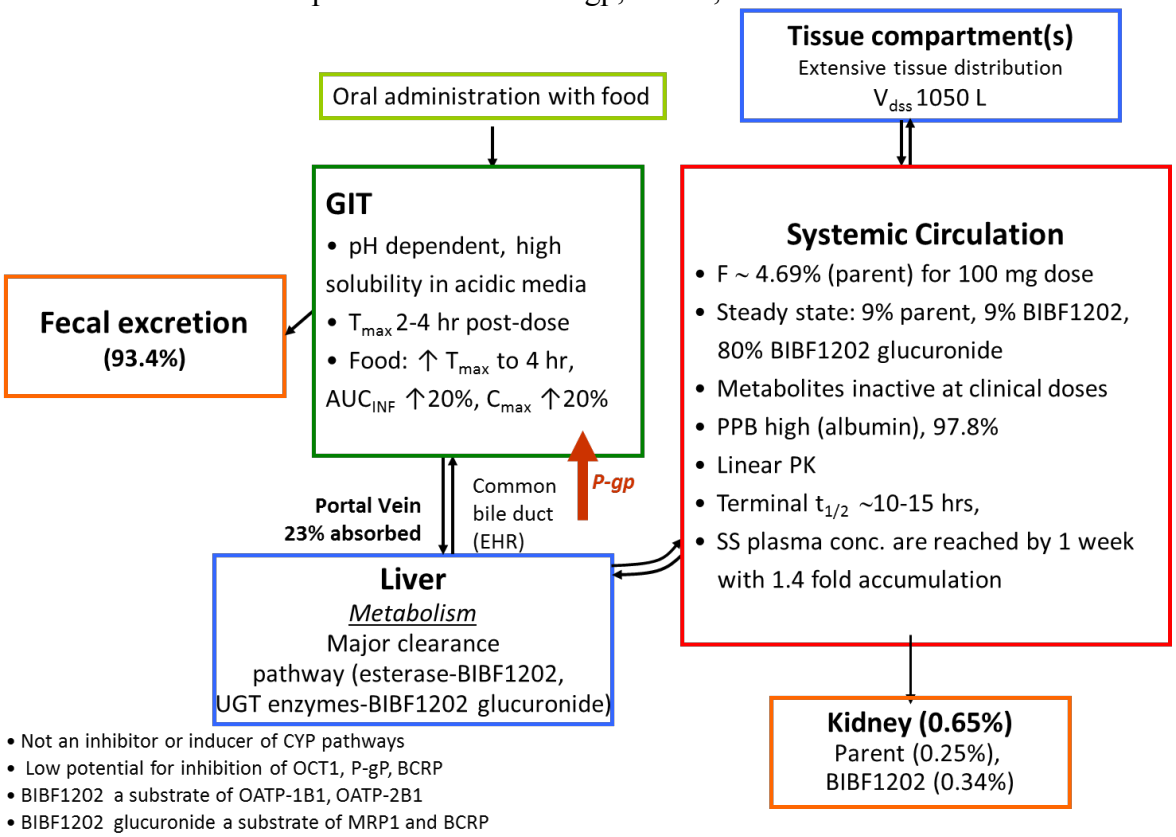
The PK characteristics of nintedanib are summarized in **Figure 3**. Sponsor states that nintedanib has low aqueous solubility under neutral pH, indicating to classification in BCS Class 2 or 4 category. After oral administration maximum concentrations (i.e., C_{max}) of nintedanib are reached in 2-4 hours under fed conditions. The absolute bioavailability of nintedanib after oral administration of 100 mg dose is approximately 4.69% under fed conditions. Data from preclinical studies indicate the involvement of P-gp transporter in absorption of nintedanib. Exposure increased by about 20% after administration under fed conditions.

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 is reported to be the major pathway of clearance for nintedanib, 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.

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. After twice-daily dosing, steady-state plasma concentrations were reached by one week, with 1.4 fold accumulation.

Nintedanib and its major metabolites are not inhibitor or inducer of CYP enzymes. Nintedanib was found to have a low potential to inhibit P-gp, OCT1, and BCRP.



↑- Increase, ↔ - no change

Figure 3: Schematic presentation of Nintedanib PK properties

Summary of Exposure Response Analysis

Sponsor conducted exposure response analysis for pharmacodynamic markers based on mechanism of action (such as VEGF, FGF and KL-6) and for safety endpoints (such as ALT, bilirubin). Sponsor reported findings from these analyses are summarized in Table 6.

Table 6. Exposure response and dose response analyses

Endpoint	Type	Study	Relationship
VEGF, FGF, DCE-MRI	Biomarker	Cancer	**ER observed for DCE-MRI; no consistent pattern for VEGF and FGF**
KL-6	Biomarker	30	**Some dose response, supportive info**
TGF-β1, 2, 3, IL-8	Biomarker	30	**No consistent pattern**
FVC	Efficacy	30	**No significant correlation within each dose group, no evaluation across dose groups**
GI AEs	Safety	Cancer	**No consistent pattern**
Liver enzyme elevation	Safety	Cancer, 30	**consistently a trend towards higher exposure with elevations of liver enzymes or bilirubin**

Mid-Cycle Deliverables

Following are the Mid-Cycle Deliverables;

- Any approvability issues
- Dose Selection
- Exposure-Response Evaluation for Efficacy and Safety
- Drug-drug Interaction and Extrinsic/Intrinsic Factors
- Labeling

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/s/

JIANMENG CHEN
06/12/2014

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