CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

205832Orig1s000

PHARMACOLOGY REVIEW(S)

Tertiary Pharmacology/Toxicology Review

Date:	September 22, 2014
From:	Timothy J. McGovern, PhD, ODE Associate Director for Pharmacology and Toxicology, OND IO
NDA:	205832
Agency receipt date:	May 2, 2014
Drug:	OVEF (nintedanib)
Sponsor:	Boehringer Ingelheim
Indication:	Treatment of idiopathic pulmonary fibrosis (IPF)
Reviewing Division:	Division of Pulmonary, Allergy, and Rheumatology Products

The primary pharmacology/toxicology reviewer and supervisor concluded that the nonclinical data support approval for the indication listed above.

The recommended pharmacologic class for nintedanib is a kinase inhibitor; nintedanib is hypothesized to exert its efficacy in IPF by inhibiting the receptor tyrosine kinase receptors FGFR, PDGFR, and VEGFR.

A complete nonclinical program was conducted including chronic toxicology studies in rats and monkeys, a genetic toxicology battery, two-year carcinogenicity studies in rats and mice, and a battery of reproductive and developmental toxicology studies. In the general toxicology studies the primary toxicities included bone, liver, kidney, ovaries and the immune system. The identified NOAELs provided exposure margins of < 1- to 2.6-fold (based on AUC) compared to the anticipated clinical exposure at the recommended dose. Based on the indicated disease, these exposure margins are considered acceptable.

The carcinogenicity studies did not produce any significant findings and nintedanib was negative in the genetic toxicity battery.

Fertility, embryo-fetal development (EFD), and pre/postnatal development studies of nintedanib were conducted in rats and an EFD study was conducted in rabbits. Nintedanib administration to rats led to a reduction in female fertility, malformations in the vasculature, skeletal system and urogenital system, and decreased post-natal viability of pups. A change in sex ratio was observed in rabbits. The Division recommended a Pregnancy Category "D" for this product based on the above findings.

Conclusion: I agree with the Division pharmacology/toxicology conclusion that nintedanib can be approved from the pharmacology/toxicology perspective. I have discussed and am in agreement with labeling revisions proposed by the Division.

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/s/

TIMOTHY J MCGOVERN
09/22/2014

Secondary Pharmacology and Toxicology Review for NDA 205-832

TO: NDA 205-832 (Boehringer Ingelheim)

FROM: Marcie Wood, Ph.D.
Supervisory Pharmacologist
Division of Pulmonary, Allergy, and Rheumatology Products

DATE: September 5, 2014

Overview: I concur with the recommendation of Dr. Luqi Pei (detailed in a nonclinical review dated August 28, 2014) that the pharmacology and toxicology of OVEF (nintedanib) have been adequately studied and the drug product should be approved from a nonclinical perspective.

Background: Nintedanib (Code name: BIBF 1120) is a kinase inhibitor. It is indicated for the treatment of idiopathic pulmonary fibrosis (IPF). The proposed clinical dosage is 300 mg/day (as 150 mg, BID). A reduced dosage (100 mg, BID) may be administered to manage adverse reactions.

Pharmacology: The pharmacodynamic effects of nintedanib were investigated both *in vitro* and *in vivo*. *In vitro* studies showed that nintedanib is an inhibitor of receptor tyrosine kinases (RTKs) [i.e., FGFR, PDGFR, VEGFR, and Flt-3] and non-receptor tyrosine kinases (nRTKs) [(b) (4), Lck, Lyn, and Src]. Nintedanib IC_{50s} ranged from 13-610 nM and 16-195 nM for RTKs and nRTKs, respectively. Nintedanib is hypothesized to exert its efficacy in IPF by inhibiting the RTKs FGFR, PDGFR, and VEGFR. *In vitro* data showed that nintedanib inhibited fibroblast migration, proliferation, and transformation of fibroblasts. *In vivo* studies showed that nintedanib treatment decreased the severity of lung fibrosis induced by bleomycin and silica in animal models.

Toxicology: The general toxicity of nintedanib was studied in mice, rats, and monkeys for up to 12 months. Chronic toxicity was evaluated in studies of 6 and 12 months in rats and monkeys, respectively. Each of these studies used the oral (gavage) route of administration. The studies identified the following target organs of toxicity: bone (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system included adrenal glands, bone marrow, spleen, and thymus.

Bone findings included dentopathy (e.g., teeth fracture and gum inflammation) and thickened epiphyseal cartilage in mice and rats, and thickening of growth plates in monkeys. Findings in the liver included extra-medullary hematopoiesis. Kidney findings included PAS-positive hyaline droplets, tubular casts, fat droplets in tubular epithelium, and tubular pigment. Changes in the ovaries included increases/decreases in the number of corpora lutea, mature corpora lutea, and a decrease in the size of corpora lutea. Adrenal gland findings included cortical peliosis/angiectesia in rats and cortical hypertrophy in mice. Changes in the bone marrow and thymus included cellular depletion, and changes in the spleen included extra-medullary hematopoiesis and lymphoid cell depletion.

The chronic rat study identified a low-dose NOAEL of 5 mg/kg/day, and the chronic monkey study failed to identify a NOAEL, though the only observation in monkeys at the low-dose of 10 mg/kg/day was growth plate thickening, which may not be relevant to an adult patient population. At the NOAEL of the chronic rat study, animal to human exposure margins are less than 1 on an AUC basis for the proposed

clinical dose of 300 mg/day. At the 10 mg/kg/day low-dose of the chronic monkey study, animal to human exposure margins range from 1.6 – 2.6 on an AUC basis. Development of nintedanib for IPF was allowed to proceed, despite lack of adequate safety margin (1 or greater on an AUC basis) in nonclinical test species. See Dr. Pei's review for further details on the toxicological characterization of nintedanib.

Genotoxicity: Nintedanib was negative in the *in vitro* bacterial mutagenicity test (Ames assay), the *in vitro* mouse lymphoma assay, and in the *in vivo* micronucleus assay in rats.

Carcinogenicity: Two 2-year carcinogenicity bioassays were conducted with nintedanib in rats and mice at oral doses up to 10 and 30 mg/kg/day, respectively. These studies did not reveal any evidence of carcinogenic potential.

Reproductive and Developmental Toxicology: Reproductive and developmental toxicity studies of nintedanib were completed in rats and rabbits via the oral route of administration. These studies evaluated the effects of nintedanib on fertility in rats, teratogenicity in rats and rabbits, and pre- and post-natal development in rats. Nintedanib was a potent teratogen and reproductive toxicant. In rats, nintedanib decreased female fertility, as evidenced by increases in resorption and post-implantation loss, and a decrease in gestation index. In chronic rodent toxicology studies, changes in the number and size of corpora lutea in the ovaries were also observed. Nintedanib had no effect on fertility in male rats. In rats and rabbits, nintedanib caused embryofetal death and teratogenic effects at maternally nontoxic doses. Malformations included abnormalities in the vasculature (e.g., missing or additional major blood vessels), skeletal system (e.g., hemivertebra, or missing or asymmetrically ossified vertebra; bifid or fused ribs; fused, split, or unilaterally ossified sternabrae), and urogenital system (e.g., missing organs in some fetuses). A sex ratio change was also observed in rabbits (e.g., shift in female:male ratio to 71%:29%). Finally, nintedanib decreased post-natal viability of rat pups during the early postnatal period.

Labeling: Section 4 (Contraindications), Section 5.3 (Embryofetal toxicity, in Warnings and Precautions), Section 8.1 (Pregnancy; Pregnancy Category D), Section 8.3 (Nursing Mothers), Section 12.1 (Mechanism of Action), and Section 13.1 (Carcinogenesis, Mutagenesis, Impairment of Fertility) have been revised to incorporate and reflect nonclinical findings discussed above. See Section 12 of Dr. Luqi Pei's review for complete product labeling details, including rationale for proposed product labeling.

There are no outstanding Pharmacology and Toxicology issues for this product.

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/s/

MARCIE L WOOD
09/05/2014

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	**NDA 205-832**
Supporting document/s:	**Sequences 0000**
Applicant's letter date:	**May 2, 2014**
CDER stamp date:	**May 2, 2014**
Product:	**Ofev (nintedanib) tablets**
Indication:	**Idiopathic pulmonary fibrosis**
Applicant:	**Boehringer Ingelheim**
Review Division:	**Pulmonary, Allergy, and Rheumatology Drug Products**
Reviewer:	**Luqi Pei, Ph.D.**
Supervisor:	**Marcie Wood, Ph.D.**
Division Director:	**Badrul Chowdhury, M.D., Ph.D.**
Project Manager:	**Jessica Lee, Pharm.D.**

Template Version: September 1, 2010

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Except as specifically identified, all data and information discussed below and necessary for approval of NDA 205-832 are owned by BI or are data for which BI has obtained a written right of reference. Any information or data necessary for approval of NDA 205-832 that BI does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as reflected in the drug's approved labeling. Any data or information described or referenced below from reviews or publicly available summaries of a previously approved application is for descriptive purposes only and is not relied upon for approval of NDA 205-832.

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LIST OF ABBREVIATIONS

Abbreviation	Definition	Abbreviation	Definition
ADME	Absorption, distribution, metabolism, and elimination	LD	Low dose
		MD	Mid dose
API	Active pharmaceutical ingredient	MRHD	Maximum recommended human dose
AUC	Area under the curve	NDA	New drug application
BI	Boehringer Ingelheim	NHLF	Normal human lung fibroblast
C	Control	nRTK	Non-receptor tyrosine kinase
CNS	Central nervous system	PCR	Polymerase chain reaction
DARRTS	Document archiving, reporting, and regulatory tracking system	PDGF	Platelet-derived growth factor
		PDGFR	PDGF Receptor
CVS	Cardiovascular system	PK	Pharmacokinetics
DPARP	Division of Pulmonary, Allergy, and Rheumatology Drug Products	PO	Oral
		PTK	Protein tyrosine kinase
DPRF	Drug product reference file	QSAR	Quantitative SAR
ECAC	Executive Carcinogenicity Assessment Committee	RTK	Receptor tyrosine kinase
		RS	Respiratory system
EOP2	End-of-Phase 2	SAR	Structural activity relationship
FCG	Fetal calf serum	TGF	Tumor growth factor
FGF	Fibroblast growth factor	TK	Tyrosine kinase
FGFR	FGF receptor	VEGF	Vascular endothelial growth factor
GD	Gestation day	VEGFR	VEFG Receptor
GLP	Good laboratory practice		
GI	Gastrointestinal		
HD	High dose		
IC50	Median inhibitory concentration		
ICH	International Conference on Harmonization		
IND	Investigational new drug		
IIG	Inactive Ingredient Guide		
IL	Interleukin		
IPF	Idiopathic pulmonary fibrosis		
IR	Information request		
IV	Intravascular		

1 Executive Summary

1.1 Introduction

This review evaluates nonclinically the safety of the Ofev Capsule (nintedanib) application (NDA 205-832). The review finds that the applicant has conducted adequate nonclinical characterizations of ingredients of the product to support the safety of its proposed use from the nonclinical perspective.

Boehringer Ingelheim (BI, the applicant) proposed to register Ofev capsules as a therapy for idiopathic pulmonary fibrosis (IPF). Ofev capsules will be manufactured in two strengths: 100 and 150-mg nintedanib/capsule. The proposed recommended human daily dose of nintedanib is 150 mg, twice daily. The 100-mg capsules will be used for dose adjustments in patients who need temporary dose reductions while on Ofev treatment.

Idiopathic pulmonary fibrosis is a serious, chronic, progressive lung disorder of unknown etiology. The disease is characterized by alveolar epithelial cell injury, formation of activated fibroblasts and myofibroblasts foci, and accumulation of extracellular matrix with subsequent destruction of the lung architecture. Proliferation and migration of lung fibroblasts and myofibroblasts appear the most prominent features in IPF. Such proliferation and migration processes require growth factors (GF) such as fibroblast growth factor (FGF) and platelet-derived growth factor (PDGF). Growth factor receptors contain tyrosine kinases (TK) for signal transductions.

Nintedanib is a TK inhibitor. There are many TKs in cells. These enzymes regulate numerous cellular functions. Tyrosine kinases are divided into receptor kinases (RTK) and non-receptor kinases (nRTKs), according to their locations and functions in the cell. Nintedanib inhibits the following TK families: FGFR, PDGFR, VEGFR (vascular endothelial growth factor receptor), Ftl-3, (b) (4) and SRC. The first four targets are RTKs while the last two are nRTKs. The nintedanib targets accounted for approximately 20% of TK families currently known. See Section 4 Pharmacology for additional information on TK classifications.

The RTK targets of nintedanib are components of GF receptors. The RTKs are activated (i.e., phosphorylated) when ligands bind to the receptor and form dimers. The activated RTKs in turn activate themselves (i.e., phosphorylate) and other enzymes. Nintedanib inhibited the RTKs (i.e., FGFR, PDGFR, and VEGFR) which are believed to play an active role in pulmonary fibrosis. Ligands for FGFR, PDGFR, and VEGFR are FGG, VEGF, and FGF, respectively.

The nRTKs are cytoplasmic enzymes that are responsible for activating (i.e., phosphorylating) other enzymes that regulate cellular activities. The nRTKs are involved primarily in signal transduction in activated T-and B-cells and hematopoietic progenitor cells. The JAK and SRC family kinases are examples of nRTKs. Because of the broad TK targets for nintedanib, BI is also developing the drug for oncological indications. Whether inhibition of nRTK contributes to the IPF efficacy of nintedanib is currently

unknown. See Section 2.2 Relevant IND and NDA applications for additional information. This application deals with the IPF indication only.

During the development of nintedanib, several code names and salt forms were used. The code names included BIBF 1120 (free base), BIBF 1120 ES (b) (4)-ethanesulfonate salt), and BIBF 1120 (b) (4) See Section 2.1 Drug for chemical structures of BIBF 1120 and BIBF 1120 ES.[1] The current NDA submission referred to the drug substance (BIBF 1120 ES) as nintedanib esilate. Nintedanib doses in the review refer to the free base.

This review uses Legacy Document Numbers (LDN, which start with a U) to identify study reports. The use of LDN keeps consistency between the review and the submission and, thus, minimizes confusion. Note that at least 3 file systems [LDN or document #, study numbers, and nonclinical document numbers] were used to identify the nonclinical studies in the NDA submission. For example, the female fertility study in rats has the following identifier: Document #U13-2650, Nonclinical Document #n00231235, and Study #12B057. Some reports have all 3 identifiers while others may have one of them. Section 3 Studies Submitted lists both Document No. and Study No. for cross references.

Nintedanib development was carried out under IND 74,683. IND 74,683 also refers to IND (b) (4) under which nintedanib is being developed for oncological indications. Portions of the nonclinical program of nintedanib were reviewed under IND (b) (4) See Section 2.7 Regulatory Background for additional information.

1.2 Brief Discussion of Nonclinical Findings

Nintedanib inhibits the following TK families: FGFR, PDGFR, VEGFR, Flt-3, (b) (4) and SRC. Nintedanib is believed to exert its efficacy in IPF by inhibiting RTKs of the following receptors: FGFR, PDFGR, and VEGFR. Nintedanib is also being investigated for therapy for cancers, based on its ability to inhibit nRTKs such as Lck, Lyn, and SRC. The role of nRTKs in IPF efficacy of nintedanib is unknown at this time.

Nintedanib is absorbed after oral administration, but the bioavailability is low (4.7% – 24%) across species. Plasma drug levels increase generally in proportion to orally administered doses in animals. Based on plasma drug AUC and C_{max} levels, nintedanib levels do not accumulate over time. The half-life of nintedanib is about 4 – 7 hours in animals and 12 - 17 hours in humans. The fraction of protein bound nintedanib ranges between 91.4% - 98.5%. The drug is metabolized in the liver and excreted mainly through feces. BIBF 1202 and BIBF 1202-Glu are two major metabolites in animals and humans. All nintedanib metabolites in humans are present in at least one animal species.

The general toxicity of nintedanib was studied in multiple nonclinical species with treatment durations up to 3, 6, and 12 months in mice, rats, and monkeys, respectively.

[1] The review does not list the structure of nintedanib (b) (4). Also, BIBF 1120 (b) (4) was used in some secondary pharmacology studies only.

These studies revealed that the target organs of nintedanib toxicity include the bones (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system included adrenal glands, bone marrow, spleen, and thymus.

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

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

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

1.3 Recommendations

1.3.1 Approvability

Approval of the application is recommended from the nonclinical perspective. The applicant proposed to register Ofev (nintedanib) capsules for idiopathic pulmonary fibrosis (IPF). The applicant has conducted adequate nonclinical characterization of the active pharmaceutical ingredient. The product contained no novel inactive ingredients. There is adequate nonclinical data to support the safety of the proposed use of the product. The review recommends approval of the product from the nonclinical perspective.

1.3.2 Additional Nonclinical Recommendations

None

1.3.3 Labeling

Below is recommended text for Sections 4, 5.1, 8.1, 8.3, 12.1, and 13.1 of the nintedanib labeling.

4 CONTRAINDICATIONS

None

5.3 Embryofetal toxicity

OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib is teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. *[See Use in Specific Populations (8.1]*

8.1 Pregnancy

Pregnancy Category D

OFEV can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV.

In animal reproductive toxicity studies, nintedanib caused embryofetal deaths and (b) (4) in rats and rabbits at approximately less than and 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). (b) (4) malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, (b) (4) or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on (b) (4) AUC basis at maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability during the first 4 post natal days in rat pups when dams were exposed to less than the MRHD (b) (4) AUC basis at maternal oral dose of 10 mg/kg/day).

8.3 Nursing Mothers

Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats (b) (4) similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because

of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue OFEV, taking into account the importance of OFEV to the mother.

12.1 Mechanism of Action

Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is (b) (4) for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of IPF pathology. Nintedanib inhibits the following nRTKs: Lck, Lyn, and Src kinases. The contribution of Flt-3 and nRTK inhibition to IPF is unknown.

13.1 Carcinogenesis, Mutagenesis, and Impairment of Fertility

Two-year oral carcinogenicity studies of nintedanib in rats and mice have not revealed any evidence of carcinogenic potential. Nintedanib was dosed up to 10 and 30 mg/kg/day in rats and mice, respectively. These doses were less than and approximately 4 times the MRHD, on a plasma drug AUC basis.

Nintedanib was negative for *genotoxicity* in the *in vitro* bacterial reverse mutation assay, the mouse lymphoma cell forward mutation assay, and the *in vivo* rat micronucleus assay.

In rats, nintedanib reduced female fertility at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day). Effects include increases in resorption and post-implantation loss, and a decrease in gestation index. Changes in the number and size of corpora lutea in the ovaries were observed in chronic toxicity studies in rats and mice. Increases in resorption only were observed at exposures approximately equal to the MRHD (on a AUC basis at an oral dose of 20 mg/kg/day). Nintedanib has no effect on male fertility in rats at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day).

2 Drug Information

2.1 Drug

CAS Registry Number: 626247-18-6

Generic Name: Nintedanib esilate or nintedanib ethanesulfonate

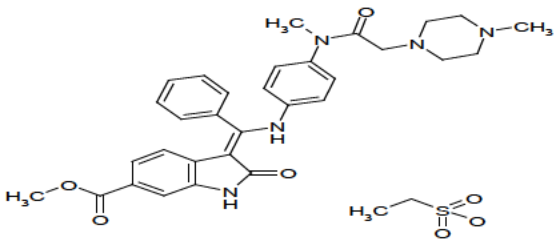
Code Name: BIBF 1120 (free base), BIBF 1120 BS (free base), BIBF 1120 ES (ethanesulfonate or esilate salt)

Chemical Name: 1H-Indole-6-carboxylic acid, 2, 3-dihydro-3-[[[4-(methyl [(4-methyl-1-piperazinyl)acetyl]amino)phenyl]amino]phenyl-methylene]-2-oxo-, methyl ester, (3Z)-, (b) (4) ethanesulfonate

Molecular Formula: $C_{31}H_{33}N_5$ and $C_{33}H_{39}N_5O_7S$ for BIBF 1120 and BIBF 1120 ES, respectively

Molecular Weight: 539.6 and 649.8 for BIBF 1120 and BIBF 1120 ES, respectively

Structure:



Pharmacologic Class: Kinase inhibitor. Nintedanib inhibits both RTKs and nRTKs. The RTK targets include the kinases of PDGFα/β (platelet derived growth factor), $VEGF_{1-3}$ (vascular endothelial growth factor), and FGF_{1-4} (fibroblast growth factor) and Flt-3. The nRTK targets include (b) (4) SRC (i.e., Lck, Lyn, and Src) families. The drug presumably exerts its efficacy in IPF primarily by inhibiting the following RTK: FGFR, PDGFR, and VEGFR.

2.2 Relevant INDs, NDAs, and DMFs

See Table 1 for these applications.

Table 1: Nintedanib Applications

Appl. No.	Division	Indication	Date of IND opening
(b) (4)	DOP1	(b) (4)	(b) (4)
IND 074,683	DPARP	Idiopathic pulmonary fibrosis	3/14/2011

2.3 Drug Formulation

OFEV capsules contain nintedanib esilate, triglyceride (b) (4), hard fat (b) (4) and lecithin. OFEV capsules will be manufactured in two strengths (i.e., 100 and 150-mg capsules). See Table 2 for the content of these capsules. The capsule shells consist of gelatin (b) (4), glycerol (b) (4) titanium dioxide (b) (4) red ferric oxide (b) (4) and yellow ferric oxide (b) (4)

Table 2: Formulation of OFEV Capsules – Filling Materials

Compound	Function	Amount per Capsule (mg)	
		100-mg Capsule	150-mg Capsule
Nintedanib esilate (BIBF 1120 ES)	(b) (4)	(b) (4)	(b) (4)
Nintedanib free base (BIBF 1120)			
Triglyceride (b) (4)			
Hard fat			
Lecithin			
Total			

2.4 Comments on Novel Excipients

The formulation contains no novel excipients. Ofev capsules contain triglyceride (b) (4) hard fat (b) (4) and lecithin as excipients. None of these are novel excipients for oral products.

2.5 Comments on Impurities/Degradants of Concern

There are no safety concerns for any of the impurities that may be present in the product. A large number of impurities were reported in the application. Except for (b) (4) none of the remaining compounds in the product had estimated exposure levels of ≥ 1.5 mcg/day, the qualification threshold for genotoxic impurities, per ICH M7 guidance.

The applicant reported approximately 40 impurities. Most of them carried structural alerts for genetic toxicity (mutagenicity), based on the structural-activity-relationship (SAR) analysis. The alerts prompted BI to conducted approximately 30 genetic toxicity assays on 21 compounds. The tests were done on a tiered approach, beginning with the Ames test for mutagenicity. Additional and follow-up tests, such as the in vivo micronucleus test and comet assay, were carried out on Ames positive compounds. Most compounds tested negative in the Ames test, but several were positive. The weight-of-evidence analysis concluded that 3 compounds (b) (4) were genotoxic. Also, the literature showed 4 more compounds (i.e., (b) (4) were mutagenic. The exposure of patients to these 7 impurities is expected to be approximately (b) (4) each, based on their specifications of not-more-than (b) (4) in the drug product and nintedanib daily dose of 300 mg. The daily exposure to (b) (4) were also deemed acceptable. See Sections 10.1 and 11.7 of the review for addition information on impurities.

2.6 Proposed Clinical Population and Dosing Regimen

Adult patients with idiopathic pulmonary fibrosis will take a 150-mg nintedanib capsule twice daily, with approximately 12 hours between doses. Those with increased liver enzymes may take the drug at a reduced dose, 100 mg, bid, for a period before returning to the regular dose of 150 mg, bid. The regular dosing schedule yields steady state plasma AUC_{0-24} of 304.2 and 2590.2 ng.h/mL for nintedanib and the sum of API and major metabolites, respectively.[2] The major metabolites are BIBF 1202 and BIBF 1202 glucuronide (or BIBF 1202-Glu) which had AUC_{0-24} of 300 and 2286 ng.h/mL, respectively.

[2] Provided by Dr. Jianmeng Chen, Clinical Pharmacology Reviewer via an email message dated July 9, 2014.

2.7 Regulatory Background

The developmental program in support of this NDA application (#205-832) was carried out under INDs 74,683 and (b) (4) The intended indication was IPF and cancers for IND 74,683 and (b) (4) respectively. IND (b) (4) supported the NDA because: 1) IND 74,683 makes reference to IND (b) (4), and 2) evaluations of some pivotal nonclinical studies of nintedanib (e.g., carcinogenicity study protocols) were reviewed under IND (b) (4). The Office of Oncological Products holds IND (b) (4) Table 3 lists regulatory milestones for these applications.

Table 3: Key Regulatory Events in IND 74,683 and NDA 208,532

Application#	Date	Events	DARRTS ID#
(b) (4)	03/08/2004	Original IND was filed	Not available
I 74,683	08/02/2006	Pre-IND meeting held	Not available
I 74,683	12/01/2010	Pre-IND/EOP2 meeting held	2,884,821
I 74,683	03/14/2011	Original IND filed	3,003,245
I 74,683	05/31/2013	IND Fast-Track designation granted	3,316,157
I 74,683	10/31/2013	Pre-NDA Meeting held	3,398,438 & 3,399,681
I 74,683	04/08/2014	Propriety name granted	3,485,297
N 208,532	05/02/2014	NDA 205-832 (Ofev) submitted	-
N 208,532	05/28/2014	Break through therapy requested	3,521,429
N 208,532	07/07/2014	Propriety name granted	3,538,159
N 208,532	07/15/2014	Break through therapy granted	3,593,404

INDs (b) (4) and 74,683 have been active since March 8, 2004, and March 14, 2011, respectively. Important regulatory events occurred prior to and after the opening of the IND 74,683. Key events included pre-IND and EOP2 meetings in IND 74,683 (b) (4)

(b) (4)

Under IND 74,683, DPARP and BI held pre-IND, EOP2, and pre-NDA meetings to discuss the development of the drug. These meetings were held on August 2, 2006, December 1, 2010, and October 31, 2013, respectively.[3] In addition to these face-to-face meetings, DPARP and BI had telephone conferences and written correspondences regarding the nonclinical developmental program of the drug. These communications dealt with a spectrum of nonclinical issues. These issues can be summarized into the following 4 areas: the overall nonclinical program, carcinogenicity, reproductive toxicity, and impurities. This section discusses each topic briefly.

Also, the Agency granted IND 74,683 a Fast-Track designation on May 31, 2013 (DARRTS ID# 3,316,157), and granted the trade name of Ofev on April 8, 2014 in IND 74,683 (DARRTS ID# 3,485,297) and July 7, 2014 in the current NDA (DARRTS ID# 3,538,159), respectively. The Agency granted the nintedanib NDA (205-832) a Breakthrough Therapy designation on July 15, 2014 (DAARTS ID# 3,593,404).

[3] Both the 02-AUG-2006 and 01-DEC-2010 meetings are referred to as pre-IND/EOP2 meetings because the meetings were held prior to the opening of IND 74,683. In the submissions and some communications, the first meeting was also referred as a pre-IND meeting and the second as an EOP2 meeting because of meeting contents. This review uses the same terminology for clarity.

Overall nonclinical developmental program: The nonclinical program in support of the IND and NDA applications were discussed in the above 3 meetings. In summary, DPARP requested BI to conduct a comprehensive nonclinical characterization of nintedanib and provide safety evaluations of impurities. The August 2, 2006 pre-IND Meeting concluded that BI apparently did not have adequate nonclinical data to support the intended clinical trial of nintedanib in humans.

The second, EOP2 meeting was held 4 years later on December 1, 2010. BI had collected additional clinical data in cancer patients over this period. BI stated in the briefing package that it intended to conduct two, phase-3, 1-year studies of nintedanib in IPF patients. Approximately 500 patients would receive 150-mg nintedanib capsules, bid, for 52 weeks. The available nonclinical data in support of the intended clinical trials included oral toxicity studies of 6 months in rats and 12 months in monkeys, respectively. Based on the summary provided in the briefing package, the nonclinical team found that the available nonclinical data were unsupportive of the intended clinical trials because of the lack of adequate safety margins. The Division determined that the available clinical data from the cancer patients appeared sufficient to evaluate the safety of the proposed dosing schedule (Ref.: DARRTS ID# 2,884,821).

BI submitted the IND 74,683 on March 14, 2011. The IND submission proposed the clinical studies as proposed in the December 1, 2010 EOP2 Meeting. Approximately 900 patients over 40 years of age would receive 150-mg nintedanib or placebo, bid, for 52 weeks. Nonclinical data in support of the proposed clinical trials included general toxicology studies up to 6 and 52 months in rats and monkeys, as indicted earlier. Dr. Luqi Pei completed a preliminary nonclinical safety review (DARRTS ID# 2,933,090) on April 14, 2011, and a comprehensive nonclinical review (DARRTS ID# 2,944,664) on May 10, 2011, respectively. The target organs of nintedanib toxicity include the bones (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system include adrenal glands, bone marrow, spleen, and thymus. The HD group rats were terminated prematurely because of severe toxicity. The review confirmed the previous determination that there was insufficient safety margin to support the proposed clinical doses.

The review team discussed the available clinical and nonclinical data in the Division IND Safety Meeting held on April 12, 2011. It was concluded that the available clinical data was sufficient to evaluate the safety of the proposed clinical trial and to alleviate nonclinical deficiencies. The Division allowed the proposed clinical trial to proceed.

Carcinogenicity: BI submitted reports of 2-year carcinogenicity studies of nintedanib in rodents in the NDA package. The Agency concurred with the designs of these studies. The Concurrence was given on September 16, 2011. (See Information Request/Advice sent by Mrs. Adele Seifried.) Table 4 provides a summary of key communications dealing with the carcinogenicity assessments of nintedanib. See the nonclinical review completed by Dr. Carol Galvis on August 22, 2014 (DARRTS ID# 3,614,801) for additional information. DPARP and BI discussed the timing for submitting the study reports and the design of the study protocols in INDs 74,683 and (b) (4).

Table 4: Major Communications in Carcinogenicity Evaluations

Date	Key Content	DARRTS ID #
08/02/2006	Discussions on timing for submitting carcinogenicity study reports	NA [a]
12/01/2010	Discussions on timing for submitting carcinogenicity study reports	2,884,821
08/02/2010	BI requested concurrence of 2-yr rodent carcinogenicity study protocols	NA
09/16/2010	Concurrence of rodent carcinogenicity study protocols (IND (b) (4)	NA
06/01/2012	BI proposed dose reductions in the 2-yr mouse carcinogenicity study (eCTD Seq. # 045)	NA
06/08/2012	FDA's response to the dose reduction proposal for the 2-year mouse carcinogenicity study	NA
10/31/2013	Discussions on timing for submitting carcinogenicity study reports	3,398,438

a. NA, Not available or applicable.

The 02-AUG-2006 pre-IND meeting: BI stated in the briefing package in IND 74,683 that they would like to submit reports of carcinogenicity studies as phase 4 commitments. The Division responded that the carcinogenicity study reports should be submitted in the NDA package (Ref.: Meeting Minutes, Question 9).

Special Protocol Assessments: The Agency assessed and concurred with the design of the 2-year rodent carcinogenicity study protocols through Special Protocol Assessment reviews under IND (b) (4) in 2010. BI requested the Agency's assessments of their protocols for 2-year carcinogenicity studies in rats and mice on August 2, 2010. The Executive Carcinogenicity Assessment Committee (ECAC) discussed the protocols and recommended modifications to the protocols on September 14, 2010. The Agency conveyed the ECAC recommendations to BI on September 16, 2010. See nonclinical reviews completed by Dr. Shwu-Luan Lee on September 27 and 30, 2010, respectively, for the Agency's evaluations of the protocols. On June 1, 2012, BI proposed (b) (4) The Agency rejected the proposal on June 8, 2014 under IND 74,683.

The 01-DEC-2010 EOP2 meeting: BI stated in the briefing package that they would like to seek guidance on the timing to submit reports of carcinogenicity studies. The Division indicated that it could be acceptable to submit the carcinogenicity study reports as Phase-4 commitments (Ref.: Meeting Minutes, DARRTS ID# 2,884,821, Question 3).

The 31-OCT-2013 Pre-NDA meeting: BI stated in the briefing package that they may submit reports of carcinogenicity studies post NDA submission. The Division accepted the approach. (Ref.: Meeting Minutes, DARRTS ID# 3,398,438, Question 3). The NDA submission contained the final reports of the rodent carcinogenicity studies. There are no longer any outstanding issues regarding the timing of submitting carcinogenicity study reports.

Reproductive toxicity: Extensive communications were held to discuss nonclinical requirements for reproductive and developmental toxicity studies of nintedanib. The communications included the 02-AUG-2006 pre-IND meeting, the 01-DEC-2010 EOP2 meeting, and 3 IR letters. The letters were issued on 19-AUG-2011, 01-DEC-2011, and 30-JAN-2012, respectively. Communications also included the meeting briefing packages and submissions of

06-SEP-2011 and 20-DEC-2011 responding to the IRs. Table 5 summarizes key contents of these communications.

Table 5: Major Communications in Reproductive Toxicity Evaluations

Date	Key Content	DARRTS ID#
08/02/2006	BI proposed not conducting any reproductive toxicity studies of nintedanib. DPARP requested BI to complete a full reproductive toxicology battery of reproductive and developmental studies.	NA
12/01/2010	BI completed limited testing (i.e., a male fertility study in rats and non-GLP dose-ranging teratology study in rats) and proposed not conducting any additional testing for reproductive and developmental toxicity studies. DAPRP requested that BI complete the battery of studies.	2,884,821
03/14/2011	BI submitted the original IND application, which included reports of the completed studies, and argued for not providing a complete battery of studies.	NA
08/19/2011	DPARP issued an IR letter responding to the 14-MAR-2011 submission. DAPRP rejected BI's arguments and retained its previous position.	3,003,245
09/06/2011	BI responded to the 19-AUG-2011 IR letter. The response contained continued arguments for not conducting any additional studies.	NA
12/01/2011	DPARP issued another IR letter rejecting BI's 06-SEP-2011 response.	3,052,263
12/20/2011	BI requested for the 3rd time the rationale for conducting reproductive toxicity studies. BI also requested comments on outlines of planned studies.	NA
01/30/2012	DPARP provided information requested in the 20-DEC-2011 submission.	3,079,191
05/02/2014	BI submitted all requested reproductive and developmental toxicity studies.	NA

The 02-AUG-2006 Pre-IND meeting: BI stated in the meeting briefing package that they did not plan to conduct any reproductive toxicity studies of nintedanib. The reason was that such studies were not required for oncological indications (Question 8). DPARP told BI that a full reproductive toxicology program was required for approval and results of the studies would be described in the product label.

The 01-DEC-2010 EOP2 meeting: BI described, in the meeting briefing package submitted on October 19, 2010, their plans for a reproductive toxicology program. DPARP outlined specific requirements for reproductive and developmental toxicity studies. Rationale for requesting the studies were also discussed.

BI did not plan to conduct any additional reproductive toxicity studies beyond what it had already completed. BI had completed a male fertility study in rats and non-GLP dose-ranging embryofetal developmental studies in pregnant rats. BI's rationale was that: 1) results of the non-GLP studies showed that nintedanib was a potent teratogen in rats, 2) BI would seek a (b) (4) for the product label, and 3) the Agency agreed to waive the requirement for

reproductive toxicity studies of nintedanib for their programs for oncological indications. BI requested that DPARP concur with its plan (Nonclinical questions 1, 2, and 8).

DPARP reiterated the need for a comprehensive nonclinical characterization of reproductive and developmental toxicity of nintedanib (Ref. Meeting Minutes, DARRTS ID# 2,884,821). DPARP told BI that a full reproductive toxicology program was required for approval and results of the studies would be described in the product label. Specifically, BI should complete the female fertility study, the embryofetal developmental studies in 2 species, and the peri- and post-natal developmental toxicity study.

***The 14-MAR-2011 Original IND* submission**: BI submitted the report of the above referenced studies and reiterated their position for not conducting any of the requested studies. Dr. Luqi Pei completed DPARP's evaluation of BI's position on May 10, 2011 (DARRTS ID 2,944,664) and found the response unsatisfactory.

***The 19-AUG-2011 IR* letter** (DARRTS ID# 3,003,245): In an IR letter, DPARP reminded BI of the need for completing the requested studies. The letter rejected BI's position for not completing the battery of reproductive and developmental toxicity studies. The comment was based on the nonclinical original IND review completed by Dr. Luqi Pei on May 10, 2011 (DARRTS ID# 2,944,664).

***The 06-SEP-2011* submission**: BI submitted a response to the August 19, 2011 IR letter. The response included additional arguments to support their previous position. Dr. Luqi Pei completed the evaluation of the response in a nonclinical review completed on November 28, 2011 (DARRTS ID# 3,050,367). The review once again found the response unsatisfactory. The review once again recommended that BI complete the previously requested studies.

The 01-DEC-2011 IR letter (DARRTS ID# 3,052,263): DPARP issued a second IR letter rejecting BI's position. The response was based on Dr. Pei's review completed on November 28, 2011 (DARRTS ID# 3050367).

The 20-DEC-2011 Submission: BI again requested rationale for the request for completing a full battery of reproductive toxicity studies. BI also requested the Division's comments on outlines of planned reproductive and developmental toxicity studies. Dr. Luqi Pei completed evaluations of BI's response in a nonclinical review completed on January 25, 2012 (DARRTS ID 3,076,935). The review provided the requested rationale, but had no comments on the proposed study outlines.

The 30-JAN-2012 IR letter (DARRTS ID# 3079191): DPARP issued an IR letter conveying the comments in the nonclinical review completed by Dr. Pei's review on January 25, 2012 (DARRTS ID 3,076,935).

The 02-MAY-2014 NDA submission: The submission contained reports of all requested reproductive and developmental toxicity studies.

Impurities: There were extensive communications on the safety evaluation and qualification of nintedanib impurities. Table 6 lists these important communications. They included the 02-AUG-2006 pre-IND meeting, Information Requests of September 9, and December 1, 2011, and the October 31, 2013 pre-NDA meeting. The communications also included the meeting

briefing packages and submissions responding to the IRs. The text below provides brief descriptions of major communications regarding impurity-related issues.

Table 6: Major Communications in Impurity-Related Issues

Date	Key Content	DARRTS ID #
08/02/2006	DPARP requested BI to assess genotoxicity of (b) (4) in a pre-IND meeting	NA
08/19/2011	DPARP requested QSAR analysis of 7 additional compounds and a completed battery of tests for (b) (4)	3,003,245
09/06/2011	BI submitted results of QSAR analysis of the nintedanib impurities using DEREK and MC4PC, as well as safety evaluations of the impurities	NA
12/01/2011	DPARP informed BI that: 1) the Division generally concurred with BI's positions on the impurities, 2) the in vivo micronucleus test with (b) (4) (b) (4) may be waved.	3,052,263
10/29/2013	DPARP and BI discussed strategy for addressing the impurity issues in the NDA submission in the pre-NDA meeting written response.	3,398,438
10/31/2013	DPARP provided clarifications to the written response in DARRTS ID # 3398438 upon BI's request on October 30, 2013.	3,399,681
05/02/2014	BI submitted its evaluations of impurity exposures based on a maximum recommended human daily dose (MRHDD) of 250-mg nintedanib	NA
06/13/2014	DAPRP issued an IR requesting BI to evaluate impurity safety based on the MRHDD of 300-mg nintedanib	3,524,164
06/20/2014	BI responded that the safety evaluation of impurities was based on a 500-mg nintedanib dose.	NA

The 02-AUG-2006 pre-IND meeting: DPARP asked BI to address nintedanib impurity issues. While reminding BI that safety evaluations and qualifications of impurities are generally addressed in the NDA stage per ICH Q3A and Q3B, DPARP asked BI to address (b) (4) in the IND submission. (b) (4) was both an intermediate and degradant of nintedanib.

***The 19-AUG*-2011 IR letter** (DARRTS ID# 3,003,245): DPARP asked BI to conduct quantitative structural activity relationship (QSAR) analysis of the following process impurities: (b) (4) . The request was issued after Dr. Yong Hu, the reviewing chemist, identified structural alerts for genetic toxicity. DPARP also asked BI to conduct a standard battery of genetic toxicity tests for (b) (4), both an impurity and a metabolite. DPARP stated that an assessment of the carcinogenicity of (b) (4) would be needed if the compound tested positive in the genetic toxicity assays. These comment were based on the nonclinical original IND review (DARRTS ID# DARRTS ID 2,944,664) completed by Dr. Luqi Pei on May 10, 2011.

The 06-SEP-2011 submission: BI submitted results of their QSAR analysis. BI indicated that they had completed the QSAR analysis of the impurities using DEREK and MC4PC software. The DEREK analysis showed no positive results for structural alerts, but MC4PC analysis revealed positive signals for several compounds. However, these compounds had the same moiety as the

API. BI stated that they would not conduct any further analysis because the impurities were part of the API analysis.

December 1, 2011 IR Letter: DPARP informed BI that the Division generally agreed with BI's position. Also, the in vivo testing of (b) (4) might not be necessary if BI could demonstrate that sufficient exposure of the compound was achieved in the chronic toxicity studies. These comments were based on the nonclinical review completed by Dr. Luqi Pei on November 28, 2011 (DARRTS ID# 3050637).

October 31, 2013 pre-NDA meeting: BI provided an overview of its strategy for addressing safety evaluations and qualifications of impurities in the drug substance and product. Two pieces of software (DEREK and MC4PC) were used to predict compounds with structural alerts for genetic toxicity. Compounds with structural alerts were evaluated in Ames tests. Additional tests were done on the compounds with positive Ames test results. The expected daily exposure for each genotoxic impurity at the maximum recommended daily nintedanib dose was below 1.5-mcg/day safety concern threshold. The impurities were not specified. DPARP commented that BI should address genotoxic materials per ICH-M7 Guidance *(DARRTS ID# 3,398,438 and 3,399,681)*.

May 2, 2104 NDA submission: BI submitted its exposure estimates and safety evaluations of the nintedanib impurities. The estimates were based on a MRHD of 250-mg nintedanib [Ref.: Subsections 8.5.8 (pages 72 – 76) and 10.8 (page 81) of Sections 2.6.6 and Subsection 4.8 (page 30) of Section 2.4]. This dose was incorrect because the MRHD in the current NDA is 300-mg/day nintedanib.

June 13, 2104 IR letter: DPARP issued an IR asking BI to reassess the impurity exposures and conduct safety evaluations accordingly (DARRTS ID# 3,524,164). BI responded to the IR on June 20, 2014, via email that its estimates were based on a daily dose of 250 mg, bid, an intended dose for oncological indications.

Outcome of the final evaluation: The estimated impurity exposures from the proposed use were less than (b) (4), so no further action is needed because there is no safety concern for the impurities at the proposed levels.

3 Studies Submitted

3.1 Studies Reviewed

Table 7 provides a list of pivotal nonclinical studies reviewed in this document.

Table 7: Pivotal Nonclinical Studies Reviewed

Document #	Study No.	Description	Location
Pharmacology			
Primary Pharmacology			
U02-1084	02-02	Receptor binding assays in vitro	4.2.1.1
U02-1109	01-02	Potency and selectivity assay in vitro	4.2.1.1
U02-1299	11-02	Selectivity and potency on PDGFR-a	4.2.1.1
U02-1301	13-02	Selectivity and potency on murine EGFR-3	4.2.1.1
U02-1310	09-02	Specificity on selected kinases in vitro	4.2.1.1
U03-1488	03-03	Wash-out period in vitro	4.2.1.1
U05-1930	02-05	Pharmacological characterization	4.2.1.1
U06-1451	6-luiii-lab3 report1	Dose-dependency in lung fibrosis in a rat model	4.2.1.1
U06-1478	2006-luiii-lab3-report3	Inhibition of TGF-ß mediated transformation of fibroblasts to myofibroblasts	4.2.1.1
U06-1479	2006-luiii-lab3-report2	Nintedanib (50mg/kg) delayed the onset of lung fibrosis in a rat model	4.2.1.1
U06-2006	8810366	Binding to 5-HT1B receptors in vitro	4.2.1.1
U08-1683	bia03-08	Inhibition of Abl kinase activity & cell proliferation in human CML cell line in vitro	4.2.1.1
U08-1946	bia09-08	Effects on kinase signaling & cell survival in several cell types in vitro	4.2.1.1
U11-1947	bircv09-11	X-ray structure analysis of VEGFR-2 complex	4.2.1.1
U12-2066	cnrs-umr6218-iem	Effect on silica induced lung inflammation and fibrosis	4.2.1.1
U12-2437	cnrs-umr7355-inem	Effect on bleomycin induced lung inflammation and fibrosis	4.2.1.1
U12-2490	university-basel-1051764	Effect on cell differentiation and on epithelial-mesenchymal unit	4.2.1.1
U12-2457	2012-rdr-ppss-lab17-report1	Potency on Inhibiting PDGFR-a/ß autophosphory-lation in human lung fibroblasts by nintedanib and its analogs	4.2.1.1
U12-2539	2012-rdr-ppss-lab17-report2	Inhibitory potency on PDGF-induced proliferation of human lung fibroblasts	4.2.1.1
U12-2598	2012-rdr-ppss-lab17-report3	Inhibitory activity on PDGFR-a/ß autophosphory-lation in human lung fibroblasts	4.2.1.1
U13-2156	2013-li-pep2-report1	Binding to immobilized human FGFR1 intracellular domain	4.2.1.1
U13-2316	2013-li-pc2-report1	X-ray structure analysis of FGFR-1 complex	4.2.1.1
Secondary Pharmacology			
U02-1248	gp2001-220-ph4	Effect on gastric secretion (intadermal) rat	4.2.1.2
U02-1258	gp2001-219-ph4	Effect on gastric emptying (po) in rats	4.2.1.2
U02-1259	gp2001-218-ph4	Effect on GI transit, rat	4.2.1.2
U02-1260	gp2001-221-222-223-ph4	Effect on renal and liver functions in conscious rat	4.2.1.2
U02-1288	gp2002-286-2001-	Effect on hERG mediated K-current current in vitro	4.2.1.2

	149-ph2		
U02-1398	gp2001-235-ph5	Effect on vital functions, telemetryplethysmography, in anesthetized conscious rats	4.2.1.2
U02-1587	gp2001-285-ph1	Effect on behavior, single dose, po, modified IRWIN-test, mouse	4.2.1.2
U02-1589	gp2001-323-ph1	Effect on nocturnal locomotion at single dose, po, mouse	4.2.1.2
U02-1674	gp2001-260-ph2	Effect on circulation + ECG in anaesthetized pigs	4.2.1.2
U04-1416	gp2003-0296-ph4	Effect on liver function in rats	4.2.1.2
Safety Pharmacology			
U03-1465	Bio-246-023329	Effect on the respiratory system in conscious rats	4.2.1.3
U03-1537	Bio-245-023142	Irwin behavioral test after PO administration in rats	4.2.1.3
Pharmacokinetics			
n00188105	b4005	Bioanalyt. assays, non BIBF1120/metabolites, overview	4.2.2.1
n00184943	b4099	Stability data overview	4.2.2.1
U02-1381	a082-01rb-a085-02rb-a093-02rb	PK after PO and IV exposure in male Wistar rat	4.2.2.2
U03-1563	a094-02rb	Whole body autoradiogr, iv (albino, pigment) / po (albino), male rat	4.2.2.3
U02-1649	a217-02te-b1785	Glucuronidation, liver, rats, dogs, monkeys, human, in vitro	4.2.2.4
U03-1150	a075-02ar-b2006	Plasma protein binding + blood cell distrib, species comparison, in vitro	4.2.2.3
U03-1296	a216-02te-b2096	Characterization + structure	4.2.2.4
U03-1355	a118-02lu	- Metabolism, hu cytochrome P450 enzymes	4.2.2.4
U03-1386	a114-02lu	Inhibition of cytochrome P450 depend paths in vitro	4.2.2.4
U03-1935	a221-02te	Metabolism, rat	4.2.2.4
U04-2195	dodf-1012-b2454	CYP inducers - Hepat. cytochrome P450 + related parameters, 4d admin, rat	
U05-1001	a227-03te-b2432	Metabolism in hepatocytes, rat, human	4.2.2.4
U05-1558	aa22653-a235-04te-b2527	PK + excretion, single dose iv + po, rhesus mo	4.2.2.5
U05-2098	a235-04te-b2582	Metabolism in rhesus monkey	4.2.2.4
U05-3076	pk05008-b4702	Hepatic + renal transporters, excretion	
U06-1105	a188-05lu	on [14C]BIBF2992 MA2 - Oxidative Metabolism, in vitro	4.2.2.4
U06-1106	a189-05lu-b2727	Metabolism, in vitro	4.2.2.4
U06-1667	a249-06te-b2886	Glucuronidation by UGT1A1, in vitro	4.2.2.4
U06-2240	a037-06bi-a254-06te-b3036	Trace metabolites, Wistar rat	4.2.2.4
U08-1144	a267-07te-b3366	Glucuronidation by microsomes+ intestinal UDP-UGTs, rat, human, in vitro	4.2.2.4
U08-1256	a219-07lu-b3300	Inhibition of cytochrome P450 depend paths, in vitro	4.2.2.4
U08-1952	a090-08fu-b3468	BIBF1202 GLUC - Plasma protein binding, rat, rhesus monkey, human, in vitro	4.2.2.3
U08-2181	pb-08-001	Plasma protein binding in rat, rhesus monkey + hu	
U09-1164	a239-08lu	Inhibition on cytochrome P450 depend metabolic paths, in vitro	4.2.2.4
U09-1949	a100-09fu-b3684	Protein binding extent, rhesus monkey plasma, in vitro	4.2.2.3

U09-1975	lpt-22057	PK, single dose, po, nu/nu mouse	4.2.2.2
U09-2019	a103-09fu-b3725	Plasma protein binding extent, CD-1 mouse, in vitro	4.2.2.3
U09-2277	a284-09te-b3867	Metabolism + excretion, mouse	4.2.2.4
U09-2517	a194-08rb-b3892	Tissue distribution & excretion in male rats (PO)	4.2.2.3
U10-2525	a181-08rb	BIBF1120, BIBF1202, BIBF1202 GLUC - PK, rat	4.2.2.7
U10-2910	a182-08rb-b4178	In situ intestinal absorpt + metab, rat	4.2.2.2
U12-1855	a196-09rb-b4579	Transfer to milk, po, lactating rats	4.2.2.3
U02-1494	b2005	Absorpt, distrib, metab, excret, rat	4.2.2.4
U12-2279	pkpr0801-b4703	Interaction with human hepato-biliary transporters in vitro	4.2.2.7
U13-2725	pk1305t	Interaction w7 human ABC + SLC transporters, in vitro	4.2.2.7

3.2 Studies Not Reviewed

Studies listed in this section were not reviewed for one of the following reasons: 1) Agency Staff had reviewed them previously, or 2) they are not pivotal in the safety evaluation of the proposed clinical use of the drug products. Table 3 lists the studies that have been reviewed previously.

Table 8: Nonclinical Studies Not Reviewed (Previously Reviewed)

Study#	Document#	Description	Location	Reference [a]
Pharmacology				
U02-1109*	01-02	Potency and selectivity, in vitro	4.2.1.1	2,944,664
U02-1310	09-02	Specificity on selected kinases, in vitro	4.2.1.1	2,944,664
U06-1479	2006-luiii-lab3-report2	Effect of 50mg/kg on lung fibrosis, delayed treatment model, rat	4.2.1.1	2,944,664
U06-1451	6-luiii-lab3 report1	Dose-dependency in lung fibrosis, rat	4.2.1.1	2,944,664
Toxicology: Repeat-dose				
U05-1843	03b073	26-week oral toxicity study w/ recovery in rats	4.2.3.2	2,944,664
U05-2245	boi-251-032137	13-week oral toxicity study in cyno. monkeys	4.2.3.2	2,944,664
U07-1875	boi-305-052470	52-week oral toxicity study in rhesus monkeys	4.2.3.2	2,944,664
U10-1798	ddb0005	13-week oral toxicity study in CD-1 mice	4.2.3.2	2,841,259
U10-1799	ddb0019	13-week oral toxicity study in Han Wistar rats	4.2.3.2	2,841,263
Genetic toxicity				
U02-1481	02b041	Ames test	4.2.3.3.1	2,841,259
U02-1512	02b121	BIBF 1120 mouse lymphoma (L5178Y) assay	4.2.3.3.1	2,841,259
U02-1650	02b079	Rat bone marrow micronucleus assay	4.2.3.3.2	2,841,259
Reproductive toxicity				
U07-1710	07b002	Dose finding for embryo-fetal developmental study in rats – high dose	4.2.3.5.2	2,944,664
U07-1814	07b030	Dose finding for embryo-fetal developmental study in rats – low dose	4.2.3.5.2	2,944,664
U10-1128	09b060	Fertility study in male rats	4.2.3.5.1	2,944,664
U13-1923	12B017	Teratogenicity study in Rat	4.2.3.5.2	3,615,202
U13-1937	12B032	Teratogenicity study in Rat Rabbit	4.2.3.5.2	3,615,202
U13-2641	DDB029	Peri- and post-natal toxicity study in rats	4.2.3.5.3	3,615,202
Carcinogenicity				
Ddb0006	N00232869	2-year oral carcinogenicity study in mice	4.2.3.4.1	3,614,801
Ddb0007	N00232871	2-year oral carcinogenicity study in rats	4.2.3.4.2	3,614,801

a. DARRTS Reference ID number.

*, file name extension. Some file names had extensions such as -01, -02 or -03 but many do not. The overwhelming majority of the extensions was -01. The extensions referred to a particular version of the study reports. Sections of 2.4 and 2.6 of the eCTD NDA submission did not use the extensions when relevant studies were referenced. This document omits the extension for clarity and to be consistent with the submission.

Some studies of nintedanib and other chemicals were not reviewed either because they do not provide information pivotal to the safety evaluation of the current NDA. Table 9 lists these studies.

Table 9: Nonclinical Studies Not Reviewed (Non-Pivotal)

Study#	Document#	Description	Location
Pharmacokinetics			
U02-1356	m087-02af-b1961	HPLC-MS/MS quantitation of BIBF1120 BS in rat & cynomolgus plasma	4.2.2.1
U02-1497	b2015	Synthesis	
U03-1161	v182-03hj-b2092	LC-MS-MS of BIBF1120 BS & (b) (4) in rat plasma	4.2.2.1
U03-1296	a216-02te-b2096	Characterization + structure	4.2.2.1
U04-1046	m119-03mi	LC-MS-MS quantitation of BIBF1120 BS, rat plasma	4.2.2.1
U04-1241	m134-03mi-b2237	HPLC-MS/MS quantitation of BIBF1120 ES in rhesus monkey plasma	4.2.2.1
U04-1873	v224-04hj-b2332	HPLC-MS/MS quantitation, validation & stability of BIBF1120ES in rhesus monkey plasma	4.2.2.1
U06-1235	m136-03mi-b2702	HPLC-MS/MS quantitation, validation & stability of BIBF1202 BW in rhesus monkey plasma	4.2.2.1
U06-1667	a249-06te-b2886	Glucuronidation by UGT1A1, in vitro	
U09-1135	m272-08mi-b3654	Quantitative validation of BIBF1120 BS & BIBF1202 ZW in rat plasma	4.2.2.1
U09-1207	m285-08mi-b3702	HPLC-MS/MS quantitation, validation & stability of BIBF1202 GLU in rhesus monkey plasma	4.2.2.1
U09-1208	m297-08mi-b3693	MS quantitation , validation + stability, rhesus monkey plasma	4.2.2.1
U09-1397	m277-08af-b3689	HPLC-MS/MS quantitation, validation & stability of BIBF1202 GLU in rat plasma	4.2.2.1
U10-1516	v327-09af-b3919	MS quantitation & validation of BIBF1120 BS, BIBF1202 ZW, & BIBF1202 GLUC in mouse plasma	4.2.2.1
U10-2072	a051-09js-b3954	Stability of BIBF1202 ZW & BIBF1202 GLUC in whole blood from humans, monkeys, and rats	4.2.2.1
U10-2653	s297-08mi-b4155	Stability of BIBF1120 BS, BIBF1202 ZW in acidified rhesus monkey plasma	4.2.2.1
U10-2664	s327-09af-b4156	Stability of BIBF1120 BS, BIBF1202 ZW in acidified mouse plasma	4.2.2.1
U11-1619	a231-10rb	metabolites - Influence of zosuquidar on exposure, po, rat	4.2.2.1
U12-2197	v383-12mi	simultaneous quantitation & validation of BIBF1120, BIBF1202, BIBF1202-gluc in rabbit plasma	4.2.2.1
U12-2271	r383-12mi	Part valid LC-MS/MS quantitation of BIBF1120, BIBF1202, & BIBF1202-gluc in rabbit plasma	4.2.2.1
U12-2290	v361-11af-b4622	Part valid LC-MS/MS quantitation of BIBF 1202 GLU in Han-Wistar rat plasma	4.2.2.1
U12-2292	v360-11af-b4621	Part valid LC-MS/MS quantitation of BIBF1120 & BIBF1202 in Han-Wistar rat plasma	4.2.2.1
U12-2309	r383-12af	Part valid LC-MS/MS quantitation of BIBF1120,	4.2.2.1

		BIBF1202, & BIBF1202-gluc in rabbit plasma	
U12-2397	r383-12dh	Part valid LC-MS/MS quantitation of IBF1120, BIBF1202, & BIBF1202-gluc in rabbit plasma	4.2.2.1
U12-2711	s383-12mi	Stability, acidified rabbit plasma	
Toxicology			
U02-1526	01b082	2-week exploratory, non-GLP oral study in rats	4.2.3.2
U02-1714	01b044	2-week exploratory, non-GLP oral study of competing candidates in male rat	4.2.3.2
U03-1326	1813-040	4-week oral toxicity study with 2-week recovery in cynomolgus monkey	4.2.3.2
U03-1707	59-553	Pilot for oral MTD determination in cynomolgus monkey	4.2.3.2
U04-1065	02b08	13-week oral toxicity study in rats	4.2.3.2
U04-1812	02b012	2-week oral toxicity study with 2-week recovery in rats	4.2.3.2
U04-1856	03b027	2-week oral toxicity study with 2-week recovery in rats	4.2.3.2
U05-2450	59-549	Preliminary 2-week oral toxicity study in Beagle dogs	4.2.3.2
U05-2452	59-558	Comparative TK after IV and PO ROA in rhesus monkeys	4.2.3.2
U05-2427	aa17740	4-week oral toxicity study with 4-week recovery in rhesus monkeys	4.2.3.2
U06-1063	59-548	Preliminary 2-week oral toxicity in rats	4.2.3.2
U07-2343	05b083	Determination of oral MTD study in minipigs	4.2.3.2
U09-1403	08b013	Range finding, IV, escalating dose study in rats	4.2.3.2
U09-1730	08b077	HP-ß-cyclodextrin feasibility, iv-infusion, rat	4.2.3.2
U09-1836	08b028	2-week intravenous (10-min infusion) in rats	4.2.3.2
U09-2398	514536	MTD after IV administration in rhesus monkeys	4.2.3.2
U10-2202	514599	2-week intravenous in rhesus monkeys	4.2.3.2
U10-1797	ddb0004	Preliminary 2-week oral toxicity in CD-1 mice	4.2.3.2
U11-1349	03b131	2-day exploratory, non-GLP oral studies in minipigs	4.2.3.2
U12-1780	aa77360	3 x 14d cycles with 4 week recovery in Wistar rats	4.2.3.2
Genetic toxicity tests of impurities		(b) (4)	
U02-1226	02b024		4.2.3.3.1
U02-1227	02b020		4.2.3.3.1
U02-1228	02b023		4.2.3.3.1
U02-1230	02b022		4.2.3.3.1
U03-1572	03b021		4.2.3.3.1
U03-1573	02b209		4.2.3.3.1
U03-1574	03b027+ 03b036		4.2.3.3.1
U05-1770	05b026		4.2.3.7.6
U05-2272	gpt-100164		4.2.3.3.1
U07-2089	07b019		4.2.3.3.2
U08-1595	08b037		4.2.3.3.1
U08-2323	08b166		4.2.3.7.6
U09-1033	08b173		4.2.3.7.6
U09-1070	08b171		4.2.3.7.6
U09-1073	08b188		4.2.3.7.6
U09-1191	08b186		4.2.3.3.1
U09-1294	08b157		4.2.3.3.2
U10-1979	10b014		4.2.3.3.1

U10-2415	8202043	(b) (4)	4.2.3.3.2
U11-2538	11b165		4.2.3.3.1
U11-2539	11b166		4.2.3.3.1
U11-2541	11b171		4.2.3.7.6
U11-2607	11b190		4.2.3.3.1
U11-2840	11b222		4.2.3.3.1
U11-2841	11b223		4.2.3.3.1
U11-2796	11b207		4.2.3.3.1
U12-1121	N/A		4.2.3.3.1
U12-1640	12b072		4.2.3.3.1
U12-1997	12b068		4.2.3.3.1
Local tolerance study of BIBF 1120			
U03-1151	02b067	Acute eye irritation after 1x in rabbits	4.2.3.6
U05-1395	03b128	Acute dermal irritation/corrosion after1x in rabbits	4.2.3.6
U08-1861	08b041	Intra-arterial local tolerance after single dose in rabbits	4.2.3.6
U08-1862	08b027	Local tolerance after 1x iv & im injection in rabbits	4.2.3.6
U08-1863	08b042	Local tolerance by 1x para-venous injection in rats	4.2.3.6
U09-1969	09b032	Hemolysis test inhuman blood in vitro	4.2.3.6
Combination tox. studies			
U06-1196	05b021	BIBW2992 + nintedanib alternating, 2-cycle DRF, po, rat	4.2.3.7.7
U06-1605	05b188	BIBW2992 + nintedanib alternating, 4-cycle, po, rat	4.2.3.7.7
U06-1606 + U06-1606-AM1	05b252	BIBW2992 + nintedanib combination, DRF, 4w, po, rat	4.2.3.7.7
U06-1624	05b190	BIBW2992 + nintedanib – combination, DRF, 2w, po, rat	4.2.3.7.7
U09-1962	08b079	BI6727 CL3 (IV) + nintedanib (PO) alternating, - 3-cycle DRF, rat	4.2.3.7.7
U11-1368	08b038	BI6727 (IV) + nintedanib (PO) alternating - 1-cycle dose-range finding, rat	4.2.3.7.7
U11-2658	aa77353	BI811283 (IV) + nintedanib (PO) alternating - 1-cycle DRF, rat	4.2.3.7.7

3.3 Previous Reviews Referenced

This review references a number of nonclinical reviews completed by Agency staff under INDs (b) (4) and 74,683. See Table 10 for the referenced reviews.

Table 10: Previously Completed Reviews Referenced

DARRTS ID #	IND/ NDA #	Date of Completion	Author	Content
2,944,664	I74,683	05/10/11	Pei	Original IND review
3,050,367	I74,683	11/28/11	Pei	Evaluation of BI's response to comments in ID# 2944664
3,076,935	I74,683	01/25/12	Pei	Need for a full reproductive toxicity program
-	(b) (4)	04/07/05	Benson	Original IND review
2,841,259	(b) (4)	09/27/10	S. Lee	Mouse carcinogenicity study protocol review
2,841,263	(b) (4)	09/30/10	S. Lee	Rat carcinogenicity study protocol review
3,593,740	N205,832	07/18/14	Jacobs	Minutes of 07/15/2014 ECAC meeting
3,614,801	N205,832	08/22/14	Galvis	Review of rodent 2-yr carcinogenicity study reports
3,594,497	N205,832	07/17/14	Zhou	Statistical review of rodent carcinogenicity data
3,615,202	N205,832	08/22/14	G. Lee	Review of teratology and developmental study reports

4 Pharmacology

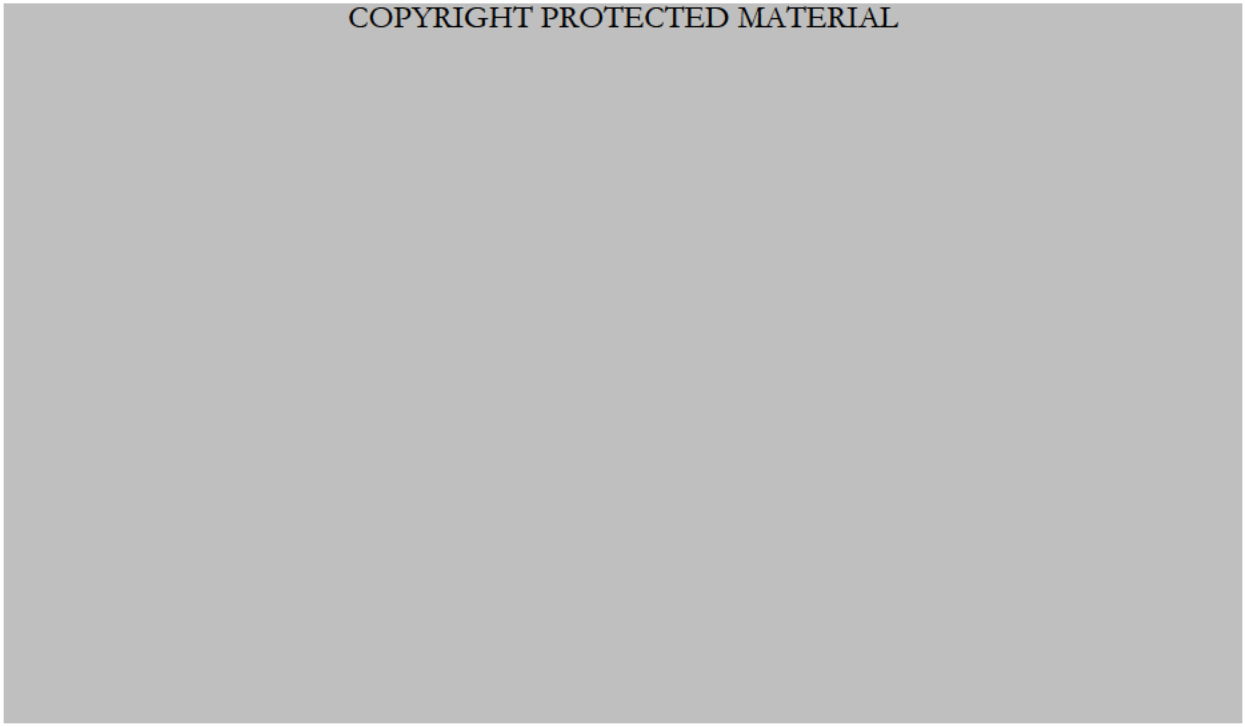
Nintedanib pharmacology was assessed in a total of 34 study reports. These reports provided information on the primary and secondary pharmacodynamic effects and safety pharmacology of nintedanib in vitro and in vivo. Results showed that nintedanib inhibited activities of several TK families in vitro. It also inhibited migration, proliferation, and transformation of fibroblasts in vitro. It attenuated lung fibrosis in animal models in vivo.

In vitro data showed that nintedanib inhibited the following TK families: FGFR, PDGFR, and VEGFR, Ftl-3, ABL, and SRC. The inhibition of the first three families may contribute to nintedanib efficacy in IPF, while the others may not. Also, nintedanib inhibited only approximately 20% of TK families currently identified. The following section provides a brief discussion of recent advances in TK research. The discussion consists of four parts: TK classifications and targets, mechanism of action, and pharmacological activity of nintedanib.

TK classifications: There are many TKs in cells. These enzymes regulate numerous cellular functions. Nintedanib inhibited approximately 20% of TK families. Currently, about 28 TK families have been identified. These TKs are divided into 2 categories according to their locations and functions in the cell: receptor tyrosine kinases (RTK) and non-receptor tyrosine kinases (nRTKs).[4] There are approximately 18 families of RTKs and 10 families of nRTKs. Each of these families of consists of several members. Table 11 presents a summary of PTK families and their family members. Nintedanib may inhibit some or all members of a RTK family (bold face).

The RTKs are components of receptors. RTKs are activated (i.e., phosphorylated) when ligands bind to their receptors and form dimers. The activated RTK in turn activate (i.e., phosphorylate) other enzymes. Ligands for RTKs are mostly growth factors as such PDGF (platelet-derived growth factor). Nintedanib inhibited TKs in the following receptors: PDGFR, VEGF (vascular endothelial growth factor), and FGFR (fibroblast growth factor).

[4] Paul and Mukhopadhyyay, Tyrosine kinase – Role and Significant in Cancer, *Int J Med Sci,* 2004;1(2):101-115.



a. Source: Lennon and Schlessinger, Cell Signaling by Receptor Tyrosine Kinases, *Cell*, 2010;141(7):1117-34.
b. Source: Neet and Hunter, Vertebrate non-receptor protein-tyrosine kinase families, *Genes to Cells*, 1992;1:147-169.
c. Highlights indicate nintedanib targets.

The nRTKs are cytoplasmic enzymes that are responsible for activating (i.e., phosphorylating) other enzymes that regulate cellular activities. The nRTKs are involved primarily in signal transduction in activated T-and B-cells and hematopoietic progenitor cells. The JAK and SRC family kinases are examples of nRTKs. The SRC family (proto-oncogene) consists of 8 PTKs.

TK targets of Nintedanib: Nintedanib inhibited both RTKs and nRTKs. The RTKs included the following receptors: PDGFR, VEGF, FGFR, and Flt-3. These RTKs (except for Flt-3) are involved in IPF pathogenesis, which includes the migration, proliferation, and transformation of fibroblasts. The nRTK targets of nintedanib included members of the ABL and SRC families. Experimental results showed that nintedanib inhibited (b) (4) Lck (lymphocyte-specific), Lyn (Lyn), and Src (proto-oncogene) genes. See Table 12 (next page) for nintedanib IC_{50s} for these enzymes.

Mechanism of Action for Nintedanib: It is hypothesized that nintedanib exerts its efficacy in IPF by inhibiting the RTKs. Nintedanib competitively bound to the ATP-site of the RTK binding pocket with high affinity. The binding prevented activation and auto-phosphorylation of RTK receptors induced by their ligands. The receptors, including PDGFRs, FGFRs, and VEGFRs, have been implicated in IPF pathogenesis. Nintedanib also inhibited several nRTKs (e.g., (b) (4) and members of the SRC family). The contribution of Flt-3 and the nRTKs in the efficacy of nintedanib is unknown.

Pharmacological activity: Nintedanib inhibited RTK and nRTK activities and cell proliferation in vitro. The nintedanib IC_{50s} for its target TKs ranged from 13 – 610 nM. The inhibition of TKs resulted in the inhibition of activation and auto-phosphorylation of TKs and subsequent inhibition of migration, proliferation, and transformation of fibroblasts.

4.1 Primary pharmacodynamic effects

The primary pharmacodynamic effects of nintedanib were evaluated both in vitro and in vivo. Results showed that nintedanib inhibited both RTKs and nRTKs in vitro and attenuated lung fibrosis in mice and rats.

4.1.1 Pharmacological Effect in Vitro

In vitro studies evaluated the TK target spectrum, IC_{50s}, the binding affinity, and effects on cell functions of nintedanib. Results showed that nintedanib inhibited both RTKs and nRTKs with the IC_{50s} that ranged from 13 – 610 and 16 – 195 nM for RTKs and nRTKs, respectively. Nintedanib inhibited auto-phosphorylation of RTK receptors and migration, proliferation, and transformation of fibroblasts.

Inhibition of PTK activity

Hilberg et al. [Cancer Res. 2008;68(12):4774-82] summarized the potency and selectivity of nintedanib on TKs and other enzymes. Table 12 (below) summarizes the nintedanib IC_{50s} for its target TKs. The IC_{50} values ranged from 13 – 610 and 16 – 195 nM for RTKs and nRTKs, respectively. The data indicate that nintedanib IC_{50s} for RTKs and nRTKs overlapped. The IC_{50s} overlap suggests that nintedanib may not be more selective to RTKs than nRTKs, as BI has indicated. Because Hilberg et al. summarized the results of the following documents: U02-1084, U02-1109, U02-1299, U02-1301, U03-1488, and U05-1930, it is unnecessary to conduct reviews of these documents which BI also submitted in the NDA submission.

a. From Hilberg et al., Cancer Res. 2008;68(12):4774-82. The table summarizes the results of the following documents: U02-1084, U-02-1109, U02-1299, U02-1301, U-03-1488, and U-05-1930. No detailed review of these documents is necessary.

b. The table did not include 31 other kinases with IC_{50s} of at least 10,000 nmol/L. These enzymes were CDK1, CDK2, CDK2/CYCLINA, CDK4, CK1, CHK1, CK2, CSK, DRYKIA, EGFR, GSK3B, HER2, HGFR, JUK1A1, MAPK2ERK2, MAPKAPK2, MSK1, PDK1, PKA, PKCA, PHK, PKBA, PP2A, PRAK, ROCKII, S6K1, SGK, SAPK2AP38, SAPK2BP38B2, SAPK3P38G, and SAPK4P38D.

c. From Document U08-1683.

The TKs inhibited by nintedanib belonged to both RTK and nRTK families. The RTKs included families of FGFRs, PDGFRs, VEGFRs, and Flt-3. Except for Flt-3, each of the RTK families has 1 – 4 members. The nRTK targets included (b) (4) and SRC (i.e., Lck, Lyn, and Src).

A number of studies were completed to evaluate the effect of nintedanib on receptor phosphorylation, the nintedanib binding site of RTKs, the effect of the drug on cell migration and proliferation, and other miscellaneous activities. Table 13 provides an overview of the studies and their findings.

Table 13: Miscellaneous Pharmacodynamic Effects

Receptor	Kinase	IC_{50} (nmol/L)	Report #
PDGFRα	Inhibition of auto-phosphorylation of PDGFRα induced by PDGF-BB	21.6	U12-2457
PDGFRβ	Inhibition of auto-phosphorylation of PDGFRβ induced by PDGF-BB	38.7	U12-2457
PDGFR α/β	Inhibition of PDGF-BB induced proliferation of NHLF cells in vitro	63.7	U12-2539
PDGFR α/β	Inhibition of TK activity of PDGFR α/β receptor lasted up to 4 days	-	U12-2598
$FGFR_1$	X-ray crystallography of nintedanib binding sites in FGFR1	NA	U13-2316
FGFR1	Nintedanib bound to the ATP-site of the binding pocket	-	U13-2316
VEFGR2	Computer modeling of the binding-site in VEFGR2	-	U11-1947
FGFR1	Binding kinetics of nintedanib to FGFR1 (K_D = 56 nM, $t_{½}$ = 13.5 S, K_{on} = 9.67 x 10^5 1/ms, K_{on} = 5.12 x 10^{-2} 1/ms)	-	U13-2516
$FGFR_1$	Nintedanib bound to intracellular domain of FGFR1 (K_D = 56 nM)	NA	U13-2156
(b) (4)		-	(b) (4)

Receptor Auto-phosphorylation

Two study reports (Documents U12-2547 and U12-2598) showed that nintedanib inhibited PDGFR auto-phosphorylation of RTKs. Normal human lung fibroblast (NHLF) cells were treated with various concentrations of nintedanib for 30 min. The cells were then stimulated with PDGF–BB (50-nmol/L for 8 min) for 0 hour to 11 days after nintedanib treatment. The cells were lysed at the end of the PDGF-BB treatment. Levels of phosphorylated PDGF receptors in the lysates were detected in ELISAs specific for human phospho-PDGFRα and phospho-PDGFRβ, respectively. Document U12-2547 showed that nintedanib (and other compounds) inhibited phosphorylation of both $PDGFR_\alpha$ and $PDGFR_\beta$ in a concentration dependent manner (Table 14 and Figure 1, n = 2 - 3).

Table 14: IC_{50} of PDGFR Antagonists

Compound	Function	IC_{50} (nmol/L)	
		$PDGFR_\alpha$	$PDGFR_\beta$
BIBF 1000	Reference	17.7	30.1
BIBF 1120	Nintedanib	21.6	38.7
BIBF 1202	Metabolite	5,717	23,510
Imatinib	Reference	1,168	718
Pazopanib	Reference	42.7	43.8

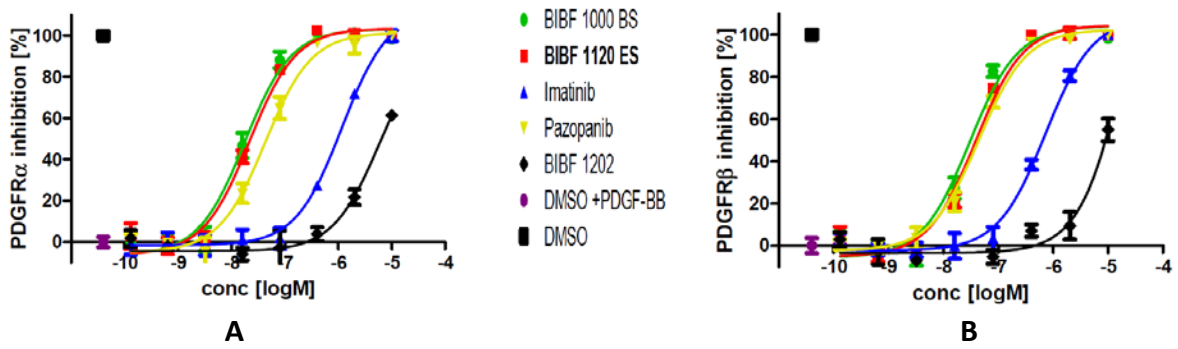


Figure 1: Inhibition of auto-phosphorylation of $PDGFR_\alpha$ (A) and $PDGFR_\beta$ (B) receptors in vitro

Document U12-2598 showed that nintedanib prevented phosphorylation of PDGF receptors for a duration of up to 4 days. Two experiments (i.e., transfer and washout) were carried out.[5] The respective inhibition of $PDGFR_\alpha$ and $PDGFR_\beta$ was 36.3% and 18.9% at day 4 in the transfer experiment and 8.6 and 16.2% at 24 hours in the washout experiment.

Nintedanib binding site of the RTK

Documents U13-2316 and U11-1947 studied the nintedanib binding sites in the kinase domain using X-ray crystallography. The crystals of intracellular domains of human FGFR1 and VEGFR were obtained. The nintedanib-kinase crystal complex was generated by soaking crystals in reservoir solution. Protein structures of the complexes were studied by X-ray crystallography. Results showed that nintedanib bound to the ATP-site in the cleft between N- and C-terminal lobes of the kinase domains (Figure 2, next page). The indolinone scaffold forms two hydrogen bonds to the backbone carbonyl oxygen of Glu562 and the backbone nitrogen of Ala564 in the hinge region. The carboxy methyl ether moiety points into the kinase specificity pocket where it forms hydrogen bonds to the backbone nitrogen of Asp641. Binding of nintedanib to the VEGFR2 was generated by computer modeling.

Document 13-2516 studied the binding of nintedanib to immobilized FGFR-1 intracellular domain ($AA_{456-765}$) using Surface Plasma Resonance on a Biocore T200 system. The nintedanib concentration ranged 0.008 – 5 µM. Results showed the following profile: K_D = 57 nM; t ½ = 13.5 s; k_{on} = 9.67 x 10^5 1/Ms, and k_{off} = 5.13 x 10^{-2} 1/s.

Effects on Cell Migration, Proliferation and Transformation:

Fibroblast migration, proliferation, and transformation are key events in IPF pathogenesis. In the presence of GFs (e.g., PDGF), fibroblasts from human lungs will migrate, proliferate, or transform into myofibroblasts in vitro. Three studies (U12-2539, U12-2490, and U06-1478) showed that nintedanib inhibited fibroblast migration, proliferation, and transformation in vitro.

[5] The transfer method referred to transferring cells to naïve wells. The method presumably eliminated any potential effects of drug residuals on the well walls during the washing process. In the washout method, cells were washed and returned to the original wells.

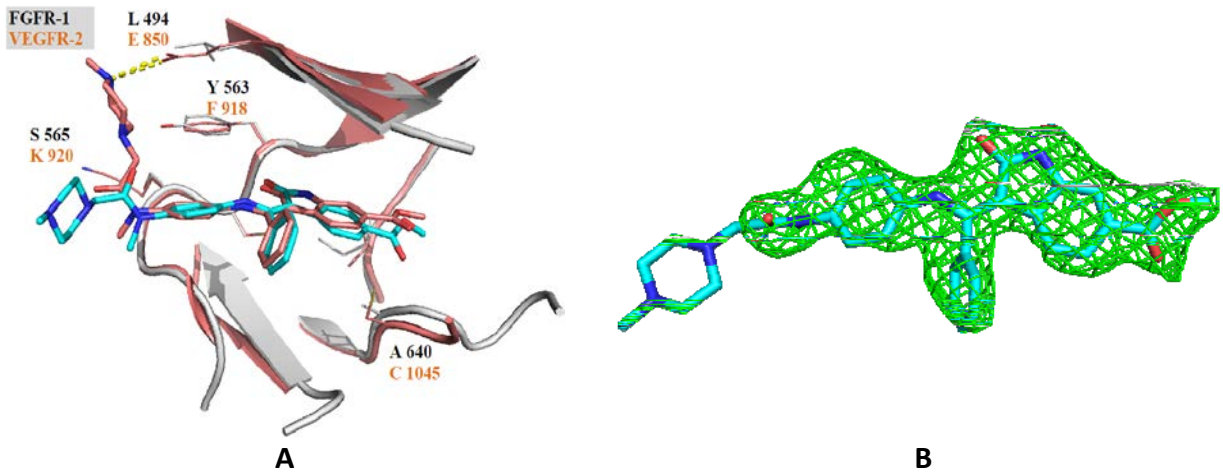


Figure 2: X-ray structure of nintedanib bound in the active site of the FGFR1 and VEGFR2 kinases.

Panel A: The inhibitor and residues that line the active site are shown in stick representation.
Panel B: The methyl piperacinyl-group points into the solvent region and is disordered in the crystal structure of FGFR1.

Document U12-2539 showed that nintedanib inhibited PDGF-induced proliferation of NHLF in vitro. Fibroblasts were isolated from human lungs. The proliferation of the cells was induced by 50-ng/mL PDGF-BB. Nintedanib concentrations ranged between 0.32 – 1000 nmol/L. The rate of cell proliferation was determined by a colorimetric immunoassay for BrdU incorporation during DNA synthesis. Nintedanib produced a concentration-dependent inhibition of cell proliferation (Figure 3). The IC_{50} was 63.7 nmol/L.

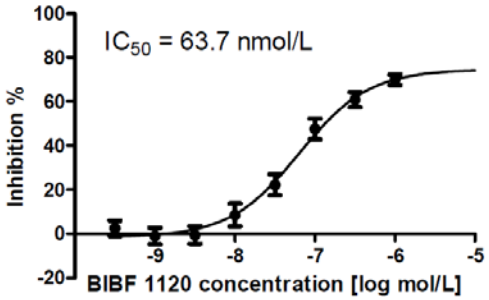


Figure 3: Dose-response relationship of inhibition of PDGF–BB-induced proliferation of NHLF cells by nintedanib (BIBF 1120) in vitro.
The cell proliferation was determined by the rate of BrdU incorporation during DNA synthesis (n = 5).

Document 12-2490 compared the effect of nintedanib on inhibition on GF-induced proliferation and migration of fibroblasts derived from IPF and non-fibrotic human lungs. Fibroblasts were treated with various nintedanib concentrations in the presence of GFs (PDGF-BB, bFGF, or VEGF) for 30 minutes (n = 4/group). Cell proliferation was assessed by the number of cells at 48 hours after nintedanib treatment. Results showed that nintedanib treatment decreased cell numbers

in all cases (Figure 4). The effect was concentration-dependent with the exception of the non-fibrotic cells treated by VEGF which failed to show a concentration-response relationship.

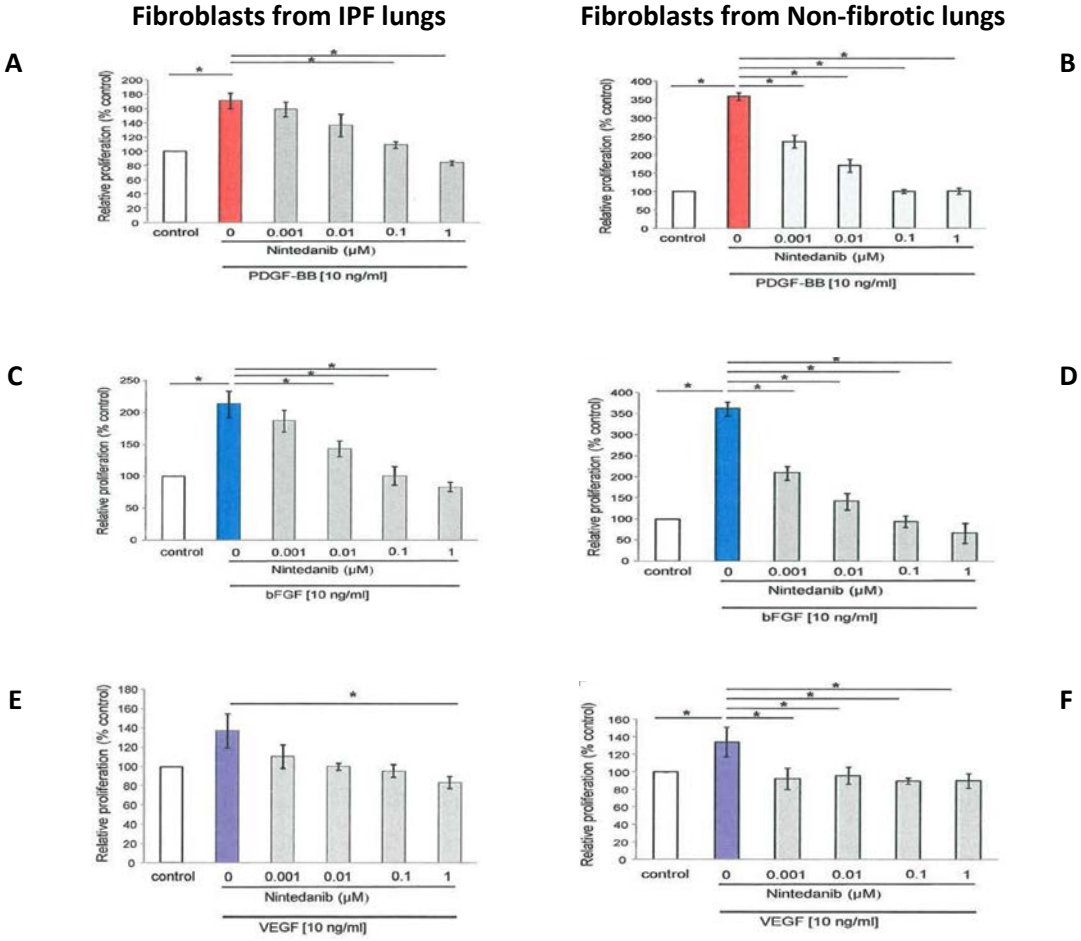


Figure 4: Inhibition of GF-induced fibroblast proliferation by nintedanib.

*, $p < 0.05$ in paired t test.

Cell migration was evaluated by the number of fibroblasts having crossed over a coated membrane within a 4-hour period. Nintedanib decreased the number of migrated cells in a concentration-dependent manner in both IPF and non-fibrotic (i.e., control) lungs (Figure 5, next page). Also, the fibroblasts from IPF lungs appear to be more responsive to GF treatment than the fibroblasts from non-fibrotic lungs. The results showed that nintedanib inhibited both proliferation and migration of fibroblasts derived from both IPF and non-fibrotic human lungs.

Document U06-1478 showed that nintedanib inhibited TGF-beta-induced transformation of fibroblasts to myofibroblasts. The expression of alpha smooth muscle actin was used as a marker for the cell transformation. The expression of the marker was quantified using a real time polymerase chain reaction (PCR) assay. Three different isolates of human primary lung fibroblasts were tested. Nintedanib at 0.4 nM inhibited TGF-beta-mediated transformation of fibroblasts to myofibroblasts. The drug, however, did not block TGF-beta-mediated SMAD2 phosphorylation.

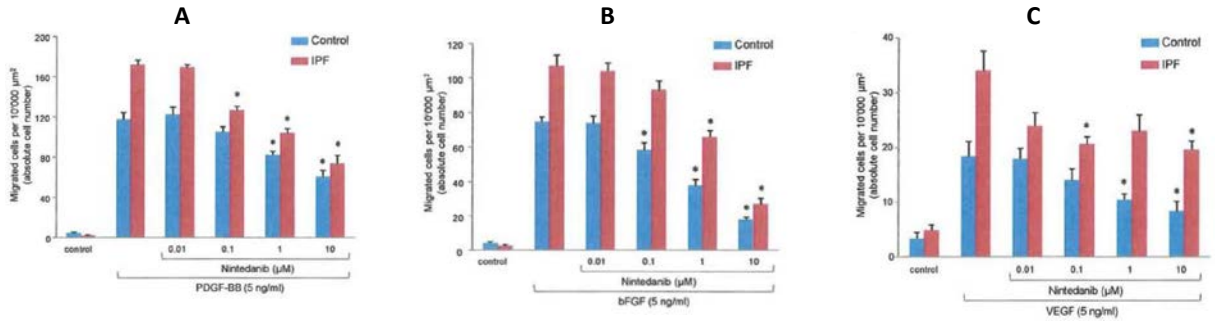


Figure 5: Inhibition of GF-induced fibroblast proliferation by nintedanib.

The GFs were PDGF-BB, bFGF, and VEGF (Panels A, B, and C, respectively).
*, $p < 0.05$ in paired t test.

4.1.2 Pharmacological Effect in Vivo

Nintedanib attenuated lung fibrosis in animal models. Lung fibrosis was induced by intratracheal and intranasal instillations of bleomycin or silica in rats and mice. Nintedanib treatment was initiated on the day of or a period after the dosing of a scorching agent. The severity of lung fibrosis was evaluated microscopically. Concentrations and gene expressions of some inflammatory makers were also evaluated. Results showed that nintedanib treatment decreased the severity of lung fibrosis regardless of the initiation time of nintedanib treatment. Table 15 provides an overview of nintedanib efficacy in animal fibrotic lung models.

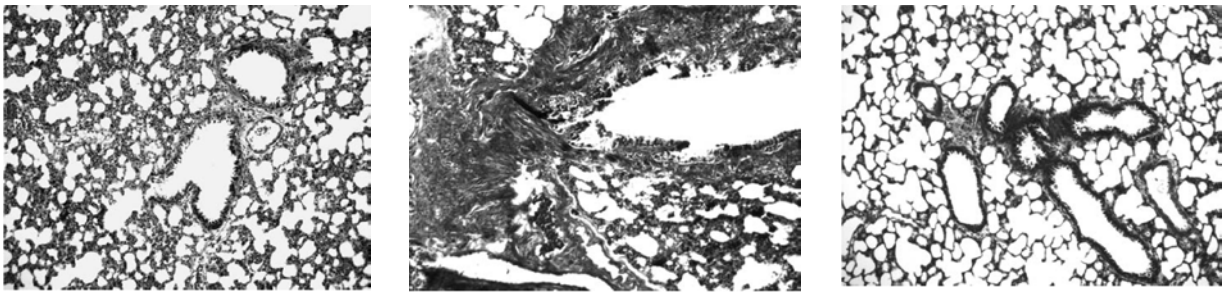
Table 15: Efficacy in Animal Fibrotic Lung Models

Document Number	Species	Scorching agent		Nintedanib treatment		Finding
		Name	mg/kg	mg/kg/day	Days	
06-1451	Rat	Bleomycin	2.2	0, 10, 30, 50	21 [a]	↓ fibrosis scores and expressions of procollagen and TGFβ genes
06-1479	Rat	Bleomycin	2.2	50	11 [b]	Same as the above
12-2066	Mouse	Silica	2.5	0, 30, 100	10 – 20 [c]	↓ fibrosis scores and gene expressions of fibrotic and inflammatory markers
12-2437	Mouse	Bleomycin	3.0	0, 30, 60	14 [d]	Same as the above

a. Nintedanib treatment was started on the day of bleomycin dosing.
b. Nintedanib treatment was started 10 days after bleomycin dosing.
c. Nintedanib treatment was started 10 or 20 days after silica dosing.
d. Nintedanib treatment was started 0 or 7 days after the bleomycin dosing.

Document #U06-1451 studied the ability of nintedanib to prevent bleomycin-induced lung fibrosis in rats. Male Wistar rats (10/dose) were dosed by intra-tracheal instillation of 2.2-mg/kg bleomycin to induce lung fibrosis. The rats were also given 0, 10, 30, or 50-mg/kg oral nintedanib daily for 21 days. The first nintedanib dose was given on the day that the animals were dosed with bleomycin. The vehicle for bleomycin was 0.1% Natrol. Another group received saline to serve as a control for the vehicle. Rats were sacrificed at the end of the nintedanib treatment for efficacy evaluations. Efficacy was evaluated by morphological

changes under microscope and real time PCR analysis for expressions of pro-collagen 1 and TGFb1 genes. Nintedanib prevented lung fibrosis formation. Figure 6 presents microscopic comparisons of lungs in the control and nintedanib treated animals. Only the HD group is shown as an example.

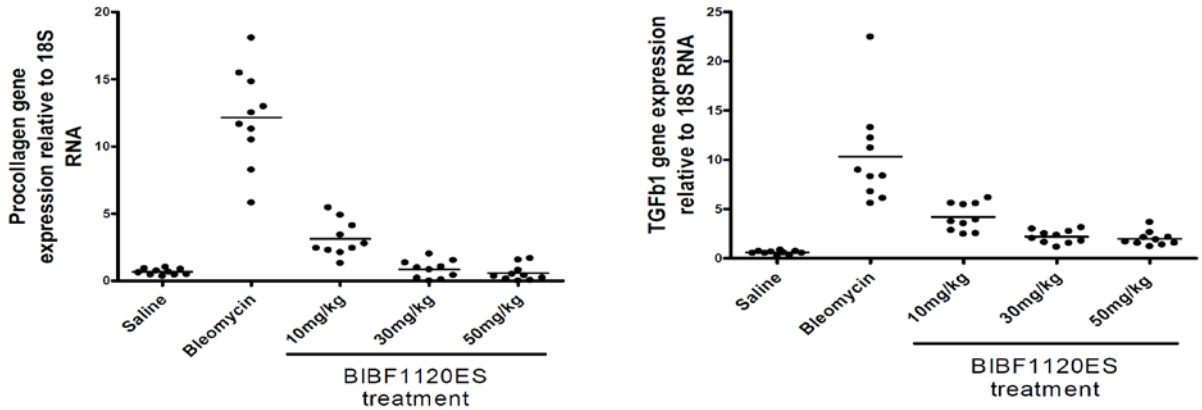


A B C

Figure 6: Effect of nintedanib treatment on lung histology in rats

Treatments in Panels A, B, and C were saline, vehicle, and 50-mg/kg/day nintedanib for 21 days

Figure 7 presents the results of gene expression assays. Nintedanib treatment resulted in dose-related decreases in the expression of both pro-collagen and TGFb1 genes.



A B

Figure 7: Inhibition of bleomycin-induced gene expression by nintedanib.

Document U06-1479 showed that nintedanib attenuated bleomycin-induced lung fibrosis in rats when the treatment is delayed for 10 days. Rats (10/group) were treated with 50-mg/kg/day nintedanib for 11 days after intratracheal instillation of 2.2-mg bleomycin. The nintedanib dose was given 10 days after the bleomycin instillation. The efficacy endpoints were identical to Document #U06-1451. The results were also similar to the previous study.

Document U12-2066 showed that nintedanib attenuated silica-induced lung fibrosis in mice. Mice (BL6, 10/group) were dosed intranasally with 2.5-mg silica to induce lung fibrosis. They were also dosed by oral gavage with 0, 30, or 100-mg/kg/day nintedanib starting on the day of the silica exposure, or days 10 or 20 after the silica exposure. All mice were sacrificed on day 30 post silica instillation. Lungs were lavaged and examined microscopically. BALF was examined for inflammation markers such as IL-1 and IL-6. Results showed that nintedanib decreases lung

histology scores for findings such as granuloma, inflammation, and collagen deposition (Figure 8). The level of some inflammation markers was also decreased.

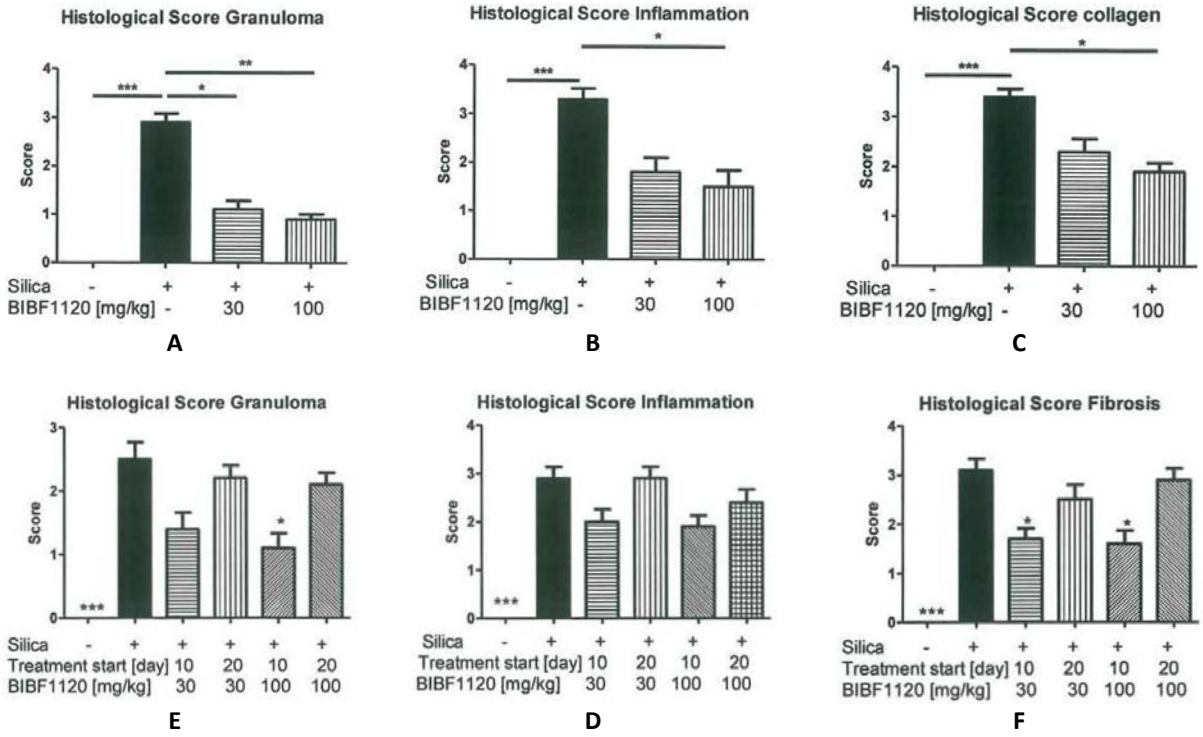


Figure 8: Lung histology scores in a silica-induced pulmonary fibrosis model in mice

Panels A, B, and C: Nintedanib treatment was started on the day of silica dosing.
Panels E, D, and F: Nintedanib treatment was started on days 10 or 20 post silica dosing.

Document U12-2437 showed that nintedanib attenuated bleomycin-induced lung fibrosis in mice. Mice (BL6, 10 Fs/group) were dosed intranasally with 3-mg/kg bleomycin to induce lung fibrosis. They were also dosed by oral gavage with 0, 30, or 60-mg/kg/day nintedanib starting on days 0 or 7 after the bleomycin exposure. Mice were sacrificed after treatment with bleomycin for 14 days. Lungs were lavaged and examined microscopically in a similar manner as Document U12-2066. Results showed that nintedanib at 60-mg/kg/day was effective in reducing lung fibrosis. The time of the nintedanib treatment initiation was not a major factor in the drug efficacy.

4.2 Secondary pharmacodynamic effects

Hilberg et al. (Cancer Res, 2008;68(12):4774-82) summarized the findings related to the effects of nintedanib on tumor cell growth as of 2008. The article included summaries of Document U08-1946. Nintedanib inhibited proliferation of a number of cancer cells induced by FGF, PDGF and VEGF, but not by fetal calf serum (FCS) in vitro (Table 16, next page). The IC_{50s} were approximately 8, 74, and 290 nmol for VEGF, PDGF, and FGF, respectively.

Table 16: Inhibition of GF-Dependent Cell Proliferation in Vitro [a]

Cell lines	Cell type	Growth factor	IC_{50} (nmol/mL)	Report #
HUVEC [a]	Human umbilical vascular epithelial cells	VEGF,	9 ± 13	Hilberg et al
		bFGF	290 ± 160	Hilberg et al
			80 ± 64	U05-1930
		VEGF-2	62	U05-1930
		VEGF-3	14.5	U05-1930
		PDGFα	433	U05-1930
		bFGF	3361 ± 1525	U05-1930
HSMEC	Human microvascular skin endothelial cells	VEGF	7 ± 5	Hilberg et al
BRP	Pericyte	PDGF BB	79 ± 21	Hilberg et al
HUASMC	Human umbilical artery smooth muscle cells	PDFG BB	69 ± 29	Hilberg et al
FaDu/CuLa	Endothelial cancer cells	VEGF1	34 ± 15	U02-1109
		VEGF2	14 ± 4	U02-1109
		VEGF3	46 ± 9	U02-1109
FaDu	Endothelial cancer cells	10% FCS	> 4,500	Hilberg et al
Calu-6	Endothelial cancer cells	10% FCS	> 4,500	Hilberg et al
HeLa	Endothelial cancer cells	10% FCS	> 3,500	Hilberg et al

a. Cell proliferation is measured by the rate of [^{3}H-thymidine] incorporation.

Report U02-1084 determined the non-specific binding of nintedanib to a battery of receptors and ion channels using the CEREP screening package in vitro. Nintedanib at the concentration of 5 μM inhibited binding of the following receptors and channels by their ligands: A3 receptors - ↓ 66%, NK2 receptors - ↓84%, $5HT_{IB}$ receptors - ↓ 102%, and Ca^{++} channels (L-site) - ↓ 65%.

Document U06-2006 showed that nintedanib at 0.1 μM did not bind to 5-HT1B receptor, but the finding was not considered of importance because the study used a lower nintedanib concentration.

4.3 Safety Pharmacology

Nintedanib had no significant effects on safety pharmacology parameters. Safety pharmacology studies were conducted to evaluate the effects of nintedanib on the central nervous system (CNS), cardiovascular system (CVS), respiratory system (RS), gastrointestinal tract (GI), liver, kidney, and locomotor activity. Table 17 summarizes the safety pharmacology studies submitted in the NDA package. The core battery of the safety pharmacology tests, which were GLP-compliant, evaluated the effect of the drug on behavior in the Irwin test in rats (U03-1537), on respiratory patterns in rats (U03-1645), and on the cardiovascular system in monkeys (U02-1326). Nintedanib was administered by oral administration. The core battery of studies revealed no remarkable findings.

Table 17: Pivotal Safety Pharmacology Studies

Species	System	Nintedanib [a] (mg/kg/day)	Observation	Document #
-	hERG	0.1 – 10 μM	IC_{50} = 4.0 μM in HEK293 cells	U02-1288
Mouse	CNS [b]	0, 50, 100, 300 [c]	No effects in Irwin behavioral test	U02-1587
Mouse	CNS	0, 50, 100, 300 [c]	No effects on nocturnal motility	U02-1589
Rat	CNS	0, 3, 20, 100	No effects in modified Irwin behavioral test	U03-1537
Rat	RS	0, 3, 20, 100	No effects on respiratory parameters	U03-1465
Rat	CVS/RS	0, 10, 30, 100 [c]	Increased arterial blood pressure and respiratory rate at 100 mg/kg	U02-1398
Rat	GI	10, 30, 100 [c]	Dose-dependent inhibition of GI motility and gastric emptying time	U02-1259
Rat	Liver	30, 100, 300	Slight increase in ALT, GLDH, triglycerides, Ca^{++} at 300 mg/kg	U04-1416
Rat	Renal, liver	10, 30, 100	Modest increase (1.3 – 2.3 x) in GPT and beta-NAG (beta-N-acetyl-glucosaminidase)	U02-1260
Pig	CVS	0, 3, 10, 30 (IV) [c]	Dose-related increases in heart rate and systolic and diastolic pressures	U02-1674
Money [d]	CVS	0, 3, 15, 60	No significant effects on cardiovascular parameters	U03-1326

a. Oral route of administration unless specified.
b. CNS, CVS, GI, and RS stand for the central nervous system, cardiovascular system, gastrointestinal tract, and respiratory system, respectively.
c. Nintedanib chloride (BIBF 1120 CL) was the testing material.
d. A 4-week oral toxicity study.

Other non-GLP-compliant studies evaluated the effect of nintedanib on body temperature and locomotion in mice, renal and hepatic functions and gastrointestinal function in rats, and cardiovascular system in pigs. Nintedanib did not affect body temperature or locomotor activity in mice. Rats showed dose-dependent and modest changes in renal and hepatic functions. Also, gastric emptying and gastrointestinal transit were inhibited at the highest dose tested in rats. The hERG assay showed an IC_{50} of 4.0 μM, but there was no effect on repolarization action potential.

5 Pharmacokinetics and Toxicokinetics

Pharmacokinetics and toxicokinetics of nintedanib were studied in mice, rats, and monkeys after single-dose or repeat-dose administration via the intravenous injection, oral gavage, and in-situ infusion routes. The studies evaluated the absorption, distribution, metabolism and elimination of the drug. Results showed that nintedanib was bioavailable after oral administration in animals, but its bioavailability was low. The nintedanib metabolic profiles were similar between animals and humans. The drug did not accumulate in animals.

5.1 PK/ADME

Nintedanib is absorbed after oral administration, but its bioavailability is low: approximately 12%, 24%, and 4.7% in rats, monkeys, and humans, respectively. Nintedanib had half-lives of about 4 – 7 hours in animals and 12-17 hours in humans. The drug is metabolized in the liver and excreted mainly through feces. Approximately 80% of intravenously administered drug is

excreted into feces in rats, monkeys, and humans. Table 18 summarizes key pharmacokinetic parameters of nintedanib in animals and humans.

Table 18: Pharmacokinetic Parameters [a]

Report [b]	U09-1975	U02-1381		U04-1067		U05-2452		U10-1400	
				Monkey					
Species	**Mouse**	**Rat**		**Cynomolgus**		**Rhesus**		**Human**	
Route of administration	oral	oral	IV	oral	IV	oral	IV	oral	IV
Nintedanib (mg/kg)	50	50	2	40	5	40	5	1.29	0.078
Cmax (ng/mL)	547	105	124	175	1300	311	1090	8.43	12.3
t ½ (h)	5.15	- [c]	3.95	-	5.95	-	7.09	11.7	17.9
AUC (ng.h/mL)	2720	375	181	2390	2260	4440	2830	56.2	71.9
Clearance (mL/(min.kg)	-	-	202	-	37.5	-	30.2	-	18.0
MRT (h)	5.19	-	3.25	-	3.82	-	5.70	13.9	12.6
Vss (L/kg)	-	-	41.2	-	8.64	-	10.4	-	13.6
Bioavailability (%)	-	11.9	-	13.2	-	23.8	-	4.7	-
Protein binding (in vitro, %) [d]	97.2	98.5	-	92.9	-	91.4	-	97.8	-

a. Extracted from Section 2.6.4 (Table 1:1, p 7).
b. From eCTD Section 2.6.5 Pharmacokinetics Tabulated Summary (p47).
c. -, Not determined not or Not applicable.
d. Extracted from Table 4:1.1 (p17) of eCTD Section 2.6.4.

5.1.1 Absorption

The pharmacokinetic profile of nintedanib after a single-dose administration was studied in mice (U09-1975 & U09-2277), rats (U02-1381 & U10-2910), and monkeys (U04-1067 & U05-2452). Table 18 summarizes the important pharmacokinetic parameters of nintedanib in different species. The drug had half-lives of about 4 – 7 hours in animals and more than 12 - 17 hours in humans. Its volume of distribution at steady state (V_{ss}) was approximately 41, 9, and 14 L/kg in rats, monkeys, and humans, respectively. The clearance was approximately 200, 35, and 20 L/(min.kg) in rats, monkeys, and humans, respectively. The bioavailability was approximately 12.0%, 18%, and 5% in rats, monkeys, and humans, respectively. The $AUC_{0\text{-}24h}$ and C_{max} generally increased in a dose-proportional manner in all species.

Nintedanib was absorbed via non-transport mechanisms. Nintedanib absorption was studied by assessing membrane permeability in vitro and the absorption in *in situ* perfused rat intestine. The bio-membrane permeability of nintedanib was investigated in cells expressing P-gp, MRP2, or BCRP [U05-3076] and in rat and human hepatocytes [U05-1001]. Upon incubation with suspended hepatocytes, the concentration of $^{[14C]}$nintedanib in the tissue culture medium declined at a very high rate. At the earliest possible sampling time (2 min), 55% - 99% of the radioactivity was found in the cell fraction. This rapid uptake suggests little involvement of drug transporters. Further, BIBF 1120 was a substrate of P-gp while BIBF 1202 was not.

In the *in situ* perfusion study, isolated intestinal loops of male Wistar rats were perfused with $^{[14C]}$nintedanib (0.23 - 0.27 µmol) in the absence or presence of Zosuquidar (0.3 mmol/L), a P-gp-inhibitor that blocked the biliary excretion of nintedanib (U10-2910). Blood drug concentration was determined in both conditions. Approximately 8.6% and 18.2% of the

administered dose was absorbed into the blood in the absence and presence of zosuquidar, respectively. Similar results were observed in rats (50 mg/kg) that were pre-treated with 2.6 mg/kg zosuquidar (U11-1619). Rats pre-treated with zosuquidar showed 1.5 – 2.3 fold increases in plasma drug (and metabolites) AUCs.

5.1.2 Distribution

Nintedanib was extensively distributed into tissues. The volumes of distribution were high in all investigated species (V_{ss} > 8 L/kg, Table 18). Tissue distribution of nintedanib was also studied by whole body autoradiography after intravenous and oral administrations of radiolabeled-nintedanib in rats (U03-1563). Male rats were dosed with 5 (IV) or 30-mg/kg (PO) nintedanib. Tissue drug (radioactivity) levels were determined at various time points post dosing: 5 minutes (IV only), 0.5 (PO only), and 1, 8, 48, and 168 hours. After intravenous administration, most of the tissues took up radioactivity very rapidly. Tissue drug levels were well above blood levels as early as 5 minutes after administration. After oral administration, the concentration of radioactivity in most tissues followed a time course with maximum concentrations 8-h post dose. Significant radioactivity was still present in the salivary gland, liver, spleen, and thymus at 48 hours post doing. Figure 9 is a whole body autoradiogram of a rat receiving oral nintedanib treatment. In contrast, radioactivity showed an early peak in blood (0.5 h post dose) and in liver (2 h post dose). Little radioactivity was found in the CNS tissues. Although the elimination was complete by 168 hours post dosing, results suggested a long residual time for nintedanib in rats.

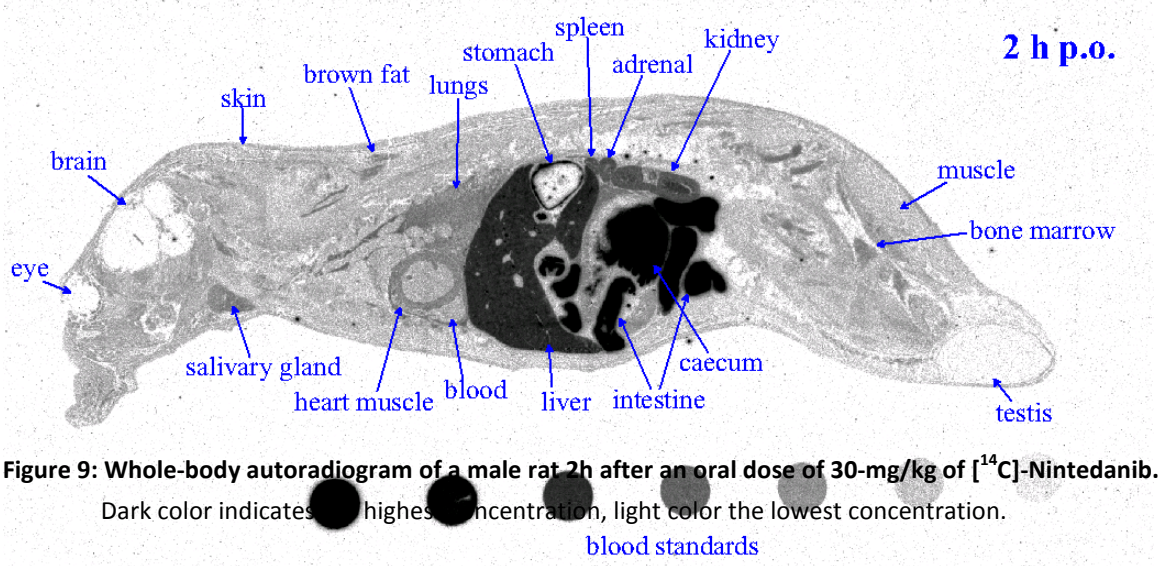


Figure 9: Whole-body autoradiogram of a male rat 2h after an oral dose of 30-mg/kg of [^{14}C]-Nintedanib.

Dark color indicates highest concentration, light color the lowest concentration.

The long residual time of nintedanib in rats prompted evaluations of tissue distribution of the drug after repeat-dose administration (U09-1527). Male rats were dosed with 30-mg/kg/day ^{14}C-nintedanib for 13 days. Tissue radioactivity was determined at various time points (1 – 14 days) post treatment. Table 19 (next page) summarizes the results. Statistically significant increases in tissue drug concentrations were observed in the following organs: brain and heart. The reason for the increases is unknown.

Table 19: Tissue Drug Concentration at 30-mg/kg/day for 13 days in Male Rats

Sample	24 h (Day 2)	144 h (Day 7)	168 h (Day 9)	240 h (Day 11)	312 h (Day 14)	Accu-mulation factor*
	ng-eg/g					
Liver	1090	1740	2320	3110	3650	3.3
Brain	18.7	19.6	34	44.9	NC	2.4**
Lymph node	1040	1230	NC	2270	2350	2.3
Epididymis	162	271	381	359	521	3.2
Heart	52.2	76.8	115	133	NC	2.5**
Kidneys	560	756	976	1070	1150	2.1
Lungs	239	316	488	459	704	2.9
Pancreas	194	180	289	246	368	1.9
Spleen	522	795	1200	1160	1320	2.5
PLASMA	12.4	11.7	10.3	18.5	18.9	1.5
BLOOD	22.4	31.4	23.7	34	24.9	1.1
Submandibular gland	1350	3030	4690	2940	5690	4.2
Bone marrow	299	432	471	589	613	2.1
Testes	60.8	162	248	339	479	7.9
Adrenal glands	408	336	362	477	494	1.2
Skin	102	142	133	174	166	1.6
Brown Fat	211	241	475	405	304	1.4
Fat	NC	68.3	NC	NC	67.1	-
Muscle	42.6	50.7	57.2	55.5	52.7	1.2
Pituitary	4480	7290	NC	8020	9150	2.0
Thyroid	733	1180	1390	726	1180	1.6
Thymus	277	388	NC	527	607	2.2

Nintedanib was secreted into the milk in rats [U12-1855]. Nursing rats were dosed orally with 30-mg/kg radio-labelled nintedanib on day 12 of lactation. The concentrations of total radioactivity in plasma and in the milk of the dams were measured at 1, 6, and 24 hours post dosing. Figure 10 (below) presents the time-course of the concentration of total nintedanib-related compounds in the plasma and milk. The respective drug concentration at 1, 6, and 24 hours post dosing was 269, 1060, and 106 ng/mL in the milk and 2260, 478, and 7.92 ng/mL in the plasma. The mean $AUC_{0\text{-}24}$ was 12,400 and 14,000 ng.h/mL in the plasma and milk, respectively. The $t_{½}$ was approximately 5.5 and 3.3 hours in the milk and plasma, respectively. It was estimated that 0.18 - 0.5% of administered dose was secreted into milk within a period of 24 hours (36 mL milk).

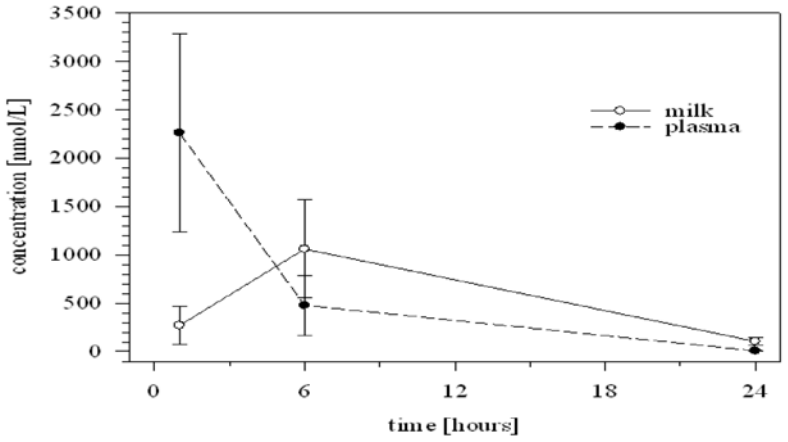


Figure 10: Concentration-time course of Nintedanib-related compounds in plasma and milk in lactating rats

Protein binding: The binding of nintedanib and its metabolites to plasma protein was determined in mouse, rat, monkey, and human plasma *in vitro* (U03-1150, U09-1949, U08-2181, and U08-1952). Table 20 summarizes the results. The protein binding was the highest for BIBF 1120 (92.9% - 97.8%) and lowest for BIBF -1202 (55% - 77.8%). BIBF 1202-Glu ranked in between (84.0% - 97%). Albumin was the major binding protein. Report U03-1150 also found that BIBF 1120 was found to be unstable in plasma of rats and mice, but the degradation can be stopped by paraoxon, a cholinesterase inhibitor.

Table 20: Plasma Binding (%) of Nintedanib and its Metabolites [a]

Species	Rat	Mouse	Monkey		Human
			Cynomolgus	Rhesus	
BIBF 1120	95.8	97.2	92.9	91.4	97.8
BIBF 1202	77.2	ND [b]	ND	55.0	77.8
BIBF 1202-Glu	96	ND	ND	84.0	97.0

a. Source: Table 4:1.1 of eCTD Section 2.6.4 (p 17).
b. ND, not determined.

5.1.3 Metabolism

Nintedanib metabolism was studied in vitro and in vivo. The in vitro studies used liver microsomes (human only) and hepatocytes from rats and humans. In vivo studies (e.g., subchronic and chronic toxicity studies) measured plasma levels of major metabolites in rats and monkeys. Figure 11 is a schematic presentation of BIBF 1120 pathways. BIBF 1202 is a major metabolite of nintedanib in animals and humans. Hydrolysis and desmethylation of nintedanib resulted in formation of BIBF 1202. Esterase and CYP 3A4 are responsible for hydrolysis and desmethylation of nintedanib. BIBF 1202 is further conjugated with glucoronide to form BIBF 1202-Glu. The latter is conjugated with glucuronidate to form BIBF 1202-Glu.

The in vitro metabolism studies showed that esterase and CYP 3A4 hydrolyzed and desmethylated nintedanib to form BIBF 1202 (U03-1355). The BIBF 1202 was then glucoronidated to form BIBF 1202-glucuronide. The glucuronidation rate was high in the rat, intermediate in humans, and low in dogs [U02-1649]. Freshly prepared rat and human hepatocytes took up BIBF 1120 rapidly (U05-1001). Both rat and human intestine tissue can metabolize nintedanib to form BIBF 1202-Glu [U08-1144 and U10-2910].

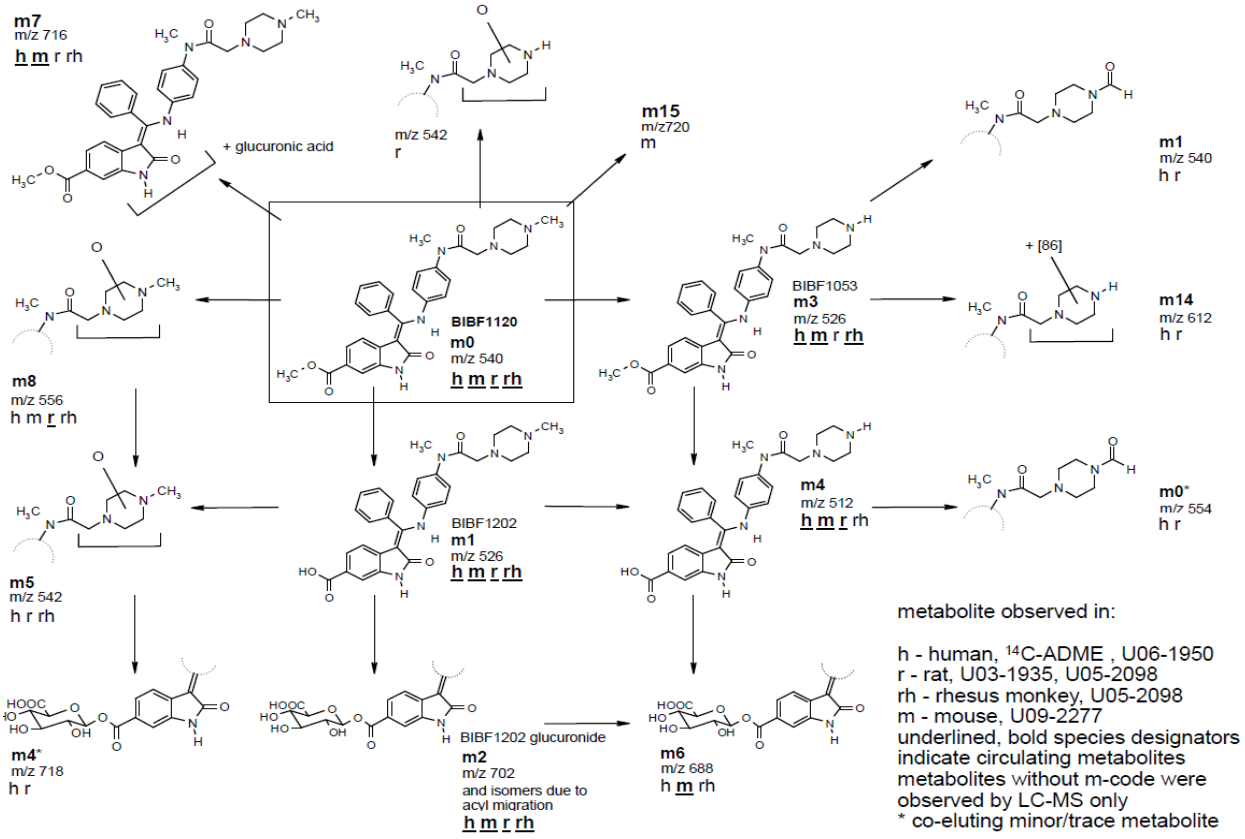


Figure 11: Hypothesized metabolic pathways

In vivo studies evaluated the metabolic profile of nintedanib after single oral and intravenous doses of $^{14\text{-}C}$nintedanib in mice (U09-2277), rats (U03-1935 & U06-2240), and monkeys (U06-2098). Table 21 (below) summarizes the plasma levels of nintedanib and its major metabolites in animals and humans. All major metabolites of nintedanib in humans were detected in animals.

Table 21: Nintedanib and Its Metabolite Levels in Animal and Human Plasma (% of Radioactivity) [a]

Species	Mouse				Rat				Rhesus monkey				Human		
Dose	30 mg/kg				5 mg/kg		30 mg/kg		5 mg/kg		20 mg/kg		100 mg/subject		
Route/sex	oral/male		oral/female		intravenous/m&f		oral/m&f		intravenous/m&f		oral/m&f		oral/male		
Sampling time	1h	4h	1h	4h	0.25h	4h	1h	4h	1h	6h	3h	8h	1h	2h	6h
m0 (BIBF 1120)	20.6	x	31.4	39.6	47.76	25.14	0.92	9.03	86.99	87.29	35.76	58.64	9.8	34.5	27.1
m1 (BIBF 1202)	x		x	19.4	38.58	26.74	2.93	9.65	12.1	10.24		x	32.5	38.7	25.7
m2 (BIBF 1202 glucuronide)	31.4		25.6	24.4	13.65	48.1	93	76.93	1.79	4.94	55.1	38.11	28.3	15.3	47.1
m3 (BIBF 1053)	14.3		x	x							7.6				
m4	x		x				3.18	4.36							
m7													9.2	11.6	0
m13											10.61				
total	66.3	x	57.0	83.4	99.99	99.98	100.03	99.97	100.88	102.47	109.07	96.75	79.8	100	100

a. Source: Table 10:2 of Section 2.6.4 Pharmacokinetics Written Summary (p 35); Empty space, not detected; X: trace amount.

Nintedanib also has a number of minor metabolites in animals and humans. Table 22 (next page) shows the minor metabolite levels in excreta of monkeys and humans after single dose of nintedanib. The excreta level was used because the level of these compounds in the blood was

too low to be measured. Monkeys and humans showed very similar metabolic patterns regarding the minor metabolites. Only two (M13 and M14) of the 10 minor metabolites were not detected in monkeys.

Table 22: Minor Metabolites Excreted in Urine, Feces, and Bile in Monkeys and Humans

	Percentage (%) of Orally Administered Dose [a]			
Species	**Rhesus monkey**		**Human**	
Matrix	**Urine (0-24h)**	**Feces (0-72h)**	**Urine (0-24h)**	**Feces (0-72h)**
M4	0.02	3.82	0.01	2.60
M5	0.01	2.49	0.004	0.20
M6	0.02	- [b]	0.05	-
M7	0.02	-	0.03	-
M8	0.05	-	0.01	-
M9	0.01	1.5	0.02	-
M10	0.02	-	0.04	-
M11	0.01	-	-	-
M13	-	-	0.50	-
M14	-	0.93	0.14	-

a. Extracted Table 10.1 (p 34) of Section 2.6.4 Pharmacokinetics Written Summary of the NDA submission. Nintedanib dose was 20 mg/kg and 100 mg/subject in monkeys and humans, respectively.
b. -, not detected.

M7 was not considered a major nintedanib metabolite. Data in Table 21 apparently suggest that M7 may also be a major metabolite in humans. Approximately 10% of radioactivity was detected at 1 and 2 hours post administration in humans, respectively, but none was detected in the animals. However, Table 22 shows that M7 accounted for only a very small portion of the metabolites in both animals and humans. Specifically, only approximately 0.02% - 0.03% of orally administered dose was discovered in the urine in monkeys and humans, respectively.

5.1.4 Elimination

Nintedanib was eliminated primarily through feces. Nintedanib elimination was studied after single oral and intravenous doses of $^{14\text{-}C}$nintedanib in mice, rats, and monkeys. Table 23 shows the amount of nintedanib-related radioactivity recovered in feces, urine, and bile in animals and humans. After oral administration, >90%, 67%, 88%, and 85% of the administered dose was recovered in feces in mice, rats, monkeys, and humans, respectively. Only 2% or less was recovered in the urine of any species.

Table 23: Excretion of Nintedanib and its Metabolites in Animals and Humans [a]

Species	**Report #**	**Sex**	**ROA**	**Nintedanib (mg/kg)**	**% of Administered dose**		
					Urine	**Feces**	**Bile**
Mouse	U09-2277	M	PO	30	1.9	99.3	9.1
		F	PO	30	0.8	90.7	19.5
Rat	U02-1494	M/F	IV	5.0	4.0	77.9	61.0
		M/F	PO	30	1.6	67.0	10.0
Monkey	U05-1558	M/F	IV	5.0	4.1	78.6	NE [b]
		M/F	PO	20	1.2	87.7	NE
Human	U-06-1274	M	PO	1.7 [c]	0.2	84.8	NE

a. Extracted from Table 10.1 (p 34) of Section 2.6.4 Pharmacokinetics Written Summary of the NDA submission.
b. NE, Not examined.

c. Derived from 60-kg subject taking a 100-mg nintedanib tablet.

Fecal excretion is also the major route of elimination after intravenous administration. About 78% of the administered dose was found in the feces in rats and monkeys. Approximately 4% of the radioactivity was recovered in the urine in both species. The amount of the drug recovered in the urine after IV administration was approximately 3 times the oral administration, but the urinary excretion remained a fraction of the fecal excretion.

The bile is the predominant route of elimination once the drug is absorbed. In biliary duct cannulated and anesthetized rats, 65.2% of the intravenously administered dose was recovered in the bile within 6 hours post dosing. After intra-duodenal dosing, the recovery in bile was lower with 8.3 - 15.4% in rats and 10.1 - 20.2% in mice.

5.2 Toxicokinetics

There was no significant accumulation of nintedanib or its metabolites in animals. Plasma drug levels were measured in chronic toxicity studies for up to 12 months in animals. Table 24 summarizes nintedanib AUC values in pivotal chronic toxicity studies in mice (from carcinogenicity study), rats, and monkeys. The duration of treatment was 6, 6, and 12 months in mice, rats, and monkeys, respectively. There were no apparent increases in AUC values in any of the species.

Table 24: Toxicokinetics in Animals

Nintedanib (mg/kg/day, PO)			Plasma Nintedanib AUC (ng.h/mL)							
			5	10	15	20	30 [a]	45 [a]	60 [a]	80
Mouse [b]	Day 1	M	54.3	-	560	-	1280	-	-	-
(DDB0006)		F	104	-	656	-	1590	-	-	-
	Week 26	M	41.5	-	313	-	1090	-	-	-
		F	38.8	-	368	-	1580	-	-	-
Rat	Day 1	M	13.7	-	-	154	-	-	-	1280
U05-1543		F	24.6	-	-	232	-	-	-	2430
	Day 179	M	16.4	-	-	184	-	-	-	1980
		F	29.2	-	-	316	-	-	-	3000
Monkey	Day 1	M	-	979	-	1150	-	-	5971	-
(Rhesus)		F	-	595	-	1730	-	-	6250	-
U10-1875	Day 91	M	-	809	-	1370	-	2270	-	-
		F	-	610	-	1110	-	2710	-	-
	Day 189	M	-	765	-	989	1440	-	-	-
		F	-	479	-	1370	1870	-	-	-
	Day 365	M	-	787	-	831	1100	-	-	-
		F	-	506	-	1220	1600	-	-	-

a. The dose levels in the HD group at difference times in the monkey study. The actual BIBF 1120 dose levels in the group were 60, 0 (dosing holiday), 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-29, and 30-55, respectively. Data was extracted from the nonclinical review completed by Dr. Luqi Pei on May 10, 2011 (Reference ID# 2,944,664).

b. A 2-year oral carcinogenicity study in mice. Data were taken from the nonclinical review completed by Dr. Carol Galvis on August 22, 2014 in NDA 205-832 (DARRTS Reference ID# 3,614,801).

c. -, Not applicable.

6 General Toxicology

Pivotal general toxicity studies of nintedanib have been reviewed previously by the Agency staff. See nonclinical reviews completed by Dr. Shwu-luan Lee on September 27, and 30, 2014 (DARRTS ID# 2,841,259 and 2,841,263, respectively), in IND (b) (4) and by Dr. Luqi Pei on May 10, 2010 (DARRTS IND# 2,944,664) in IND 74,683. Also see Sections 1.2 Brief Discussions of Nonclinical Findings and 11.3 Toxicity Summary for brief descriptions of the study findings.

7 Genetic Toxicology

Nintedanib tested negative in the following genetic toxicity assays: a bacterial gene mutation assay in vitro, a mammalian cell chromosomal aberration assay in mouse lymphoma cells in vitro, and in vivo micronucleus test in rats. See a nonclinical review completed by Dr. Shwu-luan Lee on September 27, 2014 in IND (b) (4) (DARRTS ID# 2,841,259) for review and evaluations of the genetic toxicity study reports.

8 Carcinogenicity

Carcinogenicity potential of nintedanib was evaluated in 2-year oral carcinogenicity studies in rats and mice (Report # DDBs 007 and 006, respectively). Each study consisted of a vehicle control group (C) and three treatment groups (i.e., LD, MD, and HD, respectively). The respective nintedanib dose in the C, LD, MD, and HD groups was 0, 2.5, 5.0, and 10 mg/kg/day in rats and 0, 5, 15, and 30 mg/kg/day in mice. There were 60 and 66 animals/sex/dose in rat and mouse studies, respectively. Dr. Carol Galvis completed the review and evaluations of the final reports of the studies on August 22, 2014 (DARRTS ID# 3,614,801). Ms. Feng Zhou completed statistical analyses of the tumorigenicity datasets on July 17, 2014 (DARRTS ID# 3,594,497). The Center's Executive Carcinogenicity Assessment Committee (ECAC) reviewed the reports on July 15, 2014 (DARRTS ID# 3,593,740). The ECAC and Dr. Galvis concluded that the 2-year rodent studies in rats and mice revealed no evidence of carcinogenicity for nintedanib under the conditions tested. See the above references for detailed reviews and evaluations of the rodent carcinogenicity study reports.

9 Reproductive and Developmental Toxicology

The reproductive and developmental toxicity of nintedanib was studied in rats and rabbits. The studies evaluated the effect of nintedanib on fertility in male and female rats (U10-1128 and U13-2650, respectively), on embryofetal development in rats and rabbits (U13-1923 and U13-1937, respectively), and on peri- and post-natal development in rats (U13-2641). This review evaluates Doc. #U13-2550 (female fertility study) only because the remaining documents have been reviewed elsewhere. See the following 2 nonclinical reviews for detailed evaluations of the remaining studies: one completed by Dr. Luqi Pei on May 10, 2010, in IND 74,683 (DARRTS ID# 2,944,664) evaluated Doc. #U10-1128 (male fertility study); the other completed by Dr.

Grace Lee on August 22, 2014, in NDA 205-832 (DARRTS ID# 3,615,202) evaluated the teratology and peri-/post-natal development effects (i.e., U13-1923, U13-1937 and U13-2641).

9.1 Fertility Studies

Study title: **BIBF 1120 ES: Study of Female Fertility and Early Embryonic Development to Implantation in Rats by Oral (gavage) Administration**

Study no.:	Legacy Doc. # U13-2650, Document # n002231235, Study# 12B057
Study report location:	Section 4.2.3.5.1 of eCTD
Conducting laboratory and location:	Boehringer Ingelheim (Nonclinical Drug Safety Germany), Birkendorfer straβe. 65, 88397 Biberach/Riss, Germany
Date of study initiation:	July 9, 2012 (start of nintedanib treatment)
GLP compliance:	Yes, statement signed on March 5, 2013
QA statement:	Yes, statement signed on March 5, 2013
Drug, lot #, and % purity:	BIBF 1120 ES, Batch# 1045986, purity 98.6%

Key Study Findings

- Nintedanib at an oral dose of 100 mg/kg/day decreased the number of liver fetuses ($P < 0.0001$) and increased the number of resorptions ($P < 0.0001$) in female rats. Thirteen of 24 rats receiving 100-mg/kg/day nintedanib were either non-pregnant or had no live fetuses. This group of rats also showed statistically non-significant decreases in fertility index (↓16.6%) and gestation index (↓37.8%).
- Nintedanib at an oral dose of 20 mg/kg/day increased the number of resorptions ($P < 0.05$) in rats.
- Nintedanib at an oral dose of 3 mg/kg/day did affect any female fertility parameters in rats.
- The 100-mg/kg/day group had a mean nintedanib AUC_{0-24} at the steady state (GD 7) of 997 ng.h/mL.
- Overall, nintedanib at the 100-mg/kg/day dose decreased fertility in female rats. This interpretation agrees with the study report but differed from that of BI (b) (4) See Sections 11.6 and 12.8 for additional information.

Study Design: Female Wistar rats (24/dose) were dosed by oral gavage with 0, 5, 20, or 100 mg/kg/day of nintedanib.[6] An additional 6 rats were used as back-ups and for toxicokinetic studies. Nintedanib treatment started 15 days prior to mating and ended 7 days after mating.

[6] Nintedanib dose selection was based on 2 dose-ranging studies in which rats were dosed with up to 180 mg/kg/day of the drug. Complete resorptions were observed at ≥ 20 mg/kg/day and malformations (e.g., vertebral bodies and great vessels) were observed at 10 mg/kg/day.

The rats were sacrificed on gestation days 14 - 16 for the examinations of uterine content and ovulation parameters. Treated female rats mated with untreated males (1:1 ratio) and the mating period was up to 14 days. Nintedanib dose selection was based on 2 dose-ranging studies in which rats were dosed with up to 180 mg/kg/day of the drug. Complete resorptions were observed at ≥20 mg/kg/day and malformations (e.g., vertebral bodies and great vessels) were observed at 10 mg/kg/day.

Methods

Doses:	0, 3, 20, and 100 mg/kg/day nintedanib (free base), or 3.61, 24.1, and 120.4 mg/kg/day nintedanib esilate
Dosing frequency:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	(b) (0.5% hydroxyethylcelluose)
Formulation stability:	Formulation was stable (± 10% target concentration). One sample (Group 2 on July 9, 2012) showed a higher concentration (20.4% of the target concentration), but the variation did not appear to affect the interpretability of the study results.
Species/Strain:	Crl:WI(Han) SPF quality
Number/Sex/Group:	24 females/dose; also included 24 untreated males/dose
Age:	M: ~ 6 weeks; F: ~ 9 weeks
Weight:	Males 218 -285 g, females 119 – 144 g
Food and water restriction:	None
Unique study design:	Only the females were treated with nintedanib during the study. Nintedanib treatment started from 15 days before mating, during mating, and continued until gestation day 7. The males were not treated. Each male co-habited with one female during the mating period. Uteri, ovaries, and mammary glands were examined microscopically. The pituitary gland was examined in males and females when cohabitation did not result in pregnancy in the female. Also examined were the reproductive organs in males whose partner did not become pregnant.
Deviation from study protocol:	No significant deviations occurred.

Observations and Results

Mortality: Mortality was observed once (weekends) or twice (weekdays) daily. No treatment-related effects were observed.

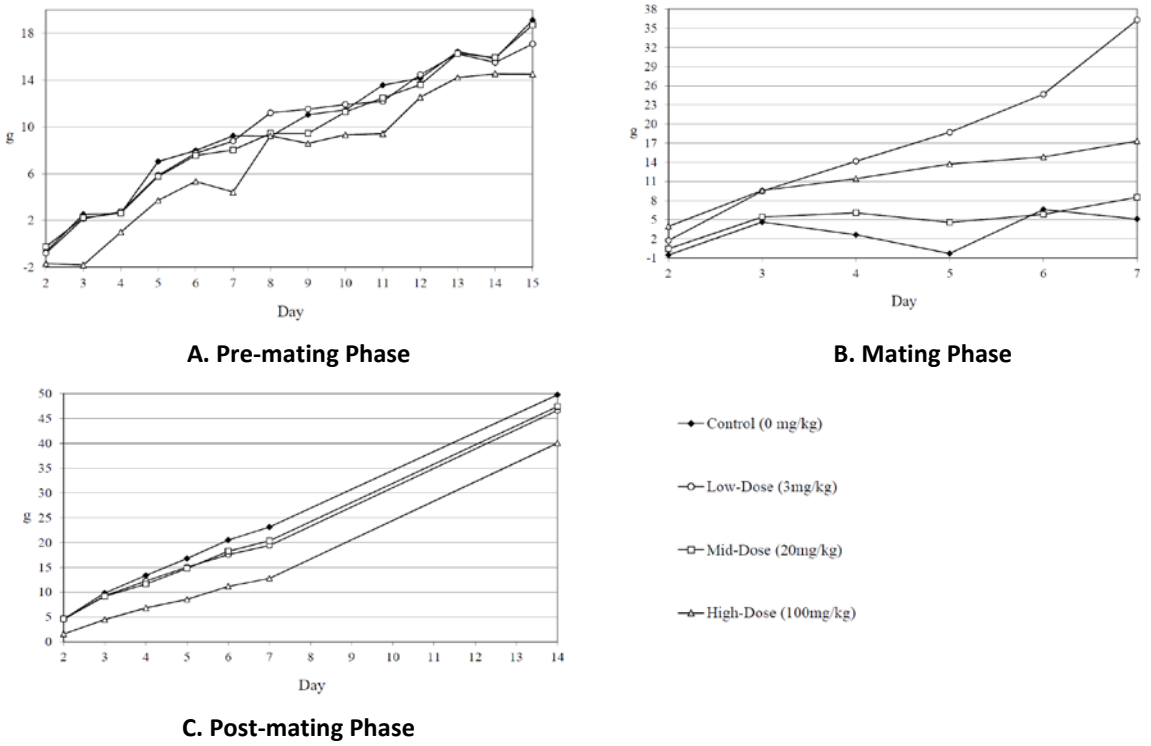
Clinical Signs: Clinical signs were observed at least once daily. No treatment-related effects were observed.

Body Weights: Body weights were measured daily. No significant effects on absolute body weight were observed. There was a dose-dependent reduction (approximately up to 3.4%) in body weight (Table 25, page 50), but the reduction did not reach statistical significance. Figure 3 showed body weight gains through the study. No constant trends were apparent over the entire study.

Food Consumption: Food consumption was measured weekly. There was a dose-dependent reduction (< 6.9%) in food consumption (Table 25), but the reduction did not reach statistical significance.

Estrus cycles: The report stated that vaginal smears were taken daily from 8 days before to 8 days after the start of drug administration. No treatment-related effects were observed based on the summary data. The estrus cycle was approximately 14 days in length in all groups. There was no line listing data of individual animals, but this deficiency does not appear to affect the overall interpretation of the study results.

Copulation: Successful copulation was determined by the presence of sperm in vaginal smears. Smears were prepared daily from the start of cohabitation between males and females. The high dose group showed a slight delay in copulation (Figure 13, below), but the delay did not achieve statistical significance.



A. Pre-mating Phase

B. Mating Phase

C. Post-mating Phase

Figure 12: Body weight gains in the female fertility study

Fertility: The gestation index was decreased (↓38.8% - 42.2%), and post-implantation loss was increased (↑41%, Table 25). Five (of 24) HD females failed to become pregnant; these rats showed positive sperm smear results, but showed no corpora lutea.[7] An additional 8 HD

[7] Rats No. 407, 410, 417, 425, and 428.

females failed to produce any fetuses because of early resorptions. Only 11 (of 24) females showed fetuses at the necropsy. These females with litters showed a statistically significant decrease in the mean number of live fetuses ($P < 0.0001$) and increases in mean resorptions ($P < 0.0001$) and post-implantation loss ($P < 0.0001$).

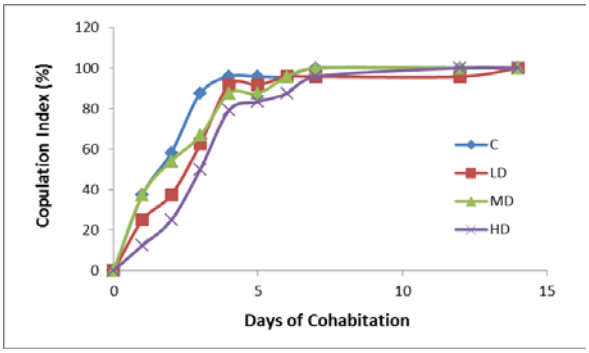


Figure 13: Cumulative copulation index as a function of time in female rats.

The figure was constructed using data in Table 3.4.3:2 (page 31) of the study report

Table 25: Summary findings of the Female Fertility Study in Rats

Nintedanib (mg/kg/day)	**0**	**3**	**20**	**100**
Maternal Data				
No. died or sacrificed	0	0	0	0
Body weight (%)	243.1 g	0.37	-0.49	-3.36
Food consumption (%)	118.6 g	1.91	-1.59	-6.86
# Females sperm-positive	24	24	24	24
# Pregnant females	23	24	23	19
Copulation index (%)	100	100	100	100
Fertility index (%)	95.8	100	95.8	79.2
Gestation index (%)	95.8	100	100	57.9
Sperm found but resorption only [a]	1	0	1	5
# Total resorption of litter	1	0	0	8*
Litter data [c]				
# of litters examined	22	24	23	11
# Corpora lutea (mean)	13.3	13.5	15.0*	12.3
# implantation (mean)	12.1	12.2	13.3	11.5
# of pre-implantation loss (mean)	8.91	10.2	10.0	4.78
# Live fetus (mean)	11.4	11.4	11.3	6.2***
# Resorption (mean)	0.68	0.75	1.91*	5.36***
Resorption (mean)	0.68	0.75	1.91*	5.36***
Late resorption	0	0	0	0
# Dead fetus (mean)	0	0	0	0
Post-implantation loss (%, mean)	5.71	7.62	13.45	46.78***

*, $p < 0.05$; ***, $P < 0.0001$.

a. These rats showed no corpora lutea.

b. Excluded the rats which showed no corpora lutea or fetus at the time of necropsy.

Litter Parameters: Five (of 24) HD females failed to become pregnant; these rats showed positive sperm smear results, but showed no corpora lutea.[8] An additional 8 HD females failed to produce any fetus because of early resorptions. Only 11 (of 24) females showed fetuses at the necropsy. These females with litters showed a statistically significant decrease in the mean number of live fetuses ($P < 0.0001$) and increases in mean resorptions ($P < 0.0001$) and post-implantation loss ($P < 0.0001$).

The statistical analysis presented in Table 25, however, are missing important data because the rats which were either non-pregnant or had no live fetuses were excluded from the statistical analysis. The treatment effects become more pronounced when the overall data is analyzed (Table 26). The HD group showed decreases in the number of live fetuses (↓75%), implantation sites (↓33%), and the number of corpora lutea (↓30%). Both the MD and HD groups showed increases in resorption rate (↑1.2 and 4.8-fold in MD and HD groups, respectively).

Table 26: Overview of Fertility Data (Including Missing Data)

Nintedanib (mg/kg/day)	0	3	20	100
# Rats/group	24	24	24	24
# Rats with no fetus	2	0	1	**13**
Corpora lutea (total/mean)	297/12.4	352/14.7	346/14.4	193/8.04
# Implantation sites (total/mean)	271/11.3	292/12.2	305/12.7	**183/7.62**
# Resorptions (total/mean)	20/0.83	18/0.75	**44/1.83**	**115/4.79**
# live fetuses (total/mean)	251/10.5	274/11.4	261/10.8	**68/2.8**

The analyses of overall and partial data of the study led to different conclusions about the potential effect of nintedanib on the number of corpora lutea and fertility. Based on the data presented in Table 25, BI stated that nintedanib at 20 mg/kg/day increased the number of corpora lutea. Table 26 shows that 1) the HD group had a 30% decreases in the number of corpora lutea, 2) there were no difference in the mean corpora lutea between the LD and MD groups, and 3) 54% of rats at the HD had no fetus (vs. ≤8.3% in the lower-dose and control groups). See Section 11.6 for additional discussions on the effect of nintedanib on the number of corpora lutea.

Histopathology

Adequate Battery: Not applicable. The report stated that pituitary (non-pregnant females) and mammary glands in all females were examined microscopically. The report also stated that no treatment-related effects were observed in the pituitary. In the mammary gland, the report stated that "[A]t 20 and 100 mg/kg evidence for low secretory activity (e.g., small diameter of glandular alveoli, few or absent secretory vacuoles in the cytoplasm) and a lower proportion of glandular tissue relative to the mammary fat pad in the majority of the dams were noted." No line-listing of the data were submitted, so the statements cannot be confirmed. The report also stated that "the histological effects on the mammary gland are … due to the pharmacodynamic activity" of

[8] Rats No. 407, 410, 417, 425, and 428.

nintedanib because VEGF and VEGFR in the mammary gland were functional during pregnancy.

Peer Review: Yes. The report contained a peer review statement signed by Dr. Dophie Bader of BI for the examination of mammary glands. The statement was of little value because the line listing data was not submitted.

Histological Findings: No treatment-related effects were observed in any of the male reproductive organs.

Histopathological evaluations: The microscopic evaluation of the study is adequate.

The NOAEL is considered 20 mg/kg/day for general toxicity and 3 mg/kg/day for the embryofetal developmental toxicity in female rats. This conclusion is in agreement with the sponsor.

Toxicokinetics: Blood nintedanib and metabolite concentrations were determined in satellite animals on treatment day 10 before mating and GD 7 at pre-dose, 1, 2, 4, 8, or 24 hours after dosing (n = 3/time point). The metabolites included BIBF 1202 and BIBF 1202-glu (glucuronide). Table 27 summarizes the results.

Table 27: Toxicokinetic Parameters in Pregnant and non-Pregnant Females

Nintedanib (mg/kg/day)	Time	BIBF 1120		BIBF 1202		BIBF 1202-Glu.	
		C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)	C_{max} (ng/mL)	AUC_{0-24} (ng.h/mL)
3	Pre-mating [a]	NC [b]	NC	2.07	NC	91.8	417
	GD 7	NC	NC	NC	NC	50.9	356
	Mean	NC	NC	NC	NC	71.3	387
20	Pre-mating	14.2	78.9	62.1	304	1,140	5,650
	GD 7	21.6	116	69.7	358	1,190	6,930
	Mean	17.9	97.6	65.9	31	1,160	6,290
100	Pre-mating	119	881	295	2,220	4,560	47,800
	GD 7	204	997	365	2,180	8,700	63,900
	Mean	162	939	330	2,200	6,630	55,800

a. Day 10 of the pre-mating treatment period.
b. NC, not calculated.

9.2 Embryofetal Developmental Studies

The effect of nintedanib on embryofetal development was evaluated in rats and rabbits (Document# U13-1923, Study 12B017). Pregnant rats and rabbits were dosed by oral gavage with nintedanib in 0.5% hydroxyethylcellulose for a period during gestation (gestation days 6 – 17 and 6 – 18 in rats and rabbits, respectively). The respective nintedanib dose in the C, LD, MD, and HD was 0, 2.5, 5, and 10 mg/kg/day in rats and 0, 15, 30, and 60 mg/kg/day in rabbits. Neither dams nor does showed maternal toxicity at the highest doses. Fetuses showed dose-related increases in the incidence of vasculature and axial skeletal malformations and variations. Neither study identified a NOAEL. See the nonclinical review completed by Dr.

Grace Lee on August 22, 2014 (DARRTS ID# 3,615,202), for a comprehensive review of the study reports. See Section 11.6 for a brief summary of study findings.

9.3 Peri-natal and Post-Natal Developmental Study

The effect of nintedanib on peri- and post-natal development was evaluated in rats (Document U13-2641, Study #DDB029). Female rats (F_0, Wistar Han) were dosed by oral gavage with 0, 2.5, 5, or 10-mg/kg/day nintedanib from GD 6 to the end of lactation except for the day of delivery. Dams were allowed to deliver naturally. Litter parameters and pup (F_1) developmental parameters were evaluated. The F_1 generation was also evaluated for reproductive parameters. The HD group showed statistically significant decreases ($p < 0.01$) in the number of pups born and the number of live pups on post natal day (PND) 4 and the post implantation survival index. See the nonclinical review completed by Dr. Grace Lee on August 22, 2014 (DARRTS ID# 3,615,202), for a comprehensive review of the study reports. See Section 11.6 for a brief summary of study findings.

10 Special Toxicology Studies

A number of studies were completed to evaluate the general toxicity of nintedanib impurities and metabolites. Short-term general toxicity studies of a few metabolites were also completed. These studies were not reviewed because they were not pivotal to the safety evaluation of the current application.

10.1 Impurities

The submission contained 30 reports of genetic toxicology tests of nintedanib impurities. These reports (i.e. studies) evaluated 22 impurities carrying structural alerts for genetic toxicity. The structural alerts were based on the structural activity relationship (SAR) analysis using DEREK and MC4PC software.[9] Genetic tests were selected on a tiered approach. Bacterial gene mutation tests (routine Ames test or modified Ames test) were done first. Additional and follow-up tests were done for compounds that tested positive in the Ames test. The additional tests included mouse lymphoma assay, in vivo micronucleus assay, comet assay, and others.

Table 28 (next page) shows that additional and follow-up tests were done for 6 compounds. Among them, BI tested the following compounds on their own: (b) (4) (b) (4) (b) (4) The Division requested testing (b) (4) of nintedanib, while (b) (4) was the first compound identified as having structural alerts for genetic toxicity.

The review did not evaluate any of the 30 genetic toxicity study reports for nintedanib impurities. The reason is that none of the impurities are expected to have daily exposure levels exceeding 1.5 mcg. The recommended daily dose of nintedanib is 300 mg. The specification for individual impurities is not more than (b) (4) This specification corresponds to daily exposures

[9] The DEREK analysis yielded no positive results for alerts for genetic toxicity while the MC4PC analysis yielded positive results for these 22 compounds.

of not more than (b) (4), a level below the genotoxicity impurity qualification threshold of 1.5 mcg per ICH M7 guidance. See Section 11.7 for additional information.

Table 28: Genotoxicity Tests of Nintedanib Impurities

Class	Compound	Ames test	L5178Y cell-line	Micro-nucleus	Comet assay	Others
II	(b) (4)	U08-2323				
		U02-1228 [a]				
		U11-2541				
V		U12-1640	U12-1997			
		U09-1033				
		U11-2539				
		U09-1070				
		U05-1770				
		U11-2067				
		U03-1572,	U03-1573	U03-1574		
		U02-1226 [a]				
		U02-1230 [a]				
		U02-1227			U07-2089	
		U10-1979				R12-0745, R12-0640
		U09-1979				
	e	U09-1073			U09-1294	
		U11-2840				
		U11-2841				
		U11-2154				
		U09-1191			U10-2415	
		U11-2538				
		U11-2796				

a. Ames II test. The test was done in (b) (4) The mix consisted of strains of TAs 7001, 7002, 7003, 7004, 7005 and 7006. The strains were used to detect base pair substitutions.

10.2 Metabolites

Nintedanib possess similar metabolic profiles between animals and humans (Ref.: Tables 21 and 22). Nintedanib is metabolized to a number of metabolites. Two of them are considered major metabolites and the rest are minor metabolites. The major metabolites are BIBF 1202 and BIBF 1202-glucoronidate. Hydrolysis and desmethylation of nintedanib resulted in formation of BIBF 1202. Esterase and CYP 3A4 are responsible for hydrolysis and desmethylattion of nintedanib. BIBF 1202 is further conjugated with glucoronidate to form BIBF 1202-Glu.

Documents U12-1640 and U12-1997 evaluated the genetic toxicity of BIBF 1202 in vitro. U12-1640 is an Ames test evaluating the mutagenicity of nintedanib in bacteria. U12-1997 studied mutagenicity and chromosomal damage in L5178Y mouse lymphoma cells. Nintedanib tested negative in both studies. The review does not evaluate the study reports because 1) nintedanib and BIBF 1202 have the same basic chemical structure and nintedanib was non-genotoxic and non-carcinogenic.

10.3 Local tolerance studies

The submission contained 6 reports of local tolerance studies. The studies evaluated the irritation potential of nintedanib to eye (U03-1151), skin (U05-1395), blood vessels (U-8-1861 and U08-1863), and muscle tissues (U08-1682) after topical and parenteral routes of administration, and hemolytic potential in vitro. There reports were not reviewed because they were not pivotal to the safety evaluation of the current submission.

11 Integrated Summary and Safety Evaluation

This application (NDA 205-832) has conducted adequate nonclinical characterization of Ofev (nintedanib) Capsules. The characterization included evaluations of pharmacological, pharmacokinetic, and toxicological profiles of the API. The toxicological characterization evaluated the general toxicity, genetic toxicity, carcinogenicity, and reproductive and developmental toxicity of nintedanib. Results showed that nintedanib was a non-genotoxic and non-carcinogenic kinase inhibitor; however, the drug was a potent teratogen when given to pregnant animals. The application has met nonclinical requirements for product approval. There are no outstanding nonclinical issues at the present time. The review recommends approval of the product from the nonclinical perspective.

Boehringer Ingelheim proposed to register nintedanib (Ofev capsules) as a therapy for IPF. Ofev capsules will be manufactured in two strengths: 100 and 150-mg nintedanib/capsule. The proposed maximum recommended human dose (MRHD) of nintedanib is 150 mg, twice daily. The 100-mg capsules will be used for dose adjustments in patients who need temporary dose reductions while on Ofev treatment.

Ofev capsules contained the following ingredients: nintedanib esilate, triglyceride (b) (4), hard fat, and lecithin. None of the excipients was novel for the oral route of administration. Therefore, the following discussions focus on the nonclinical safety evaluation of the API and API-related issues. The discussions are based on the findings and conclusions of the current and referenced reviews completed by Agency staff. See Section 3.3 for a complete list of the referenced reviews.

11.1 Pharmacology

Nintedanib is an inhibitor of the following TK families: FGFR, PDGFR, VEGFR, Flt-3, (b) (4), and SRC. These enzymes belonged to both TRK (i.e., FGFR, PDGFR, VEGFR, and Flt-3) and nRTK (e.g., (b) (4) and SRC) categories. It was hypothesized that nintedanib exerted its efficacy in IPF by inhibiting the following RTK families: FGFR, PDGFR, and VEGFR, although in vitro data showed that nintedanib lacked any selectivity between RTKs and nRTKs. The lack of selectivity was based on the observation that nintedanib had similar IC_{50s} for these enzymes. Also, the drug at similar doses is being developed as a therapy for oncological indications (b) (4). The oncological indications were based on the ability of nintedanib to inhibit the following nRTKs: (b) (4) Lck, Lyn, and Src. Table 29 provides an overview of nintedanib applications and their characteristics. The nintedanib IC_{50s} ranged from 13 – 610 nM and 16 – 195 nM for RTKs and nRTKs, respectively. The contribution of nRTK inhibition to the efficacy of nintedanib in IPF is unknown.

Nintedanib exerts its effect by inhibiting activation and auto-phosphorylation of TKs. In the RTKs, nintedanib bound to the ATP-site in the cleft between N- and C-terminal lobes of the kinase domains. In vitro data showed that nintedanib inhibited fibroblast migration, proliferation, and transformation of fibroblasts. In vivo studies showed that nintedanib treatment decreased the severity of lung fibrosis induced by bleomycin and silica in animal models.

Table 29: Indications Being Developed

Target TK		Indication	IC 50 (nmol/L)	Clinical doses	IND/NDA No.
Category	**Member**				
RTKs	PDGFRs, FGFRs, & VEGFRs	Idiopathic pulmonary fibrosis	13 - 610	150 mg, bid	N205,832, I074,683
nRTKs	(b) (4) Lck, Lyn & Src	(b) (4)	16 - 195	250 mg, bid	(b) (4)

11.2 Pharmacokinetics

Nintedanib is absorbed after oral administration, but its bioavailability is low: approximately 12%, 24%, and 4.7% in rats, monkeys, and humans, respectively. Plasma drug levels increase generally in proportion to orally administered dose in animals. There was no significant drug accumulation based on the plasma drug AUC and C_{max} parameters.

Nintedanib has a half-life of about 4 – 7 hours in animals and 12-17 hours in humans. The volume of distribution is 41.2, ~10, and 13.6 L/kg in rats, monkeys, and humans, respectively. The drug is metabolized in the liver and excreted mainly through feces. Approximately 80% of intravenously administered drug is excreted into feces in all species, including humans. Protein binding of the drug ranged from 91.4% to 98.5% in rats. The clearance is approximately 202, 35, and 18.0 mL/kg/min in rats, monkeys, and humans, respectively.

Nintedanib is metabolized to a number of metabolites in animals and humans. Major metabolites include BIBF 1202 and BIBF 1202-Glu. The former is formed when nintedanib is hydrolyzed and desmethylated. Esterase and CYP 3A4 are responsible for these reactions. BIBF 1202 is further conjugated with glucuronide to form BIBF 1202-Glu. All these metabolites are present across species, including humans. Monkeys and humans show very similar metabolic profiles.

Nintedanib is excreted into the milk in rats. A radio-labelled nintedanib study in lactating dams showed that about 0.18% - 0.5% of an orally administered dose was excreted into the milk when dams were given 30-mg/kg nintedanib on lactation day 12 (U12-1855). The respective total drug-related concentration at 1, 6, and 24 hours post dose was 269, 1060, and 106 ng/mL in the milk and 2260, 478, and 7.92 ng/mL in the plasma.

11.3 General toxicity

The general toxicity of nintedanib was studied in mice, rats, and monkeys for up to 12 months. The chronic toxicity studies included oral toxicity studies of 6 and 12 months in rats and monkeys, respectively. Each of these studies used the oral (gavage) route of administration. Table 30 lists the pivotal general toxicity studies of nintedanib. The studies identified the following as the target organs of toxicity: the bones (mice, rats, and monkeys), liver (mice and rats), kidney (rats), ovaries (mice and rats), and the immune system (mice, rats, and monkeys). The affected organs in the immune system included adrenal glands, bone marrow, spleen, and thymus.

Table 30: Overview of Pivotal General Toxicity Studies

Species	Duration (week)	BIBF 1120 (mg/kg/day, PO)	AUC_{0-24h} at NOAEL/lowest dose (ng.h/ml)	Target organs	Report #
Mouse	13	10,[a] 30, 100	233 - 242	Adrenal, bone, ovary, spleen, thymus	U10-1798
Rat	13	5, 20, 60/30	22.7 - 26.1	Adrenal, bone, spleen, thymus	U10-1799
Rat	13	**3**, 20, 100	2.3 – 8.4	Adrenal, bone, kidney, spleen, thymus	U04-1065
Rat	26	**5**, 20, 80	16.4 – 29.2	Adrenal, bone, kidney, spleen, thymus	U05-1843
Monkey [a]	13	3, 15, 30/20	305 - 345	Bone marrow, GI, thymus, pancreas	U05-2245
Monkey [b]	52	10, 20, 60/30	506 - 786	Bone	U10-1875

a. bold and highlights indicate NOAEL values.

In a **3-month mouse** study, CD-1 mice (12/sex/dose) were dosed by oral gavage at 0, 10, 30, or 100-mg/kg/day nintedanib for 13 weeks. The respective AUC_{0-24} in the LD, MD, and HD groups on day 87 was 225, 1280, and 5630 ng.h/mL in males and 231, 1350, and 3840 in females. There were dose-related decreases in absolute body weight and body weight gains. The target organs were adrenal gland, (diffused cortical hypertrophy), bone (thickening at growth plate), bone marrow (cellular depletion), liver (presence of extra-medullary hemopoiesis), spleen (increased extra-medullary hemopoiesis), teeth (dentopathy) and the ovaries (reduced numbers of mature corpora lutea and an increase incidence of luteinized follicles). No NOAEL was established.

In the **6-month rat study** (U05-1484), Wistar rats (20/sex/dose) were dosed by oral gavage at 0, 5, 20, or 80-mg/kg/day BIBF 1120 for up to 26 weeks. Additional rats were included to evaluate the reversibility of lesions (i.e., Recovery section: 10/sex in the C and HD group) and toxicokinetics (i.e., TK section: 6/sex/dose). The respective mean AUCs of BIBF 1120 in the LD, MD, and HD groups on day 179 were 16.4, 184, and 1240 ng.h/ml in males and 29.2, 316, and 1030 ng.h/ml in females.

Treatment-related effects were observed in clinical signs, body weight, macro- and microscopic examinations in the MD and HD groups. The HD group (main study only) was terminated in week 24 due to poor condition. Clinical signs included fractured teeth, gingiva swelling, and liquid feces. Body weight in male rats was decreased approximately 6% and 16% in the MD and HD groups, respectively.

Histological findings were observed in the liver, spleen, kidney, bone marrow, adrenal glands, thymus, ovaries, bile duct, and incisors in the MD and HD groups. The liver finding was periportal hemosiderosis and brown pigment in the hepatocytes, Kupffer cells and partially in

interstitial macrophages. Mineralization (minimal to moderate) of the connective tissue, depletion of the lymphoid cells (minimal or mild), and extra-medullary hematopoiesis (slight) were observed in the spleen. Tiny depositions of hyaline material or droplets were observed in the glomerular endothelial cells and podocytes in the kidney. Also observed was focal basophilic tubules (minimal to mild), tubular protein casts (minimal to mild), and dusty fat droplets and pigment storage in tubular epithelium (minimal to slight). Peliosis or angiectasis (slight to severe) and cortical tissue hyperplasia were observed in the adrenal glands. Cellular depletion of hematopoietic cells was observed in the bone marrow.

Thymus involution (moderate) partly accompanied by a mild increase in the number of apoptotic cells was observed in the HD group. In the ovaries, the size of the corpora lutea was decreased while the number of corpora lutea was increased. Some altered corpora lutea developed a liquefactive necrotic center instead of a physiological vascularization of the central cavity (corpus luteum, necrosis, liquefactive). In several cases, the internal Theca cells of sex cord stroma had pronounced hyperplasia.

In the knee (distal femur and proximal tibia), the epiphyseal cartilage was thickened in two females at 20 mg/kg and in the majority of animals at 80 mg/kg. This thickening was mainly due to an elongation of the chondral columns (hypertrophic chondrocytes). In the incisors, dysplasia (minimal to severe) was observed. Slight dysplasia exhibited irregularities of the ameloblasts and/or odontoblasts. Moderate dysplasia revealed further aggravation and first regressive lesions in the pulp cavity and/or mild inflammation and hyperplastic epithelium of the gingival sulcus and dental alveolus. The irregularities of enamel and dentin, ameloblasts and odontoblasts resulted in dental deformations and fractures. Inflammation and hyperplasia of the ductal epithelium were observed in the main bile duct. The NOAEL in the 6-month rat study was 5 mg/kg/day. This dose corresponds to mean AUCs of 16.4 and 29.2 ng.h/ml in males and females, respectively, on day 179.

In the **12-month monkey** study (Report U10-1875), Rhesus monkeys (4/sex/dose) were dosed by oral gavage with 0, 10, 20, and 60/45/30 mg/kg/day of BIBF 1120 for 52 weeks. Additional monkeys (2/sex/dose) were included in the C and HD groups to evaluate the reversibility of lesions. The BIBF 1120 dose in the HD group was started at 60 mg/kg/day but was reduced twice during the study due to overt toxicity. Specifically, the BIBF 1120 doses were 60, 0, 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-26, and 26-55, respectively. The respective mean AUCs of BIBF 1120 in the LD, MD, and HD groups on day 363 were 787, 831, and 1100 ng.h/ml in males and 506, 1220, and 1,660 ng.h/ml in females.

Treatment-related effects were seen in all BIBF 1120 dosed groups, although the effect in the LD group was limited to the bone (i.e. growth plate thickening) and changes in clinical signs and body weight were limited to the MD and HD groups. Two HD monkeys (one in each sex) were sacrificed due to poor conditions while on 45-mg/kg/day dosing. Monkeys 736 (F) and 737 (M) were killed in week 11 and 24, respectively, due to clinical signs such as liquid feces, and under-activity. Microscopic findings of these monkeys were generally similar to that of the terminally killed monkeys of the group. In addition, microscopic examination of monkey 737 revealed minimal inflammatory cells with necrotic debris at the tips of the villi in the small intestine and

the mucosal surface in the large intestine. The respective mean weight gain during the course of the study (week 0 – 52) in the C, LD, MD, and HD groups was 1.94, 1.41, 1.14 ($p < 0.05$), and 0.73 kg ($p < 0.01$) in males; and 1.51, 1.31, 1.10, and 0.88 ($P < 0.05$) kg in females.

Histological findings were present in all dose groups. These included thickening of growth plate of the bones (femur, tibia and sternum) and atrophy of the zona fasciculata in the adrenal gland. The HD group also showed cortex and trabecular bone thinning in the sternum. Growth plate thickening in the femur remained in the recovery monkeys. The respective incidence (slight in severity) in the control and HD groups was 0/2 and 1/1 in males; and 0/1 and 1/2 in females. The study did not establish a NOAEL, due to findings of growth plate thickening in the low dose group. However, the bone findings are considered irrelevant to IPF patients who are adults.

11.4 Genetic toxicity

Nintedanib tested negative in the following genetic toxicity assays: bacterial gene mutation assay in vitro, mammalian cell chromosomal aberration assay in mouse lymphoma cells in vitro, and in vivo micronucleus test in rats.

11.5 Carcinogenicity

Nintedanib was non-carcinogenic. Carcinogenicity of nintedanib was studied in 2-year oral (gavage) carcinogenicity studies in rats and mice (Study BBDs 0006 and 0007). The respective nintedanib dose was 0, 5, 15, and 30 mg/kg/day in mice and 0, 2.5, 5, and 10 mg/kg/day in rats. No evidence of tumorigenicity was observed in either study. The mean $AUC_{0\text{-}24h}$ in the HD group was 1335 and 82.9 ng.h/mL in mice and rats, respectively.[10] The AUC in mice and rats were approximately 4.4 and 0.27 times humans at the MRHDOD of 300-mg nintedanib (i.e., 304 ng.h/mL).

11.6 Reproductive and Developmental Toxicity

Reproductive and developmental toxicity of nintedanib was studied in rats and rabbits. The studies evaluated the effect of nintedanib on fertility in rats, on embryofetal development in rats and rabbits, and on pre- and post-natal development in rats. Table 31 presents an overview of these studies. Table 31 (below) summarizes nintedanib effects on fertility, embryofetal development, and post-natal development.

[10] The mean respective AUC in the HD males and females was 1090 and 1580 ng.h/mL in mice, and 78 and 87.9 ng.h/mL in rats.

Table 31: Overview of Reproductive and Developmental Studies of Nintedanib

Document #	Study#	Seg-ment	GLP	Species	Nintedanib (mg/kg/day)	Key findings
U10-1128	09B060	I	Yes	Rat, M	0, 3, 20, 100	None
U13-2650	12B057		Yes	Rat, F	0, 3, 20, 100	↑ resorptions @≥ 20mg/kg/day and above
U13-1923	12B017	II	Yes	Rat, F	0, 2.5, 5, 10	↑ variations # and malformations # @ ≥ 2.5mg/kg/day
U17-1814	07B003		No	Rat, F	0, 5 10, 20	↓ viable fetus & ↑ resorption @ 10 mg/kg/day, teratogenic @ ≥ 20mg/kg/day
U07-1710	07B002		No	Rat, F	0, 30, 75, 100	100% resorptions in all treated groups
U13-1937	12B032		Yes	Rabbit, F	0, 15, 30, 60	Δ in sex ratio & numerical ↑malformations @ 15 mg/kg/day
U13-1420	11B228		No	Rabbit, F	0, 3, 7, 15, 30, 75, 180	Total resorption @75mg/kg/day
U13-2641	DDB029	III	Yes	Rat, F	0, 2.5, 5, 10	↓ F1 fetal weight & live pup # @ 10 mg/kg/day

Effect on fertility: Nintedanib decreased female fertility in rats but had no effect in males. Effects of nintedanib on male and female fertility were studied separately in rats (U10-1128 and U13-2650). Table 32 presents an overview of these studies. Nintedanib doses were identical in the studies: 0, 3, 20, and 100 mg/kg/day. Nintedanib was administered by oral gavage prior to, during, and after mating (female fertility study only). Mating occurred between treated rats and untreated partners. Females were sacrificed 14 days after mating while males were sacrificed when mating was completed. The treatment period prior to mating was 13 and 2 weeks in males and females, respectively.

Table 32: Overview of Male and Female Fertility Studies in Rats

Document No.	U10-1128	U13-2650
Nintedanib-treated sex	**Male**	**Female**
Nintedanib (mg/kg/day)	0, 3, 20, 100	0, 3, 20, 100
Treatment period prior to mating	13 weeks	2 weeks
Treatment period after mating	None	7 days
Mating period	Up to 2 weeks	Up to 2 weeks
Sacrifice time, Female	GD 14	GD 14
End points	Male & female fertility parameters	Female fertility parameters
Other:	Histology of male reproductive organs	None
Key findings	No effect on fertility, ↓ body weight @100 mg/kg/day (P < 0.05)	↑ resorption @ ≥ 20 mg/kg/day (P < 0.05)

Nintedanib had no effects on male fertility in rats (U10-1128), but remarkable treatment-related effects were observed in females (U13-2650). Effects included statistically significant and dose-related increases in post-implantation loss and resorptions at ≥ 20 mg/kg/day (Tables 25 and 26, P < 0.05). Thirteen of the 24 HD rats had no live fetuses. Among the 13 no-litter females, 5 had no corpora lutea (P < 0.05) and 8 had total resorption of the litter (P < 0.05). Among the rats with live fetuses, the respective parameter in the C, LD, MD, and HD was 11.4, 11.4, 11.3, and 6.2 (p < 0.0001) in mean number of live fetuses/liter; 0.68, 0.75, 1.91 (P < 0.05),

and 5.36 ($p < 0.0001$) in mean number of resorptions; and 5.71%, 7.62%, 13.5%, and 46.8% ($P < 0.0001$) in mean post-implantation loss. The HD also had statistically non-significant decreases in fertility index (↓21%) and gestation index (↓ 37.9%).

Effect of nintedanib on ovaries: To assist the interpretation of results of the female fertility study in rats, the review explored the dose-relationship between nintedanib and ovary findings. The review focused on the number of corpora lutea because it was decreased in the HD group. The following is a comparison of the number of corpora lutea in the HD vs. the remaining groups:

1) Five non-pregnant HD rats showed no corpora lutea.
2) Eight pregnant HD rats had total litter losses and a mean corpora lutea number of 7.25.
3) Eleven pregnant HD rats with litters had a mean corpora lutea number of 12.3.
4) The overall mean number of corpora lutea in the HD group was 8.04.
5) The mean number of corpora lutea for the C, LD, and MD groups ranged from 13.3 – 15.0.

To assist in interpretation of the above observations, the review explored the effect of nintedanib on ovaries in general toxicity findings. Table 33 presents an overview of the ovary findings in chronic toxicity and fertility studies in rodents. Five studies were analyzed. Four of them were general toxicity studies of 13 - 26 weeks in treatment duration. One study was the fertility study in rats. Four of the studies were in rats and the remaining one in mice. Treatment-related effects were observed in all but one rat study (U10-1799) which appears to be a different strain. Effects included changes in the numbers and size of corpora lutea.

Table 33: Overview of Corpora Lutea Data in the Ovaries

Document Number	Species	Strain	Duration (Week)	Nintedanib		Noticeable Ovary Findings
				mg/kg/day	AUC (ng.h/mL)	
U10-1798	Mouse	Crl:CD1	13	0, 10, 30, 100	0, 231, 1350, 3840	↓ Mature corpora lutea numbers @100 mg/kg/day
U04-1065	Rat	Crl:WI(Han)[a]	13	0, 3, 20, 100	0, 8.4, 220, 2150	↓ Mature corpora size @100 mg/kg/day
U10-1799	Rat	HsdRccHan™	13	0, 5, 20, 60	0, 4.2, 37.6, 5730	No effect
U05-1843	Rat	Crl:WI(Han)[a]	26	0, 5, 20, 80	0, 29.2, 316, 1030	↓ Size and ↑ # of corpora lutea @ ≥20mg/kg/day
U13-2650	Rat	Crl:WI(Han)	5 (Seg. I)	0, 3, 20, 100	0, NC, 97.6, 939	↓ Corpora lutea # @ 100 mg/kg/day

a. Current nomenclature. The study report used the previous name of CrlGlxBrlHan:WI which was replaced by the current name in 2005 (Ref.: http://info.criver.com/general/documents/2005_research_model_nomenclature.pdf).

Changes in the corpora lutea numbers was inconsistent among studies: decreases were observed in the 13-week toxicity mouse study (U10-1798) and the rat fertility study (U13-2650) while increases were seen in the 26-week general toxicity study in rats (U05-1483). The increases in the corpora lutea numbers appeared to be accompanied by decreases in size (U05-1843). It is unclear at the present time whether the inconsistencies were due to variations

among studies or a treatment duration-related (compensatory) effect. Table 34 presents the incidence of ovary changes in the studies with noticeable findings. There were apparent dose-response relationships across studies. The LD group appears to be the NOAEL dose.

Table 34: Changes in Corpora Lutea in Rodent Ovaries

Document Number	Species	Duration (Week)	Nintedanib	Incidence			
			mg/kg/day	C	LD	MD	HD
Number of matured corpora lutea [a]							
U10-1798	Mouse	13	0, 10, 30, 100	9/12	5/12	5/11	3/12
U04-1065	Rat	13	0, 3, 20, 100	10/18	15/21	21/21	27/30
U05-1843	Rat	26	0, 5, 20, 80	0/20	0/20	4/19	18/21
U13-2650	Rat	5	0, 3, 20, 100	0/22	0/20	4/19	18/21
Incidence with no corpora Lutea							
U10-1798	Mouse	13	0, 10, 30, 100	0/12	0/12	2/11	1/12
U13-2650	Rat	5	0, 3, 20, 100	0/20	0/20	1/19	5/22
Incidence of ↓ corpora lutea size							
U04-1065	Rat	13	0, 3, 20, 100	0/10	0/10	0/10	10/10
U05-1843	Rat	26	0, 5, 20, 80	0/20	0/20	2/19	19/21

a. Number of moderate/marked mature corpora lutea only.

Overall evaluation of effects of nintedanib on female fertility: The available data indicate that nintedanib decreases fertility in female rats. The female fertility study (U13-2650) showed total litter loss in rats at exposures (AUC of 939 ng.h/mL at 100-mg/kg/day oral dose) approximately 3 times humans. Rats at this dose level also showed decreases in fertility and gestation indices and delayed copulation time, although none of these changes reached statistical significance. Also, ovaries were identified as a target organ of nintedanib toxicity in general toxicity studies. Finally, teratology studies (below) showed that nintedanib given to pregnant animals caused dose-related increases in the incidence of malformation, resorption, and (pre- and post-) implantation loss at exposures below the level at MRHD in humans. The available evidence suggests that nintedanib may decrease female fertility in rats.

Effect of embryofetal development: Nintedanib is a potent teratogen. Effects of nintedanib on embryofetal development were evaluated in rats (U13-1923) and rabbits (U13-1937). Rat and rabbit fetuses exposed to nintedanib maternally during pregnancy showed dose-related increases in visceral and skeletal malformations and changes in fetal sex ratios (Table 35). The visceral malformations included vasculature abnormalities in both species and missing organs in the urogenital system in rabbits. Findings in the vasculature included missing or abnormal major blood vessels. Skeletal malformations included abnormalities in the vertebrae and sternebrae in both species. The sex ratio was shifted to females in rabbits. Also, nintedanib was embryofetocidal, as indicated by litter loss and decreases in litter size. All the above effects occurred at non-maternally toxic doses.

Pregnant rats and rabbits were dosed by oral gavage with nintedanib in 0.5% hydroxyethylcellulose for a period during gestation (U13-1923, Study 12B017). The respective nintedanib dose in the C, LD, MD, and HD was 0, 2.5, 5, and 10 mg/kg/day in rats and 0, 15, 30,

and 60 mg/kg/day in rabbits. The dosing period was gestation days 6 – 17 and 6 – 18 in rats and rabbits, respectively. Plasma drug levels were determined on gestation days (GD) 6 and 10 in days and 6 and 13 in rabbits, respectively. The mean plasma nintedanib AUC_{0-24} in the LD, MD, and HD group was unknown (below lower detection limit), unknown (not calculated because of incomplete data set), and 34.2 ng.h/mL on GD 10 in rats; and 1920, 2550, and 5340 ng.h/mL on GD 13 in rabbits. Neither dams nor does showed maternal toxicity at the highest doses. Neither study identified a NOAEL.

Table 35: Summary Findings of Teratology Studies of Nintedanib in Rats

Document #	GLP	Nintedanib treatment			Noticeable Findings
		GDs	mg/kg/day	AUC [a]	
U13-1923	Yes	6 - 17	2.5	NC	Numerical ↑ in incidence of visceral and skeletal malformations
			5	NC	Numerical ↑ in incidence of visceral and skeletal malformations
			10	34.2	↑ resorption*, ↓ fetal weight*, Visceral and skeletal malformations
U13-2641[b]	Yes	6 - 20	2.5	NC	No effect
			5	NC	No effect
			10	16.5	Total resorption (3/22 litters), postnatal loss (2 litters), ↓ litter size**, ↓ pup weight**
U07-1814	No	6 - 17	5	22.6	↓ mean fetal weight * (n = 10/group)
			10	91.8	↓ Viable fetus # *, ↑ mean implantation loss*, ↑ resorption*, and ↓ mean fetal weight*
			20	566	↓ Viable fetus # & ↑ in resorption, cleft thoracic body, & blood vessel abnormality *
U07-1710	No	6 - 17	30	761	100% resorption and no live fetuses*
			75	1900	100% resorption and no live fetuses*
			100	6160	Maternally toxic dose: ↓ body weight (7.9%)*, ↓food consumption (18.3%)*, total resorption and no live fetuses

a. In ng.h/mL on GD 16.
b. A peri- and post- and post-natal developmental toxicity study:
c. *, $p < 0.05$; **, $P < 0.01$)

Fetuses showed dose-related increases in the incidence of vasculature and axial skeletal malformations and variations, with most findings occurring in the HD group (U13-1923). Vascular anomalies included missing right subclavian artery, an additional vessel at the descending aorta, an aortic arch rotation to the right side, and an increased incidence of shortened truncus brachiocephalicus. Axial skeletal anomalies were seen in mainly thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, misshaped, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). The HD group ($AUC0_{-24}$ of 34.2 ng.h/mL on day 16) also showed increases in incidences of fusion between facial bones and unossified occipital bone. A few incidences of the same axial skeletal malformations were also noted in the MD and LD groups. Other findings in the HD group included a slight increase in mean resorption rate (16.0% vs. 7.5% in the control group), a slight decrease in mean number of viable fetuses (9.8 vs. 10.8 in the control group), and a slight lower mean fetal weight (4.74 g vs. 4.98 g in the control group).

More embryofetal toxicity was observed in non-GLP compliant dose-ranging studies in rats which had higher systemic exposure of nintedanib. U07-1814 showed that dams at plasma AUC_{0-24} of 91.8-ng.h/mL nintedanib (i.e., oral dose of 10 mg/kg/day) had statistically significant decreases in fetal resorption and increases in malformations of the vasculature and skeletal (cleft thoracic body) abnormalities. Dams at plasma AUC_{0-24} of 566-ng.h/mL nintedanib (i.e., oral dose of 20 mg/kg/day) showed total litter loss. Similarly, total litter loss was observed in another dose-ranging study (U13-1710) which used higher nintedanib doses (i.e., 0, 30, 75, and 180 mg/kg/day). U13-1710 showed that maternal toxicity occurred at 180 mg/kg/day which yielded a mean plasma AUC_{0-24} of 6160-ng.h/mL nintedanib.

Rabbit fetuses (Himala yan) also showed dose-related increases in the incidence of vasculature and axial skeletal malformations and variations and fetal toxicity (U13-1937 or Study 12B032). Four of twenty-two HD does showed abortion or total resorptions and the remaining does showed an increase in mean resorption rate (42% vs. 18% in the control group). The HD group showed decreases in mean body weight of F1 at birth ($p < 0.01$) and in the number of live fetuses ($P < 0.05$). The HD group fetuses showed a decrease in mean viable fetuses (4.3 vs. 5.8 in the control group), and a lower ratio of males than females (29:71). The HD fetuses showed a statistically significant shift in mean sex ratio; there were 71% females and 29% males. Structural abnormalities mostly in the MD and HD groups were noted in the vasculature, urogenital, and axial skeletal systems. Findings in the vasculature included missing subclavian artery or aortic arch, persistent truncus arteriosus, additional vessel at truncus pulmonalis [pulmonary trunk], aortic arch, or descending aorta connected to a forelimb, thin truncus pulmonalis, shortened truncus brachiocephalicus [innominate artery], thin or displaced ductus arteriosus botalli, dilated aortic arch, and small right heart ventricle. Changes in the urogenital system included absence of kidney, ureter, ductus deferens, uterus and/or ovaries. Changes in the skeletal system included hemivertebra, or cleft, fused, displaced, or unilaterally ossified vertebrae, and fused ribs. In addition, absence of both gall bladder and ductus choledochus and additional skull bones were noted. Also, one HD fetus had open eyes, cleft palate, and neural tube, ventricular septal, axial skeletal, and limb defects. The LD and MD groups showed similar axial skeletal findings, but with lower incidences and fewer changes (vasculature and skeletal abnormalities only).

Visceral and skeletal malformations were also observed in a dose-ranging study in rabbits (13-1420). Pregnant does (6/dose) were dosed by oral gavage at 0, 3, 7, 15, 30, 75, or 180-mg/kg/day nintedanib during GDs 6 – 18. The 75-mg/kg/day group showed the following: missing gall bladder [1/20 (5%), missing kidney [1(5%)], missing ureter (1), and fused sternebrae [5/20]. The incidence of ventricular septal defect was 0/22, 1/13, 0/8, 2/12, 0/44, and 2/20 in the 0, 3, 7, 15, 30, and 75 mg/kg/day groups, respectively. Minimal changes were observed in the 15 and 30 mg/kg/day groups. No litters were produced at 180-mg/kg/day due to total resorption.

The GLP study (U13-1937) and the dose-ranging study (U13-1420) apparently show significant differences in teratogenicity of nintedanib. The status and GLP compliance and the difference in sample size do not appear to account for these differences. The review compares the plasma nintedanib AUC between the studies and finds significant differences in AUCs between the

studies (Table 36). At the same dose, the GLP study yielded higher nintedanib exposures and more teratogenicity findings in the pregnant rabbits. The reason for the difference in AUCs between the studies is unknown.

Table 36: Nintedanib Dose-Exposure relationship between Studies in Pregnant Rabbits

Nintedanib (mg/kg/day, PO)	Plasma Nintedanib AUC_{0-24} (ng.h/mL)						
	3mg	7mg	15mg	30mg	60mg	75mg	180mg
U13-1420	91.7	207	647	1710	-	3340	4270
U13-1937	-	-	1920	2520	5430	-	-

Effect of peri- and post-natal development:

Nintedanib decreased pup viability during the first 4 days of post natal age in rats. Effects of nintedanib on pre- and post-natal development were studied in rats (U13-2641, Study #DDB029). Female rats (F_0, Wistar Han) were dosed by oral gavage with 0, 2.5, 5, or 10-mg/kg/day nintedanib from GD 6 to the end of lactation except for the day of delivery. The plasma nintedanib AUC was unknown, unknown, and 16.5 ng.h/mL on lactation day (LacD) 10. Dams were allowed to deliver naturally. Litter parameters and pup (F_1) developmental parameters were evaluated. The F_1 generation was also evaluated for reproductive parameters.

Five of the 22 dams (F_0) had no live fetuses/pups by PND 4 (3 dams had no litters due to resorptions; 2 dams lost litters during the period of PNDs 1 – 4). Among the dams which delivered live pups, the HD group showed statistically significant decreases ($p < 0.01$) in the number of pups born and the number of live pups on postnatal day (PND) 4 and the post implantation survival index. The respective parameter in the C, LD, MD, and HD group was 11.7, 11.6, 10.7, and 8.9 ($P < 0.01$) in the mean number of pups/litter at birth, and 11.6, 11.5, 10.7, and 8.9 ($P < 0.01$) in the mean number of pups/litter born alive. The survival index (viability to day PND 4) was 98.8%, 98.5%, 98.7%, and 93.2% in the C, LD, MD, and HD groups, respectively. In addition, two litters lost all their pups between PNDs 1 and 4.

Nintedanib had no effects on the following parameters evaluated from PND5 and onward: survival, physical, neurobehavioral, and reproductive parameters in F_1 animals. The NOAEL for pre- and postnatal development of F_1 animals was identified as the mid dose (5 mg/kg) due to decreases in post-implantation survival index, and litter mean number of live F_1 pups on PNDs 1 and 4 in the HD group. The findings of decreases in litter size, post implantation survival index, and fetal body weights were similar to that of teratology studies and it is unnecessary to describe them in the labeling. The observation of a decrease in postnatal survivability in the HD group should be described in the product labeling.

11.7 Impurities

There are no safety concerns for the impurities in the drug product. The submission identified approximately 40 impurities (Table 37, next page). BI conducted safety evaluations of nintedanib impurities in Section 2.6.6 (subsection 8.5) of the eCTD submission. The evaluations included QSAR analysis for structural alerts for genetic toxicity, study reports evaluating the

genotoxicity profile of the impurities, and literature searches for available data on the compounds of interest. The evaluation also included comparison of the daily exposures of the impurities against the qualification threshold for genetic toxic impurities in the ICH M7 guidance.

Because of the large number of impurities, BI divided the impurities into 5 classes. The classification was based on the knowledge and understanding about their potential for genetic toxicity and carcinogenicity. See Table 37 for the definition and members of each class.

Table 37: Overview of Nintedanib Impurities

Class	Definition	Impurity
(b) (4)		

Although a number of impurities were identified in the drug product, expected daily exposures (EDE) of patients to individual impurities are generally very low. The EDE is approximately (b) (4) based on the proposed daily dose of 300-mg nintedanib/patient and the specification (b) (4) for each impurity.[11] The only exception (b) (4) which had an expected exposure of (b) (4). This amount, however, is a fraction of the acceptable daily oral intakes (b) (4) based on the drinking water standards. There are

[11] This review and BI differed in estimates of impurity exposures. The review estimated the daily impurity exposures using the proposed daily dose of 300-nintedanib of mg/day and the proposed specification of not-more-than (b) (4) for each impurity. This estimate results in exposures less than (b) (4) for each impurity. BI used human nintedanib doses different from the current NDA. The original submission conducted safety evaluations of nintedanib impurity/degradants using a MRHD of 250-mg nintedanib. See Subsections 8.5.8 (pages 72 – 76) and 10.8 (page 81) of Sections 2.6.6 and Subsection 4.8 (page 30) of Section 2.4. On June 13, 2015 (DARRTS ID 3524164), DPARP issued an IR asking BI to reassess the impurity exposures and conduct safety evaluations accordingly. BI responded to the IR on June 20, 2014 via email. The response stated that its estimates were based on a daily dose of 500-mg nintedanib, an intended dose for oncological indications. The review concludes that no further action is needed because there is no safety concern for the impurities at the proposed specification for the impurities and the MRHD of nintedanib in IPF patients.

no safety concerns about any of the impurities in the drug product based on the low levels of impurity exposures.

Also, many of the impurities (b) (4) carried structural alerts for mutagenicity, but the API was non-genotoxic and non-carcinogenic. Finally, the IPF indication of the drug further diminishes the concerns about carcinogenicity potential of the API and its impurities.

11.8 Overall Evaluation and Recommendation

The applicant has conducted adequate nonclinical characterization of the active pharmaceutical ingredient. The product contained no novel inactive ingredients. There is adequate nonclinical data to support the safety of the proposed use of the product. No additional nonclinical studies are required. The review recommends approval of the product from the nonclinical perspective.

12 Labeling Review

The review evaluates the nonclinical sections of the Ofev labeling that BI proposed on May 2, 2014. These sections are Sections 8.1 Pregnancy, 8.4 Nursing Mothers, 12.1 Mechanism of Action, and 13.1 Carcinogenesis, Mutagenesis and Impairment of Fertility. Edits are recommended to ensure labeling consistency between products of the same pharmacological class. Section 12.1 Exposure Multiples below discusses the approaches for deriving dose ratios between animals and humans in the nonclinical sections. The remaining sections discuss rationale for suggested edits.

12.1 Method for Labeling Review

The review used the labeling for several approved and marketed kinase inhibitor products for guidance. Nintedanib will be the first kinase inhibitor approved for the IPF indication, but the Agency has approved a number of kinase inhibitors for non-IPF indications. Some of the approved drugs share targets with nintedanib. Table 38 summarizes 4 drugs that share targets with nintedanib. The list includes Sunitinib (Sutent, NDA 21-938), imatinib (Gleevec, NDA 21-588), vandetanib (Caprelsa, NDA 22-405), and dasatinib (Sprycel, NDA 21-986). Nintedanib share the most number of targets with Sunitinib (i.e., PDGFR, VEGFR, and FLT3) and the least with imatinib (i.e., PDGFR). The recommended text for nonclinical sections of the labeling is based on these approved products.

Table 38: Nintedanib and Marketed Tyrosine Kinase Inhibitors

Drug Product		NDA #	Target Tyrosine Kinases	Labeling	
Brand Name	**Generic Name**			**DARRRTS Reference ID#**	**Date of Approval**
Ofev	Nintedanib	205-832	**PDGFR, FGFR, VEGFR, FLT3, SRC, LcK,** [a] LYN	NA	NA
Sutent	Sunitinib	21-938	**PDGFR, VEGFR**, KIT, **FLT3**, CSF-1R, RET	3365387	8/30/2013
Sprycel	Dasatinib	21-986	**PDGFR**, BCR-ABL, SRC family (**SRC, LCK**, YES, FYN), c-KIT, and EPHA2	3487607	4/20/2014
Caprelsa	Vandetanib	22-405	EGFR, **VEGFR,** BRK TIE2, EPH, **Src**	3480537	3/31/2014
Gleevec	Imatinib	21-588	**PDGFR**, bcr-abl, SCF, c-kit	3511243	5/22/2014

a. **Bold face** indicates common targets with nintedanib.

12.2 Exposure Multiples

This review derives nintedanib dose ratios between animals and humans using the Agency's current policies and practices for labeling reviews. Exposure multiples are expressed on either mg/m^2 or AUC bases. AUC ratios are preferred when both ratios are available. Doses on a mg/m^2 basis are converted from mg/kg in oral toxicity studies in animals using appropriate conversion factors: 3, 6, and 12 for mice, rats, rabbits, respectively. For example, a 10-mg/kg/day dose in mice is converted to 30 mg/m^2/day dose based on the following calculation: 10 (mg/kg/day) x 3 (kg/m^2) = 30 (mg/m^2/day). The following dose/exposure levels were used for humans in the calculation: $AUC_{0\text{-}24}$ of 304 ng.h/mL and surface area dose of 185 mg/m^2 [300 (mg)/60(kg) x 37 (kg/m^2) = 187 (mg/m^2)]. Table 39 summarizes the dose ratios to be used in the labeling review.

Table 39: Exposure Multiples between Animals and Humans

Section	Species	Nintedanib (PO)		AUC (ng.h/mL)	Exposure Multiples		Reference
		mg/kg/day	mg/m^2/day		Calculated [a]	Rounded to	
Pregnancy	Rat	10	NC [c]	34.2	0.1	< 1	U13-1923
	Rabbit	15	NC	1540	5.1	5	U13-1937
Fertility	Rat, M	100	600	ND	3.2 [e]	3	U10-1128
	Rat, F	100	NC	939	3.1	3	U13-2650
		20	NC	97.6	0.3	< 1	U13-2650
Post-natal dev. [b]	Rat	10	NC	16.5	0.1	< 1	U13-2641
Carcinogenesis	Mouse	30	NC	1335[d]	4.4	4	BBD0006
	Rat	10	NC	82.9	0.3	< 1	BBD0007

a. These were calculated on a AUC basis unless specified. The nintedanib AUC in humans at the MRHD of 300 mg is 304 ng.h/mL.
b. Post natal dev. = post natal development.
c. NC, not calculated; ND, not determined.
d. Average of Treatment days 1 and 13 values (1160 and 1920 ng.h/mL, respectively).
e. On a mg/m^2 basis.

12.3 Pregnancy

Three sections of the proposed labelling contain information related to nonclinical findings of nintedanib. The sections are 4 CONTRAINDICATIONS, 5.1 Embryofetal Toxicity, and 8.1

Pregnancy. See below for the proposed text for these three sections. The review evaluates these sections separately.

(b) (4)

"5 (b) (4) Embryofetal toxicity

(b) (4)

"8.1 Pregnancy

(b) (4)

Contraindication

The review recommends against Contraindications in Pregnancy Women for Ofev labeling. Effects of TK inhibitors on embryofetal developmental studies were similar among the kinase inhibitors. [12] None of the approved and marketed kinase inhibitors (i.e., Sutent, Gleevcec,

[12] Section 8.1 Pregnancy of Sutent states: "Sunitinib was evaluated in pregnant rats (0.3, 1.5, 3.0, 5.0 mg/kg/day) and rabbits (0.5, 1, 5, 20 mg/kg/day) for effects on the embryo. Significant increases in the incidence of embryolethality and structural abnormalities wereobserved in rats at the dose of 5 mg/kg/day (approximately 5.5 times the systemic exposure [combined AUC of sunitinib + primary active metabolite] in patients

Caprelsa, and Sprycel) was contraindicated in pregnancy. Each of the 3 products has a Pregnancy Category D designation. Only Ofev will have a Pregnancy (b) (4) designation if approved. BI's proposal differs significantly from others. The review, therefore, recommends removing the contraindication statement from the Ofev labeling.

Table 40: Text of Warning and Precautions about Embryofetal Toxicity of Some TK Inhibitor Labeling

Sutent (sunitinib) NDA 21-938	Gleevec (imatinib) NDA 21-588	Sprycel (dasatinib) 21-986
5.2 Pregnancy: SUTENT can cause fetal harm when administered to a pregnant woman. As angiogenesis is a critical component of embryonic and fetal development, inhibition of angiogenesis following administration of SUTENT should be expected to result in adverse effects on pregnancy. In animal reproductive studies in rats and rabbits, sunitinib was teratogenic, embryotoxic, and fetotoxic. There are no adequate and well-controlled studies of SUTENT in pregnant women. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with SUTENT. (DARRTS ID# 3,365,387)	**5.11 Embryofetal toxicity:** Gleevec can cause fetal harm when administered to a pregnant woman. Imatinib mesylate was teratogenic in rats when administered during organogenesis at doses approximately equal to the maximum human dose of 800 mg/day based on body surface area. Significant post-implantation loss was seen in female rats administered imatinib mesylate at doses approximately one-half the maximum human dose of 800 mg/day based on body surface area. Sexually active female patients of reproductive potential taking Gleevec should use highly effective contraception. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to a fetus [*see Use in Specific Populations (8.1)*]. (DARRTS ID# 3,365,387)	**5.7 Embryofetal toxicity:** SPRYCEL can cause fetal harm when administered to a pregnant woman. Adverse fetal and infant outcomes have been reported from women who have taken SPRYCEL during pregnancy. In animal reproduction studies, embryo-fetal toxicities, including skeletal malformations, were observed in rats and rabbits at plasma concentrations below those in humans receiving therapeutic doses of dasatinib. If SPRYCEL is used during pregnancy, or if the patient becomes pregnant while taking SPRYCEL, the patient should be apprised of the potential hazard to the fetus *[see Use in Specific Populations (8.1)].* Advise females of reproductive potential to avoid pregnancy, which may include the use of contraception, during treatment with SPRYCEL, *[see Use in Specific Populations (8.8)]* (DARRTS ID# 3,365,387)

Precaution and Warnings

The labeling of marketed TK inhibitors has a section under Precautions and Warning to describe effects on embryofetal development. Table 40 (above) presents the labeling section describing embryofetal toxicity for three marketed TK inhibitors. BI's proposal makes reference to the nonclinical data. This is acceptable because the labeling of currently marketed products has used the approach. The review recommends the following text for the first paragraph of Section 5.3 of the Ofev labeling:

administered the recommended daily doses [RDD]). Significantly increased embryolethality was observed in rabbits at 5 mg/kg/day while developmental effects were observed at ≥1 mg/kg/day (approximately 0.3 times the AUC in patients administered the RDD of 50 mg/day). Developmental effects consisted of fetal skeletal malformations of the ribs and vertebrae in rats. In rabbits, cleft lip was observed at 1 mg/kg/day and cleft lip and cleft palate were observed at 5 mg/kg/day (approximately 2.7 times the AUC in patients administered the RDD). Neither fetal loss nor malformations were observed in rats dosed at ≤3 mg/kg/day (approximately 2.3 times the AUC in patients administered the RDD)."

5.3 Embryofetal toxicity

OFEV can cause fetal harm when administered to a pregnant woman. Nintedanib is teratogenic and embryofetocidal in rats and rabbits at less than and approximately 5 times the maximum recommended human dose (MRHD) in adults (on a AUC basis at oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV. If OFEV drug is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient should be advised of the potential hazard to a fetus. *[See Use in Specific Populations (8.1]*

Pregnancy

The review recommends edits Section 8.1 Pregnancy of the proposed labeling. Section 11.6 of the review discusses the embryofetal developmental effects of nintedanib in rats and rabbits. The discussion concludes the following effects of nintedanib:

1) Nintedanib is a teratogen in rats and rabbits.
2) Nintedanib is embryofetocidal in rats and rabbits.
3) Nintedanib caused a shift of sex ratios of offspring to female rabbits.
4) Nintedanib decreased the viability of infant pups in rats (≤ PND 4).
5) The NOAEL for embryofetal developmental effect of nintedanib has not been established in either species.

The review finds that BI's proposal for Section 8.1 does not accurately describe the effects of nintedanib on embryofetal development in animals. Pivotal toxicity studies characterizing the effects of nintedanib on embryofetal development were the embryofetal developmental studies in rats and rabbits (U13-1923 and U13-1937, respectively). Pregnant rats and rabbits were dosed orally with nintedanib during the organogenesis period. The respective nintedanib dose in the C, LD, MD, and HD was 0, 2.5, 5, and 10 mg/kg/day in rats and 0, 15, 30, and 60 mg/kg/day in rabbits. The mean plasma nintedanib AUC_{0-24} in the LD, MD, and HD group was unknown (below lower detection limit), unknown (not calculated because of incomplete data set), and 34.2 ng.h/mL on GD 10 in rats; and 1920, 2550, and 5340 ng.h/mL on GD 13 in rabbits.

Both rat and rabbit fetuses showed dose-related increases in visceral and skeletal malformations. The visceral malformations included vasculature abnormalities in both species and missing organs in the urogenital system in rabbits. Skeletal malformations included abnormalities in the vertebrae and sternebrae in both species. The sex ratio was shifted to females at 60 mg/kg/day in rabbits. These findings were accompanied by litter loss and decreases in litter size. All the above effects occurred at non-maternally toxic doses. Neither study identified a NOAEL. Based on the above discussions, the review recommends the following text for Section 8.1 Pregnancy:

8.1 Pregnancy

Pregnancy Category D

OFEV can cause fetal harm when administered to a pregnant woman. If OFEV is used during pregnancy, or if the patient becomes pregnant while taking OFEV, the patient

should be apprised of the potential hazard to a fetus. Women of childbearing potential should be advised to avoid becoming pregnant while receiving treatment with OFEV.

In animal reproductive toxicity studies, nintedanib caused embryofetal deaths and malformations in rats and rabbits at approximately less than and 5 times the maximum recommended human dose (MRHD) in adults (on a plasma AUC basis at maternal oral doses of 2.5 and 15 mg/kg/day in rats and rabbits, respectively). Fetal malformations included abnormalities in the vasculature, urogenital, and skeletal systems. Vasculature anomalies included missing or additional major blood vessels. Skeletal anomalies included abnormalities in the thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, misshaped, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). In some fetuses, organs in the urogenital system were missing. In rabbits, a significant change in sex ratio was observed in fetuses (female:male ratio of approximately 71%:29%) at approximately 15 times the MRHD in adults (on a plasma AUC basis at maternal oral dose of 60 mg/kg/day). Nintedanib decreased post-natal viability during the first 4 post natal days in rat pups when dams were exposed to less than the MRHD (on a plasma AUC basis at maternal oral dose of 10 mg/kg/day).

12.4 Nursing mothers

The review recommends edits to the proposed text of Section 8.3 Nursing Mothers. Based on data from lactating rats, BI proposed the following statements to describe the potential for infant exposure to nintedanib though human milk.

(b) (4)

The statement that about (b) (4) is misleading. (b) (4) The proposed statement was based on the findings of Report U12-1855 which showed that 0.18 - 0.5% of the administered dose was secreted into milk within a period of 24 hours. See Section 5.1.2 of the review for a detailed description of the study. Briefly, nursing rats were dosed orally with 30-mg/kg radio-labelled nintedanib on day 12 of lactation. The concentrations of total radioactivity in plasma and in the milk of the dams were measured at 1, 6, and 24 hour post dosing. Results showed that respective drug concentrations at 1, 6, and 24 hours post dosing was 269, 1060, and 106 ng/mL in the milk and 2260, 478, and 7.92 ng/mL in the plasma. The mean AUC_{0-24} was 12,400 and 14,000 ng.h/mL in the plasma and milk, respectively.

The bioavailability of nintedanib was not determined in U12-1855. Studies in non-lactating rats showed that the nintedanib had a bioavailability of only 12% in rats. If the same bioavailability holds in lactating rats, approximately 4.2% of the absorbed drug would be excreted into milk. Given the lack of bioavailability data in Document U12-1855, it appears to be more accurate to compare the plasma and blood drug concentrations. Because the plasma and milk have

significant differences in concentration-time courses of nintedanib, the AUC values provide better comparisons. The AUC data indicated that it is reasonable to state that nintedanib concentrations in the plasma and milk were similar in lactating rats.

Nintedanib excretion into the milk has not been determined in humans, but the large V_{ss} (13.6 L/kg) suggests that nintedanib could be excreted into milk in humans. Based on the above discussions, the review recommends editing the proposed text for Section 8.3 Nursing Mothers as the following:

> Nintedanib and/or its metabolites are excreted into the milk of lactating rats. Milk and plasma of lactating rats show similar concentrations of nintedanib and its metabolites. Excretion of nintedanib and/or its metabolites into human milk is probable. There are no human studies that have investigated the effects of OFEV on breast-fed infants. Because of the potential for serious adverse reactions in nursing infants from OFEV, a decision should be made whether to discontinue nursing or to discontinue OFEV, taking into account the importance of OFEV to the mother.

12.5 Mechanism of Action

The review recommends edits to the proposed text of Section 12.1 Mechanism of Action. BI proposed the following to describe the mechanism of action for nintedanib:

(b) (4)

(b) (4)

As discussed in Section 11.1 of the review, nintedanib showed no selectivity between target RTKs and nRTKs. Specifically, nintedanib IC_{50s} ranged from 13 – 610 nM and 16 – 195 nM for RTKs and nRTKs, respectively. Inhibition of FGFR, PDGFR, and VEGFR could play important role in IPF efficacy of nintedanib, but the contribution of the nRTK inhibition to IFP efficacy is unknown.

Nintedanib will be the first kinase inhibitor approved for the IPF indication, but the Agency has approved a number of kinase inhibitors for non-IPF indications. Some of the approved drugs share targets with nintedanib. Table 38 (page 68) summarizes them. Sunitinib (Sutent) and nintedanib share the most number of targets (i.e., PDGFR, VEGFR, and FLT3). [13] Imatinib

[13] Sutent (NDA 21-938) label states: "Sunitinib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs), some of which are implicated in tumor growth, pathologic angiogenesis, and metastatic progression of cancer. Sunitinib was evaluated for its inhibitory activity against a variety of kinases (>80 kinases) and was identified as an inhibitor of platelet-derived growth factor receptors (PDGFRα and PDGFRβ), vascular endothelial growth factor receptors (VEGFR1, VEGFR2 and VEGFR3), stem cell factor receptor (KIT), Fms-like tyrosine kinase-3 (FLT3), colony stimulating factor receptor Type 1 (CSF-1R), and the glial cell-line derived neurotrophic factor receptor (RET). Sunitinib inhibition of the activity of these RTKs has been demonstrated in biochemical and

(Gleevec) and nintedanib share the least number of common targets (i.e., PDGFR only).[14] The number of shared target for dasatinib (Sprycel) is in between sunitinib and imatinib. Like nintedanib, dasatinib also inhibits both RTKs (i.e., PDGFR) and nRTKs (i.e., DRC and LCK) targets.[15] Labeling of the approved TK inhibitors will be used to guide nintedanib labeling. Based on the above discussions, the review recommends the following edits to the proposed text of Section 12.1 Mechanism of Action.

> Nintedanib is a small molecule that inhibits multiple receptor tyrosine kinases (RTKs) and non-receptor tyrosine kinases (nRTKs). Nintedanib inhibits the following RTKs: platelet-derived growth factor receptor (PDGFR) α and β, fibroblast growth factor receptor (FGFR) 1-3, and vascular endothelial growth factor receptor (VEGFR) 1-3, and Fms-like tyrosine kinase-3 (FLT3). Among them, FGFR, PDGFR, and VEGFR have been implicated in IPF pathogenesis. Nintedanib binds competitively to the adenosine triphosphate (ATP) binding pocket of these receptors and blocks the intracellular signaling which is necessary for the proliferation, migration, and transformation of fibroblasts representing essential mechanisms of IPF pathology. Nintedanib inhibits the following nRTKs: Lck, Lyn and Src kinases. The contribution of Flt-3 and nRTK inhibition to IPF is unknown.

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cellular assays, and inhibition of function has been demonstrated in cell proliferation assays. The primary metabolite exhibits similar potency compared to sunitinib in biochemical and cellular assays.

Sunitinib inhibited the phosphorylation of multiple RTKs (PDGFR1, VEGFR2, KIT) in tumor xenografts expressing RTK targets *in vivo* and demonstrated inhibition of tumor growth or tumor regression and/or inhibited metastases in some experimental models of cancer. Sunitinib demonstrated the ability to inhibit growth of tumor cells expressing dysregulated target RTKs (PDGFR, RET, or KIT) *in vitro* and to inhibit PDGFR1- and VEGFR2-dependent tumor angiogenesis *in vivo*." (Ref.: Reference ID# 3,365,387)

[14] Gleevec (NDA 21-588) label states: "Imatinib mesylate is a protein-tyrosine kinase inhibitor that inhibits the bcr-abl tyrosine kinase, the constitutive abnormal tyrosine kinase created by the Philadelphia chromosome abnormality in CML. Imatinib inhibits proliferation and induces apoptosis in bcr-abl positive cell lines as well as fresh leukemic cells from Philadelphia chromosome positive chronic myeloid leukemia. Imatinib inhibits colony formation in assays using *ex vivo* peripheral blood and bone marrow samples from CML patients.

In vivo, imatinib inhibits tumor growth of bcr-abl transfected murine myeloid cells as well as bcr-abl positive leukemia lines derived from CML patients in blast crisis.

Imatinib is also an inhibitor of the receptor tyrosine kinases for platelet-derived growth factor (PDGF) and stem cell factor (SCF), c-kit, and inhibits PDGF- and SCF-mediated cellular events. *In vitro*, imatinib inhibits proliferation and induces apoptosis in GIST cells, which express an activating c-kit mutation." (Ref.: Reference ID# 3,511,243)

[15] Sprycel (NDA 21-986) label states: "Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase.

In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCRABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression." (Ref.: Reference ID# 3,487,607)

12.6 Carcinogenesis

The review finds BI's proposal for the carcinogenesis section of the nintedanib label generally acceptable, but the review recommends edits to the dose ratios and the proposed text. Dose ratios were edited to reflect the exposure multiples based on the agency's evaluations. Text was edited to increase the clarity and readability.

> Two-year oral carcinogenicity studies of nintedanib in rats and mice have not revealed any evidence of carcinogenic potential. Nintedanib was dosed up to 10 and 30 mg/kg/day in rats and mice, respectively. These doses were less than and approximately 4 times the MRHD, on a plasma drug AUC basis.

12.7 Mutagenesis

The review recommends edits to BI's proposal for the mutagenesis section of the nintedanib label. The review finds the proposal accurately describes the findings of genetic toxicity testing and is compliant with the current labeling format. BI's proposal is as the following:

> Nintedanib was negative for *genotoxicity* in the *in vitro* bacterial reverse mutation assay, the mouse lymphoma cell forward mutation assay, and the *in vivo* rat micronucleus assay.

12.8 Impairment of fertility

The review recommends major edits to BI's proposal for the Impairment of Fertility section the nintedanib label. Edits were made to reflect the findings in fertility studies in animals which BI dismissed. BI proposed the following to describe the effect of nintedanib on fertility in animals:

(b) (4)

The review finds that the above statements do not accurately describe the effect of nintedanib on fertility in female animals. Section 11.6 of the review concludes that nintedanib impairs female fertility in rats. The conclusion was based on findings in U13-2650 and related studies. In U13-2650, females dosed with nintedanib prior to, during, and after mating showed remarkable treatment-related effects, including statistically significant, dose-related increases in post-implantation loss and resorptions at ≥ 20 mg/kg/day ($P < 0.05$). Thirteen of the 24 rats receiving 100-mg/kg/day nintedanib had no live fetuses. Among them, 5 rats had no corpora lutea ($P > 0.05$) and 8 had total resorption of the litter ($P < 0.05$). Among the rats with live fetuses, the 100-mg/kg/day group showed statistically significant decreases in the number of live fetuses ($p < 0.0001$), and increases in resorptions and post-implantation losses ($P < 0.0001$). This was accompanied by statistically non-significant decreases in fertility index (↓21%) and gestation index (↓ 37.9%). General toxicity studies showed that nintedanib affected the ovaries in female mice and rats. Effects on ovaries include changes in the number and sizes of corpora

lutea. Even U13-2650 itself states that the NOAEL for female mating and fertility was 20 mg/kg/day.

Furthermore, the effect of nintedanib on female fertility was more pronounced than tofacitinib, another approved and marketed TK inhibitor that decreases female fertility in rats. Approved on November 6, 2012, the tofacitinib labeling (Xeljanz, NDA 203-214) states that the drug decreases female fertility in rats based on the findings that rats showed increases in post-implantation losses.[16] Nintedanib causes not only implantation loss, but also a number of other effects described above. As such, the review recommends description of the above findings in the fertility section and recommends the following text for the Impairment of Fertility section:

> In rats, nintedanib reduced female fertility at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day). Effects include increases in resorption and post-implantation loss, and a decrease in gestation index. Changes in the number and size of corpora lutea in the ovaries were observed in chronic toxicity studies in rats and mice. Increases in resorption only were observed at exposures approximately equal to the MRHD (on a AUC basis at an oral dose of 20 mg/kg/day). Nintedanib has no effect on male fertility in rats at exposure levels approximately 3 times the MRHD (on an AUC basis at an oral dose of 100 mg/kg/day).

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Pharmacologist/Toxicologist

Marcie Wood, Ph.D.
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13 Appendices

Item	DARRTS ID#	Review author	Completion date	Review Content
A	2944664	L. Pei	05/10/11	Original IND review and chronic toxicity studies
B	3050367	L. Pei	11/28/11	Evaluation of BI's response to Agency comments on reproductive toxicity studies
C	3076935	L. Pei	01/25/12	Need for a full reproductive toxicity program
E	2841259	S. Lee	09/27/10	3-mouth mouse toxicity study and protocol for mouse carcinogenicity study
F	2841263	S. Lee	09/30/10	3-mouse rat toxicity study and protocol for rat carcinogenicity study

[16] In rats, tofacitinib at exposure levels approximately 17 times the MRHD (on an AUC basis at oral doses of 10 mg/kg/day) reduced female fertility due to increased post-implantation loss. There was no impairment of female rat fertility at exposure levels of tofacitinib equal to the MRHD (on an AUC basis at oral doses of 1 mg/kg/day). Tofacitinib exposure levels at approximately 133 times the MRHD (on an AUC basis at oral doses of 100 mg/kg/day) had no effect on male fertility, sperm motility, or sperm concentration (Ref.: DARRTS ID 3502430).

DEPARTMENT OF HEALTH AND HUMAN SERVICES

PUBLIC HEALTH SERVICE

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	74,683
Supporting document/s:	Vol. 7.1 – 7.70
Sponsor's letter date:	March 14, 2011
CDER stamp date:	March 15, 2011
Product:	BIBF 1020
Indication:	(b) (4) pulmonary fibrosis
Sponsor:	Boehringer Ingelheim
Review Division:	Division of Pulmonary, Allergy and Rheumatology Products
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: December 7, 2009

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1 Executive Summary

1.1 Recommendations

1.1.1 Clinical Studies Safe to Proceed:

Yes. The proposed clinical trials are safe to proceed. The available clinical data support the safety of the proposed use of BIBF 1120 although the nonclinical data in the application is deemed insufficient. The sponsor proposed to treat adult patients with idiopathic pulmonary fibrosis with BIBF 1120 for 52 weeks. Pivotal nonclinical data in support of the safety of the proposed trial are 6- and 9-month toxicity studies in rats and monkeys (one each), respectively. The NOAEL was established in rats but not in monkeys. The rat NOAEL of 5 mg/kg/day (AUCs between 16.4 – 29.2 ng.h/mL) does not provide a sufficient safety margin for the proposed clinical dose of 300 mg/day (AUC of 308 ng.h/mL), on a plasma drug AUC basis. However, there is adequate clinical experience to support the proposed use of the drug, as determined in the DPARP IND Safety Meeting held on April 12, 2011.

1.1.2 If Not Safe to Proceed, Recommendations to Allow Clinical Study to Proceed

1.1.3 Additional Recommendations

Convey the information in the External Communication section (page 36) to the sponsor.

1.2 Brief Discussion of Nonclinical Findings

BIBF 1120 is an inhibitor of tyrosine kinases of receptors of at least 3 growth factors: platelet derived growth factor (PDFG), vascular endothelial growth factor (VEGF), and fibrotic growth factor (FGF). BIBF 1120 inhibited the progression of lung fibrosis and expression of pro-fibrotic gene markers in a bleomycin-induced lung fibrosis model in rats.

General, genetic and reproductive toxicity studies of BIBF 1120 were submitted. Each of these in vivo studies used the oral (gavage) route of administration. The general toxicity studies including chronic toxicity studies identified the following target organs of toxicity: bones (including the growth plate), bile duct, liver, spleen, kidney, adrenals, thymus, and ovaries. BIBF 1120 did not affect the fertility in male rats but was teratogenic in rats.

Chronic toxicity

The chronic toxicity studies of BIBF 1120 included 6 and 12-month oral toxicity studies in rats and monkeys, respectively. In the 6-month rat study (Report U05-1484), Wistar rats (20/sex/dose) were dosed by oral gavage 0, 5, 20 and 80-mg/kg/day BIBF 1120 for up to 26 weeks. Additional rats were included to evaluate the reversibility of lesions (i.e., Recovery section: 10/sex in the C and HD group) and toxicokinetics (i.e., TK section: 6/sex/dose). The respective mean AUCs of BIBF

1120 in the LD, MD and HD groups on day 179 were 16.4, 184 and 1240 ng.h/ml in males and 29.2, 316 and 1030 ng.h/ml in females.

Treatment-related effects were observed in clinical signs, body weight, macro- and microscopic examinations in the MD and HD groups. The HD group (main study only) was terminated in week 24 due to poor condition. Clinical signs included fractured teeth, gingiva swelling and liquid feces. Body weight in male rats was decreased approximately 6% and 16% in the MD and HD groups, respectively.

Histological findings were observed in the liver, spleen, kidney, bone marrow, adrenal glands, thymus, ovaries, bile duct, and incisor in the MD and HD group. The liver finding was periportal hemosiderosis and the brown pigment in the hepatocytes, Kupffer cells and partially in interstitial macrophages. Mineralization (minimal to moderate) of the connective tissue, depletion of the lymphoid cells (minimal or mild), and extra-medullary hematopoiesis (slight) were observed in the spleen. Tiny depositions of hyaline material or droplets were observed in the glomerular endothelial cells and podocytes in the kidney. Also observed was focal basophilic tubules (minimal to mild), tubular protein casts (minimal to mild), and dusty fat droplets and pigment storage in tubular epithelium (minimal to slight). Peliosis or angiectasis (slight to severe) and cortical tissue hyperplasia were observed in the adrenal glands. Cellular depletion of hematopoietic cells was observed in the bone marrow.

Thymus involution (moderate) partly accompanied by a mild increase in the number of apoptotic cells was observed in the HD group. In the ovaries, the size of the corpora lutea was decreased while the number of corpora lutea was increased. Some altered corpora lutea developed a liquefactive necrotic center instead of a physiological vascularisation of the central cavity (corpus luteum, necrosis, liquefactive). In several cases, the internal Theca cells of sex cord stroma had pronounced hyperplasia.

In the knee (distal femur and proximal tibia), the epiphyseal cartilage was thickened in two females at 20 mg/kg and in the majority of animals at 80 mg/kg. This thickening was mainly due to an elongation of the chondral columns (hypertrophic chondrocytes). In the incisors, dysplasia (minimal to severe) was observed. Slight dysplasia exhibited irregularities of the ameloblasts and/or odontoblasts. Moderate dysplasia revealed further aggravation and first regressive lesions in the pulp cavity and/or mild inflammation and hyperplastic epithelium of the gingival sulcus and dental alveolus. The irregularities of enamel and dentin, ameloblasts and odontoblasts resulted in dental deformations and fractures. Inflammation and hyperplasia of the ductal epithelium were observed in the main bile duct.

The NOAEL in the 6-month rat study was 5 mg/kg/day. This dose corresponds to mean AUCs of 16.4 and 29.2 ng.h/ml in males and females, respectively, on day 179.

In the 12-month monkey study (Report U10-1875), Rhesus monkeys (4/sex/dose) were dosed by oral gavage with 0, 10, 20 and 60/45/30 mg/kg/day of BIBF 1120 for 52 weeks. Additional monkeys (2/sex/dose) were included in the C and HD groups to evaluate the reversibility of lesions. The BIBF 1120 dose in the HD group was started at 60 mg/kg/day but was reduced twice during the study due to overt toxicity.

Specifically, the BIBF 1120 doses were 60, 0, 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-26, and 26-55, respectively. The respective mean AUCs of BIBF 1120 in the LD, MD and HD groups on day 363 were 787, 831 and 1,100 ng.h/ml in males and 506, 1220 and 1,660 ng.h/ml in females.

Treatment-related effects were seen in all BIBF 1120 dosed groups, although the effect in the LD group was limited in the bone (i.e. growth plate thickening) and changes in clinical signs and body weight were limited to the MD and HD groups. Two HD monkeys (one in each sex) were sacrificed due to poor conditions while on 45-mg/kg/day dosing. Monkeys 736 (F) and 737 (M) were killed in week 11 and 24, respectively, due to clinical signs such as liquid feces, and under-activity. Microscopic findings of these monkeys were generally similar to that of the terminally killed monkeys of the group. In addition, microscopic examination of monkey 737 revealed minimal inflammatory cells with necrotic debris were seen at the tips of the villi in the small intestine and the mucosal surface in the large intestine. The respective mean weight gain during the course of the study (week 0 – 52) in the C, LD, MD and HD groups was 1.94, 1.41, 1.14 ($p < 0.05$) and 0.73 kg ($p < 0.01$) in males; and 1.51, 1.31, 1.10 and 0.88 ($P < 0.05$) kg in females.

Histological findings were present in all dose groups. These included thickening of growth plate of the bones (femur, tibia and sternum) and atrophy of the zona fasciculata in the adrenal gland. The HD group also showed cortex and trabecular bone thinning in the sternum. Table 3 presents the incidence and severity of these lesions. Growth plate thickening in the femur remained in the recovery monkeys. The respective incidence (slight in severity) in the control and HD groups was 0/2 and 1/1 in males; and 0/1 and 1/2 in females.

The study did not establish the NOAEL, due to findings of growth plate thickening in the low dose group. This conclusion disagrees with the study report that judged the LD as the NOAEL.

Reproductive Toxicity

BIBF 1120 did not affect the fertility in male rats but was teratogenic in rats. The submitted reproductive toxicity studies included a male fertility study and non-GLP dose range findings teratology study in rats. In the male fertility study (Report U10-1128), Wistar Rats (24 males/dose) were dosed by oral gavage with 0, 5, 20, or 100 mg/kg/day of BIBF 1120 for up to 13 weeks before they were allowed to mate with untreated females (1:1 ratio for up to 7 days). Effects on fertility were evaluated by the ability of the males to impregnate their female partners and examination of implantation loss and resorption rate in pregnant females which were sacrificed on gestation day 14. The following parameters were examined in the females: resorption, resorption rate, implantation loss, and number of corpora lutea. The reproductive organs (i.e., testes, epididymides, prostate glands, seminal vesicles and coagulating glands) in males were also evaluated microscopically. Clinical signs in the study were similar to that described previously. Loose and broken incisors in the upper and/or lower jaw (totally or partially) were detected in 4 and 23 males in the 20 and 100 mg/kg/day groups, respectively. The HD males showed statistically a significant decrease of mean body weight. No treatment-related effects were observed in male fertility parameters or morphology in the reproductive organs. The

NOAEL was 5 and 100 mg/kg/day for general toxicity and fertility potential, respectively.

BIBF 1120 caused fetal malformations when given to pregnant rats during the organogenesis period. In non-GLP dosing ranging studies (Reports U07-1710 and U07-1814), pregnant Wistar rats (10/dose) were given by orally gavage 5 – 180-mg/kg/day BIBF 1120 in Natrosol® 250 HX during the gestation period of days 7 – 16. No maternal mortality was observed at any doses, but no viable fetuses were available at ≥ 20 mg/kg/day. The 10 mg/kg/day dams showed statistically significant increases in fetal absorption and malformations: no truncus bracheocephalicus, origin of A. pulmonalis and aortic arch changed, and cleft thoracal vertebral body. No significant effect was observed at 5-mg/kg/day group.

2 Drug Information

2.1.1 CAS Registry Number (Optional)
Not available

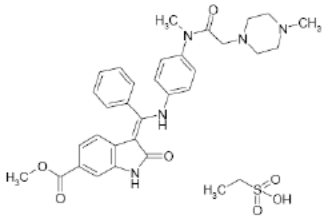
2.1.2 Generic Name
Not available

2.1.3 Code Name
BIBF 1120 (base), BIBF 1120 ES (salt, monoethanesulfonate)

2.1.4 Chemical Name
1H-Indole-6-carboxylic acid, 2, 3-dihydro-3-[[[4-(methyl [(4-methyl-1-piperazinyl)-acetyl]amino)phenyl]amino]phenylmethylene]-2-oxo-, methyl ester, (3Z)-, mono-ethanesulfonate

2.1.5 Molecular Formula/Molecular Weight
Free base: 539.6; mono-ethanesulfonate salt: 649.8

2.1.6 Structure:



2.1.7 Pharmacologic class
Inhibitor of tyrosine kinase of receptors of the following growth factors: platelet derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibrocyte growth factor (FGF). It is hypothesized that down-regulation of PDGF/R, VEGF/R and FGF/R dependent signal cascades may translate into inhibition of the fibrotic process in IPF.

2.2 Relevant IND/s, NDA/s, and DMF/s:

(b) (4)

2.3 Clinical Formulation

2.3.1 Drug Formulation

Oral capsules. Each capsule consists of 50-mg BIBF 1120 (i.e., (b) (4) BIBF 1120 ES), (b) (4) glycerides (b) (4) and (b) (4) lecithin, according to the nonclinical review completed by Dr. Kimberly Benson on April 7, 2005 (b) (4)

2.4 Proposed Clinical Population and Dosing Regimen

Two duplicate phase 3 clinical trials were proposed (Report/Study #1199.32 and #1199.34; Protocol #U11-1000-01). A total of 485 IPF patients 40 years and older (N = 291 and 194 for the treatment and placebo groups, respectively) will be enrolled in each trial. A patient will receive either 150-mg BIBF 1120 bid or placebo for 52 weeks. Men and women of child-bearing potential must use contraceptive methods to prevent pregnancy from occurring. The trials will be double-blind, randomized, placebo-controlled trials and will evaluate the safety and efficacy of BIBF 1120 in slowing decline in pulmonary function. Patients will be allowed to reduce BIBF 1120 dose to 100 mg bid if the 150-mg bid dose is not tolerated.

2.5 Regulatory Background

2.5.1 Previous Clinical Experience

The pre-IND meeting package submitted on October 19, 2010, stated that a total of 667 patients have received BIBF 1120 treatment for at least 52 weeks and 339 patients have been treated for more than 52 weeks. The sponsor has also completed a 52-week Phase-2 safety, dose-finding, proof-of-concept trial of BIBF 1120 in IPF patients in Japan (Study 1199.30). BIBF 1120 doses in the trial were 0, 50 mg qd, 50 mg bid, 100 mg bid, 150 mg bid, respectively. A total of 432 randomized patients (N = 85 – 86 per treatment group) were enrolled.

(b) (4)

2.5.1 History of Regulatory Submission

Boehringer Ingelheim (BI) has three active INDs of BIBF 1120 in the Agency. Their IND (b) (4) 74,683 (the current application) (b) (4). Table 1 (next page) presents an overview of these applications. DPARP is processing IND 74,683 (b) (4) The intended indication is (b) (4) pulmonary fibrosis (IPF) (b) (4) Further, INDs 74,683 and (b) (4) use BIBF 1120 as a monoproduct (b) (4)

DPARP held two meetings with the sponsor regarding to the development of BIBF 1120 for (b) (4) pulmonary fibrosis indication in IND 74,683. These meetings were held on August 2, 2006 and December 1, 2010, respectively. The first meeting was a pre-IND meeting that discussed the developmental strategy and nonclinical requirement for the drug development.

Table 1: BIBF 1120 INDs

IND	Division	Drug	Indication	Date of IND opening	Stage of clinical development
(b) (4)	DDOP	BIBF 1120	(b) (4)	(b) (4)	Phase 3
(b) (4)	DDOP	BIBF 1120			Phase 3
74,683	DPARP		(b) (4)	3/14/2011	Phase 2

The second meeting was an End-of-Phase 2 meeting discussed the nonclinical requirement for phase-3 clinical development. Specifically, the 01-DEC-2010 meeting discussed the following three topics:

1. Reproductive toxicity: Female fertility and 2 GLP embryo-fetal development studies (rat and rabbit each) should be completed prior to initiating Phase 3 studies. Alternatively, inclusion of two methods of birth control in the Phase 3 studies is an acceptable path forward while completing the reproductive toxicology program.
2. General toxicity: The Sponsor should provide rationale with supportive data for selection of the Rhesus monkey rather than the Cynomolgus monkey for the non-rodent species in the chronic toxicity study.
3. The timing of submitting the carcinogenicity final study reports: Whether the final report of the studies should be submitted in the DNA submission or as a phase 4 commitment is a review issue.

Also, two-year oral carcinogenicity studies of BIBF1120 in rats and mice are currently ongoing. BIBF 1120 doses were 2.5, 5 and 10 mg/kg/day in rats and 5, 15 and 30 mg/kg/day in mice, respectively. The Executive CAC concurred with the dose selections on September 14, 2010. See nonclinical reviews completed by Dr. Shwu-Luan Lee on September 30, 2010 (b) (4).

3 Studies Submitted

3.1 Studies Reviewed

Study No.	Description	Location (Vol.)
	Pharmacology	
U02-1109	Potency of BIBF 1120 on growth factors induced cell proliferation in vitro	7.3
U02-1310	Specificity of BIBF 1120 on selected kinases	7.3
U06-1479	Effect of BIBF 1220 ES on bleomycin-induced lung fibrosis in rats	7.3
U06-1451	Effect of BIBF 1220 ES on bleomycin-induced lung fibrosis in rats	7.4
	Toxicology	

Study No.	Description	Location (Vol.)
U05-1843	6-month oral gavage study in rats	7.18-22
U05-2245	3-month oral gavage study in Rhesus monkeys	7.28-30
U05-2274	12-month oral gavage study in Cynomolgus monkeys	7.31-35
U07-1128	Fertility study in male rats (also #09B060)	7.40-42
U07-1710	Non-GLP teratology dose ranging study in rats (Also #07B02)	7.39-40
U07-1814	Non-GLP teratology dose ranging study in rats (Also #07B30)	7.40

3.2 Studies Not Reviewed

Following studies were not reviewed because they had been reviewed previously.

Study No.	Description	Location in submission	Reference # in DARRTS [a]
U10-1798	13-week oral toxicity study in rats	7.36-38	2841259
U10-1799	13-week oral toxicity study in rats	7.38-39	2841263
U04-1605	13-week oral toxicity study in rats	7.16-18	
U02-1841	Ames Test (also Study# 02B41)	7.39	2841259
U02-1512	Mouse lymphoma assay (#02B079)	7.39	2841259
U01-1650	Rat micronucleus assay (#GPT-100164)	7.39	2841259

a. References 2841559 and 2841263 both were nonclinical reviews completed by Dr. Shwu-Luan Lee on September 30, 2010 (b) (4).

Following studies were not reviewed because they are not pivotal to the safety evaluation of the proposed clinical protocol.

Study No.	Description	Location (Vol.)
	Pharmacology	
U02-1084	Receptor binding of BIBF 1120, BIBF 1178 and ZD 6474	7.3
U02-1407	Efficacy of BIBF 1120 on VEGFR-2 in nude mouse xenografts and a rat tumor model	7.3
U03-1488	Wash-out experiment with VEGFR-2 in vitro	7.4
U06-1478	BIBF 1120 inhibits TGF-b-mediated transformation of fibrosis to myofibroblasts	7.4
	Safety Pharmacology	
U02-1258	Effect of BIBF 1120 CL on behaviors in mice	7.3
U06-1465	Effects of BIBF 1120 CL on respiratory parameters in conscious rats	7.4
U02-1674	Cardiovascular safety pharmacology of BIBF 1120 CL functions in anesthetized rats	7.3
U02-1288	Effect of BIBF 1120 BS on hERG channel current in vitro	7.3
U02-1288	Effect of BIBF 1120 BS on hERG channel current in vitro	7.3
U02-1260	Effect of BIBF 1120 CL on renal and liver functions in conscious rats	7.3
U02-1248	Effect of BIBF 1120 CL on gastric secretion in rats	7.3
U02-1259	Effect of BIBF 1120 CL on gastrointestinal transit in rats	7.3
U02-1258	Effect of BIBF 1120 CL on gastric emptying in rats	7.3
U06-1416	Effects of BIBF 1120 CL on liver function in conscious rats	7.4
U03-1537	Modified Irwin behavioral test in rats	7.11
	Analytic method and validation reports	
U02-1356	HPLC-MS/MS method validation – extraction procedure	7.4
U03-1161	HPLC-MS/MS method validation - stability	7.4

Study No.	Description	Location (Vol.)
U04-1406	HPLC-MS/MS method validation – sample preparation	7.5
U04-1241	HPLC-MS/MS method validation - automation	7.5
U04-1873	HPLC-MS/MS method validation – automation and extraction	7.5
U09-1135	HPLC-MS/MS method validation - quantitation	7.5
U09-1207	HPLC-MS/MS method validation - automation	7.5
U09-1208	HPLC-MS/MS method validation - acylglucuronide BIBF 1120	7.5
U09-1397	HPLC-MS/MS method validation – acylglucuronide BIBF 1120	7.6
	Absorption	
U02-1381	PK after PO and IV administration in male rats	7.6
U02-1494	Absorption, distribution, metabolic & excretion pattern in rats	7.7
U02-2128	In vitro plasma binding data in rat, monkey and human plasma	7.7
U02-1494	In vitro plasma binding data in rat, monkey and human plasma	7.7
	Distribution	
U03-1150	Species comparison in vitro plasma binding and distribution to RBC	7.7
U03-1563	Whole body autoradiography in IV administration in rats	7.7
U08-1952	Plasma binding of ^{14}C-BIBF 1202 glucuronide in rat, monkey and human plasma	
U08-2181	Plasma binding of ^{14}C-BIBF 1202 ZW in rat, monkey and human plasma	7.7
U09-1949	Plasma binding of ^{14}C-BIBF 1120 in monkey plasma	7.7
U09-2019	Plasma binding of ^{14}C-BIBF 1120 in mouse plasma	7.7
U09-2517	Distribution of ^{14}C-BIBF 1120 after multiple oral dosing in male rats	7.7
	Metabolism	7.7
U02-1649	In vitro glucuronidation of BIBF 1202 ZW in liver microsomes of rats, dogs, monkeys and humans	7.7
U03-1269	Structure and characteristics of glucuronidation of BIBF 1202 ZW	7.7
U03-1355	Role of cytochrome P450 enzymes in ^{14}C-BIBF 1120 metabolism	7.8
U03-1386	Effects P450 enzyme inhibition BIBF 1120 metabolism	7.8
U03-1935	Metabolism of BIBF 1120 in rats	7.8
U04-2195	Induction of P450 enzymes no BIBF 1120 metabolism	7.9
U05-1001	Metabolism of BIBF 1120 by rat and human hepatocytes in vitro	7.9
U05-2098	Metabolism of BIBF 1120 in Rhesus monkeys	7.9
U05-3076	Involvement of hepatic transporter in BIBF 1120 and BIBF 1120 ZW metabolism by rat and human hepatocytes in vitro	7.9
U06-1106	Effect of BIBF 2992 MA2 on BIBF 1120 metabolism	7.10
U06-1667	Metabolism of BIBF 1202 by UDP-glucuronosyltransfearse in vitro	7.10
U06-2240	Investigation of trace metabolites of BIBF 1120 in rats	7.10
U08-1140	Metabolism of BIBFs 1120 and 1202 by intestinal UDP-glucuronosyltransfearse from rat and human in vitro	7.10
U08-1256	Inhibition of BIBF 1202 metabolism by p450 dependent reactions	7.10
U09-2277	Metabolism and excretion of BIBF 1120 in mice	7.10
	Excretion	
U05-1558	PK & excretion balance of total radioactivity after IV dosing in monkeys	7.11
	Other PK studies	
U02-1497	Synthesis of [indole-3-^{14}C]BIBF 1120 ES	7.11
U09-1975	PK of BIBF 1120 ES after single oral dose in nu/nu-mice	7.11
	Toxicology	

Study No.	Description	Location (Vol.)
U04-1066	Single oral dose toxicity study in mice	7.11
U02-1491	Single oral dose toxicity study in rats	7.11
U04-1067	Toxicokinetics after single PO and IV dosing in Rhesus monkeys	7.12
U02-1526	2-week exploratory PO toxicity study in rats	7.12
U02-1724	2-week exploratory PO toxicity study of BIBF 1120 BS & other candidates in rats	7.12
U06-1063	2-week exploratory PO toxicity study of BIBF 1120 CL in rats	7.13
U04-1812	4-week PO toxicity study of BIBF 1120 ES in rats	7.14
U09-1403	IV dose range finding study in rats	7.22
U05-2450	2-week oral preliminary study of BIBF 1120 CL in dogs	7.23
U03-1707	Pilot oral preliminary study of BIBF 1120 CL in cynomolgus monkeys	7.24
U05-2452	TK of or BIBF 1120 ES after IV and PO dosing in Rhesus monkeys	7.25
U03-1326	4-week oral toxicity study of BIBF 1120 ES in cynomolgus monkeys	7.26
U05-2427	4-week oral toxicity study of BIBF 1120 ES in Rhesus monkeys	7.31
U07-2324	Oral MTD study of BIBF 1120 ES in minipigs	7.35
U09-1797	2-week preliminary oral toxicity study in mice	7.35
U03-1151	Acute eye irritation study in rabbits	7.42

3.3 Previous Reviews Referenced:

This review references nonclinical reviews completed by Dr. Wei Chen on January 30, 2004 (b) (4); and Drs. Kimberly Benson on April 7, 2005 and Shwu-Luan Lee (DARRTS Reference IDs 2841259 and 2841263) on September 30, 2010 (b) (4).

4 Pharmacology

BIBF 1120 is an inhibitor of tyrosine kinases of receptors for at least 3 growth factors: platelet derived growth factor (PDFGR), vascular endothelial growth factor (VEGF), and fibrotic growth factor (FGF). In vivo data showed that BIBF 1120 was effective in a bleomycin-induced lung fibrosis model in rats. Data also showed that intratracheal administration of BIBF 1120 inhibited the expression of pro-fibrotic gene markers in the same rat model.

4.1 Primary Pharmacology

BIBF 1120 was effective in a bleomycin-induced lung fibrosis model in rats. BIBF1120 was administered orally once daily at doses 8.3, 25 and 42 mg/kg/day for 10 days (Report U06-1451). Expression of pro-fibrotic marker genes in lung was partially and statistically significant reduced at LD and completely blocked at higher doses. Histological examination of the lungs revealed no improvement at LD, variable results at MD and improvement at HD. Therapeutic plasma concentration of BIBF 1120 in humans was expected to be 50-100 ng.h/ml for the expression of fibrotic marker genes and 200-600 ng.h/ml based on histopathological evaluations.

BIBF 1120 inhibits cell proliferation induced by VEGF and fetal bovine serum (bFGF) and kinase activities of these growth factors in vitro (Report U02-1109). Human umbilical vain endothelial cells (HUVEC) and human skin micro-vascular endothelial cells (HSMEC) fed

with VEGF or bFGF were cultured in the presence and absence of BIBF 1120. Cell proliferation was measured by the rate of [^{3}H]-thymidine incorporation. Enzymatic activity was measured by the rate of γ-^{33}P-ATP incorporation. BIBF 1120 inhibited VEGF-driven and bFGF-driven cell proliferation with respective IC50s of 9 and 341 nm in HUVEC cells; and 12 and 218 nm in HSMEC cells. The IC50 for kinase activity was 34, 21 and 46 nM for human VEGFR-1, VEGFR-2, and VEGFR-3, respectively. The IC50 for inhibiting murine VEGFR-2 (flk-1) kinase activity was 14 nM. Report U02-1310 showed that the IC50 of BIBF 1120 in inhibiting the kinase activity was 13, 59, 69, 4117, and > 50 nM for VEGFR-3, platelet derived growth factor (PDFGRα), FGFR1, insulin receptor (InsR), and her2, respectively.

Efficacy of BIBF 1120 was investigated by histology and pro-fibrotic marker genes. In Report U06-1479, rats were dosed by intratracheal instillation of 2.2 mg/kg bleomycin. BIBF 1120 ES (0 or 50-mg/kg/day) was given for 12 days starting on day 10 post-bleomycin treatment. The rats were killed on day 21 and the lung was examined microscopically. BIBF 1120 blocked bleomycin-induced lung fibrosis. In Report U06-1451, rats were treated in a similar schedule as in Report U06-1479 except that two lower doses (10 and 30 mg/kg/day BIBF 1120 ES) were included. Levels of pro-fibrotic marker genes (procollagen and TGFb1) were measured. Dose-related decreases in the levels of pro-fibrotic marker genes were observed. The gene expression was completely blocked at the MD and HD groups.

The sponsor postulated that therapeutic plasma concentration of BIBF 1120 in humans was expected to be 50-100 ng.h/ml for the expression of fibrotic marker genes and 200-600 ng.h/ml based on histopathological evaluations.

4.2 Secondary pharmacology

No secondary pharmacology studies were submitted.

4.3 Safety pharmacology

BIBF1120 had no effects on behavioral parameters, body temperature, or locomotion in mice. In rats, both renal and hepatic function was modestly affected in a dose-dependent fashion. Also, gastric emptying and gastrointestinal transit were inhibited at the highest dose tested in rats. Myocardial repolarization remained unaffected by BIBF1120 in vitro.

5 Pharmacokinetics/ADME/Toxicokinetics

5.1 PK/ADME

After intravenous administration, plasma clearance was high in the rat (~ 200 mL.kg/min) and moderate to high in both monkey species (~ 30 to 40 mL.kg/min). Half-lives of about 4, 6h and 7 h were calculated for rat, cynomolgus and rhesus monkey, respectively. The high volume of distribution (Vss) of about 41, 9 and 10 L/kg, respectively, indicated a good tissue penetration of the compound. There was no evidence for a sex-related effect; the exposure to BIBF 1120, BIBF 1202 and BIBF 1202-glucuronide increased almost proportionally with the dose in the rat. Feces were the main route of excretion. In Rhesus monkeys, cumulative fecal excretion was 85.6 % following intravenous administration and 88.9 % following oral administration. The median 168 h cumulative urinary excretion was 5.21 % following

intravenous administration and 1.54 % following oral administration. Table 2 summarizes these pharmacokinetic parameters.

Table 2: Pharmacokinetic Parameters of BIBF 1120

	Rat	Monkey		Human
		Cynomolgus	Rhesus	
t ½ (hr)	4	6	7	17.9
Vss (L/kg)	41	9	10	
Excretion: Fecal	65% (biliary)			
Urine	1.4%			0.7%
Protein Binding	97.2%	92.9%	91.4%	97.8%
Bioavailability	12%	15 - 20%	15 - 20%	5%

Metabolism pathways of BIBF 1120 in humans and major metabolism pathways in animal species have been studied. CYP 3A4 was the predominant enzyme involved in the formation of hydroxylated and desmethylated metabolites. BIBF 1202 is a major metabolite of BIBF 1120 desmethylation. BIBF 1120 was detected in toxicity studies in both rats and monkeys. Figure 1 is a schematic presentation of BIBF 1120 pathways.

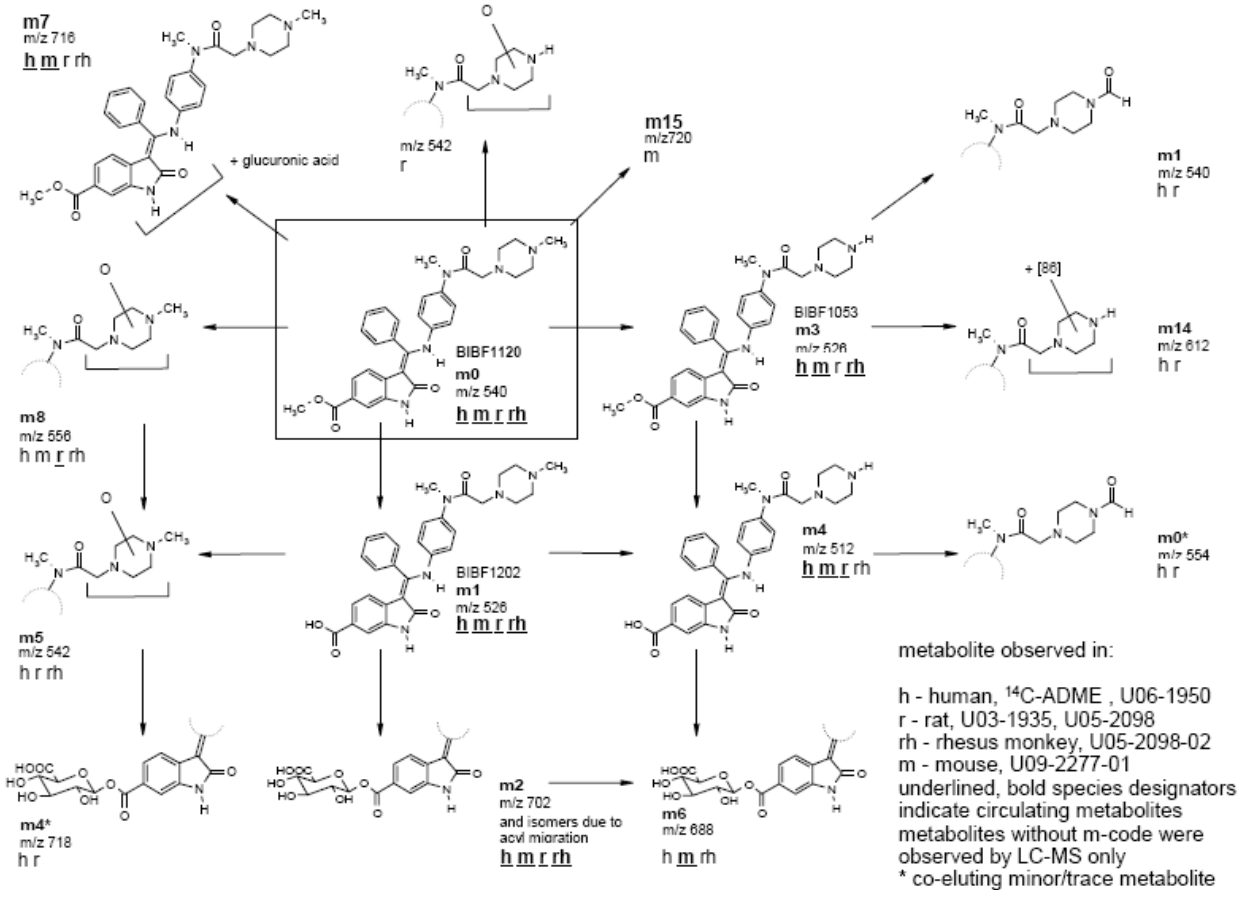


Figure 1: Metabolism pathways in humans and major metabolism pathways in animal species

5.2 Toxicokinetics

BIBF 1120 does not accumulate in the body in either rats or monkeys. Table 3 presents the BIBF AUCs in 3- and 12-month toxicity studies in monkeys. The rat data were similar (See the 6-month rat toxicity study for additional information).

Table 3: BIBF 1120 AUCs between Cynomolgus and Rhesus Monkeys

			AUC (ng.h/mL)						
BIBF 1120 (mg/kd/day, PO)			3	10	15	20	30	45	60
Cynomolgus	Day 1	M	307	979	1430		1920		
U05-2246		F	330	595	1100		2070		
	Day 91	M	305		1370	1870			
		F	345		1310	1320			
Rhesus	Day 1	M		979		1150			5971
U10-1875		F		595		1730			6250
	Day 91	M		809		1370		2220	
		F		610		1110		2710	
	Day 189	M		765		989	1440		
		F		479		1370	1870		
	Day 365	M		787		831	1100		
		F		506		1220	1600		

6 General Toxicology

6.2 Repeat-Dose Toxicity

6.2.1 6-Month Study in Rats

Study title:	**BIBF 1120 ES: 6-month oral (gavage) toxicity study in rats with an 8-week recovery period**
Study no.:	Report/Doc. # U05-1843; Report/Study No. 03B073
Study report location:	14-MAR-2011 submission, Vol. 7.18-22; or Module 4, vol. 4.16-20.
Conducting laboratory and location:	Boehringer Ingelheim (Department of Nonclinical Drug Safety), Biberach, Germany
Date of study initiation:	June 16, 2003
GLP compliance:	Yes, the statement signed
QA statement:	Yes, the statement signed
Drug, lot #, and % purity:	BIBF 1120 ES, Batches 8230091, purity of 98.3%

Key Study Findings

- Rats (20/sex/dose) were dosed by oral gavage with 0, 5, 20, or 80 mg/kg/day of BIBF 1120 for up to 26 weeks.

- The HD group was terminated in week 24 due to poor health conditions. Deaths were also observed in the MD group.
- The Target organs of toxicity included the bone, thymus, ovaries, teeth, liver and bile duct, spleen, kidney, adrenal glands.
- The NOAEL was 5 mg/kg/day that corresponded to the respective BIBF 1120 and BIBF 1202 AUCs of 16.4 and 44.1 ng.h/ml in males; and 29.2 and 67.7 ng.h/ml in females. This conclusion is in agreement with the study report.

Study Summary: Wistar Rats (20/sex/dose) were dosed by oral gavage with 0, 5, 20, or 80 mg/kg/day of BIBF 1120 for up to 26 weeks. Additional rats (10/sex/dose) were included in the C and HD groups to evaluate the reversibility of lesions after an 8-week recovery period. Each of the 4 groups also included additional 6 rats per sex to evaluate toxicokinetics of the drug. Table 4 presents the study design. The HD group was terminated in week 24 due to poor health conditions. The major findings are listed above in the Key Study Findings section.

Table 4: Design of the 6-month Oral Toxicity Study in Rats

Group	Dose (mg/kg/day)		Number of Rats/sex		
	BIBF 1120 ES	BIBF 1120	Main Study	Recovery	TK
1	0	0	20	10	6
2	6.13	5	20	-	6
3	24.5	20	20	-	6
4	98.0	80	20	10	6

Methods

Doses:	0, 5, 20, and 80 mg/kg/day
Dosing frequency:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	(b (4) (5% hydroxyethylcelluose)
Species/Strain:	CrlGlxBrlHan:WI (SPF quality)
Number/Sex/Group:	20,10 and 6/sex/dose for main study, recovery (C and HD only) and TK sections, respectively
Age:	8 – 9 weeks
Weight:	males 195.9 - 260.1 g, females 131.4 - 178.9 g
Satellite groups:	10/sex/dose for the C and HD groups for the (8-week) recovery section 6/sex/dose for the TK sections
Unique study design:	The HD group in both sexes was sacrificed in week 24 (treatment days 165-166) due to poor general condition and the lack of body weight gains.
Deviation from study protocol:	None

Observations and Results,

Mortality: Mortality was observed twice daily. Two MD rats (one in each sex on days 114 and 143, respectively) and 2 HD females (on days 162 and 157) were sacrificed prematurely due to poor weight loss and poor health conditions. Three HD rats (2 main study males and 1 kinetic section female) were found dead on days 156 – 168. The remaining HD rats were sacrificed on days 165 – 166 due to poor healthy conditions.

Clinical Signs: Clinical signs were observed daily. The MD and HD rats showed dose-related increases in the incidence of gingiva reddening and swelling, and fractures of incisors. These findings were observed from day 43 and onward (Table 5).

Table 5: Clinical Signs of the 6-month Oral Toxicity Study in Rats

	Daily dose BIBF 1120 BS [mg/kg]			
Clinical sign	**Control**	**5**	**20**	**80**
Gingiva reddening	None	None	onset Day 43 - 151 duration in all animals until end of observation / until necropsy	onset Day 31 - 78 duration in all animals until end of observation / until necropsy (including recovery phase)
Gingiva swelling	None	None	onset Day 43 - 151 duration in all animals until end of observation / until necropsy	onset Day 31 - 78 duration in all animals until end of observation / until necropsy (including recovery phase)
Fracture of incisors onset last occurrence animals affected occurrence during administration phase	None	None	 Day 43 - 165 Day 46 - 183 3/20 males, 9/20 females 1-11 x per animal	 Day 35 - 79 Day 63 - 165 (Day 184 in recovery animals) 30/30 males, 30/30 females 3-15 x per animal

Body Weights: Body weights were recorded weekly. The MD and HD males showed decreases in body weight (Table 6). The decreases in body weight in the HD rats remained after a 8-week recovery period. No treatment-related effects were observed in females.

Table 6: Mean body weight of the 6-month rat Study

BIBF 1120 (mg/kg/day)	Mean Body Weight (g)							
	Male				Female			
	0 mg	5 mg	20 mg	80 mg	0 mg	5 mg	20 mg	80 mg
Day 1	227.9	227.2	226.2	225.2	156.7	159.8	161.4	157.9
Day 162	414.3	406.5	391.4*	322.8*	229.0	232.9	231.3	224.0
Day 182	418.1	410.0	392.7*	350.2*	230.1	229.8	229.9	229.8
Day 220	449.3			390.1*	234.5			230.8

*, $p < 0.05$.

Food Consumption: The HD group showed moderate decreases in food consumption.

Ophthalmology: No treatment related effects were observed.

Hematology: A complete panel of hematological evaluations was done at pre-dosing and the end of the treatment and recovery periods. Red blood cell count was decreased in the 20 and 80 mg/kg groups, up to 26% in males and up to 20% in females on Day 86/87 and on Day 165/166 compared to Control.

Clinical Chemistry: A complete panel of hematological evaluations was done at pre-dosing and the end of the treatment and recovery periods. The HD recovery group showed increases in mean ALT (~150%), AST (~150%), and GLHD (glutamate dehydrogenase, ~200 – 480%) at the end of the recovery period.

Urinalysis: A complete panel of urinalysis evaluations was done at pre-dosing and the end of the treatment and recovery periods. A trend to slightly increased numbers of bacteria and inorganic phosphate were found on Day 163 (80 mg/kg), Day 170 (20 mg/kg) and on Day 219 (80 mg/kg) in males and females. In addition, protein concentrations (1.0 g/L or ⩾3.0 g/L) and white blood cells (ca. 500 cells/dL) were strongly increased in 3-4 of about 30 animals at 80 mg/kg on Day 163. Kidney cells were found in the female No. 358 (20 mg/kg group) on Day 170. These changes appeared to correlate with histopathological findings in the kidneys.

Toxicokinetics: Blood samples (0.3 ml) were drawn on Weeks 1, 3, 4, 13, 24 and 26. Sample time was 1, 2, 4, 8 and 24 hrs post dosing except for weeks 3 and 4 when samples were collected at 2 hours post dosing only. Both BIBF 1120 BS and 1202 were analyzed except week 3 when only [redacted] (b) (4) was analyzed. Drug levels were determined by HPLC-MS/MS with the lower limit of quantitation of 1 ng/ml. Table 7 presents the design of the toxicokinetic section of the study.

Table 7: Design of the TK section of the 6-Month Study in Rats

Sampling Time			Group	Analyte		
Week	Day	Hr (post dosing)		BIBF 1120	BIBF 1202	[redacted] (b) (4)
1	1	1, 2, 4, 8 & 24	1 - 4	X	X	
3	16	1, 2, 4, 8 & 24	1 - 4			x
4	22	2	1 - 4	X	X	
13	85	2	1 - 4	X	X	
24	164	1, 2, 4, 8 & 24	4	X	X	
26	179	1, 2, 4, 8 & 24	1 - 3	X	X	

Plasma drug levels increased super-proportionally to oral BIBF 1120 doses in both sexes. So did BIBF 1202, a major metabolite of BIBF 1120. The level [redacted] (b) (4) was below the lower limit of quantitation.

Table 8: Plasma Levels of BIBFs 1120 and 1202 in 6-month Rat Study

PK Parameter	Time (day)	Sex	Plasma Drug Level					
			BIBF 1120			BIBF 1202		
			LD [a]	MD	HD	LD	MD	HD
Cmax	1	M	3.38	29.7	378	8.84	56.5	298
	1	F	5.76	61.6	465	16.3	118	529
	179	M	5.12	41.1	173	11.9	76.2	429
	179	F	9.70	78.4	168	12.5	166	625
AUC (ng.h/ml) [a]	1	M	13.7	154	1270	38.1	333	1280
	1	F	24.6	232	1960	51.1	537	2430
	179	M	16.4	184	1240	44.1	407	1980
	179	F	29.2	316	1030	67.6	700	3000

a. The oral dose of BIBF 1120 was 5, 20 and 80 mg/kg/day in the LD, MD and HD groups, respectively.

Histopathology

Adequate Battery: Adequate. A complete panel of organ/tissues in every group was examined.

Peer Review: Yes.

Necropsy Findings: Dose-related increases in the incidence of abnormal observations were noted in spleen (mineralization of connective tissues), adrenal gland (discoloration and enlargement), bone marrow (soft or discoloration) and incisors (fractures) in the MD and HD groups. Table 9 presents in the incidence of these findings.

Table 9: Macroscopic Findings of the 6-Month Oral Study in Rats

BIBF 1120 (mg/kg/day)	0		5		20		80	
Sex	M	F	M	F	M	F	M	F
Number of monkeys examined	19	20	20	20	19	19	21	21
Spleen: Mineralization of connective tissue	0	0	0	0	1	1	18	9
Incisors/ lesions: lower jaw	0	0	0	0	3	6	17	16
Upper jaw	0	0	0	0	0	3	18	15
Bone marrow: Soft consistency and/or discoloration	0	0	0	0	0	1	4	7
Adrenal gland: Discoloration and/or enlargement	0	0	0	0	0	0	5	2
Region of the liver, pancreas and pylorus/ duodenum with noteworthy findings [a]	0	0	0	0	0	0	6	2

a, Dilatation, contents fluid, thickening, nodule.

Histological Findings: Histological findings were observed in the liver, spleen, kidney, bone marrow, adrenal glands, thymus, ovaries, bile duct, and incisor in the MD and HD group (Table 10, next page). The incidence and severity of the lesions were generally dose-related. The liver finding was periportal hemosiderosis and the brown pigment in the hepatocytes, Kupffer cells and partially in interstitial macrophages. Mineralization (minimal to moderate) of the connective tissue, depletion of the lymphoid cells (minimal or mild), and extramedullary hematopoiesis (slight) were observed in the spleen. Tiny depositions of hyaline material or droplets were observed in the glomerular endothelial cells and podocytes in the kidney. Also observed was focal basophilic tubules (minimal to mild), tubular protein casts (minimal to mild), and dusty fat droplets and pigment storage in tubular epithelium (minimal to slight). Peliosis or angiectasis (slight to severe) and cortical tissue hyperplasia were observed in the adrenal glands. Cellular depletion of hematopoietic cells was observed in the bone marrow.

Thymus involution (moderate) partly accompanied by a mild increase in the number of apoptotic cells in the HD group. In the ovaries the size of the corpora lutea was decreased while the number of corpora lutea were increased. Some altered corpora lutea developed a liquefactive necrotic center instead of a physiological vascularization of the central cavity (corpus luteum, necrosis, liquefactive). In several cases, the internal Theca cells of sex cord stroma had pronounced hyperplasia.

Table 10: Histological Findings in the 26-week Rat Study

BIBF 1120 (mg/kg/day)	0		5		20		80	
Sex	M	F	M	F	M	F	M	F
Number of monkeys examined	19	20	20	20	19	19	21	21
Liver: Hemosiderosis	0	0	0	1	1	15	15	21
Extramedullary hematopoiesis	0	1	0	2	6	10	9	13
Spleen: Mineralization of connective tissue	0	0	0	0	1	7	21	13
Depletion lymphoid	0	0	0	0	0	0	20	19
Extramedullary hematopoiesis increased	3	7	4	5	11	20	15	14
Kidney: PAS-positive hyaline droplets	0	0	1	0	3	5	21	20
Basophilic tubules, focal	5	2	3	0	3	0	11	18
Mononuclear infiltration, focal, cortical	3	1	0	2	4	1	9	9
Tubular protein casts	0	1	0	0	2	1	8	9
Increased fat droplets in tub. epithelium	0	1	0	0	0	0	11	16
Increased tubular pigment storage	8	7	5	5	5	8	12	16
Adrenal gland: Cortical peliosis/angiectasia	0	0	0	0	0	0	10	7
Diffuse cortical hyperplasia	0	0	0	0	0	0	0	0
Bone marrow: cellular depletion	0	0	0	0	16	4	21	20
Thymus: Apoptosis, increased, slight	9	4	5	7	4	7	13	9
Moderate/severe	1	0	1	0	0	0	0	3
Apoptosis, increased, slight	13	18	18	19	14	16	8	15
Moderate/severe	4	2	2	0	4	4	11	5
Ovaries: Reduced size of corpora lutea	0	0	0	0	0	2	0	19
Increased number of corpora lutea	0	0	0	0	0	4	0	18
Liquefactive necrosis in corpora lutea	0	0	0	0	0	0	0	11
Hyperplasia of sex cord stroma	0	0	0	0	0	1	0	12
Incisor: minimal to moderate dentopathy	0	0	0	0	19	19	0	0
Severe dentopathy	0	0	0	0	0	0	21	21
Main (extra-hepatic) bile duct: dilatation	0	0	0	0	0	0	3	2
Inflammation	0	0	0	0	0	0	3	2
Hyperplasia of ductal epithelium	0	0	0	0	0	0	3	2

In the knee (distal femur and proximal tibia), the epiphyseal cartilage was thickened in two females at 20 mg/kg and in the majority of individuals at 80 mg/kg. This thickening was mainly due to an elongation of the chondral columns (hypertrophic chondrocytes). In incisors, dysplasia (minimal to severe) was observed. Slight dysplasia exhibited irregularities of the ameloblasts and/or odontoblasts. Moderate dysplasia revealed further aggravation and first regressive lesions in the pulp cavity and/or mild inflammation and hyperplastic epithelium of the gingival sulcus and dental alveolus. The irregularities of enamel and dentin, ameloblasts and odontoblasts resulted in dental deformations and fractures. Inflammation and hyperplasia of the ductal epithelium were observed in the main bile duct. Table 11 presents findings in bile duct and associated tissues in individual animals.

Table 11: Table Findings of Main Duct and Associated Tissues

Microscopic finding	Animal Nos.
Main bile duct: dilatation, inflammation, hyperplasia of ductal epithelium	402, 403, 427, 456, 478
Liver: noteworthy inflammatory changes	403, 417, 420, 427, 456
Intra-hepatic bile ducts: slight or moderate hyperplasia	403, 417, 420, 427,456, 478
Pancreas: noteworthy inflammatory changes	402, 406, 417, 420, 427, 456
Intra-pancreatic ducts: hyperplasia of ductal cells	415, 417
Gastric pylorus: inflammation and/or Crypt dilatation of the mucosa	403, 406, 427, 456, 478
Duodenum: inflammation and/or crypt/gland dilatation	402, 415, 416, 417, 456, 467, 470, 478

Histopathological evaluations: The microscopic evaluation of the study is adequate. The NOAEL is considered 5 mg/kg/day.

6.2.2 3-Month Oral Study in Cynomolgus Monkeys

Study title:	**The BIBF 1120 ES Toxicity Study by Oral Gavage Administration to Cynomolgus Monkeys for 13 weeks Followed by a 4 Week Recovery Period**
Study no.:	Report/Doc # U05-2245; Study #BOI 251/032137
Study report location:	14-MAR-2011 submission, vol. 7.28-30; or Module 4, vol. 26-28.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	August 7, 2003
GLP compliance:	Yes, the statement signed
QA statement:	Yes, the statement signed
Drug, lot #, and % purity:	BIBF 1120 ES, Batches 8230071, purity 98.6%

Key Study Findings

- Cynomolgus monkeys (3/sex/dose) were dosed by oral gavage with 0, 3, 15 and 30/20 mg/kg/day of BIBF 1120 for 13 weeks. The HD BIBF 1120 dose started at 30 mg/kg/day but was reduced to 20 mg/kg/day due to toxicity. Specifically, BIBF 1120 dose in the HD group was 30 mg/kg/day during days 1 – 13, 0 mg/kg/day during days 13 – 16, and 20 mg/kg/day the remaining period of the study.
- Additional monkeys (2/sex/dose) were included in the C and HD groups to evaluate the reversibility of lesions.
- The Target organs of toxicity included the bone, thymus, and pancreas.
- The study did not establish the NOAEL. This conclusion is in agreement with the study report.

Methods

Doses:	0, 3, 15, 30/20 mg/kg/day. The HD group was given 30 mg/kg/day during days 1 – 13, 0 mg/kg/day during days 13 – 16, and 20 mg/kg/day during days 17 – 90.
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 mL/kg/day
Formulation/Vehicle:	(b) (4
Species/Strain:	Cynomolgus
Number/Sex/Group:	3/sex/group
Age:	62 – 115 weeks
Weight:	M: 2.19 – 2.85 kg; F: 1.88 – 2.79 kg
Satellite groups:	None.
Unique study design:	The BIBF 1120 dose in the HD group was adjusted. See doses section for detail.

Deviation from study protocol: No major deviations.

Observations and Results

Mortality: Mortality was observed twice daily. No deaths occurred during the study.

Clinical Signs: Clinical signs were observed daily. Loose/liquid feces were observed in the MD and HD groups. The MD group showed the findings occasionally while each HD monkey showed the finding consistently while dosed with 30-mg/kg/day BIBF 1120.

Body Weights: Body weights were recorded weekly. The HD group showed decreases in mean body weight. A loss of body weight occurred when the monkeys were dosed at 30 mg/kg/day (the first two weeks). Figure 2 (next page) shows the mean body weight curve as a function of time in males. Females behaved similarly. The respective mean weight gain during the study in the C, LD, MD and HD groups was 0.29, 0.13, 0.03 ($p < 0.05$) and -0.03 kg ($p < 0.01$) in males; and 0.19, 0.08, -0.01 ($P< 0.05$) and -0.04 ($P < 0.01$) in females.

Feed Consumption: Food consumption was recorded weekly per cage. The food intake for in the HD females was markedly lower throughout the treatment period. The mean food consumption in females in week 13 was 4,040, 3,700, 4,000, and 3,370 g in C, LD, MD and HD groups, respectively. The HD males showed smaller reductions for most of the treatment period.

Ophthalmoscopy: Ophthalmic examinations were conducted at pre-study and week 13. No treatment-related findings were observed.

ECG: ECGs (before and 2 h after dosing) were conducted at pre-study and weeks 3, 6 and 13 of the treatment. No treatment-related findings were observed.

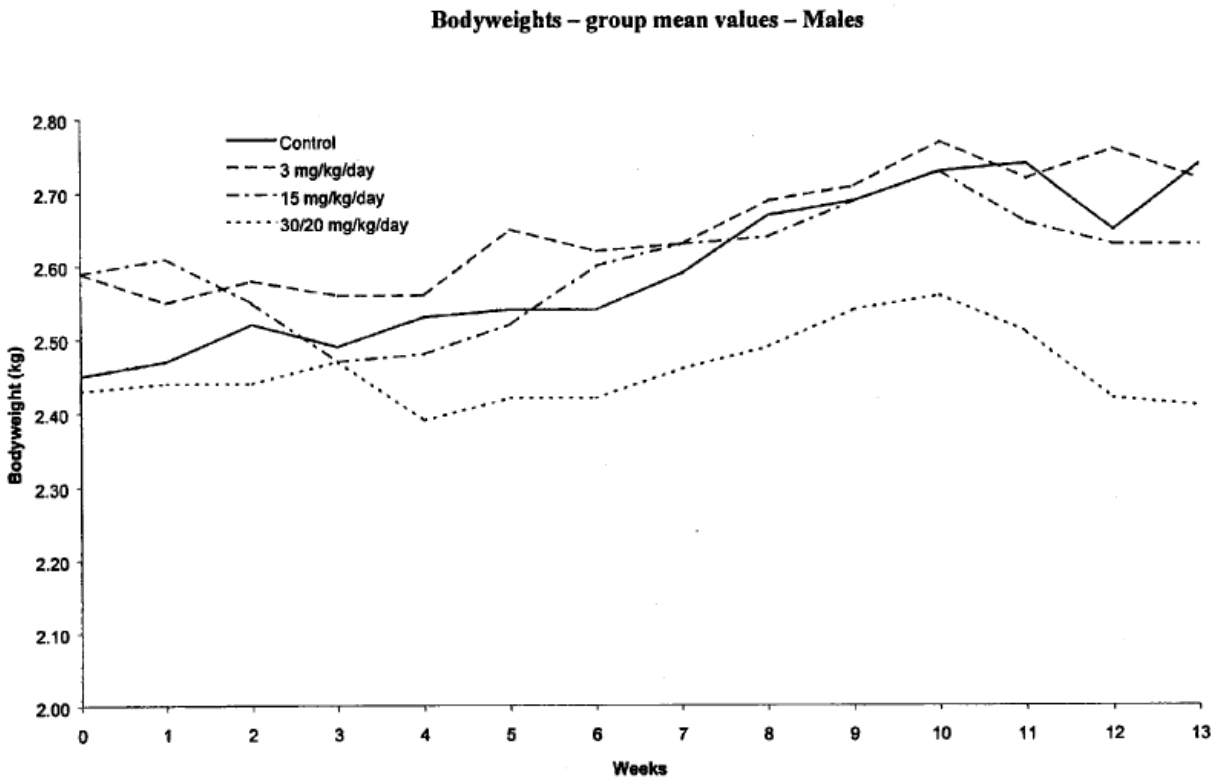


Figure 2: Mean Body Weight of the 3-Month Oral Study in Cynomolgus Monkeys

Hematology: A complete panel of hematological evaluations was done at pre-dosing and weeks 2 (C and HD only), 6 and 13. Also was flow cytometry to evaluate the following cells: T and B lymphocytes, CD4 and CD8 lymphocytes, NK cells and monocytes. No significant, treatment-related effects were observed.

Clinical Chemistry: A complete panel of hematological evaluations was done at pre-dosing and weeks 2 (C and HD only), 6 and 13. No significant, drug-treatment-related effects were observed.

Urinalysis: A complete panel of hematological evaluations was done at pre-dosing and weeks 6 and 13. No significant, drug-treatment-related effects were observed.

Toxicokinetics: Blood drug levels were determined at 0, 1, 2, 4, 8 and 24 hrs post dosing on days 1, 28 and 91 in each group; and at 0, 4 and 24 hrs post dosing on days 13 (final dose of 30 mg/kg/day) and 17 (first dose of 20 mg/kg/day) in HD group only. The limit of quantitation was 1 ng.h/ml. Table 12 (next page) shows the results. There was no apparent drug accumulation over the course of the study.

Necropsy: Necropsy was conducted at the time of sacrifice (day 91). Smaller thymus was observed in 2 HD females.

Organ weights: Organ weights were collected at the time of sacrifice (day 91). The HD group showed statistically non-significant decreases in thymus weights. For example, the respective thymus weight in the C and HD groups in males was 5.37 and 3.16 g in absolute weight and 6.03% and 4.47% in relative weights (to body weight).

Table 12: Plasma Levels of BIBFs 1120 in 3-mo. Cyno. Monkey Study

PK Parameter	Time (day)	Plasma BIBF 1120 Level					
		Male			Female		
		3-mg/kg	15-mg/kg	30/20-mg/kg	3-mg/kg	15-mg/kg	30/20-mg/kg
Cmax	1	38.5	137	224	33.5	103	177
	28	34.6	145	187	23.8	102	171
	91	38.3	140	170	37.2	131	119
AUC (ng.h/ml) [a]	1	307	1430	2300	330	1100	2070
	28	285	1400	1920	234	991	1740
	91	305	1370	1870	345	1310	1320

a. The oral dose of BIBF 1120 was 5, 20 and 80 mg/kg/day in the LD, MD and HD groups, respectively.

Histopathology

Adequate Battery: Adequate. A complete panel of organ/tissues in every group was examined.

Peer Review: Yes.

Histological Findings: Dose-related abnormal findings were observed in the bone marrow (fatty replacement), thymus (decreases in cellularity) and pancreas (acinar cell degranulation). Table 13 presents the incidence and severity of these findings.

Table 13: Histological Findings in the 3-mo Monkey Study – Main study

Sex	Male						Female					
Study section	Main				Recov'y		Main Study				Recov'y	
BIBF 120 (mg/kg/day)	0	3	15	30/20	0	30/20	0	3	15	30/20	0	30/20
Number of monkeys examined	3	3	3	3	2	2	3	3	3	3	2	2
Femur: fatty replacement of marrow: slt/min	0	0	0	0	1	0	0	2	0	1	0	2
Moderate	0	3	3	3	0	2	0	1	3	1	0	0
Marked	0	0	0	0	0	0	0	0	0	1	0	0
Total	0	3	3	3	1	2	0	3	3	3	1	2
Sternum: fatty replacement of marrow: min	1	2	3	3	0	1	1	2	3	3	0	2
Slight	0	1	1	1	0	0	0	0	0	0	0	0
Total	1	3	3	3	0	1	1	2	3	3	0	2
Thymus/cortex: ↓ cellularity - min	0	0	1	2	0	0	1	1	1	1	0	0
Pancreas: acinar cell degranulation - min	0	1	3	3	0	1	1	0	3	2	0	0

Histopathological evaluations: The microscopic evaluation of the study is adequate. The study did not establish the NOAEL. This conclusion is in agreement with the study report.

6.2.3 12-Month Oral Study in Rhesus Monkeys

Study title:	**12-Month Oral Toxicity Study in Cynomolgus Monkeys with a 4-Week Recovery period**
Study no.:	Report/Doc #U05-2274; Report/Study #BOI/305
Study report location:	14-MAR-2011 submission, vol. 7.31 – 35; or module 4, vol. 29 – 33.
Conducting laboratory and location:	(b) (4)
Date of study initiation:	November 3, 2004
GLP compliance:	Yes, the statement signed
QA statement:	Yes, the statement signed
Drug, lot #, and % purity:	BIBF 1120 ES, Batches 8230091, Purity 98.5%

Key Study Findings

- Rhesus monkeys (4/sex/dose) treated with ≥ 10-mg/kg/day BIBF 1120 orally for 12 months showed thickening of growth plate of the bone (slight to moderate) and adrenal gland atrophy.
- The study did not establish the NOAEL, due to findings of growth plate thickening in the low dose group. This conclusion disagrees with the study report that considered the LD was NOAEL. The report argued the changes in this group were "slight, of unknown relationship to treatment or were pharmacologically mediated". It is unclear at present whether the argument was valid. Also, one (of 4) LD male showed moderate growth plate thickening.
- BIBF 1120 doses were 0, 10, 20 and 60/45/30 mg/kg/day in the C, LD, MD and HD groups, respectively. The BIBF 1120 dose in the HD group was started at 60 mg/kg/day but was reduced twice during the study due to overt toxicity. Specifically, the BIBF 1120 doses were 60, 0, 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-26, and 26-55, respectively.

Methods

Doses:	0, 10, 20 and 60/45/30 BIBF 1120. The BIBF 1120 in the HD group was adjusted twice during the study. The final dose level was reported as 60, 45 and 30 for weeks of 1-3, 4-26, and 27-52. Such reporting did not include 3-week off drug period (week 4 – 6). The actual BIBF 1120 dose levels in the HD group was 60, 0, 45, and 30 mg/kg/day during weeks 1-3, 4-6, 7-29, and 30-55, respectively.
Frequency of dosing:	Once daily
Route of administration:	Oral gavage
Dose volume:	5 mL/kg/day

Formulation/Vehicle:	[redacted]
Species/Strain:	Rhesus monkeys
Number/Sex/Group:	4/sex/group
Age:	123 – 143 weeks
Weight:	M: 2.75 – 4.10 kg; F: 1.42 – 3.88 kg
Satellite groups:	Recovery groups: 1 - 2/sex/group in the control and HD groups.
Unique study design:	The BIBF 1120 dose in the HD group was adjusted. See doses section for detail.

Deviation from study protocol: No major deviations occurred.

Observations and Results

Mortality: Mortality was observed twice daily. Two HD monkeys [Monkeys 736 (F) and 737 (M)] were sacrificed in week 11 and 24, respectively, when they were dosed at 45-mg/kg/day, due to clinical signs such as liquid feces, and under-activity.

Monkey 736 (F) had dark, enlarged adrenal glands with high weights and low spleen, thymus, thyroid and parathyroid weights with the spleen and thymus also appearing small. Microscopic examination revealed thymic atrophy and the presence of inflammatory cells in the liver, gall bladder and parotid salivary glands, centrilobular atrophy of the liver, hemorrhage in the lungs and bronchi and the lamina propria of the ileum & Peyer's patch, congested spleen and adrenal cortical hypertrophy. Gastrointestinal tract showed no pathological findings but bacteria *coliform Spp.* and Shigella Spp types were present.

Monkey 737 (M) showed low spleen and thymus weights. Findings in the sternum, femur and adrenals were similar to these in other animals of the group. Microscopic examination revealed minimal inflammatory cells with necrotic debris were seen at the tips of the villi in the small intestine and the mucosal surface in the large intestine.

Two LD group monkeys (one in each sex) were killed at weeks 7 and 14 due to dosing errors.

Clinical Signs: Clinical signs were observed daily. Loose/liquid feces were observed in the MD and HD groups. The MD group showed the findings occasionally while each HD monkey showed the finding consistently, especially when they were dosed with 60-mg/kg/day of the drug.

Body Weights: Body weights were recorded weekly. The HD group showed decreases in mean body weight. Figure 3 shows the mean body weight curve as a function of time in males. Females behave similarly. The respective mean weight gain during the study (week 0 – 52) in the C, LD, MD and HD groups was 1.94, 1.41, 1.14 ($p < 0.05$) and 0.73 kg ($p < 0.01$) in males; and 1.51, 1.31, 1.10 and 0.88 ($P < 0.05$) kg in females.

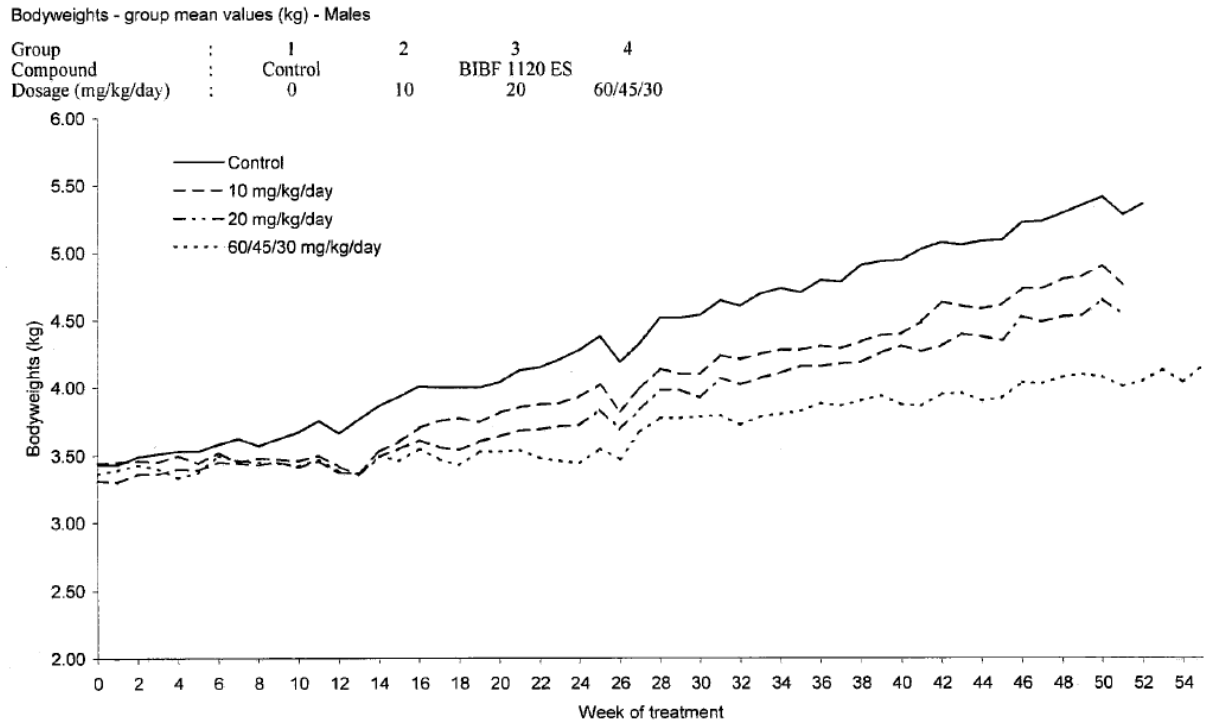


Figure 3: Body weight as a function as time in males in the 52-week study in monkeys.

Feed Consumption: not measured.

Ophthalmoscopy: Ophthalmic examinations were conducted at pre-study, and ends of the treatment and recovery periods, respectively. No treatment-related findings were observed.

ECG: ECGs (before and 2 h after dosing) were conducted at pre-study and week 4 of the treatment. No treatment-related findings were observed.

Hematology: A complete panel of hematological evaluations was done at pre-dosing and the end of the treatment and recovery periods. No significant, drug-treatment-related effects were observed.

Clinical Chemistry: A complete panel of clinical chemistry evaluations was done at pre-dosing and the end of the treatment and recovery periods. No significant, drug-treatment-related effects were observed.

Urinalysis: A complete panel of urinalysis evaluations was done at pre-dosing and the end of the treatment and recovery periods. No significant, treatment-related effects were observed.

Toxicokinetics: Blood drug levels of BIBFs 1120 and 1202 were determined on day 1 and weeks 4, 7 (Group 4 only), 13, 26, 42 and 52. The time of sampling was 0, 0.5, 1, 2, 4, 8 and 24 hrs post dosing. The limit of quantitation was 1 ng.h/ml each. Table 14 summarizes the Cmax levels of these compounds on these days. The Cmax of both compounds generally increases with the oral dose.

Table 14: Plasma Cmax of BIBFs 1120 and 1202 in 1-year Monkey Study

Time (day)	Sex	Plasma Cmax (ng/ml)					
		BIBF 1120			BIBF 1202		
		LD [a]	MD	HD	LD	MD	HD
1	M	120	133	442	8.21	8.39	32.6
1	F	67.8	189	427	4.32	12.0	32.5
22	M	155	187	304	9.92	14.3	21.0
22	F	78.3	207	384	4.64	11.2	41.4
49	M	ND [b]	ND	336	ND	ND	19.9
49	F	ND	ND	329	ND	ND	23.0
91	M	83.7	156	186	6.21	7.72	10.4
91	F	78.3	120	221	4.78	9.78	17.1
189	M	88.8	121	133	5.95	6.52	8.70
189	F	88.8	163	187	5.19	8.03	14.2
288	M	90.2	128	148	6.21	6.59	9.09
288	F	50.8	150	170	3.28	8.67	10.7
363	M	77.6	92.0	92.0	5.95	4.80	5.60
363	F	53.7	132	160	3.64	7.17	8.70

a. The oral dose of BIBF 1120 was 5 and 20 mg/kg/day in the LD and MD groups, respectively. The BIBF 1120 dose in the HD group was 60, 45, and 30 mg/kg/day on days 1, 22 - 91, and 189 – 363, (weeks 1-3, 4-26, and 26-52) respectively.
b. ND = not determined.

Table 15 summarizes the AUC values of BIBFs 1120 and 1202. The BIBF 1120 AUC generally increases with the oral dose. The AUC of BIBF 1202 is approximately 1/10 of the BIBF 1120 in monkeys.

Table 15: Plasma BIBFs 1120 and 1202 AUCs in 1-year Monkey Study

Time (day)	Sex	AUC (ng.h/ml)					
		BIBF 1120			BIBF 1202		
		LD [a]	MD	HD	LD	MD	HD
1	M	979	1150	5970	85.9	85.4	438
1	F	595	1730	6250	50.8	147	487
22	M	1350	1650	3760	102	123	272
22	F	671	2040	5870	56.2	156	610
49	M	ND [b]	ND	4030	ND	ND	277
49	F	ND	ND	3940	ND	ND	311
91	M	809	1370	2220	71.4	93.4	157
91	F	610	1110	2710	53.2	95.3	241
189	M	765	989	1440	70.5	71.4	110
189	F	661	1370	1870	58.3	95.9	164
288	M	856	1150	1910	82.0	81.1	141
288	F	479	1630	1960	43.3	125	145
363	M	787	831	1100	85.7	59.7	76.0
363	F	506	1220	1660	47.9	90.9	111

a. The oral dose of BIBF 1120 was 10 and 20 mg/kg/day in the LD and MD groups, respectively. The BIBF 1120 dose in the HD group was 60, 45, and 30 mg/kg/day on days 1, 22 - 91, and 189 – 363, respectively.
b. ND = not determined

Histopathology

Adequate Battery: Adequate. A complete panel of organ/tissues in every group was examined.

Peer Review: Yes.

Histological Findings: Histological findings were limited to the all group. All HD males and females showed growth plate thickening of the bones (femur, tibia and sternum) and atrophy of the zona fasciculata in the adrenal gland. The HD group also showed cortex and trabecular bone thinning in the sternum. Table 16 presents the incidence and severity of these lesions.

Table 16: Histological Findings in the 52-week Monkey Study – Main study

	Males				Female			
BIBF 120 (mg/kg/day)	0	10	20	60/30	0	10	20	60/30
Number of monkeys examined	4	4	4	4	4	4	4	4
Femur: Growth plate thickening: minimal	0	2	3	0	0	3	1	0
Slight	0	1	0	3	0	0	1	1
Moderate	0	1	1	1	0	0	2	2
Total	0	4	4	4	0	4	4	4
Sternum: cortex/trabecular bone thinning	0	0	0	1	0	0	0	1
Slight	0	0	0	1	0	0	0	1
Total	0	0	0	2	0	0	0	2
Growth plate thickening (minimal)	0	2	4	4	0	2	2	3
Adrenal gland: zona fasciculata atrophy: minimal	0	3	1	3	0	0	2	2
Slight	0	0	0	1	0	0	0	0
Total	0	3	1	4	0	0	2	2

Recovery animals: Growth plate thickening (slight in severity) in the femur remained in the recovery monkeys. The respective incidence in the control and HD groups was 0/2 and 1/1 in males; and 0/1 and ½ in females.

Histopathological evaluations: The microscopic evaluation of the study is adequate. The NOAEL is considered 10 mg/kg/day. The Target organs of toxicity included the bones and adrenal gland. The study did not establish the NOAEL, due to findings of growth plate thickening in the low dose group. This conclusion disagrees with the study report considers the LD was NOAEL. The report argued the changes in this group were "slight, of unknown relationship to treatment or were pharmacologically mediated". It is unclear at present whether the argument was valid. Also, one (of 4) LD male showed moderate growth plate thickening.

7 Genetic Toxicity

BIBF 1120 ES tested negative in the following assays: Ames test and mouse lymphoma (9L5178Y) assay *in vitro*, and *in vivo* micronucleus test in rats (bone marrow). See the nonclinical review completed by Dr. Shwu-Luan Lee on September 30, 2010 (b) (4).

9 Reproductive Toxicity

The evaluation of reproductive toxicity of BIBF 1120 was limited. The sponsor has completed a male fertility study and dose-ranging (non-GLP) studies of teratology in rats. Table 17 presents an overview of these studies. BIBF 1120 did not affect the male fertility but appeared teratogenic in rats.

Table 17: Reproductive Toxicity studies of BIBF 1120

Species	Study	BIBF 1120 (mg/kg/day)	Finding	Report #
Rat	♂ Fertil.	10, 30, 100	No effect at up to 100 mg/kg/day	U10-1128
Rat	Seg. II	5, 10, 20	Visceral malformation & fetal absorption at ≥ 10 mg/kg/day (Non-GLP)	U07-1814
Rat	Seg. II	30, 75, 180	No fetuses available at all doses (Non-GLP)	U07-1710

9.1.1 Male Fertility Study in Rats

Study title:	**BIBF 1120 ES: Study of Male Fertility and Early Embryonic Development to Implantation in Rats by Oral (gavage)**
Study no.:	Report/Doc# U07-1128. Report/Study# 09B060
Study report location:	14-MAR-2011 submission, vol. 7.40 - 42; or module 4, vol. 38 – 40.
Conducting laboratory and location:	Boehringer Ingelheim (Department of Nonclinical Drug Safety), Birkendorfer straβe. 65, 88397 Biberach an der Riss, Germany
Date of study initiation:	May 11, 2009
GLP compliance:	Yes, the statement signed
QA statement:	Yes, the statement signed
Drug, lot #, and % purity:	BIBF 1120 ES, Batch# 10, purity 98.3%

Key Study Findings

- Rats (24 males/dose) treated by oral gavage with 0, 3, 20, or 100 mg/kg/day of BIBF 1120 for 13 weeks showed no treatment-related effects on male fertility

parameters. Neither were there effects on morphology of reproductive organs upon microscopic examinations.
- The NOAEL was 3 mg/kg/day for generally toxicity and 100 mg/kg/day for male reproductive toxicity.

Study Design: Wistar Rats (24 males/dose) were dosed by oral gavage with 0, 5, 20, or 100 mg/kg/day of BIBF 1120 for up to 13 weeks before they mated with untreated females (1:1 ratio for up to 7 days). Males were sacrificed after mating and were evaluated for copulation parameters and histological evaluations were done on the reproductive organs: testes, epididymides, prostate glands, seminal vesicles and coagulating glands. Pregnant females were sacrificed on gestation day 14 for the evaluation of fertility parameters: resorption, resorption rate, implantation loss, and number of corpora lutea.

Methods

Doses:	0, 3, 20, and 100 mg/kg/day BIBF 1120
Dosing frequency:	Once daily
Route of administration:	Oral gavage
Dose volume:	10 ml/kg
Formulation/Vehicle:	(b (4) (5% hydroxyethylcelluose)
Species/Strain:	Crl:WI(Han)
Number/Sex/Group:	24 males/dose; also included 24 untreated females/dose
Age:	M: 5 - 6 weeks; F: 9 weeks
Weight:	males 128 - 172 g, females 154 - 179 g
Unique study design:	Only the males were treated with BBF 1120 for 13 weeks before mating. The females were not treated. Each male co-inhabited with one female during the mating period.

Deviation from study protocol: None

Observations and Results,

Mortality: Mortality was observed twice daily. No treatment-related effects were observed.

Clinical Signs: Loose and broken incisors in the upper and/or lower jaw (totally or partially) were detected in 4/24 of the 20 mg/kg dose group and in 23/24 (except in male No. 473) animals of the 100 mg/kg dose group.

Body Weights: Body weights were recorded weekly. The HD males showed significant decreases in mean body weight (Figure 3).

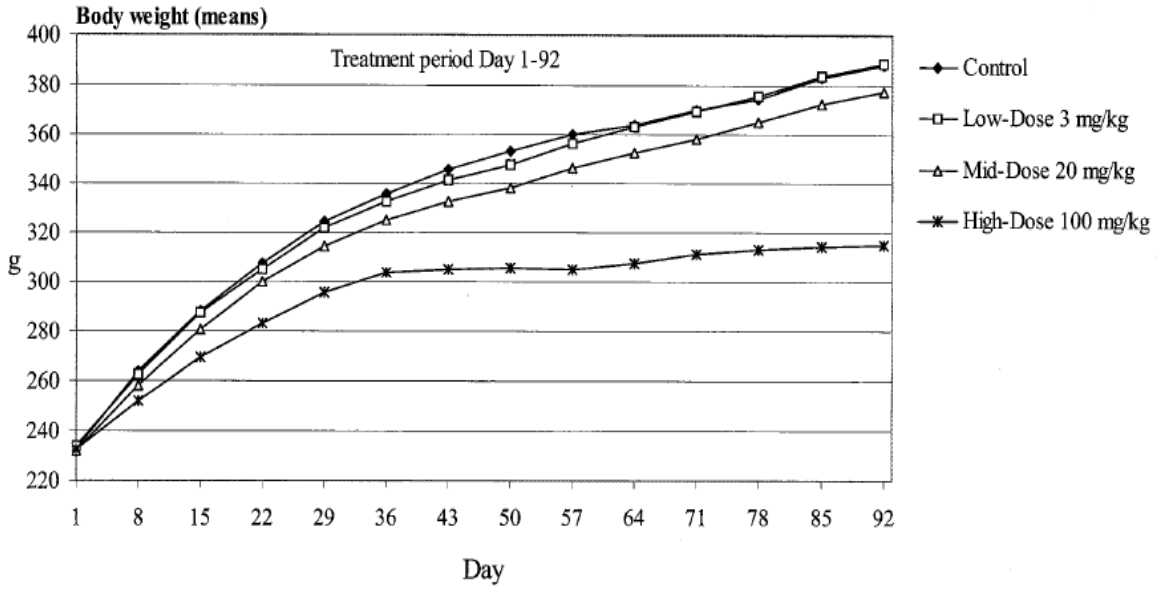


Figure 3: Mean Body Weight of the Male Fertility Study in Rats

Food Consumption: The HD group showed significant decreases in food consumption. Table 18 presents the mean food consumption during the pre-mating phase.

Table 18: Food Consumption of the Males Treated with BIBF 1120

Group	BIBF 1120 (mg/kg/day)	Mean food consumption (g) [a]					
		Day 8	Day 22	Day 50	Day 57	Day 78	Day 92
1	0	154.4	150.9	142.7	142.8	137.0	139.1
2	3	154.5	155.6	140.3	143.3	139.2	139.7
3	20	150.0	148.0	133.7*↓	131.6	131.5	133.1
4	100	141.8*↓	141.2*↓	112.4*↓	110.1*↓	111.9*↓	106.0*↓

*↓, significantly decreased from the control ($P < 0.05$).
a, n = 19 – 24.

Toxicokinetics: Not measured.

Male fertility: No treatment-related effects were observed in copulation index, fertility index. All males were fertile.

Females: No treatment-related effects were observed in pre-implantation loss, resorption rate, copulation index, fertility index, litter sizes, gestation index.

Histopathology

Adequate Battery: Adequate. A complete panel of organ/tissues in every group was examined.

Peer Review: Yes.

Necropsy Findings: No treatment-related effects were observed.

Histological Findings: No treatment-related effects were observed in any of the male reproductive organs.

Histopathological evaluations: The microscopic evaluation of the study is adequate. The NOAEL is considered 3 mg/kg/day for general toxicity and 100 mg/kg/day for the reproductive toxicity in male rats. This conclusion is in agreement with the sponsor.

9.1.2 Embryofetal developmental dosing ranging Studies in Rats

Two non-GLP dose ranging studies (Reports #U07-1710 and Report U07-1814) showed that BIBF 1120 was teratogenic in rats. Pregnant rats (Crl:WI(Han), 10/dose) were given by orally gavage BIBF 1120 in Natrosol® 250 HX during the gestation period of days 7 – 16. They were sacrificed on gestation day 22 for fetal examinations. The first study (Report #U07-1710, Study #07B02, vol. 7.39-40) failed because it used excessive high BIBF 1120 doses (30, 75 and 180 mg/kg/day) which resulted in no vital fetuses. Consequently, a second study (Report U07-1814) was initiated at low BIBF 1120 doses (5, 10 and 20 mg/kg/day). No detailed reviews of these non-GLP reports are needed. The following is a brief summary of the results of Report U07-1814 (Study #07B30, Vol. 7.40).[1]

No maternal mortality was observed at any doses. The HD dams showed statistically significant decreases in the mean body weight, blood at the orifice of vagina (4/10), and total fetal absorption. The MD dams showed increased statistically significant increases in fetal absorption. Visceral and skeletal examinations revealed the following in the MD group fetus (one each): no truncus bracheocephalicus [Origin of A. subclavia (right) at the base of the A. carotis (right) near the aortic arch], small distance between the carotids, enlarged distance between left A. carotis left A. subclavia, common trunk of pulmonary arteries at the A. pulmonalis, blunt edge of liver, and small testes. Thirty eight percent of the MD fetus showed cleft thoracal bodies. Table 19 presents the noticeable findings. The study report argued that the fetal findings were not treatment-related because of the lack of dose-response. Such argument is flawed because the HD group has no fetuses for examination.

Table 19: Noticeable Findings of the Teratology Dose-Ranging Study

BIBF 1120	0 mg/kg/day	5 mg/kg/day	10 mg/kg/day	20 mg/kg/day
Maternal (n =)	10	10	10	10
Viable fetuses (/litter)	10.9 (9 – 13) [a]	10.6/7-13	8.0 (0- 14)*	0
Total resorption	0.50 (0 – 2)	0.7 (0 – 2)	4.5 (0 – 14)*	11.25 (5-14)*
Early resorption	0.50 (0 – 2)	0.7 (0 – 2)	4.5 (0 – 14)*	11.25 (5-14)*
Resorption rate	4.5%	5.48%	35.3%*	100%*
Fetal: No truncus bracheocephalicus	0/52	0/50	1/38	-
Cleft thoracal body	0/57	1/56	12/38*	-
Blood vessel abnormality. [b]	0/52	0/50	4/38*	-

*, Significantly different to control.

a. Numbers in parenthesis indicate range.

b. Origin of A. Pulmonalis and aortic arch changed.

[1] This study was conducted by the Boehringer Ingelheim (Department of Nonclinical Drug Safety, Biberach, Germany).

Plasma BIBF 1120 levels were determined on gestation days 7 and 16. Table 20 presents the Cmax and AUC values on these days. The AUC increased super-proportional to dose on both days.

Table 20: Plasma BIBF 1120 Levels in Pregnant Rats.

Gestation Days	Camx (nmol/L)			AUC_{0-24h} (nmol.h/L)		
	5 mg/kg	10 mg/kg	20 mg/kg	5 mg/kg	10 mg/kg	20 mg/kg
7	3.04	14.2	43.4	15.6	61.2	288.0
16	3.76	18.9	110.0	22.6	91.8	566.0

10 Carcinogenicity

The 2-year oral carcinogenicity studies of BIBF 1120 in rats and mice are currently ongoing. The respective BIBF 1120 doses were 2.5, 5 and 10 mg/kg/day in rats and 5, 15 and 30 mg/kg/day in mice. The Executive CAC concurred with the dose selections on September 14, 2010. See nonclinical reviews completed by Dr. Shwu-Luan Lee on September 30, 2010 (b) (4).

11 Integrated Summary and Safety Evaluation

Summary

The proposed clinical trial may be allowed to proceed because there are sufficient clinical data to evaluate the safety of the proposed use of BIBF 1120 although the nonclinical data in the application is deemed insufficient. The sponsor proposed to treat adult patients with idiopathic pulmonary fibrosis with BIBF 1120 for 52 weeks. Pivotal nonclinical data in support of the safety of the proposed trial are 6- and 9-month toxicity studies in rats and monkeys (one each), respectively. The NOAEL was established in rats but not in monkeys. The rat NOAEL does not provide a sufficient safety margin for the proposed clinical dose, on a plasma drug AUC basis. However, there is adequate clinical experience to evaluate the proposed use of the drug. The proposed clinical trials may be allowed to proceed from the nonclinical perspective.

Evaluation

There is sufficient clinical data to support the proposed trials although the nonclinical data in the application is deemed insufficient. BI proposed 2 identical phase-3 clinical trials of BIBF 1120 in IPF patients (Protocol #U11-1000-01; Studies 1199.32 and 1199.34). A total of 485 IPF patients 40 years and older (N = 291 and 194 for the treatment and placebo groups, respectively) will be enrolled in each trial. A patient will receive either 150-mg BIBF 1120 (free base) bid or placebo for 52 weeks. Men and women of child-bearing potential must use contraceptive methods during sexual intercourses to prevent pregnancy from occurring. The trials will be double-blind, randomized, placebo-controlled trials and will evaluate the

safety and efficacy of BIBF 1120 in slowing decline of pulmonary function. Patients will be allowed to reduce the BIBF 1120 dose to 100 mg bid if the 150-mg bid dose is not tolerated.

A total of 667 IPF patients have received BIBF 1120 treatment for at least 52 weeks and 339 IPF patients have been treated for more than 52 weeks. The drug is also being investigated oncological indications (b) (4).

Nonclinical data submitted by BI included general, genetic and reproductive toxicity studies of BIBF 1120. Table 21 presents an overview of the general toxicity studies of BIBF 1120. Pivotal nonclinical data supporting the above proposed clinical trials included studies of chronic toxicity and reproductive toxicity. The chronic toxicity studies included oral toxicity studies of 6 and 12 months in rats and monkeys, respectively. Each of these in vivo studies used the oral (gavage) route of administration. The chronic studies identified the following organs as the target organs of toxicity: bones (including the growth plate), bile duct, liver, spleen, kidney, adrenals, thymus, and ovaries. Reproductive studies included an oral fertility study in male rats and a dose-ranging teratology study (non-GLP) in pregnant female rats (Table 17). BIBF 1120 did not affect the fertility in male rats but was teratogenic in rats. The NOAEL of BIBF 1120 for general toxicity was 5 mg/kg/day and not-established in rats and monkeys, respectively. BIBF 1120 at $\geqslant$ 10 mg/kg/day appears teratogenic in rats. See section 1.2 – Brief Discussion of Nonclinical Findings for detailed summary of the toxicology findings.

Table 21: Overview of General Toxicity Program of BIBF 1120

Species	Duration (week)	BIBF 1120 (mg/kg/day, PO)	AUC0-24hr at NOAEL or lowest dose (ng.h/ml)	Target organs	Report #
Mouse	13	**10**,[a] 30, 100	233 - 242	Adrenal, bone, ovary, thymus, spleen …	U10-1798
Rat (Wistar)	13	5, 20, 60/30	22.7 - 26.1	Adrenal, bone, thymus, spleen	U10-1799
Rat (Wistar)	13	**3**, 20, 100	2.3 – 8.4	Adrenal, bone, kidney, thymus, spleen …	U04-1065
Rat (Wistar)	26	**5**, 20, 80	16.4 – 29.2	Adrenal, bone, kidney, thymus, spleen	U05-1843
Monkey (C)	13	3, 15, 30/20	305 - 345	GI, Bone Marrow, Thymus, pancreas	U05-2245
Monkey (R)	52	10, 20, 60/30	506 - 786	Bone	U10-1875

a. bold and highlights indicate NOAEL values.

DPARP in the 01-DEC-2010 meeting requested BI to provide rationale with supportive data for selection of the Rhesus monkey rather than the Cynomolgus monkey for the non-rodent species in the chronic toxicity study. BI stated that the dose-response of cynomolgus and rhesus monkeys were similar. The explanation seems acceptable. Table 22 presents major findings between the species of monkeys.

Table 22: Microscopic Findings in Cynomolgus and Rhesus Monkeys (Male)

	Cynomolgus (3-month)				Rhesus (12 month)			
BIBF 1120 (mg/kg/day)	0	3	15	30/20	0	10	20	60/30
AUC (ng.h/ml) of last day	0	305	1370	1870	0	787	831	1440
Femur: fatty replacement/marrow	0/3	3/3	3/3	3/3				
Growth plate thickening					0/4	4/4	4/4	4/4
Thymus: ↓ cellularity	0/3	0/3	3/3	3/3				
Pancreas: acinar cell degranulation	0/3	1/3	3/3	3/3				
Adrenal: zona fasciculata atrophy					0/4	3/4	1/4	4/4

Safety Margins

This review calculates safety margins of BIBF 1120 on a plasma drug AUC basis. The NOAEL of BIBF 1120 in animals is 5 and <10 mg/kg/day in rats and monkeys, respectively. The rat NOAEL corresponds to plasma AUCs of 16.4 and 29.3 ng.h/ml in males and females, respectively. Monkeys at the toxic dose of 10-mg/kg/day BIBF 1120 (AUCs of 787 and 506 ng.h/ml in males and females, respectively) showed thickening of growth plate in the bones. Rats at AUCs of 184 – 316 ng.h/ml (20 mg/kg/day) showed lesions in multiple organs (i.e., teeth, liver, spleen, bone, ovaries). Clinical data showed that the proposed clinical dose of 300-mg/day BIBF 1120 yielded a mean plasma AUC of 308 ng.h/ml in IPF patients. The above data shows that the safety margin of the proposed use of BIBF 1120 is less than one. Table 23 contains additional exposure margins between animals and humans.

Table 23: Exposure Margins of BINF 1120 between Animals and Humans

	BIBF 1120 mg/kg/day	AUC (ng.h/mL)		Ratio (animal/ human)	Findings
		M	F		
Rat	5	12.4	29.3	0.04 – 0.10	NOAEL
	20	184	316	0.5 - 1.0	Growth plate thickening (GPT), lesions in multiple organs (LIMO)
	80	1240	1030	3.3 – 4.0	Moribund, LIMO
Monkey	10	787	506	1.6 – 2.6	GPT
	20	831	1220	2.7 – 4.0	GPT, Adrenal atrophy (AA)
	30	1100	1660	3.6 – 5.4	GPT, AA
	60	5970	6250	-	
Human	5	308		-	Diarrhea and nausea [a]

a. See clinical review for detailed descriptions of findings in humans.

Impurities

Dr. Yong Hu, the chemist reviewer, identified both BIBF 1120 and its salt (ethanesulfonic acid or ES) have structural alerts for genotoxicity. BIBF 1120 (free base) is the active pharmaceutical ingredient (API) and ES the salt form. All nonclinical studies used BIBF 1120 ES as the testing material. A battery of standard genetic toxicity testing of BIBF 1120 ES did not show any genetic toxicity potential, according to the nonclinical review completed

by Dr. Shwu-Luan Lee on September 30, 2010 (b) (4). BIBF 1120 ES tested negative Ames test and mouse lymphoma (9L5178Y) assay in vitro, and in vivo micronucleus test in rats (bone marrow). There is no nonclinical safety concerned about the genetic toxicity of either BIBF 1120 or ethanesulfonic acid.

Dr. Hu also identified the following impurities of BIBF 1120 as having structural alerts for genetic toxicity: (b) (4) He further indicated that these compounds are (b) (4) The estimated total exposure of the group of impurities was approximately (b) (4) (based on the specifications of (b) (4) (b) (4) has been identified as a major metabolite in monkeys and rats. Expected exposure levels of the impurities are (b) (4) the allowable level of 5 µg/day for clinical trials up to 12 months in duration. This issue, however, is not considered a major safety concern in the IPF indication. The sponsor should be asked to conduct QSAR analyses of these impurities, test impurities as needed in the in vitro bacterial reverse mutation assay, and lower levels as appropriate (per the Draft Genotoxic Impurities Guidance). Further, the sponsor should assess the genetic toxicity profile and carcinogenicity of (b) (4) parallel to the proposed clinical trial.

Conclusion

The proposed trial may be allowed to proceed from the nonclinical perspective. This IND was discussed in the Divisional Safety Meeting on April 12, 2011. It was determined that the available clinical experience was sufficient to evaluate and support the safety of the proposed use of BIBF 1120, although the nonclinical data did not provide adequate safety margins as discussed previously in the Safety Margins section. See Section 2.5.1 – Previous Clinical Experience for brief description of the available clinical data.

Teratology studies in rats showed that BIBF 1120 is embryocidal and teratogenic when given in pregnant females rats. These findings should be described in the investigator's brochure and Informed Consent Form.

Internal Recommendations:

1. The proposed trials may be allowed to proceed from the nonclinical perspective, based on the decision of the Divisional Safety Meeting on April 12, 2011.
2. It is recommended that the Investigator's Brochure and Informed Consent Form include the embryocidal and teratogenic findings of BIBF 1120 in pregnant rats. Pregnant rats were given by orally gavage BIBF 1120 during the gestation period of days 7 – 16. There were no viable fetuses at ≥20 mg/kg/day. Fetal malformations were observed at 10 mg/kg/day. No effects were observed at 5 mg/kg/day.
3. The sponsor should be reminded to conduct a comprehensive evaluation of reproductive toxicity of BIBF 1120 ES in parallel to the proposed phase 3 clinical trials. The sponsor has evaluated only the male fertility of BIBF 1120 in rats.
4. The sponsor should be asked to reduce the level of impurities. The sponsor should also assess the genetic toxicity profile and carcinogenicity of (b) (4) in parallel to the proposed clinical trial.

External Recommendations:

1. Describe the embryocidal and teratogenic findings of BIBF 1120 in pregnant rats (Report/Doc #U07-1814) in the Investigator's Brochure and Informed Consent Form.
2. Conduct a comprehensive evaluation of reproductive toxicity of BIBF 1120 ES in parallel to the proposed phase 3 clinical trials.
3. Several impurities [redacted] (b) (4)) were identified as carrying structural alerts for genetic toxicity. Conduct QSAR analyses for these impurities and qualification studies (in vitro bacterial reverse mutation assay) if applicable. See Draft FDA Guidance for Industry: Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008). These impurities possess [redacted] (b) (4) for comparison to the qualification threshold in the Guidance and daily exposure lowered as appropriate. The agency also plans to conduct QSAR analyses of these impurities and may communicate further regarding this issue.
4. [redacted] (b) (4) possesses a structural alert for genotoxicity and has been identified as both an impurity and metabolite. Evaluate the genotoxic potential of this impurity/metabolite in the standard battery of genotoxicity test (per the ICH S2A and S2B Guidance). If [redacted] (b) (4) is positive for genotoxicity, develop and propose plans to assess the carcinogenicity of [redacted] (b) (4)

Luqi Pei, Ph.D.
Senior Pharmacologist

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/s/

LUQI PEI
05/10/2011

TIMOTHY W ROBISON
05/10/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	74,683
Supporting document/s:	SN 045
Sponsor's letter date:	September 6, 2011
CDER stamp date:	September 7, 2011
Product:	BIBF 1120
Indication:	(b) (4) pulmonary fibrosis
Sponsor:	Boehringer Ingelheim
Review Division:	Pulmonary, Allergy and Rheumatology Products
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: December 7, 2009

SUMMARY: This review evaluates adequacy of the Sponsor's 06-SEP-2011 responses to the nonclinical comments of the Agency's 19-AUG-2011 letter. The letter contains 4 nonclinical comments. The review finds the sponsor's responses to Agency's Comments 1 and 3 satisfactory while responses to Comments 2 and 4 unsatisfactory. See the External Communication section for information to be conveyed to the sponsor.

INTRODUCTION

This review evaluates nonclinically the correspondence of Boehringer Ingelheim (BI) submitted to IND 74,683 on September 06, 2011. The correspondence address the DPARP's comments issued on August 16, 2011 letter. The letter was Advice/Information Request letter for the original IND that was submitted on March 14, 2011. The letter contains following 4 nonclinical comments.[1] Specifically, the letter states:

"1. Describe the embryocidal and teratogenic findings of BIBF 1120 in pregnant rats (Report/Doc #U07-1814) in the Investigator's Brochure and Informed Consent Form.
2. Conduct a comprehensive evaluation of reproductive toxicity of BIBF 1120 ES in parallel to the proposed Phase 3 clinical trials.
3. Several impurities (b) (4) were identified as possessing structural alerts for genetic toxicity. Conduct QSAR analyses for these impurities and qualification studies (b) (4) if applicable. See the Draft FDA Guidance for Industry: *Genotoxic and Carcinogenic Impurities in Drug Substances and Products: Recommended Approaches (2008)*. These impurities possess essentially the same structural alert for genotoxicity and levels of those found to be positive for genotoxicity should be summed together for comparison to the qualification threshold in the Guidance and daily exposure lowered as appropriate. The Agency also plans to conduct QSAR analyses of these impurities and may convey further information regarding this issue.
4. (b) (4) possesses a structural alert for genotoxicity and has been identified as both an impurity and metabolite. Evaluate the genotoxic potential of this impurity/metabolite in the standard battery of genotoxicity test (per the ICH S2A and S2B Guidance). If (b) (4) is positive for genotoxicity, develop and propose plan to assess the carcinogenicity of (b) (4)

EVALUATION

Comment 1: The Division letter requests BI to describe the embryocidal and teratogenic findings of BIBF 1120 in pregnant rats (Report/Doc #U07-1814) in the Investigator's Brochure and Informed Consent Form. BI stated that its current version of the approved Informed Consent Form complies with the request. The IC states: "BIBF 1120 has been shown to cause embryo/fetal lethality and teratogenic effects in rats at dose levels resulting in plasma drug concentrations comparable or below those in humans. Angiogenesis is critical to fetal development and the inhibition of angiogenesis following administration of BIBF 1120 was shown in rats to result in absorption of fetuses and increased incidence of

[1] See nonclinical original IND review completed by Dr. Luqi Pei on May 10, 2011 for bases of the comments.

malformations." The above statements comply with the Division's request. The review considers the BI response satisfactory.

Comment 2: This comment requests BI to "conduct a comprehensive evaluation of reproductive toxicity of BIBF 1120 ES in parallel to the proposed phase 3 clinical trials". BI stated in the response that BI does not plan to conduct any additional reproductive toxicity studies beyond those that have been completed.[2] BI provided the following argument for not conducting additional studies:

> "Due to the high sensitivity to the effects BIBF 1120/ (b) (4) the conduct of reproductive toxicity studies for effects on embryo-fetal development and for effects on pre- and postnatal development are not warranted, because the exploratory reproductive toxicity studies in rats clearly demonstrate that BIBF 1120 is teratogenic at an exposure below those encountered in humans and that at an exposure comparable to human exposure the required number of evaluable litters would not be obtained and thus further studies are likely to be uninformative.
>
> It is also BI's perspective that the conduct of a study for effects on embryo-fetal development in rabbits would not provide any added value, because the teratogenicity of BIBF 1120 at subtherapeutic exposure has already been shown in the first test species, i.e. in rats [P04-6491, P11-0881, P11-0882].
>
> Therefore, BI proposes not to conduct further studies for effects on early development/fertility in female rats, for effects on embryo-fetal development and for effects on pre- and postnatal development in rats with BIBF 1120.
>
> If 'comprehensive evaluation' is meant to include additional repro tox studies, the extent of such studies will need to be assessed. We do not believe that additional repro tox studies will provide any insight that might translate into possible guidance for physicians using the drug in the IPF population"

The above response is unsatisfactory. The Division and BI have had extensive discussions about the nonclinical requirement of BIBF 1120 ES for the IPF indication. These discussions were held in the August 2, 2006 pre-IND meeting and December 1, 2011 pre-IND/EOP2 meeting. The December 1, 2011 meeting minutes states:

> "**Question 2 [of BI]: Does the Agency agree with BI's approach to reproductive toxicology?**
>
> *Division Response:*
>
> *Based on the summary data you provided, additional reproductive studies are needed to complete your reproductive toxicology program. Completion of the fertility study battery (fertility study in females) is recommended prior to initiating Phase 3 clinical studies. Additionally, completion of two GLP teratogenicity studies (1 rat and 1 rabbit) is needed. Although the pilot teratogenicity study in rats showed a positive signal, dose reduction in this study may allow for longer exposure and better characterization of the potential teratogenic effects. Additionally, the rabbit teratogenicity study may reveal different findings. Lastly, if the teratogenicity studies in rat can be completed at lower BIBF 1120 doses, then completion of the peri/post-natal studies is expected. Consideration of the GLP rat teratogenicity study results will be taken to determine the feasibility of conducting a pre- and post-natal development study in this species.*

[2] The completed reproductive toxicity studies were two non-GLP teratology studies in rats. These studies showed that BI1120 ES was a potent teratogen. See nonclinical review completed by Dr. Luqi Pei on May 10, 2011 for additional information.

BI Clarifying Comment and Question:

BI acknowledges the reproductive toxicology liabilities of BIBF 1120 at doses resulting in exposure well below the therapeutic range, and assumes respective restrictions in the use of BIBF 1120 including requiring two methods of birth control for WoCBP in the Phase 3 studies.

We would like to understand more fully the objective of the FDA for conducting additional reproductive toxicology studies using lower doses.

Would the Division provide clarification for the rationale around the suggestions for completion of the reproductive toxicology battery?

Discussion:

The Division informed BI that for IPF patients a full reproductive toxicity battery is expected (completion of the fertility, embryo-fetal development, and peri- and post-natal studies) prior to Phase 3 with two teratogenicity studies, particularly since there was a strong signal in the preliminary teratogenicity study. The study results should be submitted with the IND, although since two forms of birth control are required, the Phase 3 studies may be initiated. The Division further acknowledged the feasibility limitations to performing the complete reproductive toxicity study battery, noting that other species may be considered (i.e., rabbit). The Division indicated that a NOAEL was not identified in the preliminary teratogenicity study in rats and adequate safety margins for their findings need to be provided. The Division recommended that BI choose a dose level that is high enough to characterize the toxicity by BIBF 1120, as well as a dose level that is low enough to determine a NOAEL so that the risk/benefit ratio can determined. BI stated that they were surprised that the teratogenic effects were observed early on in the reproductive toxicology program, and further concluded that the value of additional studies may be very limited. The Division replied that BI still needs to submit the data to support their conclusions and that the findings in the pilot teratogenicity study in rats do not eliminate the need to conduct the standard fertility study in female rats and teratogenicity studies in rats and rabbits. If it is found to be unfeasible to complete the full reproductive study battery, a thorough justification should be provided for consideration during the formal review. BI agreed to further investigate the feasibility of additional reproductive toxicology studies and repeated that they will require two methods of birth control in their clinical trials. The Division responded that all available information regarding the toxicology/safety studies should be submitted.

The above statements have clearly delineated the Agency's position and thinking about the requirements for a comprehensive evaluation of the reproductive toxicity of BIBF 1120 ES. They also document BI's understanding of the situation. There is no need for any additional discussion on the issue. BI should comply with the Divisional recommendations. If BI continues to refuse to comply with the Agency's request by conducting any of the requested studies, it will become a review issue in future submissions.

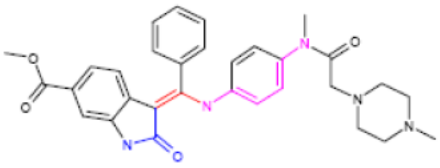
As a follow up item to its response, BI states that Comment 2 was "unclear to us what, exactly, is being requested". It appears necessary to repeat and list the required studies in the next Advice/Information Request letter. Briefly, the study include a female fertility study in rats, teratology studies in rats and rabbits (one each), a pre and post – natal development study in rats. A list of these studies is provided in the External Comments section.

Comment 3: This comment requests BI to conduct QSAR analysis of genotoxicity potential of several impurities. BI completed QSAR analysis (DEREK and MC4PC) of these impurities and found no positive signal in DEREK analysis, but several of them have

moieties with structural alerts in MC4PC analysis. These moieties, however, were the same one of the API that tested negative in a standard testing battery. Because these moieties have been tested in the API genotoxicity testing battery, there are no safety concerns about them. BI stated that they would not conduct any additional QSAR analysis. This response is satisfactory.

Comment 4: This comment requests BI to complete a standard battery of genetic toxicity testing to evaluate the genotoxicity potential of BIBF 1120, a metabolite of the API. BI stated that it does not have any genotoxicity data on the compound. Figure 1 presents chemical structures of BIBF 1120 (API) and (b) (4) BI does not want to conduct any additional testing based on the following arguments:

> "BIBF 1120 was tested in the Ames (U02-1481) and mouse lymphoma assay (U02-1512) with and without a metabolic activation system (Aroclor 1254-induced rat liver microsomal fraction and co-factors (b) (4) (b) (4)



BIBF 1120

(b) (4)

Figure 1: Chemical Structures of BIBF 1120 and (b) (4)

The above arguments are insufficient to address Comment 4 of the letter. BIBF1120 and (b) (4) are chemically two different compounds. The negative responses obtained with BIBF 1120 in the standard battery of genetic toxicology tests does not necessarily demonstrate that (b) (4) would also be non-genotoxic (i.e., the levels of (b) (4) in the in vitro tests with BIBF 1120 may have been inadequate for detection), although BI's argument for not conducting an in vivo micronucleus test of (b) (4) is reasonable. The reason was that there was sufficient (b) (4) exposures in the repeat-dose toxicity studies in rats. Table 1 (next page) provides the BIBFs 1120 and (b) (4) exposures in the 6-month oral toxicity study of BIBF 1120 in rats (Report #U05-1843). It seems reasonable to suspect that (b) (4) might be present in the in vitro genetic toxicity testing due to the presence of liver microsomes; however, BI needs to provide evidence that sufficient (b) (4) (b) (4) concentrations were present in the tests that they have completed with BIBF 1120. Overall, BI needs to conduct the in vitro genetic toxicity testing with (b) (4) or provide evidence that sufficient concentrations of (b) (4) were present in the tests with BIBF 1120.

Table 1. Plasma BIBF 1120 and (b) (4) Levels in a 6-Month Oral toxicity Study in Rats

PK Parameter	Time (day)	Sex	Plasma Drug Level			(b) (4)
			BIBF 1120			
			LD [a]	MD	HD	
Cmax	1	M	3.38	29.7	378	
	1	F	5.76	61.6	465	
	179	M	5.12	41.1	173	
	179	F	9.70	78.4	168	
AUC (ng.h/ml) [a]	1	M	13.7	154	1270	
	1	F	24.6	232	1960	
	179	M	16.4	184	1240	
	179	F	29.2	316	1030	

a. The oral dose of BIBF 1120 was 5, 20 and 80 mg/kg/day in the LD, MD and HD groups, respectively.
b. The table was taken from the nonclinical review completed by Dr. Luqi Pei on May 10, 2011.

CONCLUSION

BI has adequately addressed Comments 1 and 3 of the May 15, 2011 Advice/Information Request Letter. The responses to Comments 2 and 4 were unsatisfactory. Comments in the External Comments section should be conveyed to BI.

EXTERNAL COMMENTS:

We have completed the preclinical section of your September 7, 2011 submission to IND 74,683. We make references to the Agency's Advice/Information Request letter of May 15, 2011 and minutes of the August 16, 2006 pre-IND meeting and December 1, 2010 Pre-IND/EOP2 meeting. We have the following comments.

1. We consider your responses to Comments 1 and 3 of the Agency's Advice/Information Request letter dated May 15, 2011 satisfactory.
2. You have not provided satisfactory response to the Comment 2 of the Advice/Information Request letter dated May 15, 2011. You must complete the reproductive toxicity studies of BIBF 1120 listed below and submit reports of these studies in your NDA.
    a. A (1) female fertility study in rats,
    b. Two (2) teratology studies in rats and rabbits (one each)
    c. A pre and post – natal development study in rats.

    Each of the above studies must be fully GLP-compliant. We consider the lack of the above studies a review issue in our evaluations of your future submissions.
3. Complete the in vitro genetic toxicity testing (i.e., a bacterial gene mutation assay and a mammalian chromosomal aberration assay). Such tests may not be necessary

if you demonstrate that sufficient (b) (4) exposures (concentrations) were achieved in the in vitro genetic toxicity tests that you have completed with BIBF 1120. Ideally, the (b) (4) exposures must meet the current testing standards for the test of interest.

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/s/

LUQI PEI
11/28/2011

TIMOTHY W ROBISON
11/28/2011
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY IND REVIEW AND EVALUATION

Application number:	74,683
Supporting document/s:	SDN 091 (DARRTS); Submission #0082
Sponsor's letter date:	December 20, 2011
CDER stamp date:	December 20, 2011
Product:	BIBF 1120
Indication:	(b) (4) pulmonary fibrosis
Sponsor:	Boehringer Ingelheim
Review Division:	Pulmonary, Allergy and Rheumatology Products
Reviewer:	Luqi Pei, Ph.D.
Team Leader:	Timothy Robison, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Sadaf Nabavian

Template Version: December 7, 2009

SUMMARY: This review evaluates BI's 20-DEC-2011 responses to the Division's 01-DEC-2011 Information Request Letter. BI requested in its responses that the Division: 1) provide rationale for asking additional animal reproductive toxicity studies of BIBF 1120, and 2) comment on conceptual designs for reproductive toxicity studies that BI planed to conduct. The review contains the draft responses to be sent to BI.

BACKGROUND

BI and the Division have been discussing the nonclinical requirements for reproductive and developmental toxicity studies of BIBF 1120 since 2006.[1] Until recently, BI had maintained a position that no additional reproductive toxicity studies of BIBF 1120 were needed because preliminary non-GLP dose-ranging studies had clearly shown that BIBF 1120 was a potent teratogen in animals. See the briefing packages of the 02-AUG-2006 pre-IND meeting and 01-DEC-2010 pre-IND/EOP2 meeting and submissions of 14-MAR-2011 (original submission), 06-SEP-2011 (SDN 055), and 20-DEC-2011 (SDN 091) for additional information of BI's position.

DPARP disagreed with the above position and requested BI to conduct a complete characterization of the reproductive and developmental toxicity profile of the drug in animals. See the following documents for the Division's rationale and positions on the issue: the minutes of 02-AUG-2006 pre-IND meeting and 01-DEC-2010 pre-IND/EOP2 meeting and information requests of 15-MAY-2011 and 01-DEC-2011.

The 01-DEC-2011 IR letter and the 20-DEC-2011 submission reflected the most recent positions of BI and the Division, respectively. In response to BI's 06-SEP-2011 request, the Division in the 01-DEC-2011 IR letter identified the following studies to-be-submitted in the NDA submission:

a. One female fertility study in rats,
b. Two teratology studies in rats and rabbits (one each)
c. One pre and post – natal development study in rats.

BI in the 20-DEC-2011 submission finally agreed to conduct the above studies; however, BI maintained a position that no nonclinical toxicity studies should be required for the drug. BI requested that the Division: 1) provide rationale for requiring the above studies, and 2) comment on conceptual designs of the to-be-conducted studies.

RATIONALE FOR REQUESTING TOXICITY STUDIES

Boehringer Ingelheim is developing BIBF 1120 for the (b) (4) pulmonary fibrosis and other indications. A complete nonclinical characterization of the toxicological profile of BIBF 1120 is needed in its NDA application. Assessments of effects of BIBF 1120 on reproduction and development are a key segment of the nonclinical safety characterization

[1] This application is currently in clinical phase-3 developmental stage. The sponsor is conducting two phase-3 52-week clinical trials of BIBF 1120 in (b) (4) pulmonary fibrosis (IPF) patients. Nonclinically, the sponsor is conducting 2-year oral carcinogenicity studies of BIBF 1120 in rats and mice.

of the drug. Adequate assessments of the effect of BIBF1120 on reproductive and development should include evaluations of the drug in fertility in both males and females and its effects on embryofetal, peri-natal, and post-natal developments in animals. Results of the animal studies will be described in the drug product labeling. Information in the product labeling should be based on well-designed GLP compliant toxicity studies in animals. These studies should investigate the dose-response relationship of BIBF 1120 in animals. Ideally, the study should identify both the no-adverse-effect level (NOAEL) and minimally toxic doses.

BI has completed a male fertility study in rats and 2 non-GLP compliant dose-ranging teratology studies of BIBF 1120 in rats. Results of the studies showed that BIBF 1120 was potent teratogen. BI has not evaluated the effect of BIBF 1120 on female fertility, nor did it conduct a GLP-compliant, well-designed adequate embryofetal development studies to study the dose-response relationship of the drug in 2 animal species, or peri-natal and post-natal studies in any animal species. The lack of the above information precludes an adequate safety assessment and proper labeling review. As such, BI must complete the requested studies and submit the reports to the Division for review in its new drug application of BIBF 1120.

DESIGNS OF REPRODUCTIVE TOXICITY STUDIES

BI submitted conceptual designs of 4 reproductive and developmental toxicity studies of BIBF 1120 in animals for the Division to comment. These studies were a female fertility study in rats, two teratology studies in rats and rabbits (one each), and a pre and post – natal development study in rats. Each study will include a vehicle control group and 3 BIBF 1120-treatment groups (low, mid and high dose). BIBF 1120 dose level for each treatment group are to be decided.

The to-be-conducted studies are commonly-designed reproductive and developmental toxicity studies that are routinely performed by toxicological research and testing laboratories. No detailed reviews of these proposals for conceptual study designs are needed. BI should be informed that each of the studies should be completed in a manner that reflects the current practices. The Division will determine the adequacy of the studies once the reports are submitted.

INTERNAL COMMENTS:

A general advice/information request letter should be send to BI, the sponsor of BIBF 1120 (IND 74,683). The letter will provide response to BI's 20-DEC-2011 request. Specifically, the letter will provide the Division's rationales for requesting reproductive and developmental toxicity studies in a BIBF 1120 NDA application. It will also contain the Division's comment of the conceptual designs of the to-be-completed reproductive toxicity study protocols. See the External Comments section for the information to be conveyed to BI.

EXTERNAL COMMENTS:

We have completed the preclinical section of your December 20, 2011 submission to IND 74,683. We have the following comments.

1. We provide the following responses to your request for our rationale for requesting that you conduct additional reproductive and developmental toxicity studies of BIBF 1120 in animals.

   We have determined that BIBF 1120 is a new molecular entity (NME). An NDA submission of a NME indicated for (b) (4) pulmonary fibrosis should include a complete nonclinical characterization of the toxicological profile of the drug. The nonclinical characterization of the toxicological profile for BIBF 1120 should include adequate assessments for effects on: 1) fertility and reproductive performance in both male and female rats, 2) embryofetal development in rats and rabbits, and 3) peri-natal, and post-natal development in rats. Key findings of these animal studies will be described in the potential product labeling (i.e., Sections 8.1 and 13.1), which conveys safety information to the patient. Information in the potential BIBF 1120 product labeling should be based on well-designed, GLP-compliant animal toxicity studies. A well-designed study should investigate the dose-response relationship of BIBF 1120 and attempt to identify the no-adverse-effect level (NOAEL) and minimally toxic doses.

   To date, you have completed only a GLP-compliant male fertility study in rats and 2 non-GLP compliant dose-ranging teratology studies of BIBF 1120 in rats. Results of the studies showed that BIBF 1120 was a potential teratogen. We request that you complete the four remaining studies listed in the first paragraph.

2. We have no specific comments on the conceptual designs for any of the 4 reproductive and developmental toxicity studies. We will evaluate the adequacy of the studies once the final reports are submitted.

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/s/

LUQI PEI
01/25/2012

TIMOTHY W ROBISON
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08/28/2014

MARCIE L WOOD
08/28/2014
I concur

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 205-832
Supporting document/s:	SDN 1
Applicant's letter date:	May 2, 2014
CDER stamp date:	May 2, 2014
Product:	Ofev (nintedanib) tablets
Indication:	Idiopathic pulmonary fibrosis
Applicant:	Boehringer Ingelheim
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products
Reviewer:	Grace S. Lee, Ph.D., D.A.B.T.
Supervisor/Team Leader:	Marcie Wood, Ph.D.
Division Director:	Badrul Chowdhury, M.D., Ph.D.
Project Manager:	Jessica K. Lee, Pharm.D.

Template Version: September 1, 2010

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1 Executive Summary

1.1 Introduction

A battery of reproductive and developmental toxicity studies of BIBF 1120 was completed in rats and rabbits. These studies evaluated the effect of BIBF 1120 on fertility in rats, embryo-fetal developmental toxicity in rats and rabbits, and pre- and post-natal development in rats. In this review, embryo-fetal developmental (EFD) studies and a pre- and post-natal developmental (PPND) study were evaluated. The results from the EFD studies showed teratogenic effects of BIBF 1120 in both rats and rabbits, and the vasculature and axial skeletons were mainly affected in both species. In addition, anomalies in the urogenital system were clearly noted in rabbits. Increased resorption rate and reduced number of viable fetuses were also observed at the high dose of these studies. These embryo-fetal findings were demonstrated in the absence of maternal toxicity. NOAELs could not be identified in the EFD studies in rats and rabbits due to teratogenic effects seen in all test article-dosed groups. Although obvious embryo-fetal developmental effects of BIBF 1120 were observed in the EFD studies, BIBF 1120-related effects in the PPND rat study (with the same dose levels that were used the EFD rat study) were limited to slightly increased mean gestation days, increased mean postimplantation loss, and decreased litter mean number of live F_1 pups on postnatal day (PND) 1 and 4 in the HD group. Most likely, pups with anomalies were not alive at the delivery or died shortly after they were born, and apparently, there were no test article-related effects on the development of pups that survived.

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2 Drug Information

BIBF1120. See the nonclinical original NDA review for complete drug information.

3 Studies Submitted

3.1 Studies Reviewed

Study #	Title	EDR Location
12B017	BIBF 1120: Study for effects on embryo-fetal development in rats by oral (gavage) administration	4.2.3.5.2
12B032	BIBF 1120: Study for effects on embryo-fetal development in rabbits by oral (gavage) administration	4.2.3.5.2
DDB0229	BIBF 1120: Study for effects on pre- and postnatal development in the Han Wistar rat by oral gavage administration	4.2.3.5.3

3.2 Studies Not Reviewed

The following three studies were not reviewed because they do not provide a considerable amount of additional information in the nonclinical safety evaluation of

BIBF 1120. The studies were non-GLP compliant, dose-ranging teratology studies in rats and rabbits. Fully GLP-compliant teratology studies in each species are available. However, major findings from these dose-ranging studies in rats and rabbits were cursorily reviewed and summarized under the section of Justification of Dose Selection in the review of GLP EFD studies in rats and rabbits, respectively.

Study #	Title	EDR Location
07B002	BIBF 1120 ES: Preliminary study for effects on embryo-fetal development in rats by oral (gavage) administration (non-GLP)	4.2.3.5.2
07B030	BIBF 1120 ES: Preliminary study for effects on embryo-fetal development in rats by oral (gavage) administration (non-GLP)	4.2.3.5.2
11b228	BIBF 1120: Dose range finding study for effects on embryo-fetal development in rabbits by oral (gavage) administration (non-GLP)	4.2.3.5.2

3.3 Previous Reviews Referenced

IND 74,683 (BIBF 1120 Boehringer Ingelheim) PharmTox Review by Dr. Luqi Pei dated May 10, 2011

9 Reproductive and Developmental Toxicology

9.2 Embryonic Fetal Development

Study title: BIBF 1120: Study for effects on embryo-fetal development in rats by oral (gavage) administration

Study no.:	12B017 [Document No. U13-1923-01]
Study report location:	EDR
Conducting laboratory and location:	Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Str. 65 88397 Biberach an der Riss Germany
Date of study initiation:	Not stated; February 9, 2012 (day of animal delivery)
GLP compliance:	Yes; in accordance with the OECD Principles of Good Laboratory Practice
QA statement:	Yes
Drug, lot #, and % purity:	BIBF 1120 ES, batch No. 1045986, 98.6% purity; All concentrations refer to the free base equivalent BIBF 1120 BS of the test article BIBF 1120 ES using the conversion factor of 1.204.

Key Study Findings

- In the embryo-fetal developmental (EFD) toxicity study in the rat, time-mated Han Wistar rats were administered BIBF 1120 at oral (gavage) doses of 0 (0.5% hydroxyethylcellulose), 2.5 (LD), 5 (MD), or 10 (HD) mg/kg/day from Gestation Day [GD] 7 through 16 (day of confirmed mating = GD 1).
- Test article-related maternal toxicity was not observed in the study.
- Embryo-fetal developmental effects of BIBF 1120 were demonstrated in the study. In the HD group, slightly increased resorption rate (16.0% vs. 7.5% in the control group), slightly reduced number of viable fetuses (9.8 vs. 10.8 in the control group), and slightly lower mean fetal weight (4.74 g vs. 4.98 g in the control group) were observed.
- Test article-related teratogenic effects were observed in all BIBF 1120-dosed groups, although most obvious effects were noted in the HD group. The vasculature and axial skeleton were mainly affected in the HD group. Vascular anomalies included missing right subclavian artery, an additional vessel at the descending aorta, aortic arch rotation to the right side, and an increased incidence of shortened truncus brachiocephalicus [innominate artery]. Axial skeletal anomalies were seen mainly in thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, misshaped, or asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). Slightly increased incidences of fusion between facial bones and unossified occipital bone were also observed in the HD group. A few incidences of the same axial skeletal malformations were also noted in the MD and LD groups.
- TK analysis showed that systemic exposures to BIBF 1120 and its metabolites, BIBF 1202 and BIBF 1202 GLUC, increased with dose. The plasma levels of metabolites were higher than those of BIBF 1120, especially BIBF 1202 GLUC which was much higher than BIBF 1120 and BIBF 1202.
- The NOAEL for maternal toxicity was the high dose (10 mg/kg) as there was no maternal toxicity, but the NOAEL for embryo-fetal developmental toxicity could not be identified in the study as teratogenic effects were observed in all test article-dosed groups. This agrees with the sponsor's determination.

Methods

Doses:	0 (G1, control group), 2.5 (G2, LD), 5 (G3, MD), and 10 (G4, HD) mg/kg
Frequency of dosing:	Once daily from Gestation Days 7 to 16
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Natrosol® 250 HX (0.5% aqueous hydroxyethylcellulose solution in demineralized water)
Species/Strain:	Han Wistar rats [Crl:WI(Han)]
Number/Sex/Group:	27 mated females in G1, 30 mated females/group in G2-4

Satellite groups:	3 mated females in G1 and 6 mated females/group in G2-4 for toxicokinetic evaluation
Study design:	The day when sperm and/or a vaginal plug were observed was designated Gestation Day 1 (GD 1). Plasma was prepared and analyzed for BIBF 1120 as well its metabolites BIBF 1202 and BIBF 1202-glucuronide.
Deviation from study protocol:	There were no deviations that affected the integrity of the study or impacted the study design.

Justification of Dose Selection

Dose levels in the GLP definitive EFD rat study were based on the findings from two non-GLP dose-ranging EFD rat studies. In the first non-GLP dose-ranging EFD rat study [Study No. 07B002], time-mated Han Wistar rats were administered BIBF 1120 at oral (gavage) doses of 0, 30, 75, or 180 mg/kg/day from GD 7-16 (day of confirmed mating = GD 1). All test article-dosed rats had complete resorptions. Thus, the second dose-ranging EFD rat study [07B030] was conducted with lower dose levels (0, 5, 10, and 20 mg/kg/day). Completely resorbed litters were observed at 20 mg/kg, and an increased resorption rate was also observed at 10 mg/kg (35% vs. 4.5% in the control group), which led to a lower number of viable fetuses (8.0 fetuses vs. 10.9 fetuses in the control group). Teratogenic effects were observed in viable fetuses in the 5 and 10 mg/kg groups of the second dose-ranging EFD study, with the aortic arch and axial skeleton being the mainly affected structures. Vasculature anomalies were observed only in the 10 mg/kg group, and these included missing right subclavian artery (1/38 fetuses), changed origin of arteria pulmonalis and aortic arch (4/38), inversion of the aortic arch to the right lateral (1/38) and additional vessel originating at the aortic arch (1/38), shortened truncus brachiocephalicus (3 /38), and no truncus bracheocephalicus (1/38). Axial skeletal findings observed only in the 10 mg/kg group are as follows: sternebra (asymmetrically ossified, split or dorsal-ventrally split), thoracic vertebral body (partly not ossified), and lumbar vertebral body findings (cleft, flat, asymmetrically ossified, dumbbell-shaped). These findings were also noted in low incidences (1-3 fetuses for each finding). In addition, the following skeletal findings were observed in the 5 and 10 mg/kg groups: unilaterally ossified cervical vertebral body (1/56 and 12/42 fetuses in 5 and 10 mg/kg groups, respectively), cleft thoracic vertebral body (3/56 and 9/42, respectively), dumbbell-shaped thoracic vertebral body (8/56 and 13/42, respectively), asymmetrically ossified thoracic vertebral body (5/56 and 15/42, respectively), and flat lumbar vertebral body (1/56 and 2/42, respectively). In this study, TK analysis of BIBF 1120 was included, and $AUC_{(0\text{-}24h)}$ values at 5 mg/kg were 15.50 and 22.60 nmol·h/L on GDs 7 and 16, respectively. These values were similar to the $AUC_{(0\text{-}24h)}$ values at 10 mg/kg in the GLP EFD rat study.

Observations and Results

Mortality

Viability was checked once daily, except on working days during the dosing period, when it was checked at least twice daily.

There was no mortality in the study. All animals were terminally sacrificed.

Clinical Signs

Clinical observations were performed once daily, except on working days during the dosing period, when it was checked at least twice daily.

Clinical observation data are not included in the study. The study report states that no adverse clinical signs were noted.

Body Weight

Body weights were measured on GDs 1, 7-16, and 21.

There were no test article-related effects on mean body weight or body weight gain.

Feed Consumption

Food consumption was determined weekly on GDs 7, 14, and 21.

There were no test article-related effects on mean food consumption.

Toxicokinetics

Blood samples for toxicokinetic (TK) analysis were collected from the retrobulbar venous plexus of pregnant females on GDs 7 and 16 under light isoflurane anesthesia at the following time points: 2 hr postdose from the control group, and predose, 1, 2, 4, 8, and 24 hr postdose from test article-dosed groups.

Plasma concentrations of the parent compound BIBF 1120 and its metabolites, BIBF 1202 and BIBF 1202-glucuronide (BIBF 1202 GLUC), were analyzed using a validated HPLC-MS/MS method. The lower limit of quantification (LLOQ) was 1.00 ng/mL for BIBF 1120 and BIBF 1202 GLUC and 2.00 ng/mL for BIBF 1202.

BIBF 1120, BIBF 1202, and BIBF 1202 GLUC were not detected in any samples from the control group.

The TK data from BIBF 1120-dosed groups are shown in Table 1. The plasma levels of metabolites were higher than those of BIBF 1120, especially BIBF 1202 GLUC which was much higher than BIBF 1120 and BIBF 1202.

The plasma levels of BIBF 1120 and BIBF 1202 were below LLOQ for all samples from the LD group, whereas only 2 and 4 samples from the MD group had levels above

LLOQ for BIBF 1120 and BIBF 1202, respectively. Based on comparison of C_{max} values, the exposure to BIBF 1120 and BIBF 1202 increased in a greater than dose-proportional manner where detection was possible. The dose effect for $AUC_{(0-24h)}$ could only be estimated for BIBF 1202 GLUC. The exposure to BIBF 1202 GLUC increased with dose. Slight increases in BIBF 1120 and BIBF 1202 plasma concentrations were observed after repeated dosing, whereas no consistent change was observed for BIBF 1202 GLUC.

Table 1 Mean toxicokinetic parameters from the EFD study in rats (doses are reported as BIBF 1120) [taken directly from the study report, pp. 25]

		BIBF 1120		BIBF 1202		BIBF 1202 GLUC*	
Dose [mg/kg]	Dosing Day	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
2.5	1	NC	NC	NC	NC	45.7	325
2.5	10	NC	NC	NC	NC	53.2	399
2.5	1&10	NC	NC	NC	NC	49.5	362
5.0	1	1.10	NC	3.04	NC	60.2	496
5.0	10	1.85	NC	6.24	50.4	102	875
5.0	1&10	1.47	NC	5.17	50.4	80.9	686
10	1	3.83	17.5	13.2	51.2	317	1760
10	10	6.97	34.2	19.2	125	288	2000
10	1&10	5.40	25.8	16.2	80.5	302	1880

NC: not calculated
* BIBF 1202-glucuronide
Day 1= GD 7; Day 10 = GD 16

Dosing Solution Analysis

All test article dosing formulations were prepared as suspensions in the vehicle. The concentrations of BIBF 1120 (test article calculated as free base) in the formulations were determined by (b) (4)

All samples were within a range of 10% of the nominal concentrations.

Necropsy

Animals were sacrificed on GD 22 and were macroscopically examined. Macroscopic findings were filed in the raw data and not reported.

Two, one, five, and one animals in the control, LD, MD, HD groups, respectively, were not pregnant.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

For pregnant rats, the number of corpora lutea, number and position of implantation sites, early or late resorptions, and live and dead fetuses were counted.

The Cesarean section data are shown in Table 2. In the HD group, test article-related effects were observed in the following parameters: increased resorption rate (16.0% vs. 7.5% in the control group), reduced number of viable fetuses (9.8 vs. 10.8 in the control group), and lower mean fetal weight (4.74 g vs. 4.98 g in the control group). The magnitude of these changes was slight.

Table 2 Cesarean section data from the EFD rat study [taken directly from the study report, pp. 27]

Parameter (means and ranges)	BIBF 1120 BS				Spontaneous incidences from the evaluation study [U03-1549-01]
	G 1	G 2	G 3	G 4	
	Dose [mg/kg]				
	Control	2.5	5	10	
Total number of litters	**22**	**23**	**19**	**23**	**85**
	mean/ range				mean/ range
Corpora lutea	12.6/ 5-15	13.0/ 10-15	13.3/ 10-16	13.0/ 10-16	12.0/ 9-15
Implantations	11.4/ 2-15	11.7/ 2-15	11.8/ 5-15	11.6/ 4-16	11.1/ 5-15
Viable fetuses	10.8/ 1-15	11.0/ 2-14	11.2/ 5-15	9.8/ 2-14	10.5/ 5-14
Dead fetuses	0	0	0.1/ 0-1	0	0
Male fetuses (%)	44.03/ 0.00-100.00	51.87/ 16.67-100.00	51.73/ 25.00-81.82	54.23/ 22.22-90.91	49.41/ 18.18-80.00
Female fetuses (%)	55.97/ 0.00-100.00	48.13/ 0.00-83.33	48.27/ 18.18-75.00	45.77/ 9.09-77.78	50.59/ 20.00-81.82
Total resorptions	0.64/ 0-3	0.70/ 0-4	0.58/ 0-2	**1.78**/ 0-8	0.65/ 0-6
Early resorptions	0.59/ 0-3	0.70/ 0-4	0.53/ 0-2	**1.78**/ 0-8	0.60/ 0-6
Late resorptions	0.05/ 0-1	0	0.05/ 0-1	0	0.05/ 0-1
Fetal weight [g]	4.98/ 4.51-6.35@	4.93/ 4.30-5.64	4.88/ 4.30-5.21	**4.74**/ 4.22-5.18	5.03/ 4.20-5.73
Pre-implantation loss (%)	10.83/ 0.00-60.00	9.17/ 0.00-86.67	10.13/ 0.00-66.67	10.92/ 0.00-71.43	7.57/ 0.00-61.54
Resorption rate	7.49/ 0.00-50.00	5.21/ 0.00-30.77	4.69/ 0.00-18.18	**15.95**/ 0.00-80.00	5.70/ 0.00-54.55

Statistically significant differences between test item treated and Control group are printed in bold.
@ Body weight of fetus 111R03 was excluded from the calculation because it was accidentally injected during anesthesia of its mother.

Offspring (Malformations, Variations, etc.)

The weight and sex of the fetuses were recorded and these data are shown in Table 2. Anomalies of fetuses were determined by external, skeletal, and visceral examinations.

For skeletal examinations, approximately half of the fetuses from each litter were randomly selected, eviscerated and processed using the Alizarin Red S staining method. The remaining fetuses were prepared for visceral examination (formalin fixation 12%). The fixed heads were examined using the Wilson's sectioning technique (freehand razor blade sections), and the thorax and abdomen were dissected under a stereoscopic microscope for visceral changes.

The study report does not state that the litter served as the unit of analysis, but it appears that the litter was the unit of analysis.

Selected organs (not specified in the study report) were fixed, sectioned, and stained with hematoxylin and eosin (H&E) and then microscopically examined. However, the histopathological findings were filed in the raw data and not reported.

Fetal visceral and skeletal findings are presented in Tables 3 and 4, respectively. Test article-related teratogenic effects were observed in all BIBF 1120-dosed groups, although most obvious effects were noted in the HD group. The aortic arch and axial skeleton were mainly affected by the test article. As BIBF 1120 caused a wide range of skeletal findings and these skeletal findings were related to each other, each finding was not considered as a separate finding. Instead, related findings were analyzed together. This is also true for BIBF 1120-induced vasculature defects.

The vasculature anomalies were observed only in the HD group, and included single incidences of missing right subclavian artery, additional vessel at the aorta descendens (descending aorta) connected to the right side, and aortic arch rotated to the right side. An increased incidence of shortened truncus brachiocephalicus [innominate artery] was also observed in the HD group. Most of these findings were also noted in the 10 mg/kg group in the dose-ranging EFD study.

The test article-related axial skeletal findings in the HD group are as follows: fused, split, or abnormally ossified (unilaterally, partly or asymmetrically) sternebra; bifid or fused ribs; cervical vertebral bodies <7; missing thoracic vertebra or thoracic hemivertebra, or cleft, displaced, abnormally ossified (unilaterally or asymmetrically), or dumbbell-shaped thoracic vertebral body; fused lumbar vertebral arches or lumbar hemivertebra, or enlarged, flat, dumbbell-shaped, or asymmetrically ossified lumbar vertebral body; cleft, fused, displaced or unilaterally ossified caudal vertebral body. In addition, slightly increased incidences of fusion between facial bones (processus zygomaticus of maxillar bone and jugal bone; unilateral or bilateral) and unossified occipital bone were observed in the HD group.

Single incidences of flat thoracic vertebral body, and split or dumbbell-shaped sternebra in the MD group appeared to be test article-related as these findings were also noted in higher incidences in the 5 mg/kg group in the second dose-ranging study. Additionally, dumbbell-shaped or asymmetrically ossified thoracic vertebral body (8/56 and 5/56 fetuses, respectively) and flat lumbar vertebral body (5/56 fetuses) were also observed in the 5 mg/kg group in the dose-ranging study.

Only a few incidences of skeletal findings (flat or cleft thoracic vertebral body; fused, split, or unilaterally ossified sternebra) were observed in the LD group. These findings were observed in the HD group, and some of these findings were also noted in the MD group in this study or the LD group (5 mg/kg) in the dose-ranging study. Thus, these findings in the LD group are considered test article-related.

A few incidences of unilateral or bilateral distal anterior or posterior phalanges less than 5 were only observed in the test article-dosed groups, however, the incidences were not dose-related. Moreover, proximal anterior or posterior phalanges less than 4 or 3, respectively, frequently occurred even in the control group. Thus, limb digit findings were not considered test article-related in this study. However, note that a few incidences of test article-induced short digits were observed in the EFD rabbit study of BIBF 1120 as described below.

Table 3 Visceral findings from the EFD rat study [number of affected fetuses/% incidence]

Parameter	BIBF 1120				Study # U03-I549-01*
	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)	
No. of fetuses/No. litters observed	113/21	122/23	101/19	105/23	424/85
Missing A. subclavian right	0	0	0	**1/1.0**	0
Additional vessel at the aorta descendens connected to the right side	0	0	0	**1/1.0**	0
Aortic arch rotated to the right side	0	0	0	**1/1.0**	0
Shortened truncus brachiocephalicus	2/1.8	0	2/2.0	**5/4.8**	1/0.2

*As a reference point, the sponsor included spontaneous findings from Study No.U03-1549-01 (Evaluation of the rat strain CrlGlxBrlHan:WI in a study for effects on embryo-fetal development by oral administration of Natrosol 250 HX, gavage).

Table 4 Skeletal findings from the EFD rat study [number of affected fetuses/% incidence]

Parameter	BIBF 1120				Study # U03-I549-01*
	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)	
No. of fetuses/No. litters observed	124/22	132/23	112/19	120/23	465/85
Processus zygomaticus of maxillar bone and jugal bone fused-bilateral	2/1.6	1/0.8	0	**8/6.7**	0
Processus zygomaticus of	3/2.4	5/3.8	3/2.7	**10/8.3**	0

Parameter	BIBF 1120				Study # U03-I549-01*
	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)	
maxillar bone and jugal bone fused-unilateral					
Occipital bone not ossified	6/4.8	1/0.8	3/2.7	**14/11.7**	11/2.4
Sternebra fused	0	**1/0.8**	0	0	0
Sternebra split	0	0	**1/0.9**	**2/1.7**	0
Dorsal-ventrally split sternebra	0	**2/1.5**	0	0	1/0.2
Sternebra partly not ossified	14/11.3	20/15.2	18/16.1	**26/21.7**	0
Sternebra asymmetrically ossified	0	3/2.3	2/1.8	**17/14.2**	11/2.37
Sternebra unilaterally ossified	0	**1/0.8**	0	**1/0.8**	0
Sternebra dumbbell-shaped	0	0	**1/0.9**	0	0
Rib bifid-unilateral	0	0	0	**1/0.8**	0
Ribs fused-unilateral	0	0	0	**1/0.8**	0
Cervical vertebral bodies <7	13/10.5	14/10.6	14/13.4	**47/39.2**	76/16.3
Cervical vertebral arch narrow-unilateral	0	0	0	**1/0.8**	0
Thoracic vertebral body cleft	0	1/0.8	0	**17/14.2**	1/0.2
Thoracic vertebral body unilaterally ossified	0	0	0	**2/1.7**	0
Thoracic vertebral body displaced	0	0	0	**1/0.8**	0
Thoracic vertebra missing	0	0	0	**1/0.8**	0
Thoracic hemivertebra	0	0	0	**2/1.7**	0
Additional thoracic vertebra	0	0	0	1/0.8	1/0.22
Thoracic vertebral body asymmetrically ossified	0	0	0	**13/10.8**	0
Thoracic vertebral body dumbbell-shaped	0	0	0	**13/10.8**	3/0.7
Thoracic vertebral body flat	0	2/1.5	1/0.9	**9/7.5**	1/0.2
Lumbar hemivertebra	0	0	0	**3/2.5**	0
Lumbar vertebral arches fused	0	0	0	**1/0.8**	0
Lumbar vertebral arches fused in combination with fused lumbar bodies	0	0	0	**1/0.8**	0
Additional lumbar vertebra	1/0.8	0	0	**4/3.3**	0
Lumbar vertebral body enlarged	0	0	0	**1/0.8**	0
Lumbar vertebral body flat	0	0	0	**1/0.8**	0

Parameter	BIBF 1120				Study # U03-I549-01*
	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)	
Lumbar vertebral body dumbbell-shaped	0	0	0	**1/0.8**	0
Lumbar vertebral body asymmetrically ossified	0	0	0	**1/0.8**	0
Caudal vertebral body cleft	0	0	0	**1/0.8**	0
Caudal vertebral body unilaterally ossified	0	0	0	**2/1.7**	0
Caudal vertebral body displaced	0	0	0	**1/0.8**	0
Caudal vertebral bodies fused	0	0	0	**1/0.8**	0
Distal anterior phalanges <5-bilateral	0	3/2.3	2/1.8	0	4/0.9
Distal anterior phalanges <5-unilateral	0	2/1.5	1/0.9	1/0.8	
Distal posterior phalanges < 5-bilateral	0	4/3.0	2/1.8	0	1/0.2
Distal posterior phalanges < 5- unilateral	0	0	2/1.8	0	

*As a reference point, the sponsor included spontaneous findings from Study No.U03-1549-01 (Evaluation of the rat strain CrlGlxBrlHan:WI in a study for effects on embryo-fetal development by oral administration of Natrosol 250 HX, gavage).

Study title: BIBF 1120: Study for effects on embryo-fetal development in rabbits by oral (gavage) administration

Study no.:	12B032 [Document No. U13-1937-01]
Study report location:	EDR
Conducting laboratory and location:	Boehringer Ingelheim Pharma GmbH & Co. KG Birkendorfer Str. 65 88397 Biberach an der Riss Germany
Date of study initiation:	Not stated; February 16, 2012 (start day of animal delivery)
GLP compliance:	Yes; in accordance with the OECD Principles of Good Laboratory Practice
QA statement:	Yes
Drug, lot #, and % purity:	BIBF 1120 ES, batch No. 1045986, 98.6% purity; All concentrations refer to the free base equivalent BIBF 1120 BS of the test article BIBF 1120 ES using the conversion factor of 1.204.

Key Study Findings

- In the embryo-fetal developmental (EFD) toxicity study in the rabbit, time-mated Himalayan rabbits were administered BIBF 1120 at oral (gavage) doses of 0 (0.5% hydroxyethylcellulose), 15 (LD), 30 (MD), or 60 (HD) mg/kg/day from GDs 6 through 18 (day of confirmed mating = GD 0).
- Similar to the EFD study in rats, test article-related maternal toxicity was not observed in this rabbit study.
- Test article-related embryo-fetal developmental effects were demonstrated in the study. In the HD group, there were one doe with abortion and three does with all resorptions. In addition, increased resorption rate (42% vs. 18% in the control group), reduced number of viable fetuses (4.3 vs. 5.8 in the control group), and lower ratio of males versus females (29:71) were also noted in the HD group.
- Test article-related teratogenic effects were observed in all BIBF 1120-dosed groups. Mainly affected structures in the MD and HD groups were the vasculature (absence of the subclavian artery or aortic arch), urogenital system (absence of kidney, ureter, ductus deferens, uterus and/or ovaries), and axial skeletal system (e.g., hemivertebra, or cleft, fused, displaced, or unilaterally ossified vertebrae, fused ribs). In addition, absence of both gall bladder and ductus choledochus, and additional skull bone were noted. One HD fetus had open eyes, cleft palate, and neural tube, ventricular septal, axial skeletal, and limb defects. Some of the same axial skeletal findings were also observed in the LD group.
- The systemic exposure to BIBF 1120 increased from 30 to 60 mg/kg, but was similar at the 15 and 30 mg/kg dose levels. The systemic exposure to the metabolites BIBF 1202 and BIBF 1202 GLUC increased roughly in a dose-proportional manner from 15 to 60 mg/kg. The plasma levels of BIBF 1202 GLUC were slightly lower than those of BIBF 1120, but plasma levels of BIBF 1202 were higher than those of BIBF 1120.
- The NOAEL for maternal toxicity was the high dose (60 mg/kg) as there was no maternal toxicity, but the NOAEL for embryo-fetal developmental toxicity could not be identified in the study as teratogenic effects were observed in all test article-dosed groups. This agrees with the sponsor's determination.

Methods

Doses:	0 (Control group), 15, 30, and 60 mg/kg
Frequency of dosing:	Once daily from Gestation Days 6 to 18
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Natrosol® 250 HX (0.5% aqueous hydroxyethylcellulose solution in demineralized water)
Species/Strain:	Himalayan rabbits [Crl:CHBB(HM)]
Number/Sex/Group:	21 mated females/group

Satellite groups:	None
Study design:	The day of mating evidence was designated Gestation Day (GD) 0.
Deviation from study protocol:	There were no deviations that affected the integrity of the study or impacted the study design.

Justification of Dose Selection

Dose levels in the GLP definitive EFD rat study were based on the findings from a non-GLP dose-ranging EFD rabbit study. In the non-GLP dose-ranging EFD study [Study No. 12B032], Himalayan rabbits were administered BIBF1120 at oral (gavage) doses of 0, 3, 7, 15, 30, 75, or 180 mg/kg from GD 6-18 (day of confirmed mating = GD 0). All litters were completely resorbed at 180 mg/kg and a marked increase in resorption rate was also observed at 75 mg/kg (34% vs. 5.5% in the control group).

Teratogenic effects of BIBF 1120 were noted in all test article-dosed groups. One female fetus in the 3 mg/kg dose group exhibited absence of head and right forelimb, malrotated left forelimb with absence of 5th digit, and thoracic/abdominal schisis. In the same group, another female fetus had skull hernia and a male fetus had ventricular septal defect.

Axial skeletal findings included asymmetrically ossified or split sternebra in the 7, 15, and 75 mg/kg groups, additional lumbar vertebra in the 30 and 75 mg/kg groups, and fused sternebrae in the 75 mg/kg group. One fetus in the 15 mg/kg dose group showed unilateral brachydactyly (short digits).

In addition to one fetus in the 3 mg/kg dose group, ventricular septal defect was also noted in the 15 mg/kg (2 fetuses) and 75 mg/kg (2 fetuses) groups. Aorta arch findings included missing right subclavian artery and additional vessel at the truncus pulmonalis connected to right forelimb in the 30 mg/kg group, and shortened truncus brachiocephalicus in the 15 and 30 mg/kg groups.

There was one fetus with absence of left kidney and ureter and another fetus with shortened ductus choledochus in the 75 mg/kg group.

TK data from the dose-ranging rabbit study are presented in Table 5.

Table 5 Mean toxicokinetic parameters (doses are reported as BIBF 1120) [taken directly from the study report, pp. 23]

		BIBF 1120		BIBF 1202 GLUC		BIBF 1202	
Dose [mg/kg]	Day	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
3	1	18.4	99.5	28.2	153	112	508
3	13	16.5	91.7	31.9	258	129	650
3	1&13	17.4	95.6	30.1	205	120	579
7	1	46.4	229	76.2	372	406	1510
7	13	50.9	207	48.9	273	400	1490
7	1&13	48.6	218	62.6	322	403	1500
15	1	194	673	146	694	1430	4400
15	13	173	647	176	984	1230	4620
15	1&13	183	660	161	839	1330	4510
30	1	636	2810	383	2290	3490	15100
30	13	427	1710	390	2340	2610	10900
30	1&13	531	2260	387	2310	3050	13000
75	1	498	2290	223	1700	6970	30000
75	13	619	3340	268	2550	6180	36900
75	1&13	559	2810	246	2130	6570	33500
180	1	1730	14300	713	7400	9600	59100
180	13	412	4270	265	4410	3150	28500
180	1&13	1400	11800	601	6660	7990	51400

Observations and Results

Mortality

Viability was checked once daily, except on working days during the dosing period, where it was checked at least twice daily.

There was no mortality in the study. All animals were terminally sacrificed.

Clinical Signs

Clinical observations were performed once daily, except on working days during the dosing period, where it was checked at least twice daily.

Only a summary table of clinical signs (below) was included in the study report, but line listings of the individual data were not provided in the study report.

There were no test article-related clinical signs.

Table 6 Summary of clinical signs from the embryo-fetal developmental toxicity study in rabbit [taken directly from the study report, pp.23]

Dose Group	Clinical Sign	GD
G1 0 mg/kg		
No. 102[#]	Blood on cage tray	23, 24
No. 121	Blood on cage tray	10
	Few feces	19-23, 26-28
	Bladder stone excreted (diameter about 1 cm)	GD 22
G2 15 mg/kg		
	No findings	
G3 30 mg/kg		
	No findings	
G4 60 mg/kg		
No. 417	Abortion, 3 placentae recovered	20
No. 420	Blood on cage tray	19-21, 23, 25

[#] Animal used for blood sampling

Body Weight

Body weights were measured on GD 1, 6-18, 21, and 28. One non-pregnant female in the control group and one non-pregnant female, one aborted female, and three females with no viable fetuses were excluded from mean values.

There were no test article-related effects on mean body weight or body weight gain.

Feed Consumption

Food consumption was determined weekly on GD 6, 14, 21, and 28.

There were no test article-related effects on mean food consumption.

Increased mean food consumption was noted in the HD group on GD 28 (26% increase relative to the control group). However, there were no test article-related effects during the dosing period and individual variations on food consumption were relatively large within each group, including the control group. Thus, the change was considered incidental.

Toxicokinetics

Blood samples for toxicokinetic (TK) analysis were collected via the ear vein of 3 pregnant females per group on GDs 6 and 18 at the following time points: 2 hr postdose from the control group and predose, 1, 2, 4, 8, and 24 hr postdose from test article-dosed groups.

Concentrations of BIBF 1120 and the metabolites BIBF 1202 and BIBF 1202-glucuronide (BIBF 1202 GLUC) in the plasma samples were determined

using a validated HPLC-MS/MS assay. The lower limit of quantification (LLOQ) was 1.00 ng/mL for BIBF 1120 and 2.00 ng/mL for BIBF 1202 and BIBF 1202 GLUC.

TK data are shown in Table 7. The C_{max} and $AUC_{(0-24h)}$ values of BIBF 1120 increased from 30 to 60 mg/kg, but C_{max} and $AUC_{(0-24h)}$ values of BIBF 1120 were similar at 15 mg/kg and 30 mg/kg. The C_{max} and $AUC_{(0-24h)}$ values of BIBF 1202 and BIBF 1202 GLUC increased roughly in a dose-proportional manner from 15 to 60 mg/kg. The plasma levels of BIBF 1202 GLUC were slightly lower than those of BIBF 1120, but plasma levels of BIBF 1202 were higher than those of BIBF 1120. Slight accumulation over the repeat dosing period was observed for BIBF 1120 (AUC accumulation ratio [AR] of 1.3-2.2), BIBF 1202 (AR of 1.3-1.5), and BIBF 1202 GLUC (AR of 1.4-3.4).

The inter-individual variability of plasma concentrations was considered to be moderate for BIBF 1120 (CV of 41-90% AUC) and low to moderate for the metabolites BIBF 1202 (CV of 6-67% AUC) and BIBF 1202 GLUC (CV of 6-63% AUC).

Table 7 Mean toxicokinetic parameters (doses are reported as BIBF 1120) [taken directly from the study report, pp. 233]

		BIBF 1120		BIBF 1202 GLUC*		BIBF 1202	
Dose [mg/kg]	Day	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
15	1	329	1160	144	604	2010	6250
15	13	461	1920	246	1470	2100	9320
15	1&13	395	1540	195	1040	2060	7790
30	1	344	1150	190	1100	2850	10500
30	13	562	2550	449	3540	3330	15800
30	1&13	453	1850	319	2320	3090	13200
60	1	840	4170	433	2700	5470	22200
60	13	1140	5340	534	3870	5760	29000
60	1&13	990	4760	483	3290	5610	25600

* BIBF 1202 GLUC = BIBF 1202-glucuronide
Day 1 = GD 6; Day 13 = GD 18

Dosing Solution Analysis

All dose formulations of BIBF 1120 were prepared as suspensions in the vehicle. Samples collected at the beginning and the end of the dosing period were analyzed for concentrations and homogeneity of the formulations by reverse phase HPLC with UV detection.

All samples were within a range of 10% of the nominal concentrations.

Necropsy

Animals were sacrificed on GD 29 and were macroscopically examined.

One animal each in the control and HD groups was not pregnant. In the HD group, there were one doe with abortion and three does with all resorptions.

There were no test article-related macroscopic findings.

Cesarean Section Data (Implantation Sites, Pre- and Post-Implantation Loss, etc.)

For pregnant rabbits, the number of corpora lutea, number and position of implantation sites, early or late resorptions, and aborted, live, and dead fetuses were counted.

Cesarean Section data are shown in Table 8. In the HD group, only 16 litters were analyzed for reproductive parameters in the table because there was one non-pregnant doe, one aborted doe, and three completely resorbed does. In the 16 analyzed litters in the HD group, test article-related effects were observed in the following parameters: increased resorption rate, reduced number of viable fetuses (4.3 vs. 5.8 in the control group), and lower ratio of males than females (29:71). The increase in total resorption rate in the HD group (42.2% vs. 18.4% in the control group) was mainly due to increased early resorptions (3.06 vs. 1.20 in the control group). Late resorptions were slightly increased in the HD group (0.44 vs. 0.10 in the control group).

Table 8 Cesarean section data [taken directly from the study report, pp. 26]

Parameter (means)	BIBF 1120				Historical Data+	Spontaneous incidences from the evaluation study [U05-1804-01]
	G 1	G 2	G 3	G 4		
	Dose [mg/kg]					
	Control	15	30	60		
Total number of litters	**20**	**21**	**21**	**16**	**158**	**60**
	Means (individual ranges)				Means (ranges of means)	
Corpora lutea	8.7 (6-11)	8.5 (5-14)	9.0 (5-12)	9.1 (6-11)	7.5 (6.4-8.4)	7.6 (7.6-7.8)
Implantations	7.1 (2-11)	7.3 (4-12)	7.6 (2-12)	7.9 (4-11)	7.0 (6.1-7.8)	7.3 (7.2-7.4)
Viable fetuses	5.8 (1-10)	6.0 (1-11)	6.6 (1-11)	4.3 (1-10)	6.5 (5.3-7.4)	6.9 (6.8-7.2)
Dead fetuses	0.1 (0-1)	0.1 (0-2)	0.0 (0)	0.1 (0-1)	0.01 (0-0.08)	<0.1 (0-0.1)
Male fetuses %	51.01 (0.00-100.00)	42.57 (0.00-100.00)	42.03 (0.00-100.00)	**29.05 (0.00-66.67)**	51 (48-59)	42.93 (39.38-48.30)
Female fetuses %	48.99 (0.00-100.00)	57.43 (0.00-100.00)	57.97 (0.00-100.00)	**70.95 (33.33-100.00)**	49 (41-52)	57.07 (51.70-60.62)
Total resorptions	1.30 (0-6)	1.14 (0-6)	0.95 (0-3)	**3.50 (0-10)**	0.5 (0.2-1.2)	0.32 (0.15-0.45)
Early resorptions	1.20 (0-6)	1.10 (0-6)	0.76 (0-3)	**3.06 (0-9)**	0.4 (0.1-1.1)	0.28 (0.15-0.40)
Late resorptions	0.10 (0-1)	0.05 (0-1)	0.19 (0-2)	0.44 (0-4)	0.1 (0-0.1)	0.03 (0-0.05)
Fetal weight g	37.62 (17.51-44.55)	37.97 (31.14-45.00)	37.77 (26.77-49.26)	37.32 (27.55-46.33)	38.3 (35.9-40.3)	34.88 (34.29-35.30)
Pre-implantation loss %	17.90 (0.00-66.67)	13.13 (0.00-60.00)	17.18 (0.00-77.78)	12.53 (0.00-60.00)	6.5 (1.7-13.1)	4.46 (3.48-5.94)
Resorption rate %	18.35 (0.00-85.71)	16.46 (0.00-85.71)	14.10 (0.00-50.00)	**42.16 (0.00-90.91)**	7.3 (4.2-14.4)	4.67 (1.91-7.19)

Significant differences between dose groups and Control group are printed in bold type.
+ These data originate from an internal historical data set from 10 Control groups in 10 embryo-fetal studies performed before 1998 [U93-2032, U94-2044, U94-2119, U94-2192, U95-2127, U95-2267, U96-2578, 97B102, 43S , 97B057]. They are filed in the Teratology Laboratory at Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach.

Offspring (Malformations, Variations, etc.)

The weight and sex of the fetuses were recorded, and these data are shown in Table 8. Anomalies of fetuses were determined by external, skeletal, and visceral examinations. The skeletal examination was performed radiographically. The fixed heads (Davidson fixation and storage in 12% formaldehyde) were examined using Wilson's sectioning technique (freehand razor-blade sections). *In situ* examination of the unfixed thorax and abdomen was carried out to determine visceral anomalies and sex of the fetuses.

The study report does not state that the litter served as the unit of analysis, but it appears that the litter was the unit of analysis.

At the external examination, short tail was observed in a single fetus each in the MD and HD groups. Brachydactyly (short digits) was observed in one LD fetus and also one HD fetus. The HD fetus also had a number of other anomalies as described below.

Fetal visceral and skeletal findings are presented in Tables 9 and 10. Multiple abnormalities were observed in the MD and HD groups. Mainly affected structures were the vasculature (e.g., missing subclavian artery or aortic arch, or persistent truncus arteriosus), the urogenital system (missing kidney, ureter, uterus, ductus deferens [vas deferens], and/or ovaries) and the axial skeletal system (e.g., hemivertebra, or cleft, fused, displaced, and/or unilaterally ossified vertebral body). One MD fetus with missing kidney, ureter, and uterus, and one HD fetus with missing ductus deferens also had diaphragmatic hernia. One LD fetus had skull hernia with some regions of the brain missing. Absence of gall bladder was observed across the groups, including the control group. However, 3 HD fetuses with missing gall bladder also did not have ductus choledochus. Cysts were observed proximate to the ovary in the MD and HD fetuses and to the epididymis in HD fetuses.

As BIBF 1120 caused a wide range of vasculature defects and these findings were related to each other, each finding was not considered as a separate finding. Instead, related findings were analyzed together. Similar to findings in rats, test article-related vasculature findings in the rabbit EFD study included missing subclavian artery or aortic arch, persistent truncus arteriosus, additional vessel at truncus pulmonalis [pulmonary trunk], aortic arch, or descending aorta connected to a forelimb, thin truncus pulmonalis, shortened truncus brachiocephalicus [innominate artery], thin or displaced ductus arteriosus botalli, dilated aortic arch, and small right heart ventricle.

Skeletal findings included additional sutura (frontal bone), unilateral ossification in the cervical, thoracic, lumbar, and caudal vertebral body, hemivertebra, additional vertebra, misshapen or displaced vertebra in the thoracic and/or lumbar region, and fused ribs. All these findings were observed in the HD group, with low incidences for certain findings and higher incidences for the some other findings. Some findings were occasionally observed in the LD and/or MD groups as well. Single incidences of horseshoe-shaped xiphoid cartilage and duplicated sternebrae and absence of lumbar vertebra were also observed in the LD group. Similar to findings in rats, BIBF 1120 caused a wide range of skeletal findings, but these skeletal findings were related to each other. Thus, each finding should not be considered as a separate finding. Instead, related findings should be analyzed together.

One HD fetus had multiple malformations, including open eyes, encephalocele, spina bifida, cleft palate, abdominal schisis, ventricular septal defect, fused cervical vertebral bodies, shortened and bent long bones (radius, ulna, tibia, fibula), and brachydactyly (short digits of 4^{th} and 5^{th} in the left forelimb and 4^{th} in hindlimbs). These teratogenic findings were considered test article-related as similar findings were observed in the

previous dose-ranging study. In the 3 mg/kg group of the dose-ranging study, there were severely malformed fetuses (one female fetus with absence of head and right forelimb and thoracic/abdominal schisis, another female fetus with skull hernia, and a male fetus with ventricular septal defect).

Increased incidences of additional sutura (nasal/frontal bone) were observed in the LD and HD groups in this study. In the dose-ranging study, 3 out of 44 control fetuses (14%) had the same finding. Thus, this finding was not considered test article-related in the definitive study.

Table 9 Visceral findings from the EFD rabbit study [number of affected fetuses/% incidence]

Parameter	BIBF 1120				HCD[a]	Study No. U05-1804-01[b]
	0 (control)	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day		
No. of fetuses/No. litters observed	115/20	126/21	139/21	69/16	1028/158	416/60
Missing parts of the brain	0	**1/0.8**	0	0	0	6/1.4
Truncus arteriosus persistens	0	0	0	**2/2.9**	1/0.1	0
Missing A. subclavia right	0	0	**3/2.2**	**7/10.1**	0	2/0.5
Missing A. subclavia left	0	0	**1/0.7**	0	0	0
Add. vessel at the Truncus pulmonalis connected to the right forelimb (sensu subclavia)	0	0	0	**1/1.4**	0	2/0.5
Add. vessel at the Truncus pulmonalis connected to the left forelimb (sensu subclavia)	0	0	**1/0.7**	0	0	0
Add. vessel at the Aorta descendens connected to the right forelimb (sensu subclavia)	0	0	**3/2.2**	**5/7.2**	0	0
Add. vessel at the Aortic arch connected to the right forelimb (sensu subclavia)	0	0	0	**1/1.4**	0	0
Apex of heart flattened, funnel-	0	0	**1/0.7**	0	0	0

Parameter	BIBF 1120				HCD[a]	Study No. U05-1804-01[b]
	0 (control)	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day		
shaped opening in left ventricle, closed by membrane						
Missing Aortic arch (Aorta leads into the carotids)	0	0	**1/0.7**	0	0	0
Anterior part of the heart turned to the left side	0	0	0	**2/2.9**	0	0
Aortic arch turned to the right side, left A. subclavia retroesophagial	0	0	0	**1/1.4**	0	0
Dilated aortic arch	0	0	0	**5/7.2**	0	0
Truncus pulmonalis thin	0	0	0	**2/2.9**	0	0
Shortened Truncus brachiocephalicus	0	**2/1.6**	0	**3/4.3**	0	0
Ductus arteriosus botalli thin	0	0	0	**6/8.7**	0	0
Ductus arteriosus botalli displaced	0	0	0	**2/2.9**	0	0
Heart ventricle small right	0	0	**1/0.7**	**2/2.9**	0	0
Diaphragm hernia	0	0	**1/0.7**	**1/1.4**	0	0
Missing gall bladder	6/5.2	5/4.0	5/3.6	6/8.7	0	6/1.4
Missing ductus choledochus	0	0	0	**3/4.3**	0	0
Kidney displaced caudally and changed in shape and proportion-unilateral	0	0	1/0.7	0	0	0
Missing kidney-bilateral	0	0	0	**2/2.9**	0	1/0.2
Missing kidney-unilateral	0	0	**2/1.4**	**5/7.2**	0	0
Missing ureter-bilateral	0	0	0	**2/2.9**	0	1/0.2
Missing ureter-unilateral	0	0	**2/1.4**	**5/7.2**	0	0
Missing uterus-bilateral	0	0	0	**1/1.4**	0	0
Missing uterus-unilateral	1/0.9	0	1/0.7	**3/4.3**	0	1/0.2
Missing ductus	0	0	0	**1/1.4**	0	0

Parameter	BIBF 1120				HCD[a]	Study No. U05-1804-01[b]
	0 (control)	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day		
deferens-bilateral						
Missing ductus deferens-unilateral	0	0	**1/0.7**	**3/4.3**	0	0
Missing ovary-bilateral	0	0	0	**1/1.4**	0	1/0.2
Cyst near ovary-unilateral	0	0	**2/1.4**	**1/1.4**	0	0
Cyst near epididymis-unilateral	0	0	0	**2/2.9**	0	0

[a]Historical Control Data (HCD) from an internal historical data set from 10 control groups in 10 embryo-fetal studies performed before 1998
[b]As a reference point, the sponsor included spontaneous findings from Study No. U05-1804-01 (Evaluation of the rabbit strain Chbb:HM in a study for effects on embryo-fetal development by oral administration of Natrosol 250 HX, gavage).

Table 10 Skeletal finding from the EFD rabbit study [number of affected fetuses/% incidence]

Parameter	BIBF 1120				HCD[a]	Study U05-1804-01[b]
	0 (control)	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day		
No. of fetuses/No. litters observed	115/20	126/21	139/21	69/16	1028/158	416/60
Additional sutura (nasal/frontal bone) - bilateral	1/0.9	3/2.4	0	6/8.7	0	0
Additional sutura (frontal bone) - bilateral	0	0	0	1/1.4	0	0
Additional sutura (parietal bone) - unilateral	0	0	2/1.4	1/1.4	0	0
Xiphoid cartilage horseshoe-shaped and sternebra duplicated	0	**1/0.8**	0	0	0	0
Fused ribs (unilateral)	0	0	0	**3/4.3**	0	0
Cervical vertebral body unilaterally ossified	0	**1/0.8**	0	**3/4.3**	0	0
Cervical vertebral body asymmetrically ossified	0	0	**1/0.7**	**1/1.4**	0	0

Parameter	BIBF 1120				HCD[a]	Study U05-1804-01[b]
	0 (control)	15 mg/kg/day	30 mg/kg/day	60 mg/kg/day		
Cervical vertebral body flat	0	0	0	**1/1.4**	0	0
Additional thoracic vertebra with ribs	0	0	3/2.2	**7/10.1**	2/0.2	1/0.2
Thoracic Hemivertebra	0	0	0	**3/4.3**	0	0
Thoracic vertebral body unilaterally ossified	0	0	0	**1/1.4**	0	0
Thoracic vertebral body dumbbell-shaped	0	0	**1/0.7**	0	0	0
Lumbar vertebral body displaced	0	0	**1/0.7**	**1/1.4**	0	0
Lumbar vertebra missing	0	**1/0.8**	0	0	1/0.1	0
Lumbar vertebral body cleft	0	0	0	**1/1.4**	0	0
Lumbar vertebral body unilaterally ossified	0	0	**1/0.7**	**1/1.4**	0	0
Lumbar vertebral bodies fused	0	0	0	**2/2.9**	0	0
Lumbar hemivertebra	0	0	0	**2/2.9**	0	0
Additional lumbar vertebra	0	0	1/0.7	**13/18.8**	2/0.2	0
Caudal vertebral body unilaterally ossified	0	0	**1/0.7**	**1/1.4**	0	0
Caudal vertebral arches fused	0	0	0	**1/1.4**	0	0
Caudal vertebrae fused	0	**1/0.8**	0	0	0	0
Caudal vertebra displaced	0	**1/0.8**	**1/0.8**	**2/2.9**	0	0
Caudal vertebrae <10	0	0	0	**1/1.4**	0	0

[a]Historical Control Data (HCD) from an internal historical data set from 10 control groups in 10 embryo-fetal studies performed before 1998
[b]As a reference point, the sponsor included spontaneous findings from Study No. U05-1804-01 (Evaluation of the rabbit strain Chbb:HM in a study for effects on embryo-fetal development by oral administration of Natrosol 250 HX, gavage).

9.3 Prenatal and Postnatal Development

Study title: BIBF 1120: Study for Effects on Pre- and Postnatal Development in the Han Wistar Rat by Oral Gavage Administration

Study no.:	DDB0229
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 6, 2012 (protocol signed by Study Director)
GLP compliance:	Yes, in compliance of UK GLP regulations and OECD Principles of GLP
QA statement:	Yes
Drug, lot #, and % purity:	BIBF 1120 ES, batch # 1045986, and 100.3% purity; All concentrations refer to the free base equivalent BIBF 1120 BS of the test article BIBF 1120 ES using the conversion factor of (b) (4)

Key Study Findings

- In the pre- and postnatal developmental (PPND) toxicity study in the rat, mated F_0 female Han Wistar rats were administered BIBF 1120 at oral (gavage) doses of 0, 2.5 (LD), 5 (MD), or 10 (HD) mg/kg/day from Gestation Day (GD) 6 to Lactation Day (LacD) 20 (day of confirmed mating = GD 0).
- Test article-related maternal toxicity was not observed in F_0 females in the study.
- In F_0 females in the HD group, mean gestation days were slightly increased (23.0 days vs. 22.5 days in the control group). Moreover, there was an increase in mean postimplantation loss, including 3 litters with total resorption in the HD group. This resulted in decreased mean postimplantation survival index and a lower litter mean number of total pups on postnatal day (PND) 1 in the HD group (71.5% and 8.9, respectively, excluding 3 litters with total resorption), compared to the control group (89.2% and 11.7, respectively). In addition, two litters lost all their pups between PNDs 1 and 4. From PND 5, there were no test article-related effects on the survival rate of delivered pups, physical, neurobehavioral, and reproductive parameters in F_1 animals.
- There were no test article-related effects on viability of F_2 fetuses in any dose group, as examined on GD 14.
- TK analysis showed that systemic exposure to BIBF 1120, BIBF 1202, and BIBF 1202 GLUC generally increased dose proportionally from 2.5 to 10 mg/kg, except that the increase of BIBF 1202 GLUC was more than dose-proportional from 2.5 to 5 mg/kg.

- The NOAEL for pre- and postnatal development of F_1 animals was identified as the mid dose (5 mg/kg) due to decreases in postimplantation survival index and litter mean number of live F_1 pups on PNDs 1 and 4 in the HD group.

Methods

Doses:	0 (control), 2.5 (LD), 5 (MD), and 10 (HD) mg/kg/day
Frequency of dosing:	Once daily from Gestation Day 6 to Lactation Day 20
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	Natrosol® 250 HX (0.5% hydroxyethylcellulose solution in demineralized water)
Species/Strain:	Han Wistar rats (RccHan; WIST)
Number/Sex/Group:	22 mated females
Satellite groups:	3 mated females/group for toxicokinetic evaluation
Study design:	The day of mating evidence was designated Gestation Day (GD) 0. Approximately 24 hours after birth was designated Lactation Day (LacD) 1 for F_0 females and Postnatal Day (PND) 1 for F_1 animals.
Deviation from study protocol:	There were no deviations that affected the integrity of the study or impacted the study design.

Observations and Results

F_0 Dams

Survival: Viability was checked at least twice daily.

There was no test article-related mortality.

One female in the control group was sacrificed due to poor clinical condition on GD 20.

Clinical signs: Clinical observations were performed at least twice daily. In addition, a more detailed physical examination was performed on each F_0 animal on GDs 0, 5, 12, 18, and 20, and LacDs 1, 7, 14, and 21.

There were no test article-related clinical signs.

Body weight: Body weights were measured on GDs 0, 3, 6, 10, 14, 17, and 20, and LacDs 1, 4, 7, 11, 14, 18, and 21.

There were no test article-related adverse maternal effects on mean body weight or body weight gain of F_0 females.

Decreased mean body weight gain was observed in the HD group from GDs 14 to 20 (33% decrease relative to the control group), but there was no effect on mean body weight gain prior to GD 14 or during the lactation period. On LacD 1, the mean body weight of the HD group (244 g) was similar to the control group (243 g). The decrease in body weight gain in the HD females from GDs 14 to 20 appeared to be a secondary effect from increased postimplantation loss and decreased litter mean number of total pups born in the HD group as described below.

A slight decrease in mean body weight gain was observed in the MD group from GDs 6 to 20 (9% decrease from GDs 6 to 14 and 15% decrease from GDs 14-20 relative to the control group). On LacD 1, the mean body weight of the MD group (237 g) was slightly lower than the control group (243 g). There was no decrease in mean body weight gain in the MD group during the lactation period. Slightly decreased mean food consumption was observed in the MD group during the gestation period (21 g/animal/day vs. 23 g/animal/day in the control group from GDs 10 to 13, 22 g/animal/day vs. 24 g/animal/day in the control group from GDs 14 to 16, and 23 g/animal/day vs. 25 g/animal/day in the control group from GDs 17 to 19) and from LacD 1 to 3 (32 g/animal/day vs. 36 g/animal/day in the control group). The litter mean number of total pups born in the MD group was slightly lower than the control group (10.7 vs. 11.6 in the control group). As the

magnitude of decreased body weight gain of F_0 females in the MD group was slight and this decrease was partly affected by decreased total pups born, the decrease in mean body weight gain in the MD group was not considered an adverse maternal effect.

There were no test article-related effects on mean body weight or body weight gain in any test article-dosed group during the lactation period.

Feed consumption: Food consumption was measured for the following intervals: GD 0-2, 3-5, 6-9, 10-13, 14-16, and 17-19, and LacDs 1-3, 4-6, 7-10, 11-13, 14-17, and 18-20. The mean daily consumption (g/rat/day) was calculated for each animal.

There was no test article-related adverse maternal effect on mean food consumption.

A slight decrease in mean food consumption was observed in the MD and HD group from GDs 10 to 19 (1 or 2 g/animal/day less than the respective food consumption values in the control group) and from LacDs 1 to 3 (32 g/animal/day vs. 36 g/animal/day in the control group). However, as the magnitude of the decreased food consumption was slight, the change was not considered adverse.

Uterine content: F_0 females surviving until the scheduled necropsy were sacrificed on LacD 21. Females that failed to produce a viable litter were sacrificed on presumed GD 25. Females whose litter died before LacD 21 were sacrificed on the day the last offspring died.

The numbers of implantation sites in each uterine horn was counted. For females failing to produce a viable litter, the number of uterine implantation sites was re-checked after staining with ammonium sulfide.

No abnormal findings were recorded.

Necropsy observation: A full macroscopic examination of the tissues was performed. Any abnormality in the appearance or size of any organ and tissue was recorded. Pituitary glands and ovaries were collected from F_0 females that failed to produce a viable litter, and the mammary tissues (caudal) were collected from F_0 females whose litter died before weaning. Retained mammary tissues were stained with hematoxylin and eosin and then microscopically examined.

Two females in the HD group and one female in the control group had macroscopic mammary findings in mammary tissues (inactive and pale), but there were no test article-related histological findings in mammary tissues.

Reproductive assessment: From GD 20, F_0 females were inspected 3 times daily for evidence of parturition. The progress and completion of parturition was monitored, numbers of live and dead offspring were recorded, and any difficulties observed were noted.

Reproductive data of F_0 females are shown in Table 11. Mean gestation days were slightly increased in the HD group (23.0 days vs. 22.5 days in the control group). Three litters in the HD group had complete resorption. Moreover, postimplantation loss was higher in the HD group, leading to decreases in postimplantation survival index and litter mean number of total pups on PND 1, and litter mean number of live pups on PND 4 (before culling) (71.5%, 8.9, and 9.2, respectively, excluding 3 litters with total resorption), compared to the control group (89.2%,11.7, and 11.5, respectively).

Table 11 Reproductive assessment of F_0 females from the PPND rat study

Parameter	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)
No. of pregnant rats	20	21	22	22
No. of live litters delivered	20	21	22	19[a]
Mean gestation period (days)	22.5	22.5	22.5	23.0
Litter mean no. of implant sites	13.0	12.2	12.0	12.6
Litter mean no. of total pups on Day1	11.7	11.6	10.7	8.9**
Litter mean no. of live pups on Day1	11.6	11.5	10.7	8.9**
Litter mean no. of live pups on Day 4 (before culling)	11.5	11.4	10.5	9.2*
Fetal sex ratio (M%:F%) on Day 1	48:52	49:51	53:47	51:49
Postimplantation survival index (%)[b]	89.2	94.0	87.8	71.5**
Viability of F_1 pups on Day 1 (%)[c]	99.7	99.3	99.5	98.2

Parameter	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)
Viability of F_1 pups on Day 4 (%)[d]	98.8	98.7	98.7	93.2
Viability of F_1 pups on Day 21 (%)[e]	98.1	100.0	99.4	100.0

* $p<0.05$
** $p<0.01$
[a]There were one total litter loss between PNDs 1 and 4 (before culling) and another total litter loss on PND 4. Thus, from PND 4 (after culling), there were only 17 litters with live pups in the HD group.
[b]Postimplantation survival index (%) = (Total No. of offspring born/ Total No. of implantation sites) x 100
[c]Viability of F_1 pups on Day 1 (or live birth index) (%) = (No. live pups on PND 1/ Total No. of pups born) x 100
[d]Viability of F_1 pups on Day 4 (%) = (No. live pups on PND 4/ No. live pups on PND 1) x 100
[e]Viability of F_1 pups on Day 21 (or lactation index) (%) = (No. live pups on PND 21/ No. live pups on PND 4) x 100

Table 12 Mean toxicokinetic data of F_0 animals on LacD 20 (doses are reported as BIBF 1120) [taken directly from the study report, pp. 446]

		BIBF 1120		BIBF 1202		BIBF 1202 GLUC	
Dose [mg/kg]	Phase	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
2.5	3	NC	NC	NC	NC	55.7	188
5	3	1.52	NC	13.3	37.6	243	775
10	3	4.55	16.5	23.3	78.8	424	1450

NC not calculated

Toxicokinetics: Blood samples were collected from F_0 satellite animals on GD 6 (at 2 and 4 hr postdose; Phase 1) and LacD 20 (at 1, 2, 4, 8, and 24 hr postdose; Phase 3). In addition, blood samples were obtained from 10 main study females per group on LacD 4 (at 2 hr postdose) for exposure assessment, and from their culled offspring at PND 4 (at 6 hr postdose [after maternal dosing]; Phase 2). For the culled pups, plasma samples were pooled within each litter.

Plasma concentrations of the parent compound BIBF 1120 and its metabolites, BIBF 1202 and BIBF 1202-glucuronide (BIBF 1202 GLUC), were analyzed using a validated HPLC-MS/MS method. The lower limit of quantification (LLOQ) was 1.00 ng/mL for BIBF 1120 and BIBF 1202 GLUC and 2.00 ng/mL for BIBF 1202.

BIBF 1120, BIBF 1202, and BIBF 1202 GLUC were not detected in any samples from the control group. TK data of BIBF 1120-dosed F_0 females on LacD 20 are shown in Table 12. In general, C_{max} and $AUC_{(0\text{-}24h)}$ of BIBF 1120, BIBF 1202, and BIBF 1202 GLUC increased dose proportionally from 2.5 to 10 mg/kg, except that the increase of BIBF 1202 GLUC was more than dose-proportional from 2.5 to 5 mg/kg. The inter-individual variability of plasma concentrations was considered to be high for BIBF 1120 (CV of 81% AUC) and low to moderate for the metabolites BIBF 1202 (CV of 31-35% AUC) and BIBF 1202 GLUC (CV of 12-38% AUC). There was no apparent accumulation over repeat dosing, comparing C_{max} data on GD 6 and LacD 20.

The plasma levels of BIBF 1120 were much lower than those of metabolites BIBF 1202 and BIBF 1202 GLUC. BIBF 1120 was only above the LLOQ in one LD animal at 2 hours postdose on GD 6, and all other samples from the LD group were below the LLOQ. The plasma levels of BIBF 1102 from the MD animals were measurable at 2 and 4 hours postdose on GD 6, and occasionally at 2 hours on LacD 4 or 20. Almost all samples from HD animals had measurable levels of BIBF 1202 GLUC at 2 and/or 4 hours postdose on GD 6 and LacDs 4 and 20, but no samples at 8 and 24 hours postdose (except for one sample at 8 hours) had measurable levels of BIBF 1202 GLUC.

Exposure of the F_1 pups: The exposures of F_1 pups to BIBF 1120 and its metabolites were low. No or only very low concentrations of BIBF 1120 and BIBF 1202 were found in the plasma of F_1 pups. The same holds for the low and mid doses of BIBF 1202 GLUC. In F_1 pups in the HD group, however, measureable, but low concentrations of BIBF 1202 GLUC were found in most samples.

Dosing Solution Analysis: The dosing formulations prepared for use in the first and last weeks of dosing were analyzed for test article concentration and homogeneity by reverse phase HPLC with UV detection.

There was no test article in samples from the control group. The concentrations of BIBF 1120 (test article calculated as free base) in all analyzed test article dose formulation samples (taken from the top, middle and bottom strata of each formulation vessel) from this study were within a range of 10% of the nominal concentrations.

F_1 Generation Survival: All litters were examined at approximately 24 hours after birth (PND 1) and then daily thereafter. On PND 4, litters were culled to keep eight offspring (4 males and 4 females in each litter if possible). Offspring were weaned on PND 21.

Survival data of F_1 pups until PND 21 are presented in Table 11 above. As mentioned above, due to lower numbers of live pups born, litter mean number of live pups on PNDs 1 and 4 was lower in the HD group. In addition, there were one total litter loss between PNDs 1 and 4 (before culling) and another total litter loss on PND 4. From PND 5, there was no test article-related effect on the survival rate of delivered pups.

Clinical signs: Clinical observations were performed at least twice daily. In addition, a more detailed physical examination was performed once each week after weaning for all animals of the F_1 generation, and on GDs 0, 6, and 14 for F_1 females.

There were no test article-related clinical signs.

Body weight: Individual offspring body weights were recorded on PND 1, 4 (before culling), 7, 11, 14, 18, and 21. For selected F_1 offspring and spares only, body weights were also measured on PND 25.
Selected F_1 males were weighed twice weekly until scheduled termination, and selected F_1 females were weighed twice weekly until mating was detected and on GDs 0, 3, 6, 10, and 14. Unselected offspring were weighed weekly until terminal examination.

There were no test article-related effects on mean body weight or body weight gain throughout the study.

Feed consumption: Not included.

Neurological assessment: Pre-weaning reflex developmental tests were performed on each offspring as follows:
(1) Surface righting: assessed daily from PND 2 until achieved.
(2) Air righting: assessed daily from PND 14 until achieved or PND 19. Those not passed by PND 19 recorded as fail.
(3) Auditory function: the startle response to a sudden sharp sound was assessed on PND 20.
(4) Visual function: the pupil closure response of dark adapted eyes to a bright point source of light was assessed on PND 20.

Post-weaning neurobehavioral tests were performed as follows:
(1) Motor activity: motor activity over a 1-hour period was assessed with an automated activity monitoring system collecting data over successive 6-minute intervals on PND 25. Ambulatory activity was monitored by low-level beam detectors, and rearing activity was monitored by high-level beam detectors.
(2) Learning and memory: Morris water maze was performed on PND 31±1. A series of three trials was conducted on each of four consecutive days.

There were no test article-related effects on any neurobehavioral assessments evaluated in the study.

Reproduction: For sexual maturation assessment, balano-preputial separation was checked daily from PND 38 for all selected males, and body weight was recorded on the day of completion of separation. Similarly, vaginal opening was checked daily from PND 28 for all selected females, and body weight was recorded on the day of vaginal opening.

For reproductive assessment, males and females (at least 9 weeks of age) from the same dose groups were paired on a one-to-one basis for a period of up to two weeks. Pairing siblings was avoided. The day on which evidence of mating was found was designated GD 0, and the males and females were separated. F_1 females were sacrificed on GD 14 and evaluated for the following parameters: the number of corpora lutea, implantation sites and the number and distribution of resorption sites (classified as early or late), and live and dead embryos. For apparently non-pregnant animals and apparently empty uterine horns, the number of uterine implantation sites was checked after staining with ammonium sulfide.

There were no test article-related effects on sexual maturation or mating parameters examined in the study.

Reproductive data of F_1 animals are shown in Table 13 below. There were no test article-related effects on pre- and post-implantation

losses, number of corpora lutea, and implantation sites.

Other: Unselected offspring on PND 4 that were externally abnormal were examined macroscopically. All other offspring dying before weaning were macroscopically examined. However, missing offspring and those grossly autolysed or grossly cannibalized could not be examined.

The majority of offspring that were not selected on PND 21 were sacrificed, and a limited number were retained as possible replacements until completion of the selection process and formal start of the F_1 generation.

For one male and one female unselected pups in each litter on PND 21, body weight and length of left ulna were recorded and the ulna was retained. In addition, one knee joint (femur/joint/ tibia, the left where possible) from F_1 PND 21 pups and F_1 adult animals was retained in 10% neutral buffered formalin and histologically examined.

Selected F_1 adult females surviving until the scheduled necropsy were sacrificed on GD 14, with the exception of 3F 223 (evidence of mating was not detected, but the animal was found to be pregnant). Selected F_1 adult males were sacrificed after the necropsy of the majority of the females. A full macroscopic examination of the tissues was performed on selected F_1 adult animals.

For all animals examined, samples of any abnormal tissues were retained. In addition, ovaries, pituitary gland, ovaries, and uterus were retained from F_1 females that failed to mate, whereas pituitary gland and male reproductive tissues were retained from F_1 males that failed to mate or sire a pregnancy. These tissues were not microscopically examined.

There were no test article-related macroscopic findings.

Ulna lengths for male and female offspring, measured at scheduled termination on PND 21, were similar across all groups. No test article-related histologic findings were noted in the knee joints of the F_1 PND 21 pups or F_1 adult animals. The only histologic finding in the epiphyseal plate of the femur was minimal or slight focal acute hemorrhage in adult animals (three control females, one LD male, one HD male, and one HD female).

Table 13 Reproductive assessment of F_1 animals from the PPND study

Parameter	0 (control)	2.5 mg/kg/day (LD)	5 mg/kg/day (MD)	10 mg/kg/day (HD)
Mating index (%)[a]	100 (20/20)	100 (20/20)	100 (20/20)	100 (20/20)
Fertility index (%)[b]	100 (20/20)	95 (19/20)	90 (18/20)	95 (19/20)
Mean litter no. of corpora lutea	14.0	13.9	13.2	13.2
Mean litter no. of implantation	11.9	12.8	12.2	11.7
Mean litter no. of total resorption	1.2	0.9	1.2	0.6
Mean litter no. of live fetuses	10.7	11.9	11.0	11.1
Mean preimplantation loss per litter (%)	14.8	7.4	7.1	11.0
Mean postimplantation loss per litter (%)	10.6	7.0	9.6	4.4

[a]Mating Index (%) = (No. of pairs copulated/No. of pairs cohabited) x 100
[b]Fertility Index (%) = (No. of pregnant females/No. of mated females) x 100

For the F_2 generation, only viability of fetuses was evaluated on GD 14 as shown in Table 13.

11 Integrated Summary and Safety Evaluation

Reproductive and developmental toxicity studies of BIBF 1120 using the oral (gavage) route of administration were as follows: fertility and early embryonic developmental toxicity studies in rats, embryo-fetal developmental toxicity studies in rats and rabbits, and a pre- and postnatal development study in rats. The fertility studies were evaluated by Dr. Luqi Pei elsewhere. In this review, embryo-fetal developmental (EFD) toxicity studies and the pre- and postnatal development (PPND) study were evaluated, and the major findings from these studies are presented below. Note that all dose levels are expressed as free base concentrations of BIBF 1120.

In an EFD toxicity study in the rat [Study No. 12B017, GLP], time-mated Han Wistar rats were administered BIBF 1120 at oral (gavage) doses of 0 (0.5% hydroxyethylcellulose), 2.5 (LD), 5 (MD), or 10 (HD) mg/kg/day from Gestation Day [GD] 7 through 16 (day of confirmed mating = GD 1). Test article-related maternal toxicity was not observed in the study, however, embryo-fetal developmental effects of the test article were demonstrated in the study. In the HD group, slightly increased resorption rate (16.0% vs. 7.5% in the control group), slightly reduced number of viable fetuses (9.8 vs. 10.8 in the control group), and slightly lower mean fetal weight (4.74 g vs. 4.98 g in the control group) were observed. Test article-related teratogenic effects were observed in all BIBF 1120-dosed groups, although most obvious effects were noted in the HD group. The vasculature and axial skeleton were mainly affected in the HD group. Vascular anomalies included missing right subclavian artery, an additional vessel at the descending aorta, an aortic arch rotation to the right side, and an increased incidence of shortened innominate artery. Axial skeletal anomalies were seen mainly in thoracic, lumbar, and caudal vertebrae (e.g., hemivertebra, missing, misshaped, or

asymmetrically ossified), ribs (bifid or fused), and sternebrae (fused, split, or unilaterally ossified). Slightly increased incidences of fusion between facial bones and unossified occipital bone were also observed in the HD group. A few incidences of the same axial skeletal malformations were also noted in the MD and LD groups. TK analysis showed that systemic exposure of BIBF 1120, BIBF 1202, and BIBF 1202 GLUC increased with dose. The plasma levels of metabolites were higher than those of BIBF 1120, especially BIBF 1202 GLUC which was much higher than BIBF 1120 and BIBF 1202. The NOAEL for maternal toxicity was the high dose (10 mg/kg) as there was no maternal toxicity, but the NOAEL for embryo-fetal developmental toxicity could not be identified in the study as teratogenic effects were observed in all test article-dosed groups.

In an EFD toxicity study in the rabbit [Study No. 12B032, GLP], time-mated Himalayan rabbits were administered BIBF 1120 at oral (gavage) doses of 0 (0.5% hydroxyethylcellulose), 15 (LD), 30 (MD), or 60 (HD) mg/kg/day from GDs 6 through 18 (day of confirmed mating = GD 0). Similar to the EFD study in rats, test article-related maternal toxicity was not observed in this rabbit study, however, embryo-fetal developmental effects of the test article were demonstrated. In the HD group, there was one doe with abortion and there were three does with all resorptions. In addition, increased resorption rate (42% vs. 18% in the control group), reduced number of viable fetuses (4.3 vs. 5.8 in the control group), and lower ratio of males than females (29:71) were also noted in the HD group. Test article-related teratogenic effects were observed in all BIBF 1120-dosed groups. Mainly affected structures in the MD and HD groups were the vasculature (absence of the subclavian artery or aortic arch), urogenital system (absence of kidney, ureter, ductus deferens, uterus and/or ovaries), and axial skeletal system (e.g., hemivertebra, or cleft, fused, displaced, or unilaterally ossified vertebrae, and/or fused ribs). In addition, absence of both gall bladder and ductus choledochus and additional skull bone were noted. One HD fetus had open eyes, cleft palate, and neural tube, ventricular septal, axial skeletal, and limb defects. Some of same axial skeletal findings were also observed in the LD group. The systemic exposure to BIBF 1120 increased from 30 to 60 mg/kg, but was similar at the 15 and 30 mg/kg dose levels. The systemic exposure to the metabolites BIBF 1202 and BIBF 1202 GLUC increased roughly in a dose-proportional manner from 15 to 60 mg/kg. The plasma levels of BIBF 1202 GLUC were slightly lower than those of BIBF 1120, but plasma levels of BIBF 1202 were higher than those of BIBF 1120. The NOAEL for maternal toxicity was the high dose (60 mg/kg) as there was no maternal toxicity, but the NOAEL for embryo-fetal developmental toxicity could not be identified in the study as teratogenic effects were observed in all test article-dosed groups.

In a PPND toxicity study in the rat [Study No. DDB0229, GLP], mated F_0 female Han Wistar rats were administered BIBF 1120 at oral (gavage) doses of 0, 2.5 (LD), 5 (MD), or 10 (HD) mg/kg/day from Gestation Day (GD) 6 to Lactation Day (LacD) 20 (day of confirmed mating = GD 0). Test article-related maternal toxicity was not observed in F_0 females in the study, however, for F_0 females in the HD group, mean gestation days were slightly increased (23.0 days vs. 22.5 days in the control group). There was an increase in mean postimplantation loss, including 3 litters with total resorption in the HD group. This resulted in decreased mean postimplantation survival index and a lower

litter mean number of total pups on postnatal day (PND) 1 in the HD group (71.5% and 8.9, respectively, excluding 3 litters with total resorption), compared to the control group (89.2% and 11.7, respectively). In addition, two litters lost all their pups between PNDs 1 and 4. From PND 5, there were no other test article-related effects on survival, physical, neurobehavioral, and reproductive parameters in F_1 animals. There were no test article-related effects on viability of F_2 fetuses in any dose group, as examined on GD 14. TK analysis showed that systemic exposure to BIBF 1120, BIBF 1202, and BIBF 1202 GLUC generally increased in a dose-proportional manner from 2.5 to 10 mg/kg, except that the increase of BIBF 1202 GLUC was more than dose-proportional from 2.5 to 5 mg/kg. The NOAEL for pre- and postnatal development of F_1 animals was identified as the mid dose (5 mg/kg) due to decreases in postimplantation survival index and litter mean number of live F_1 pups on PNDs 1 and 4 in the HD group.

In summary, teratogenic effects of BIBF 1120 were demonstrated in both rats and rabbits, and the vasculature and axial skeletons are mainly affected in both species. In addition, anomalies in the urogenital system were clearly noted in rabbits. A few incidences of limb defects were also seen in rabbits. Increased resorption rate and reduced number of viable fetuses were also observed at the high dose of these studies. These embryo-fetal findings were demonstrated in the absence of maternal toxicity. NOAELs could not be identified in the EFD toxicity studies in rats and rabbits due to teratogenic effects seen in all test article-dosed groups. The effects of BIBF 1120 on embryo-fetal development were expected as BIBF 1120 inhibits a number of different tyrosine kinases, including PDGFR, VEGFR, FGFR, and Flt-3. Although obvious embryo-fetal developmental effects of BIBF 1120 were observed in the EFD studies, BIBF 1120-related effects in the PPND rat study (with the same dose levels that were used the EFD rat study) were limited to decreases in postimplantation survival index and litter mean number of live F_1 pups on PNDs 1 and 4 in the HD group. Most likely, pups with anomalies were not alive at the delivery or died shortly after they were born, and apparently, there were no test article-related effects on the development of survived pups.

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/s/

GRACE S LEE
08/22/2014

MARCIE L WOOD
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PHARMACOLOGY/TOXICOLOGY NDA/BLA REVIEW AND EVALUATION

Application number:	NDA 205-832
Supporting document/s:	SDN 1
Applicant's letter date:	5/2/2014
CDER stamp date:	5/2/2014
Product:	BIBF 1120 (Nintedanib) Oral Capsules
Indication:	Idiopathic Pulmonary Fibrosis (IPF)
Applicant:	Boehringer Ingelheim Pharmaceuticals, Inc.
Review Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Reviewer:	Carol M. Galvis, Ph.D.
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List of Abbreviations

ADME	Absorption, Distribution, Metabolism, Excretion
ALP	Alkaline phosphatase
ALT	Alanine transferase
APTT	Activated partial thromboplastin time
AUC	Area under the curve
B	Benign
C_{max}	Maximal drug concentration in plasma
CMC	Chemistry, Manufacturing, and Controls
ECAC	Executive Carcinogenicity Assessment Committee (FDA)
EDR	Electronic Document Room
EDTA	Ethylenediaminetetraacetic acid
ES	Ethanesulfonate
F	Female
FGF	Fibroblast growth factor
g	Grams
GLP	Good Laboratory Practice
HD	High-dose
HPLC	High-performance Liquid Chromatography
hr	Hour
i.e.	*Id est* (That is)
IND	Investigational New Drug
IPF	Idiopathic pulmonary fibrosis
kg	Kilogram
L	Liter
LC/MS/MS	Liquid chromatography with tandem mass spectrometry
LD	Low-dose
LLOQ	Lower limit of quantitation
LUC	Large unstained cells
M	Male or malignant (neoplastic findings table)
MCH	Mean cell hemoglobin
MCV	Mean cell volume
MD	Mid-dose
mg	Milligram
mL or ml	Milliliter
MS	Mass spectrometry
MTD	Maximum tolerated dose
N (or no.)	Number
NC	Not calculated
NDA	New Drug Application
ng	Nanogram
NOAEL	No observed adverse effect level
PDGF	Platelet-derived growth factor
PK	Pharmacokinetics
PTP	Prothrombin time

QA	Quality assurance
SPA	Special protocol assessment
TK	Toxicokinetics
T_{max}	Time to maximal drug concentration in plasma
VEGF	Vascular endothelial growth factor

1 Executive Summary

1.1 Introduction

This review evaluates the carcinogenicity potential of BIBF 1120 (nintedanib). Nintedanib is a kinase inhibitor. Nintedanib inhibits the tyrosine kinase receptors for platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and fibroblast growth factor (FGF) and also inhibits (b) (4) kinase and members of Src family of kinases. It is being developed by Boehringer Ingelheim Pharmaceuticals for the treatment of Idiopathic Pulmonary Fibrosis (IPF).

Nintedanib was negative in a full battery of genetic toxicology studies (*in vitro* Ames and mouse lymphoma assays and *in vivo* micronucleus assay in rats).

The applicant conducted two carcinogenicity bioassays (2-year oral studies in CD-1 mice and Han Wistar rats) to assess the carcinogenic potential of nintedanib. Both study protocols were discussed with the Executive Carcinogenicity Assessment Committee (ECAC) in a meeting held on September 14, 2010. The doses used in the studies were the same doses recommended by the ECAC. In addition, for the mouse study, the Division provided recommendations for the early termination of a group based on mortality via email on June 8th, 2012.

The results from the two bioassays were discussed with the ECAC during a meeting held on July 15, 2014. The ECAC concluded that the two studies were acceptable, noting prior Committee concurrence with the study protocols, and that there were no drug-related neoplasms in mice or rats.

1.2 Brief Discussion of Nonclinical Findings

In a 2-year bioassay (study number DDB0006), CD-1 mice (66/sex/group) received 0 (vehicle control, 0.5% hydroxyethyl cellulose in demineralized water), 5, 15, or 30 mg/kg/day nintedanib (BIBF 1120) orally once daily for 102 (males) or 104 (females) weeks. The doses were selected based on the maximum tolerated dose (MTD) identified in a 13-week oral toxicity study in CD-1 mice (*i.e.*, 100 mg/kg/day due to findings of broken teeth).

No statistically significant neoplastic findings were observed in male or female mice. Increased mortality was observed in the HD male group starting approximately on study week 76 and led to termination of this group on study week 102 based on recommendations provided by the Division via email (*i.e.*, to terminate a group when the number animals remaining reached 15). The other male groups (control, LD, and MD groups) were terminated on study week 103.

In females, mortality was higher at all BIBF 1120 doses compared to controls but did not follow a dose-response and was not statistically significant. All the female groups were maintained until scheduled necropsy. Treatment-related non-neoplastic findings were observed in male and female mice in the following tissues: gallbladder (fibrosis and

ulceration), skin (dermal inflammation, epidermal ulceration and hyperplasia, edema, and scabs), uterus (arteritis/periarteritis/vascular mural fibrinoid necrosis), and adipose tissue (inflammation and necrosis).

Results of TK analysis in the mouse showed that BIBF 1120 C_{max} and AUC increased in a greater than dose-proportional manner across doses. Also, there was not a clear gender difference in exposure or evidence of drug accumulation over time. The systemic exposure (AUC_{0-24}) at the highest dose of 30 mg/kg/day (1,335 ng·hr/mL in males and females combined) was used to calculate the exposure margins to the maximum proposed human dose of 300 mg/day (AUC_{0-24} = 327 ng·hr/mL). The mouse:human exposure margin for carcinogenicity is approximately 4.

In a 2-year bioassay (study number DDB0007), HsdHan™;WIST rats (60/sex/group) received 0 (vehicle control, 0.5% hydroxyethyl cellulose in demineralized water), 2.5, 5, or 10 mg/kg/day nintedanib (BIBF 1120) orally once daily for 104 weeks. Doses were selected based on a MTD identified in a 13-week oral toxicity study in Wistar Han rats (*i.e.*, 20 mg/kg/day due to findings of broken teeth).

Nintedanib was not carcinogenic in male or female rats. In addition, mortality or body weights were not affected by treatment with nintedanib. Non-neoplastic histopathology findings were observed in rats in the lungs (aggregation of alveolar macrophages, cholesterol cleft granuloma, granulomatous inflammation, and perivascular mononuclear cell inflammation), the liver (increased pigment in Kupffer cells), thyroid (focal C cell hyperplasia), kidney (increased incidence and severity of chronic progressive nephropathy) and teeth (dentopathy). In addition, arteritis/periarteritis was observed in the tongue, testes, pancreas, and spleen.

Results of the TK analysis in the rat showed that systemic exposure (C_{max} and AUC) of BIBF 1120 increased in a greater than dose-proportional manner across doses and there was evidence of drug accumulation over time. There was not a clear gender difference in exposure. The AUC_{0-24} at 10 mg/kg/day (82.95 ng·hr/mL in males and females combined) was used to calculate the exposure margins to the maximum human dose of 300 mg/day. The rat:human exposure margin for carcinogenicity is approximately 0.25.

2 Drug Information

2.1 Drug

CAS Registry Number: 656247-18-6 (Ethanesulfonate or ES) or 656247-17-5 (base)

Generic Name: Nintedanib

Code Name: BIBF 1120 ES

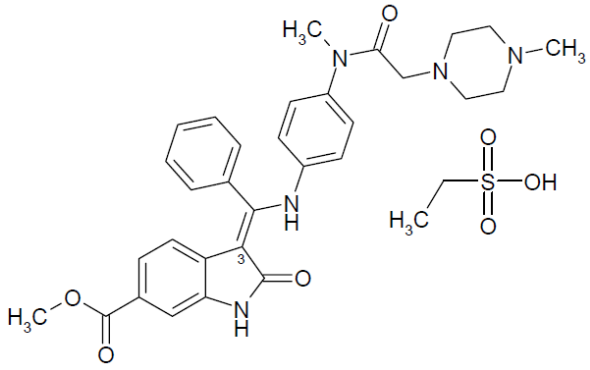
Chemical Name: 1*H*-indole-6-carboxylic acid, 2,3-dihydro-3-[[[4-[methyl[(4-methyl-1-piperazinyl)acetyl]-amino]phenyl]amino]phenylmethylene]-2-oxo-,methyl ester, (3*Z*)-, ethanesulfonate

Molecular Formula: $C_{31}H_{33}N_5O_4 \cdot C_2H_6O_3S$ or $C_{33}H_{39}N_5O_7S$

Molecular Weight: 649.76 (ES) or 539.62 (base)

Structure or Biochemical Description

Figure 1: BIBF 1120 ES Structure.



Pharmacologic Class: Kinase inhibitor

2.2 Relevant INDs, NDAs, BLAs and DMFs

Application #	*Sponsor*	*CDER OND Division*
(b) (4)	Boehringer Ingelheim Pharmaceuticals	DDOP
74,683	Boehringer Ingelheim Pharmaceuticals	DPARP

2.3 Drug Formulation

BIBF 1120 is being formulated as soft gelatin capsules for oral administration. Two strengths are available: 100 mg and 150 mg capsules. Additional information regarding the drug product formulation will be included in the CMC review.

2.6 Proposed Clinical Population and Dosing Regimen

Boehringer Ingelheim is seeking approval under this NDA for patients with IPF (a specific form of chronic, progressive fibrosis interstitial pneumonia of unknown cause). The proposed dosing regimen is 150 mg orally twice daily for symptomatic treatment of IPF or 100 mg twice daily if any adverse reactions are observed at the higher dose.

2.7 Regulatory Background

IND 74,683 was originally submitted on March 14, 2011 to develop BIBF 1120 for the treatment of IPF. BIBF 1120 is also being developed by Boehringer Ingelheim for oncology indications (b) (4) (Division of Oncology Products 1).

The special protocol assessments (SPAs) for the two 2-year bioassays were reviewed by Dr. Shwu-Luan Lee (b) (4) (refer to PharmTox reviews dated 9/30/2010 and ECAC meeting minutes dated 9/16/2010). The two bioassays were conducted using the dose levels recommended by the ECAC.

On June 1, 2012, and June 8, 2012; Boehringer Ingelheim submitted two requests for feedback under IND 74,683 regarding proposals for modifying the dosing schedule of the 2-year mouse bioassay (due to increased mortality in male mice). The Division's recommendations were communicated to Boehringer Ingelheim via email on June 8, 2012.

For the full regulatory history, refer to Dr. Pei's integrated PharmTox review under this NDA.

3 Studies Submitted

3.1 Studies Reviewed*

Study Number	*Title*	*Location*
DDB0006	BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 Weeks	EDR 4.2.3.4.1
DDB0007	BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to Han Wistar Rats for 104 Weeks	EDR 4.2.3.4.1

* Other nonclinical pharmacology and toxicology studies submitted under this NDA will be reviewed by Dr. Luqi Pei.

3.3 Previous Reviews Referenced

Application #	*Studies Reviewed*	*Reviewer Name*	*Review Date*
(b) (4)	Genetic Toxicology and Mouse SPA	Shwu-Luan Lee, Ph.D.	9/30/2010
	Rat SPA	Shwu-Luan Lee, Ph.D.	9/30/2010
	ECAC Meeting Minutes	Abigail Abby Jacobs, Ph.D.	9/16/2010
IND 74,683	Preliminary Safety Review	Luqi Pei, Ph.D.	4/14/2011
IND 74,683	Chronic Toxicity and Male Fertility Studies	Luqi Pei, Ph.D.	5/10/2011

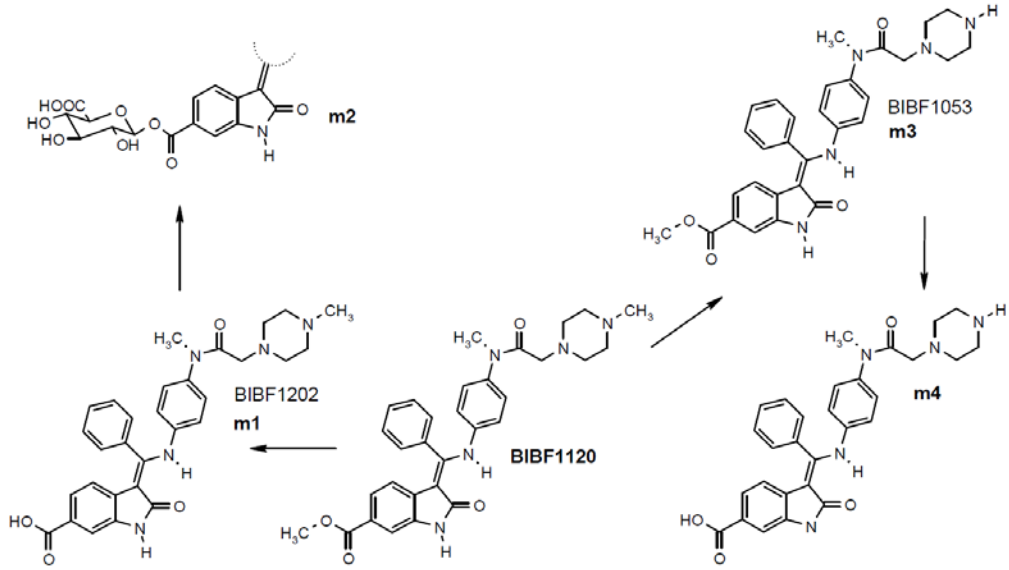
4 Pharmacology

BIBF 1120 is a kinase inhibitor. BIBF 1120 is an inhibitor of tyrosine kinase receptors for PDGF, VEGF, and FGF, and is also an inhibitor of (b) (4) and Src kinases. For specific details refer to Dr. Pei's integrated review under this NDA.

5 Pharmacokinetics/ADME/Toxicokinetics

Figure 2 below (excerpted from the applicant's submission) presents the metabolic pathway of BIBF 1120. As shown, the main metabolite is BIBF 1202 and it is present in human, mouse, and rat (and also in monkey). Toxicokinetic parameters (C_{max}, T_{max}, and AUC) for both BIBF 1120 and BIBF 1202 were evaluated in the carcinogenicity studies discussed herein. For additional details on BIBF 1120's metabolism, refer to Dr. Luqi Pei's integrated review under this NDA.

Figure 2: BIBF 1120 Metabolism.



6 General Toxicology

Oral toxicity studies were conducted in rats (up to 26 weeks) and monkeys (up to 52 weeks) and were previously reviewed by Dr. Luqi Pei (refer to Dr. Pei's review dated 5/10/2011). A brief summary of noteworthy findings follows.

Wistar rats (20/sex/group) received 0 (vehicle control), 5, 20, or 80 mg/kg/day BIBF 1120 for 26 consecutive weeks. The 80 mg/kg/day group was sacrificed early on study week 24 due to poor clinical condition (clinical signs included fractured teeth, gingiva swelling, and liquid feces). Additionally, drug-related histological findings were observed in animals at ≥ 20 mg/kg/day in the liver (periportal hemosiderosis and brown pigment in hepatocytes, Kupffer cells, and interstitial macrophages), spleen (mineralization of the connective tissue, lymphoid depletion, and extra-medullary hematopoiesis), kidney (hyaline deposition in glomerular endothelial cells and podocytes, focal basophilic tubules, tubular protein casts, and dusty fat droplets and pigment storage in tubular epithelium), bone marrow (hematopoietic cell depletion), adrenal glands (peliosis/angiectasis and cortical tissue hyperplasia), thymus (involution and increase number of apoptotic cells), ovaries (decreased size and increased number of corpora lutea), bone (epiphyseal plate thickening), bile duct (inflammation and

hyperplasia of the ductal epithelium), and incisors (dysplasia). The NOAEL was identified in rats at the 5 mg/kg/day dose level based on the aforementioned findings.

Rhesus monkeys (4/sex/group) received 0 (vehicle control), 10, 20, or 60/45/30 mg/kg/day BIBF 1120 for 52 consecutive weeks. The high-dose group started with a BIBF 1120 dose of 60 mg/kg during study weeks 1-3 but this dose was then reduced due to overt toxicity. The high-dose group was then treated with 45 mg/kg BIBF 1120 during study weeks 7-26. Two animals at this dose level were sacrificed early on study weeks 11 and 24 due to poor condition (liquid feces and decreased activity). The high-dose was then lowered again to 30 mg/kg during study weeks 27-55. Drug-related histological findings were observed in animals at all dose groups in the bone (thickening of the epiphyseal growth plate and cortex and trabecular bone thinning only at the high-dose), and in the adrenal gland (atrophy of the zona fasciculata). A NOAEL was not defined due to thickening of the epiphyseal growth plate in the low-dose group.

7 Genetic Toxicology

The following genetic toxicology studies were conducted and reviewed (b) (4) *in vitro* Ames and mouse lymphoma assays and an *in vivo* micronucleus assay in rats. BIBF 1120 tested negative for genetic toxicity. Refer to PharmTox review (b) (4) dated 9/30/2010 for additional details.

8 Carcinogenicity

Study title: BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to CD-1 Mice for 104 Weeks.

Study no.:	DDB0006
Study report location:	EDR
Conducting laboratory and location:	(b) (4)
Date of study initiation:	September 16, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BIBF 1120, Batch number 1045986, 100.3%
CAC concurrence:	Yes. Refer to Executive CAC meeting minutes dated 09/16/2010.

Key Study Findings

- CD-1 mice (66/sex/group) were treated with 0 (vehicle control), 5, 15, or 30 mg/kg/day BIBF 1120 for 102 weeks (males) or 103 weeks (females).
- There was increased mortality in the HD males group starting approximately on study week 76 and until the group was terminated on study week 102 [based on recommendations provided by the Division via email on June 8th, 2012 (*i.e.*, when the number animals remaining reached 15)]. The control, LD, and MD groups in

males were terminated on study week 103. In females, mortality was higher at all BIBF 1120 doses compared to controls but did not follow a dose-response and all the groups were maintained until scheduled necropsy.

- There were no statistically significant BIBF 1120-related neoplastic findings in males or females.
- Treatment-related non-neoplastic findings were observed in the gallbladder (fibrosis and ulceration), skin (dermal inflammation, epidermal ulceration and hyperplasia, edema, and scabs), uterus (arteritis/periarteritis/vascular mural fibrinoid necrosis), and adipose tissue (inflammation and necrosis).
- Toxicokinetics parameters were analyzed for BIBF 1120 and two main metabolites, BIBF 1202 ZW and BIBF 1202 GLUC. Results show that the T_{max} was 1-2 hours post-dose for BIBF 1120 and BIBF 1202 and 1-4 hours post-dose for BIBF 1202 GLUC. The C_{max} and AUC increased in a greater than dose-proportional manner for all the analytes. There was not a clear gender difference in exposure or evidence of drug accumulation over time.

Adequacy of Carcinogenicity Study

The study was considered adequate to assess the carcinogenic potential of BIBF 1120 in mice. The doses used were the ones recommended by the ECAC (refer to the ECAC meeting minutes dated 9/16/2010). Although the HD males group had to be terminated early on study week 102 due to increased mortality, the duration of exposure was considered adequate. The termination of this group also followed the recommendations provided by the Division via email communication on June 8th, 2012.

Appropriateness of Test Models

The test model was considered appropriate. The study design was evaluated by the ECAC in a meeting held on September 14, 2010. The ECAC was in agreement with the sponsor's proposal and recommended the doses used in the study (*i.e.*, 5, 15, and 30 mg/kg/day).

Evaluation of Tumor Findings

No statistically significant BIBF 1120-related neoplastic findings were observed in mice.

Methods

Doses:	0 (vehicle control), 5 (low-dose, LD), 15 (mid-dose, MD), or 30 (high-dose, HD) mg/kg/day
Frequency of dosing:	Once daily for 102 (males) or 104 (females) weeks
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxyethyl cellulose (Natrosol® 250 HX) in demineralized water
Basis of dose selection:	In a 13-week oral toxicity study, the MTD was identified at 100 mg/kg/day due to broken teeth
Species/Strain:	Crl:CD-1 mouse strain
Number/Sex/Group:	66 mice/sex/group
Age:	35 to 41 days old at study start
Weight:	Males: 24.3-37.4 g Females: 17-26 g
Animal housing:	Males were individually housed. Females were housed three per cage unless this number was reduced by mortality.
Paradigm for dietary restriction:	None.
Dual control employed:	Only one control (vehicle) was included in the study
Interim sacrifice:	Main study males were terminated on study week 102 when the number of males remaining in the high dose group reached 15, as recommended by the ECAC.
Satellite groups:	A satellite group of 18 males and females (9 in the vehicle control group) was included for toxicokinetic sampling (refer to Table 1 below excerpted from the study report).
Deviation from study protocol:	Protocol deviations were reviewed and judged not to affect the integrity of study data.

Table 1: Study DDB0006 Design - Mouse.

Group	Treatment	Dosage (mg/kg/day) #	Number of animals			
			Main study		Satellite study†	
			Male	Female	Male	Female
1	Control	0	66	66	9	9
2	BIBF 1120 ES	5	66	66	18	18
3	BIBF 1120 ES	15	66	66	18	18
4	BIBF 1120 ES	30	66	66	18	18

Dosages are expressed as free base. A conversion factor for salt/base ratio was used to convert to salt form (1.000 g of the base corresponds to 1.204 g of the salt form).
† Satellite animals used for toxicokinetic sampling.

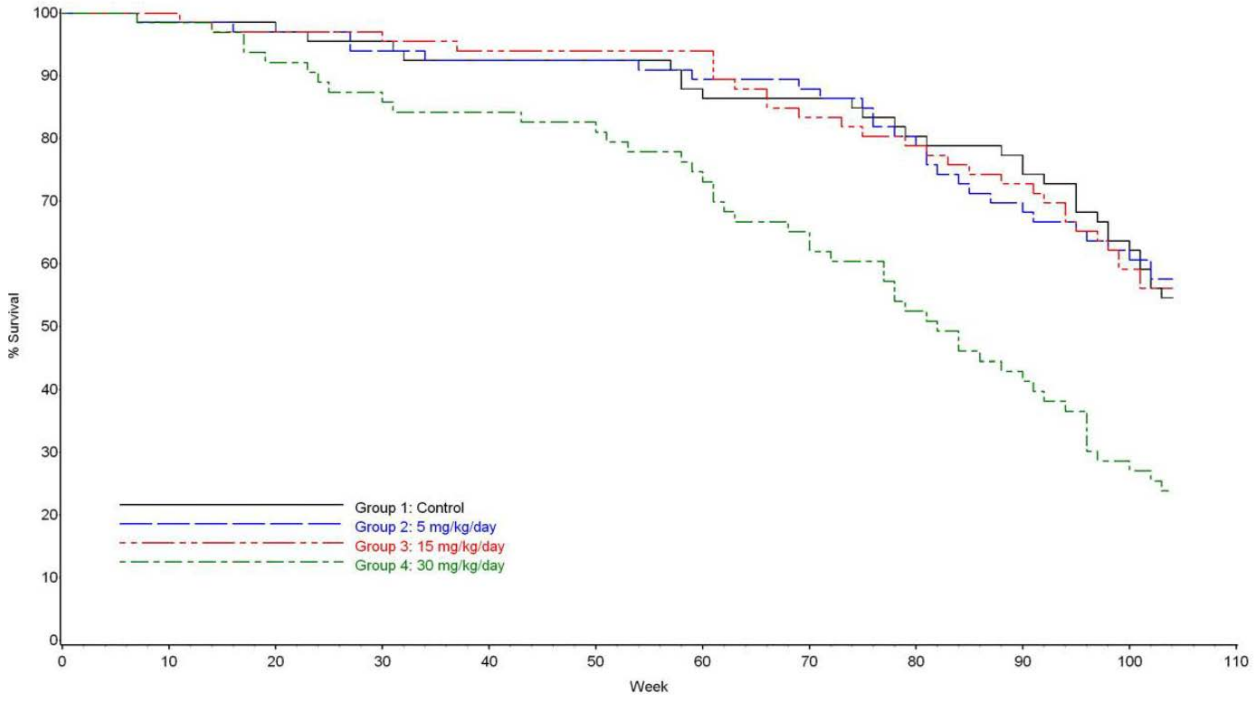
Observations and Results

Mortality

A viability check was performed near the start and end of each working day. Animals were observed at least twice daily (in the morning and afternoon) for any signs of moribundity. Cages were inspected daily for evidence of animal ill-health amongst the occupants.

Mortality was higher in males treated with 30 mg/kg BIBF 1120 (the HD) relative to the controls. Deaths in this group started on study week 6 and continued to increase until the group was terminated early on study week 102 when the number of animals remaining in this group reached 15 (23% survival). This was based on guidance provided by the Division via email after consultation with ECAC members. The males in the control, LD, and MD groups were terminated on study week 103 with a percent survival of 55%, 58%, and 56%; respectively (see Figure 3 below, excerpted from the applicant's submission). The mortality in the high dose group reached statistical significance (trend test) when compared to the vehicle controls.

Figure 3: Kaplan-Meier Survival Function – Male Mice.



In females, mortality was similar in all groups (vehicle control and treatment groups) until approximately study week 78, where a slight increase in mortality was observed in the HD group females relative to the vehicle controls (see Figure 4 below, excerpted from the applicant's submission). Towards the end of the study, an increase in mortality was observed in all treatment groups relative to controls. The percent survival on study

week 104 was 50% for the vehicle control group, 33% for the LD group, 38% for the MD group, and 30% for the HD group. The difference in mortality in females was statistically significant at the HD (refer to statistical review by Feng Zhou).

Figure 4: Kaplan-Meier Survival Function – Female Mice.

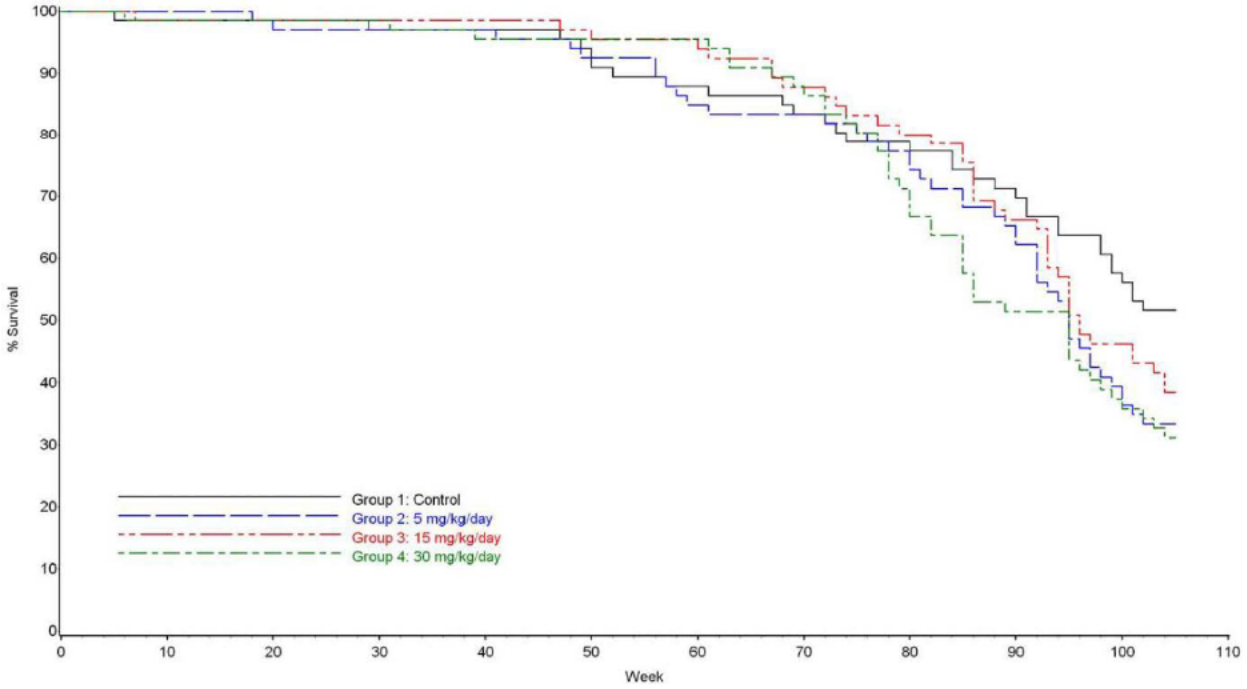


Table 2 below presents a summary of the number of early decedents (main study animals sacrificed early or found dead during the study) and the number of animals at termination in both males and females.

Table 2: Summary of Early Decedents, Number of Animals at Termination, and % Survival - Mouse.

BIBF 1120 (mg/kg)	Males			Females		
	Early Decedents	Termination	% Survival	Early Decedents	Termination	% Survival
0 (vehicle control)	30	36	55%	33	33	50%
5	28	38	58%	44	22	33%
15	29	37	56%	41	25	38%
30	51	15	23%	46	20	30%

Clinical Signs and Palpable Masses

Detailed observations were performed to establish and confirm a pattern of signs at the following: daily on study week 1, twice weekly on study weeks 2-4, once weekly on study weeks 5-13, once every two weeks on study weeks 14-52, and once every four weeks on study week 53 and onwards. In addition, a more detailed weekly physical examination, which included palpation, was performed on each animal to monitor general health. Particular attention was paid to any superficial or palpable swellings, for

which the location, size, consistency, time of first observation and subsequent history were recorded.

A number of drug-related signs of toxicity were observed, primarily at the highest dose. These included fast or irregular breathing, piloerection, hunched posture, pale skin, and colorless teeth. A summary of findings is presented below in Table 3.

Table 3: Clinical Observations in CD-1 Mice – (Weeks 1-105).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**5**	**15**	**30**	**0**	**5**	**15**	**30**
Number of animals examined	**66**	**66**	**66**	**66**	**66**	**66**	**66**	**66**
OBSERVATION								
Breathing								
Fast	10	8	5	14	12	11	11	18
Irregular	7	3	12	13	16	14	5	19
Coat								
Piloerection	20	27	28	36	13	24	14	26
Posture								
Hunched	4	11	6	16	11	12	10	22
Skin color								
Pallor, whole body	8	7	4	17	11	23	18	21
Teeth								
Abnormal color, colorless	0	4	12	20	0	8	3	15
General poor clinical condition	10	13	10	20	13	18	19	23

Below is Table 4 (excerpted from the study report) that presents palpable swellings (group distribution, multiplicity, and mean time of onset). As shown, there was not much difference in terms of group distribution of masses. However, the mean time of onset was slightly earlier in HD males, which may have contributed to the increased mortality in this group.

Table 4: Palpable Masses in CD-1 Mice – Group Distribution, Multiplicity, and Time of Onset.

Group /Sex	Group size	Multiplicity∅ 0	1	2	3	4 or more	Number of animals with swellings	Total number of swellings	Mean time of onset*
1M	66	51	12	3	0	0	15	18	66
2M	66	60	5	1	0	0	6	7	60
3M	66	47	17	2	0	0	19	21	78
4M	66	59	6	1	0	0	7	8	57
1F	66	54	10	1	0	1	12	17	76
2F	66	57	7	1	1	0	9	12	60
3F	66	60	3	1	1	1	6	14	80
4F	66	53	11	1	1	0	13	16	76

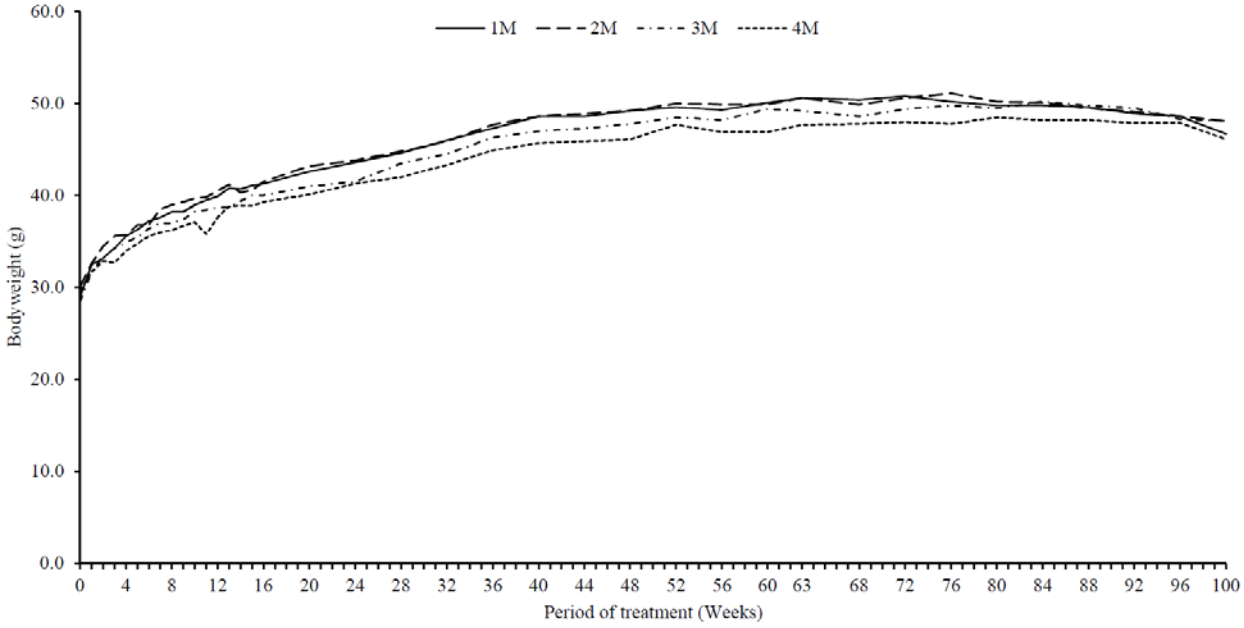
\+ Including swellings which regressed or were not positively identified at *post mortem* examination
∅ Expressed as number of animals bearing the indicated number of swellings
* In weeks to onset of first recorded swelling including those found at necropsy examination

Body Weights

Body weights were recorded one week before dosing, on the first day of dosing, at weekly intervals for the first 16 weeks of dosing, once every four weeks thereafter, and before necropsy. More frequent body weights were recorded, when appropriate, for animals displaying ill-health so that the progress of the observed condition could be monitored.

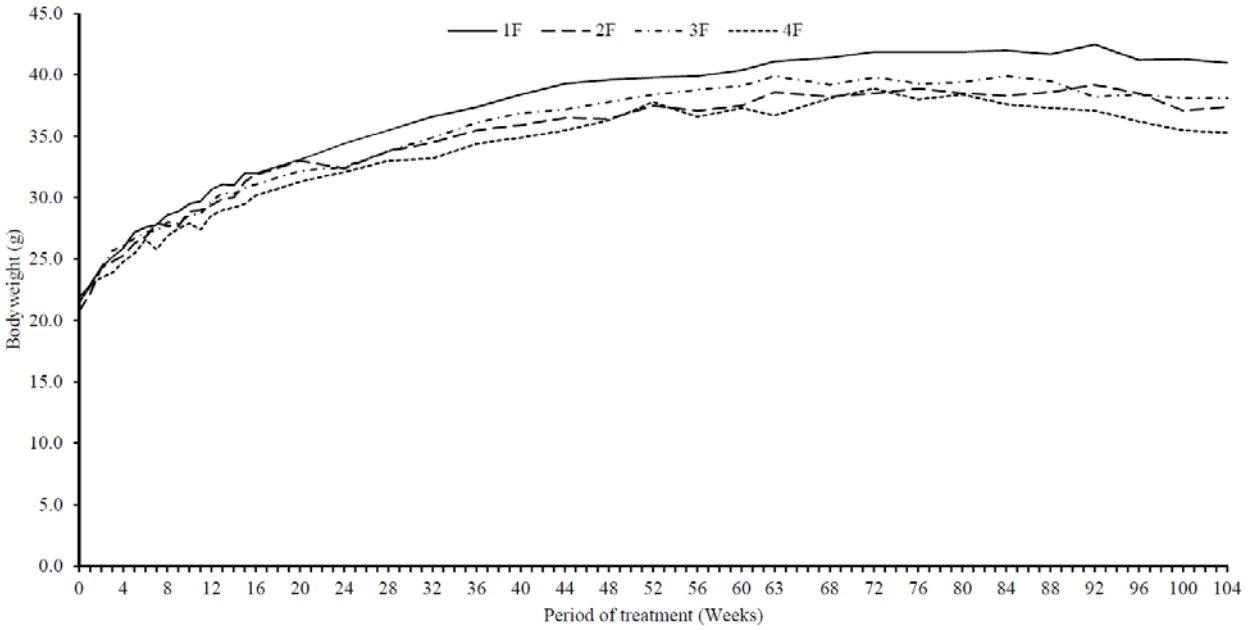
Bodyweight gain was lower in HD males and females. In HD males, the difference was more pronounced during study weeks 1-76, approximately, and was statistically significant ($p<0.05$). In HD females, the difference was observed throughout the study and was considered statistically significant ($p<0.01$). Figures 5 and 6 below present group mean body weights versus period of treatment (in weeks) for males and females, respectively.

Figure 5: Group Mean Body Weights (g) Versus Period of Treatment (Weeks) – Male Mice.



1M = vehicle control; 2M = LD; 3M = MD; 4M = HD

Figure 6: Group Mean Body Weights (g) Versus Period of Treatment (Weeks) – Female Mice.



1F = vehicle control; 2F = LD; 3F = MD; 4F = HD

Feed Consumption

The weight of food supplied to each cage, remaining food, and an estimate of any spilled food was recorded for the week before dosing started, weekly for the first 16 weeks, and once every four weeks thereafter. The mean weekly consumption per animal (g/mouse/week) was calculated for each cage.

Food consumption was variable throughout the study for all groups. There was no drug-related effect on food consumption.

Hematology

Blood samples were collected without overnight withdrawal of food and prior to dosing on study week 103 from twenty males and females with the lowest animal numbers in each group and a full battery of hematology parameters was evaluated. Blood samples were collected from all the remaining animals and a limited battery of hematology parameters was evaluated (only red blood cell count and total and differential white blood cell count).

A number of drug-related changes were observed (refer to Table 5 below). Mean cell hemoglobin and mean cell volumes were increased in MD and HD males and females. In addition, neutrophils were increased in males at all doses (no dose-response) and lymphocyte counts were increased in MD and HD females. Eosinophil counts were also increased in males at all doses (no dose-response), and large unstained cells were increased in MD and HD males (no dose-response) and in females at all doses.

Statistically significant changes are identified with asterisks as follows: * p<0.05 and ** p<0.01.

Table 5: Summary of Drug-related Changes in Hematology Parameters Relative to Controls – Mouse.

	Males			Females		
BIBF 1120 (mg/kg/day)	**5**	**15**	**30**	**5**	**15**	**30**
MCH (pg)	-	+7%**	+13%**	-	+9%**	+9%**
MCV (fL)	-	+7%**	+12%**	-	+10%**	+10%**
Neutrophil ($x10^9$/L)	+62%*	+45%*	+40%*	-	-	-
Lymphocyte ($x10^9$/L)	-	-	-	-	+61%	+74%*
Eosinophil ($x10^9$/L)	+25%*	+92%*	+42%*	-	-	-
LUC ($x10^9$/µL)	-	+100%*	+89%*	+43%	+100%	+157%*

MCH = mean cell hemoglobin
MCV = mean cell volume
LUC = large unstained cells
(-) = no drug-related change observed
* p<0.05; ** p<0.01

Gross Pathology

All animals were subject to a detailed necropsy. After a review of the history of each animal, a full macroscopic examination of the tissues was conducted. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ or tissue (external and cut surface) was recorded and the required tissue samples preserved. As mentioned before under "Mortality", main study males were killed following 102 weeks of treatment when the number of males remaining in the high dose group reached 15. Main study females were killed following completion of the full 104 weeks of treatment. Carbon dioxide asphyxiation with subsequent exsanguination was used to euthanize the animals.

The following gross lesions were observed (refer to Table 6 below): thickened mammary in two LD and four HD females (but also in one female control); increased incidence of skin abrasions at all doses in males and females; increased incidence of abnormal contents in the GI tract (stomach, duodenum, jejunum, ileum, cecum, and colon) that could be related to the oral gavage administration; fluid in the abdomen and thorax in HD males and females; dark liver in males at all doses (also in females but similar incidence relative to controls); edema in the pancreas in HD males and females (also in come control females); granular and/or pale kidney in HD males and females; edema in the thymus in HD males and in females at all doses; pale extremities in HD males and MD/HD females; and broken, maloccluded, or pale incisors at all doses in males and females (but no dose-response in females).

Table 6: Gross Observations in CD-1 Mice (All Animals).

	Males	Females

BIBF 1120 (mg/kg/day)	0	5	15	30	0	5	15	30
Number of animals examined	66	66	66	66	66	66	66	66
GROSS OBSERVATIONS								
Mammary								
Thickened	0	0	0	0	1	2	0	4
Skin								
Abrasion(s)	7	9	9	10	1	3	5	7
Jejunum								
Abnormal contents	4	4	2	6	1	4	3	7
Distended	2	2	1	5	1	1	1	3
Ileum								
Abnormal contents	1	2	0	4	1	1	1	5
Distended	0	2	0	3	1	0	1	1
Cecum								
Abnormal contents	1	4	2	6	2	2	1	8
Colon								
Abnormal contents	1	3	1	5	1	2	0	1
Distended	1	2	0	4	0	0	0	0
Liver								
Dark	0	2	1	7	2	5	3	3
Pancreas								
Oedematous	0	2	0	6	5	6	4	10
Kidney								
Granular	2	0	3	10	8	9	12	10
Pale	2	7	5	12	14	20	18	20
Thymus								
Oedematous	1	1	0	5	0	1	2	6
Stomach								
Abnormal contents	5	4	1	12	1	4	2	7
Distended	1	3	0	5	0	2	2	2
Duodenum								
Abnormal contents	1	2	0	7	1	2	0	1
Distended	0	1	0	5	0	0	0	0
Teeth								
Incisor(s) broken	0	0	0	2	0	0	1	0
Incisor(s) maloccluded	0	1	0	2	0	1	1	0
Incisor(s) pale	1	0	1	4	0	0	2	0
Abdomen								
Contained fluid	1	2	2	5	8	8	11	13
Thorax								
Contained fluid	2	5	2	8	9	7	10	11
General comments								
Extremities pale	5	1	1	10	9	11	14	14

Histopathology

A full battery of tissues was collected at necropsy and examined microscopically. In addition, skin lesions in the ear/head/neck area were collected and examined for all decedent animals and for all terminal animals that showed a history of skin lesions in the ear/head/neck region. From study week 25, multiple sectioning was performed

across two margins between the affected and normal skin to show a transition from normal to abnormal tissue on each slide. Sections were stained using hematoxylin and eosin.

Peer Review: In addition to the study pathologist, two additional pathologists from the sponsor conducted a peer review of the histological findings.

Neoplastic Findings

There were no BIBF 1120-related neoplastic findings that were statistically significant. A few findings were observed at a slightly higher incidence in treated animals compared to the vehicle control group. These are summarized below in Table 7. In the lungs and bronchi, the incidence of benign bronchioalveolar adenoma and malignant bronchioalveolar adenocarcinoma was slightly increased in the LD and MD males compared to the controls. To understand better the carcinogenic potential in the lungs, the two tumors types were combined as suggested in published guidelines[1]. No drug-related effect was observed when the two tumors were combined.

In the mammary gland, the following tumors were observed in females: benign adenoepithelioma in one HD female; malignant adenocarcinoma in two LD, one MD, and four HD females; and malignant adenoacanthoma in one LD and one HD females. The adenomas (observed in one control female), adenocarcinomas, and adenoacanthomas were combined to have a better understanding of the neoplastic findings in this tissue and to determine whether there was a masked drug-related effect. These mammary tumor types were also combined for the statistical analysis performed by Dr. Feng Zhou, statistical reviewer. The statistical review found that there was not a drug-related effect in the mammary gland (refer to the full statistical review by Dr. Zhou). The neoplastic findings in the lungs and mammary gland were considered by the applicant as incidental. This reviewer agrees with this conclusion based on the lack of statistical significance.

Finally, it was noted that the number of lymphomas was slightly increased in MD and HD males and LD and MD females compared to the controls. However, the statistical analysis conducted by Dr. Zhou found that the increase was not statistically significant. Thus, the malignant lymphomas have been considered as incidental.

Table 7: Histological Observations in CD-1 Mice – Neoplastic (All Animals).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**5**	**15**	**30**	**0**	**5**	**15**	**30**
Number of animals examined	**66**	**66**	**66**	**66**	**66**	**66**	**66**	**66**
NEOPLASTIC OBSERVATIONS								

[1] McConnell EE, Solleveld HA, Swenberg JA, and Boorman GA. *Guidelines for Combining Neoplasms for Evaluation of Rodent Carcinogenesis Studies.* (1986) Journal of the National Cancer Institute 76(2); pages 283-289.

Lungs with bronchi								
B-Bronchioalveolar adenoma	13	14	22	8	14	8	9	8
M-Bronchioalveolar adenocarcinoma	5	8	7	2	6	1	3	4
Lungs with bronchi								
Total (adenoma+adenocarcinoma)	18	22	29	10	20	9	12	12
Mammary								
B-Mammary adenoma	0	0	0	0	1	0	0	0
B-Adenomyoepithelioma	0	0	0	0	0	0	0	1
M-Mammary adenocarcinoma	0	0	0	0	0	2	1	4
M-Mammary adenoacanthoma	0	0	0	0	0	1	0	1
Mammary								
Total								
(adenoma+adenocarcinoma+adenoacanthoma)	0	0	0	0	1	3	1	5
Hematopoietic Tumor								
M-Malignant lymphoma	3	4	5	5	14	17	17	11
M-Plasma cell lymphoma	0	0	0	0	0	0	0	1
Hematopoietic Tumor								
Total (all malignant lymphomas)	3	4	5	5	14	17	17	12

B = benign
M = malignant

Because there was a statistically significant increase in mortality in HD males relative to controls, the incidence of neoplastic findings in animals found dead or sacrificed early was analyzed (Table 8 below). A number of neoplastic findings were observed at a slightly higher incidence in these animals (bronchioalveolar adenomas and adenocarcinomas in the lungs/bronchi, mammary adenoepithelioma and adenocarcinomas, and malignant lymphomas). However, there was not a clear response that would suggest that these tumors were the cause of death in these animals. Therefore, the increased mortality observed in HD males was not adjudicated to any neoplastic findings.

Table 8: Histological Observations in CD-1 Mice – Neoplastic (Animals Sacrificed Early or Found Dead During the Study).

	Males				**Females**			
BIBF 1120 (mg/kg/day)	**0**	**5**	**15**	**30**	**0**	**5**	**15**	**30**
Number of animals examined	**30**	**28**	**29**	**51**	**33**	**44**	**41**	**46**
NEOPLASTIC OBSERVATIONS								
Lungs with bronchi								
B-Bronchioalveolar adenoma	5	3	4	4	4	4	4	6
M-Bronchioalveolar adenocarcinoma	1	3	5	1	5	1	2	4
Lungs with bronchi								
Total (adenoma+adenocarcinoma)	6	6	9	5	9	5	6	10
Mammary								
B-Adenomyoepithelioma	0	0	0	0	0	0	0	1
M-Mammary adenocarcinoma	0	0	0	0	0	2	1	2
Hematopoietic Tumor								
M-Malignant lymphoma	2	2	4	5	8	14	10	9

Non Neoplastic Findings (Table 9)

The following non-neoplastic findings were observed at all doses but with increased incidence and/or severity in drug-treated animals compared to vehicle controls: fibrosis and ulceration in the gallbladder; dermal inflammation; epidermal hyperplasia and ulceration; skin edema and scabs; and arteritis/periarteritis/vascular mural fibrinoid necrosis in the uterus. In addition, in the adipose tissue, inflammation was observed in HD males and all doses in females; and necrosis was observed in one HD male and MD and HD females. These target organs are different from the rat (see below).

Table 9: Histological Observations in CD-1 Mice – Non-Neoplastic (All Animals).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**5**	**15**	**30**	**0**	**5**	**15**	**30**
Number of animals examined	**66**	**66**	**66**	**66**	**66**	**66**	**66**	**66**
NON-NEOPLASTIC OBSERVATIONS								
Gall Bladder								
Fibrosis								
Slight	0	1	2	0	1	0	0	2
Moderate	0	0	2	1	0	1	3	5
Marked	0	0	0	0	0	0	0	2
Severe	0	0	0	0	0	0	1	1
Ulceration								
Minimal	0	0	0	1	0	0	0	0
Slight	0	1	0	1	3	0	2	2
Moderate	0	0	3	0	0	1	4	4
Skin								
Dermal inflammation								
Slight	3	4	2	1	4	6	5	5
Moderate	6	7	10	8	0	3	4	5
Marked	3	2	2	6	1	1	1	2
Epidermal hyperplasia								
Slight	3	3	3	6	2	1	0	4
Moderate	8	8	11	8	1	2	3	3
Marked	0	1	0	1	0	0	2	1
Epidermal Ulceration								
Slight	1	0	2	1	0	0	0	0
Moderate	5	4	9	6	0	4	2	5
Marked	4	5	3	7	1	1	2	2
Oedema								
Slight	2	3	2	3	2	2	6	8
Moderate	7	8	7	9	9	9	11	11
Marked	2	0	0	0	0	0	0	0
Scab								
Slight	2	2	3	1	1	1	1	1
Moderate	6	8	5	10	3	4	2	3
Marked	4	2	4	4	0	0	3	3
Uterus								
Arteritis/Periarteritis/Vascular Mural								

Fibrinoid Necrosis								
Minimal	-	-	-	-	0	2	0	0
Slight	-	-	-	-	3	3	6	4
Moderate	-	-	-	-	0	1	2	5
Marked	-	-	-	-	0	0	0	1
Adipose tissue	(8)	(4)	(5)	(9)	(6)	(13)	(20)	(10)
Inflammation								
Minimal	0	1	0	0	0	0	0	0
Slight	1	0	0	3	0	1	0	0
Moderate	0	0	0	2	0	1	2	1
Necrosis								
Slight	0	0	0	0	0	0	0	1
Moderate	0	0	0	1	0	0	1	1

Toxicokinetics

Blood samples were collected from satellite animals at 1, 2, 4, 8, or 24 hours post-dose on study weeks 1 and 26 and at 1 hour post-dose at necropsy (study week 103 for males and study week 105 for females) for toxicokinetic (TK) analysis. Animals were anesthetized with isoflurane and blood was collected from the retro-orbital sinus into tubes containing potassium EDTA as anticoagulant. Analysis of BIBF1120 and its metabolites (BIBF 1202 ZW and the acylglucuronide form, or BIBF 1202 GLUC) was performed. Samples were extracted using a validated solid-phase extraction method and were analyzed using a validated high performance liquid chromatography (HPLC) coupled with tandem mass spectrometry (LC/MS/MS). The lower limits of quantification (LLOQs) are: 2.5 ng/mL for BIBF 1120, 5 ng/mL for BIBF 1202 ZW, and 5 ng/mL for BIBF 1202 GLUC.

Tables 10, 11, and 12 below (from the study report) include the mean PK parameters for BIBF 1120, BIBF 1202 ZW, and BIBF 1202 GLUC; respectively, in mouse plasma. There was no drug in plasma samples from vehicle control animals. BIBF 1120, BIBF 1202 ZW, and BIBF 1202 GLUC C_{max} and AUC_{0-24} increased more than dose-proportional across doses. The T_{max} was 1-2 hours post-dose for BIBF 1120 and BIBF 1202 and 1-4 hours post-dose for BIBF 1202 GLUC. There was not a clear gender effect in PK parameters and there was no evidence of drug accumulation over time.

Table 10: Mean BIBF 1120 Pharmacokinetic Parameters in CD-1 Mice – Study Weeks 1 and 26.

Group	Dose [mg/kg]	Week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	5	1	m	1	16.1	54.3
G2	5	1	f	2	35.6	104
G2	5	26	m	1	20.4	41.5
G2	5	26	f	1	17.1	38.8
G3	15	1	m	2	151	560
G3	15	1	f	2	155	656
G3	15	26	m	1	84.2	313
G3	15	26	f	2	80.2	368
G4	30	1	m	2	314	1280
G4	30	1	f	2	344	1590
G4	30	26	m	1	308	1090
G4	30	26	f	2	215	1580

m = males; f = females

Table 11: Mean BIBF 1202 ZW Pharmacokinetic Parameters in CD-1 Mice – Study Weeks 1 and 26.

Group	Dose [mg/kg]	Week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	5	1	m	NC	NC	NC
G2	5	1	f	2	4.91	7.36
G2	5	26	m	1	2.32	2.32
G2	5	26	f	1	4.96	8.59
G3	15	1	m	2	21.5	56.0
G3	15	1	f	2	32.2	99.8
G3	15	26	m	1	13.0	27.5
G3	15	26	f	2	53.4	195
G4	30	1	m	2	40.2	130
G4	30	1	f	2	59.0	213
G4	30	26	m	1	58.7	136
G4	30	26	f	1	83.6	653

NC = not calculated
m = males; f = females

Table 12: Mean BIBF 1202 GLUC Pharmacokinetic Parameters in CD-1 Mice – Study Weeks 1 and 26.

Group	Dose [mg/kg]	Week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	5	1	m	1	18.3	59.3
G2	5	1	f	2	26.6	90.6
G2	5	26	m	1	16.6	26.6
G2	5	26	f	2	16.3	58.7
G3	15	1	m	1	83.7	406
G3	15	1	f	2	143	577
G3	15	26	m	1	79.0	254
G3	15	26	f	2	78.2	545
G4	30	1	m	2	153	548
G4	30	1	f	1	251	882
G4	30	26	m	1	194	881
G4	30	26	f	4	233	1700

m = males; f = females

Dosing Solution Analysis

A stability test of dosing formulations at 24 hours at ambient temperature followed by 8 days refrigerated (4ºC) was conducted during the study. Stability of the dosing formulations at concentrations of 2-12 mg/mL after 8 days of storage at room temperature was conducted for a previous study performed at the same laboratories. In addition, homogeneity tests were conducted for dosing formulations prepared during study weeks 1, 13, 26, 39, 53, 65, 78, 91, and 103 (samples from top, middle, and bottom of the bottle). A validated (b) (4) method was used to measure the analyte (BIBF 1120) in the samples.

All the results for stability and homogeneity were within (b) (4) of nominal (pre-specified acceptance criteria based on FDA Guidance for Industry: “Bioanalytical Method Validation”).

Study title: BIBF 1120: Carcinogenicity Study by Oral Gavage Administration to Han Wistar Rats for 104 Weeks.

Study no.:	DDB0007
Study report location:	EDR
Conducting laboratory and location:	(b) (4) [redacted]
Date of study initiation:	September 30, 2010
GLP compliance:	Yes
QA statement:	Yes
Drug, lot #, and % purity:	BIBF 1120, Batch number 1045986, 100.3% pure
CAC concurrence:	Yes. Refer to Executive CAC meeting minutes dated 09/16/2010.

Key Study Findings

- Wistar rats (60/sex/group) were treated with 0 (vehicle control), 2.5, 5, or 10 mg/kg/day BIBF 1120 for 104 weeks (males and females).
- There were no BIBF 1120-related neoplastic findings observed in male or female rats.
- Treatment-related non-neoplastic findings were observed in the lungs (aggregation of alveolar macrophages, cholesterol cleft granuloma, granulomatous inflammation, and perivascular mononuclear cell inflammation), the liver (increased pigment in Kupffer cells), thyroid (focal C cell hyperplasia), kidney (increased incidence and severity of chronic progressive nephropathy), and teeth (dentopathy). In addition, arteritis/periarteritis was observed in the following tissues: tongue, testes, pancreas, and spleen.
- TK parameters were analyzed for BIBF 1120, BIBF 1202 ZW and BIBF 1202 GLUC. Results show that the T_{max} was 1-4 hours post-dose for BIBF 1120 and 1-2 hours post-dose for the two metabolites. The C_{max} and AUC of BIBF 1120 and BIBF 1202 ZW increased in a greater than dose-proportional manner across doses. BIBF 1202 GLUC systemic exposure increased in a dose-proportional manner across doses. There was not a clear gender difference in exposure. There was some evidence of drug accumulation for BIBF 1120, BIBF 1202 ZW, and BIBF 1202 GLUC.

Adequacy of Carcinogenicity Study

This study was considered adequate to assess the carcinogenic potential of BIBF 1120 in rats. BIBF 1120 doses used were recommended by the ECAC (refer to ECAC meeting minutes dated 9/16/2010). (b) (4)

Appropriateness of Test Models

The test model was considered appropriate by the ECAC. The study design (Table 13 below, excerpted from the study report) was discussed with the ECAC in a meeting held

on September 14, 2010. The Committee recommended the doses used in the study (*i.e.*, 2.5, 5, and 10 mg/kg/day).

Evaluation of Tumor Findings

There were no BIBF 1120-related neoplastic findings observed in rats.

Methods

Doses:	0 (vehicle control), 2.5 (LD), 5 (MD) or 10 (HD) mg/kg/day BIBF 1120
Frequency of dosing:	Once daily for 104 weeks
Dose volume:	10 mL/kg
Route of administration:	Oral gavage
Formulation/Vehicle:	0.5% hydroxyethyl cellulose (Natrosol® 250 HX) in demineralized water
Basis of dose selection:	A 13-week oral toxicity study in rats
Species/Strain:	Han Wistar rats
Number/Sex/Group:	60/sex/group
Age:	33-40 days old at study start
Weight:	Males: 93-164 g Females: 85-141 g
Animal housing:	Males and females were blocked by sex and the cages constituting each group were dispersed in batteries so that possible environmental influences arising from their spatial distribution were equilibrated, as far as it was practicable. There were five animals of the same sex per cage unless this number was reduced by mortality or isolation
Paradigm for dietary restriction:	None.
Dual control employed:	Only one control was included (vehicle)
Interim sacrifice:	There was no interim sacrifice in this study
Satellite groups:	A satellite group of 10 rats/sex/treatment group was included for TK analysis (5/sex for the control group). Refer to Table 13 below for the study design.
Deviation from study protocol:	Protocol deviations were reviewed and judged not to affect the quality or integrity of study data.

Table 13: Study DDB0007 Design - Rat.

Group	Treatment	Dose (mg/kg/day) #	Number of animals			
			Main study		Satellite study†	
			Male	Female	Male	Female
1	Control	0	60	60	5	5
2	BIBF 1120 ES	2.5	60	60	10	10
3	BIBF 1120 ES	5	60	60	10	10
4	BIBF 1120 ES	10	60	60	10	10

A conversion factor for salt/base ratio was used. 1.000 g of the base corresponds to 1.204 g of the salt form
† Satellite animals used for toxicokinetic sampling only

Observations and Results

Mortality

Animals were observed twice daily near the start and end of each working day for signs of moribundity. Animals were sacrificed for reasons of animal welfare as necessary.

There were no drug-related deaths in the study. In fact, the percent survival was higher in the treatment groups compared to the vehicle controls (refer to Figures 7 and 8, and Table 14 below).

Figure 7: Kaplan-Meier Survival Function – Male Rats.

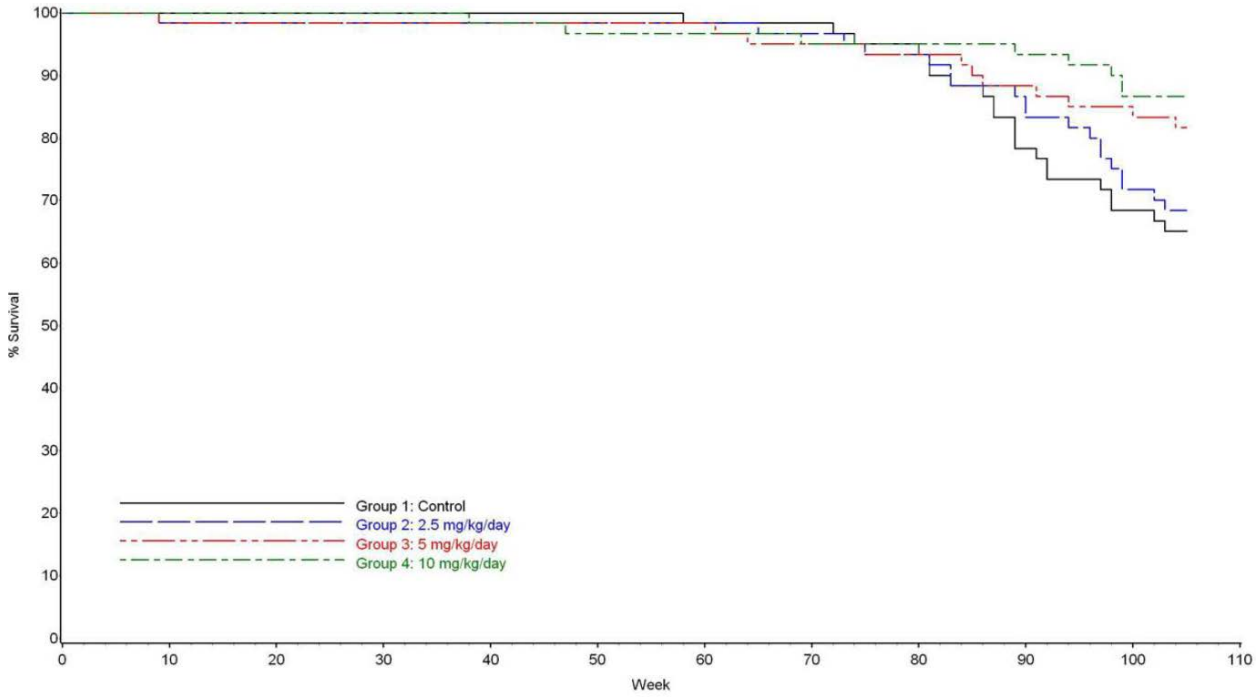


Figure 8: Kaplan-Meier Survival Function – Female Rats.

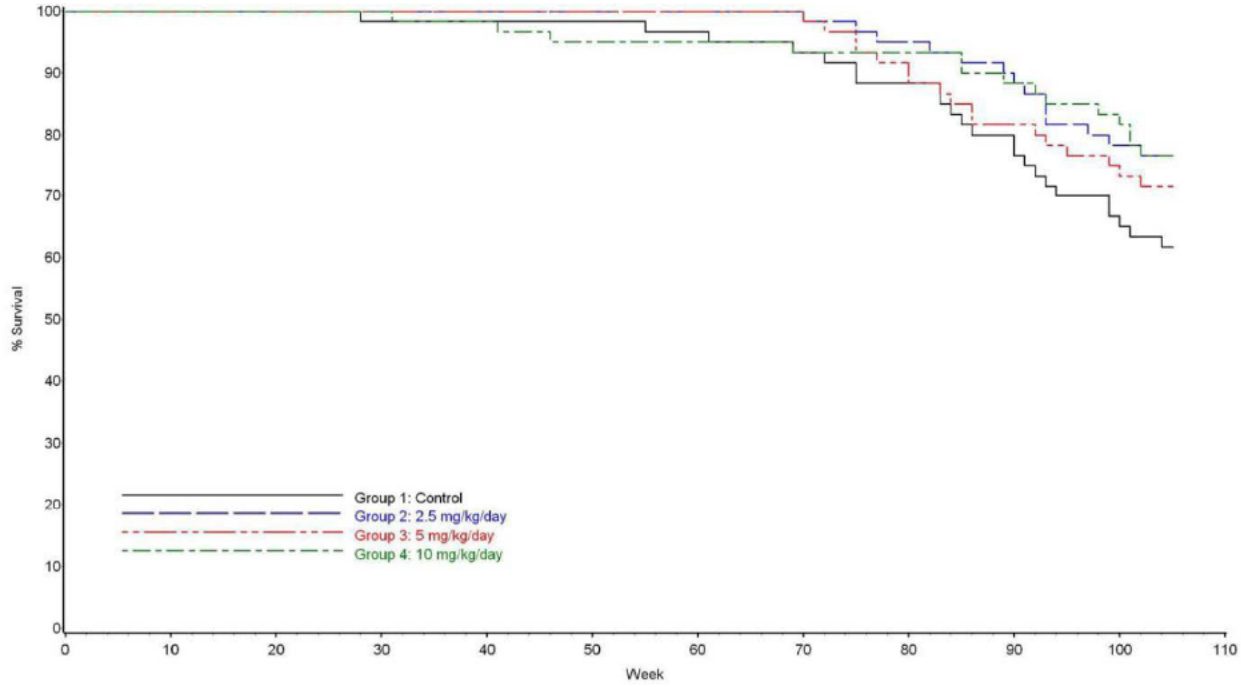


Table 14 below includes a detailed summary of the number of early decedents (sacrificed early or found dead during the study), the number of animals at termination, and the % survival in males and females.

Table 14: Summary of Early Decedents, Number of Animals at Termination, and % Survival - Rats.

BIBF 1120 (mg/kg)	Males			Females		
	Early Decedents	Termination	% Survival	Early Decedents	Termination	% Survival
0 (vehicle control)	21	39	65%	23	37	62%
2.5	19	41	68%	14	46	77%
5	11	49	82%	17	43	72%
10	8	52	87%	14	46	77%

Clinical Signs

Animals were inspected visually at least twice daily for signs of ill-health or reactions to treatment. Cages were inspected daily for evidence of animal ill-health amongst the occupants. In addition, detailed observations were conducted daily on study week 1, twice weekly on study weeks 2 to 4, once weekly on study weeks 5 to 13, once every two weeks on study weeks 14 to 52, and once every four weeks on study weeks 53 onwards. Also, a more detailed weekly physical examination that included palpation was conducted on each animal to monitor general health. Particular attention was paid to any superficial or palpable swellings; for which the location, size, consistency, time of first observation, and subsequent history were recorded.

A few signs of toxicity were observed with higher incidence in drug-treated animals compared to controls (Table 15). These include prominent eyes at all doses in females (but no dose-response); skin encrustation in HD males; and pale/white teeth, absent teeth, broken teeth, maloccluded teeth, or overgrown teeth at all doses in males and females.

Table 15: Clinical Observations in Wistar Rats – (Weeks 1-106).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Number of animals examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
OBSERVATION								
Eyes								
Prominent	7	4	2	3	7	14	13	11
Skin								
Encrustation, ventral body surface	9	11	10	17	1	2	1	0
Teeth								
Abnormal color, pale	0	0	2	2	0	2	0	9
Abnormal color, white	0	0	0	2	0	0	0	6
Absent	0	0	0	2	1	0	0	5
Broken	5	3	4	11	1	2	1	11
Broken, lower jaw (left)	0	0	0	0	0	0	0	1
Maloccluded	0	0	0	1	0	1	0	1
Overgrown	0	0	0	0	0	1	1	0

Table 16 below, excerpted from the study report, presents a summary of palpable swellings (group distribution, multiplicity, and mean time of onset). Neither the number of palpable swelling nor the time of onset were affected by BIBF 1120.

Table 16: Palpable Masses in Wistar Rats – Group Distribution, Multiplicity, and Time of Onset.

Group	:	1	2	3	4
Compound	:	Control	BIBF 1120 ES	BIBF 1120 ES	BIBF 1120 ES
Dosage (mg/kg/day)	:	0	2.5	5	10

Group /Sex	Multiplicity∅ 0	1	2	3	4 or more	Number of animals with swellings	Total number of swellings	Mean time of onset*
1M	30	13	9	5	3	30	59	58
2M	29	22	4	4	1	31	47	67
3M	29	16	7	6	2	31	56	64
4M	31	14	10	4	1	29	50	60
1F	29	18	11	1	1	31	48	83
2F	29	17	9	5	-	31	50	78
3F	33	19	7	1	-	27	36	85
4F	44	9	6	1	-	16	24	86

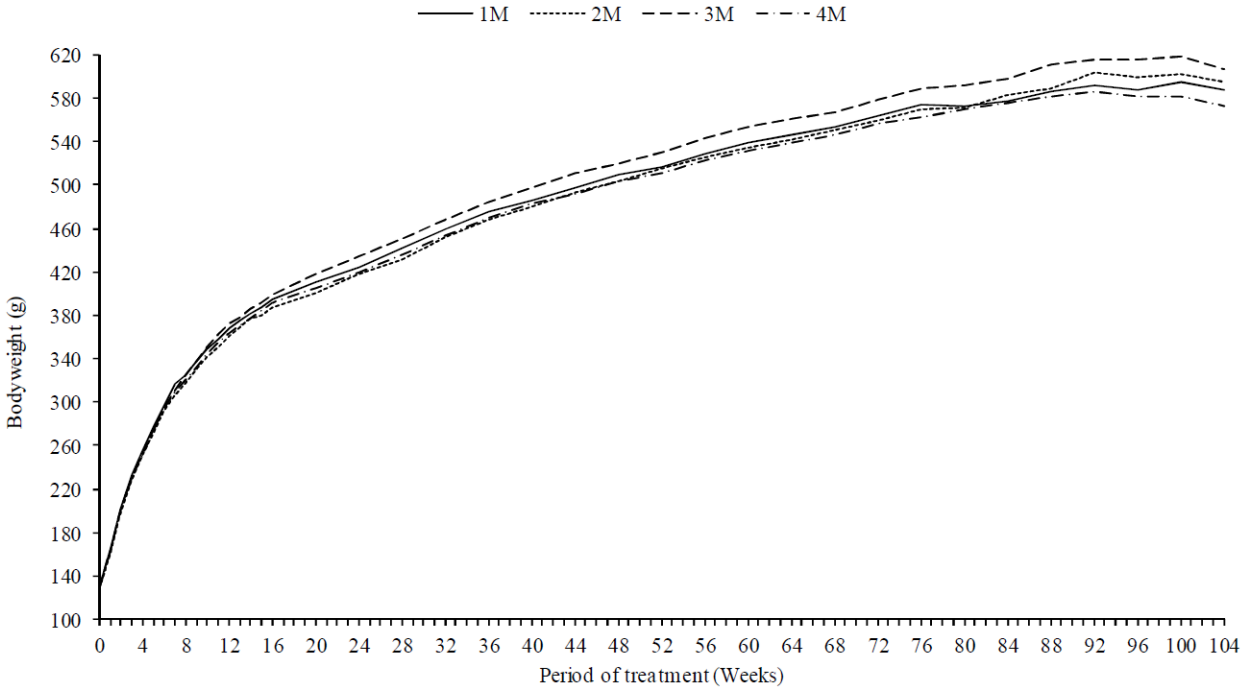
\+ Including swellings which regressed or were not positively identified at *post mortem* examination
∅ Expressed as number of animals bearing the indicated number of swellings
* In weeks to onset of first recorded swelling including those found at necropsy examination

Body Weights

Body weights were recorded one week before treatment, on the first day of treatment, at weekly intervals for the first 16 weeks of treatment (study weeks 1-16), once every four weeks thereafter, and before necropsy (terminal weight).

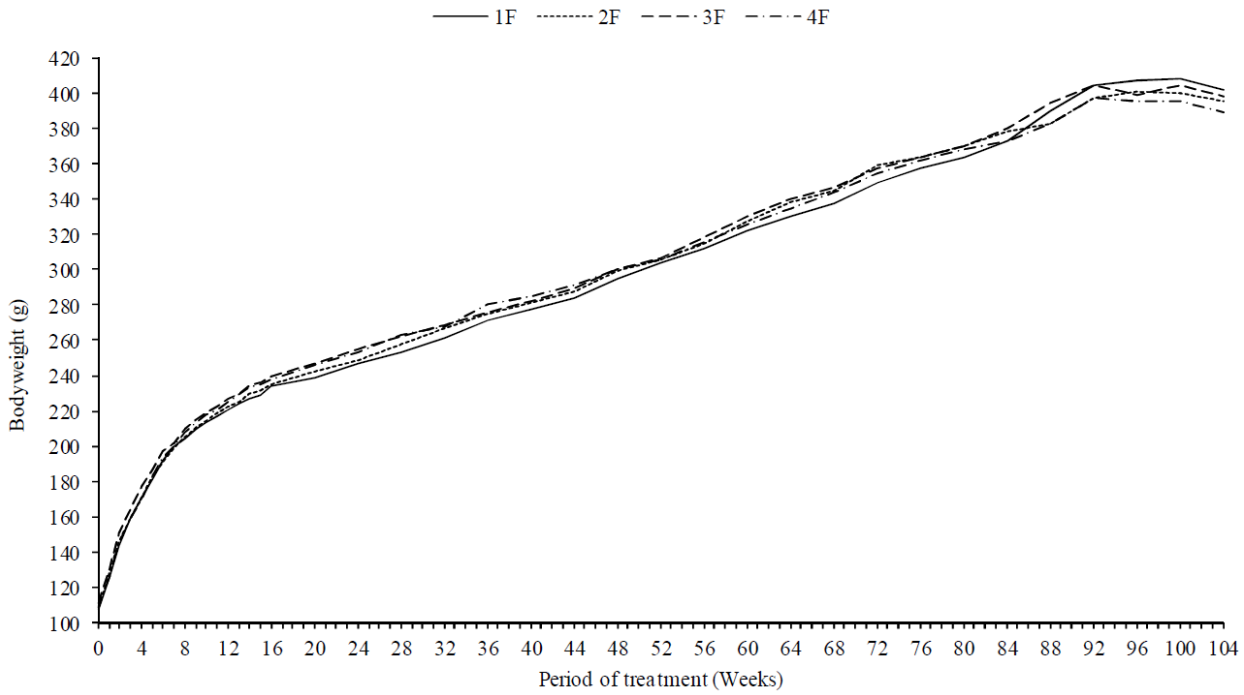
Figures 9 and 10 below present group mean body weights (in grams) for males and females, respectively. Body weights were not affected by BIBF 1120.

Figure 9: Group Mean Body Weights (g) Versus Period of Treatment (in Weeks) – Male Rats.



1M = vehicle control; 2M = LD; 3M = MD; 4M = HD

Figure 10: Group Mean Body Weights (g) Versus Period of Treatment (in Weeks) – Female Rats.



1F = vehicle control; 2F = LD; 3F = MD; 4F = HD

Feed Consumption

Food consumption per cage was evaluated by measuring the food supplied to each cage, the food remaining, and an estimate of any food spilled. The mean weekly consumption per animal (g/rat/week) was estimated from these measurements. Food consumption was recorded for the week before treatment started, weekly for the first 16 weeks of treatment (study weeks 1-16) and once every four weeks thereafter.

There was no drug-related change in food consumption in treated animals relative to controls.

Ophthalmology

Ophthalmic examinations were conducted using a binocular indirect ophthalmoscope at the following timepoints: before treatment (all animals), and on study weeks 52 and 100 (20 males and 20 females with the highest animal number from each group). Prior to each examination, the pupils of each animal were dilated using tropicamide ophthalmic solution (Mydriacyl). The adnexae, conjunctiva, cornea, sclera, anterior chamber, iris (pupil dilated), lens, vitreous and ocular fundus were examined.

There were no ophthalmic changes in drug-treated animals compared to controls.

Hematology

Blood samples were collected for hematology analysis after an overnight fast and prior to dosing on study week 104 (end of treatment period) from 20 males and 20 females

(with the lowest animal number) from each group. Blood samples were collected from all remaining animals for a limited list of hematology parameters (red blood cell count, total white blood cell count, and differential white blood cell count). Animals were held under light general anesthesia (isoflurane) while blood samples were collected from the sublingual vein into tubes containing EDTA as anticoagulant. Additional blood samples were collected into tubes containing citrate anticoagulant for analysis of coagulation parameters (prothrombin time and activated partial thromboplastin time).

A summary of drug-related changes is presented below in Table 17. Red blood cell counts were decreased in MD females and HD males and females. This was associated with an increase in reticulocytes in females but not in males. In addition, mean cell hemoglobin was increased at all doses in males and in MD/HD females. Mean cell volume was also increased at all doses in males and females. Finally, neutrophils were slightly increased in HD females and prothrombin time was slightly decreased in HD males and females. Statistically significant changes are identified with asterisks as follows: * $p<0.05$ and ** $p<0.01$.

Table 17: Summary of Drug-related Changes in Hematology Parameters Relative to Controls – Rats.

	Males			Females		
BIBF 1120 (mg/kg/day)	**2.5**	**5**	**10**	**2.5**	**5**	**10**
Red blood cells ($x10^{12}$/L)	-	-	-7%**	-	-6%**	-14%**
Reticulocytes (%)	-	-14%*	-5%**	+22%*	+37%**	+79%**
MCH (pg)	+5%**	+5%**	+12%**	-	+6%**	+14%**
MCV (fL)	+3%*	+6%**	+12%**	+4%*	+8%**	+17%**
Neutrophil ($x10^{9}$/L)	-	-	-	-	-	+13%*
PTP (sec)	-	-	-15%**	-	-	-12%**

MCH = mean cell hemoglobin
MCV = mean cell volume
PTP = prothrombin time
(-) = no drug-related change observed
* $p<0.05$; ** $p<0.01$

Serum Chemistry

Blood samples were collected after an overnight fast and prior to dosing on study week 104 from 20 males and 20 females with the lowest animal numbers from each group for analysis of serum chemistry. Animals were held under light general anesthesia using isoflurane and blood samples were collected from the sublingual vein into tubes containing lithium heparin as anticoagulant. Plasma was analyzed for a full battery of serum chemistry parameters.

A number of changes were observed in drug-treated animals relative to vehicle controls. These are summarized below in Table 18. Many of the changes were associated with nephropathy observed histologically. The findings include: increased liver enzymes (ALP and ALT) in HD females; increased urea and cholesterol in HD males and

females; increased creatinine and phosphate in MD/HD males and females; increased glucose in HD females; increased triglycerides in males at all doses (no dose-response); increased potassium in HD males and females at all doses (no dose-response); and increased magnesium in HD males. In addition, albumin (and albumin/globulin ratio) was decreased in MD/HD males and females. Statistically significant changes are identified with asterisks as follows: * p<0.05 and ** p<0.01.

Table 18: Summary of Drug-related Changes in Serum Chemistry Parameters Relative to Controls – Rats.

	Males			Females		
BIBF 1120 (mg/kg/day)	**2.5**	**5**	**10**	**2.5**	**5**	**10**
ALP (U/L)	-	-	-	-	-	+62%**
ALT (U/L)	-	-	-	-	-	+70%
Urea (mmol/L)	-	-	+29%*	-	-	+8%
Creatinine (µmol/L)	-	+23%**	+33%**	+9%*	+14%*	+23%**
Cholesterol (mmol/L)	-	-	+44%**	-	-	+31%**
Glucose (mmol/L)	-	-	-	-	-	+13%*
Triglycerides (mmol/L)	-	-	-	+14%	+44%	+42%
Potassium (mmol/L)	-	-	+13%**	+13%*	+8%*	+15%**
Phosphate (mmol/L)	-	+11%*	+23%**	+9%	+12%*	+10%*
Magnesium (mmol/L)	-	-	+9%**	-	-	-
Albumin (g/L)	-	-10%**	-13%**	-	-5%*	-13%**
Alpha-1 globulin (g/L)	-	-	+25%**	-	-	+8%*
Alpha-1 globulin (g/L)	-	-	-	-	+25%**	+25%**
Albumin/Globulin ratio	-	-14%**	-20%**	-	-10%**	-20%**

ALP = alkaline phosphatase
ALT = alanine aminotransferase
(-) = no drug-related change observed
* p<0.05; ** p<0.01

Urinalysis

Urine samples were collected over approximately 16 hours on study week 103 from 20 males and 20 females with the lowest animal number from each group. Animals were placed in an individual metabolism cage overnight without food or water for urine sample collection. Samples were examined for the following: appearance, volume, pH, specific gravity, glucose content, ketones, bilirubin/bile pigments, blood pigments, protein, sodium, potassium, and chloride. In addition, a microscopic examination of the urine sediment was performed.

The following changes were observed at the HD (Table 19): increased protein in urine in males and females, decrease urine volume in females, and decreased urine sodium and chloride in females. These changes are associated with the increased nephropathy observed at this dose level in both genders (see histopathology table below). Statistically significant changes are identified with asterisks as follows: * p<0.05 and ** p<0.01.

Table 19: Summary of Drug-related Changes in Urinalysis Parameters Relative to Controls – Rats.

	Males			Females		
BIBF 1120 (mg/kg/day)	**2.5**	**5**	**10**	**2.5**	**5**	**10**
Protein (g/L)	-	-	+399%**	-	+346%	+1821%**
Volume (mL)	-	-	-	-	-	-17%*
Sodium (mmol)	-	-	-	-	-	-22%*
Chloride (mmol)	-	-	-	-	-	-32%**

(-) = no drug-related change observed
* p<0.05; ** p<0.01

Gross Pathology

All surviving main study animals were sacrificed following 104 weeks of treatment using carbon dioxide asphyxiation with subsequent exsanguination. All main study animals were subjected to a detailed necropsy at the end of the treatment period or after being found dead or sacrificed. After review of the history of each animal, a full macroscopic examination of tissues was conducted. All external features and orifices were examined visually. Any abnormality in the appearance or size of any organ or tissue (external and cut surface) was recorded and the appropriate tissue samples were collected.

Table 20 below summarizes the macroscopic observations in the study. The following findings were observed with increased incidence in drug-treated animals compared to controls: hair loss in MD and HD males and females; masses in the preputial glands in MD and HD males; pale areas in the liver in HD males and MD/HD females; granules, masses, and pale areas in the kidneys in MD/HD males and females; thickened capsule in testes at all doses (no dose-response); pale areas in the lungs at all doses in males and females (no dose-response); and prominent blood vessels in one HD male and a few MD/HD females.

Table 20: Summary of Macroscopic Observations in Wistar Rats (All Animals).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Number of animals examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
MACROSCOPIC OBSERVATIONS								
Skin								
Hair loss	9	9	17	16	6	2	9	7
Preputial glands								
Mass(es)	9	6	14	15	-	-	-	-
Liver								
Pale area(s)	16	16	17	21	17	16	21	21
Kidneys								
Granular	0	0	2	7	0	0	0	5
Mass(es)	0	0	0	1	0	0	0	2
Pale	1	0	3	4	0	0	1	2

Pale area(s)	3	4	4	9	3	4	3	4
Testes								
Capsule thickened	3	9	6	9	-	-	-	-
Lungs and bronchi								
Pale area(s)	48	56	52	60	46	52	58	58
Blood vessels								
Prominent	0	0	0	1	0	0	2	3

Histopathology

A full battery of tissues was collected from all main study animals (premature deaths and animals that survived to the scheduled necropsy) at necropsy and examined microscopically. Sections were stained using hematoxylin and eosin.

Peer Review: A reviewing pathologist undertook a peer review of the findings.

Neoplastic Findings (Table 21)

No drug-related neoplastic findings were observed in male or female rats. Because malignant lymphomas were increased in drug-treated mice, the incidence of this tumor type was analyzed in detail for the rat. However, only one MD female and two HD females presented this neoplastic finding. This low incidence is not statistically significant.

Table 21: Histological Observations in Wistar Rats – Neoplastic (All Animals).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Number of animals examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
NEOPLASTIC OBSERVATIONS								
Hematopoietic tumor								
M-Malignant lymphoma	2	0	0	1	0	0	1	2

Non Neoplastic Findings (Table 22)

Non-neoplastic microscopic findings were observed in the lungs (aggregation of alveolar macrophages, cholesterol cleft granuloma, granulomatous inflammation, and perivascular mononuclear cell inflammation), liver (increased pigment in Kupffer cells), and thyroid (focal C cell hyperplasia). Although these findings were also observed in some control animals, they were observed with increased incidence and/or severity in drug-treated animals. Dentopathy was observed in HD males and MD/HD females and correlates with findings observed in other toxicity studies. In addition, arteritis/periarteritis was observed in drug-treated animals in the following tissues: tongue, testes, pancreas, and spleen. Further, there was increased incidence and severity of chronic progressive nephropathy (CPN) in males and females. The target

organs observed in this study correlate with the target organs already identified in the chronic toxicity studies in the rat (see above under section 6, "General Toxicology").

Table 22: Histological Observations in Wistar Rats – Non-Neoplastic (All Animals).

	Males				Females			
BIBF 1120 (mg/kg/day)	**0**	**2.5**	**5**	**10**	**0**	**2.5**	**5**	**10**
Number of animals examined	**60**	**60**	**60**	**60**	**60**	**60**	**60**	**60**
NON-NEOPLASTIC OBSERVATIONS								
Lungs and bronchi								
Alveolar macrophages aggregation								
Minimal	35	38	38	31	31	41	35	26
Slight	3	12	9	10	10	5	10	17
Moderate	0	0	0	5	1	1	2	5
Marked	1	0	0	0	0	0	0	0
Cholesterol cleft granuloma(ta)								
Minimal	3	10	7	12	8	9	12	17
Slight	0	1	2	7	1	0	2	8
Moderate	0	0	0	0	0	0	1	0
Granulomatous inflammation								
Minimal	0	0	1	1	1	0	0	5
Slight	0	0	0	0	0	1	0	0
Perivascular mononuclear cell inflammatory infiltrate								
Minimal	7	17	16	22	10	13	24	25
Slight	0	0	2	0	0	0	0	0
Moderate	0	0	0	0	1	0	0	0
Liver								
Pigment in Kupffer cells/macrophages, periportal								
Minimal	2	0	0	3	9	16	11	25
Slight	0	1	1	0	1	4	3	8
Moderate	0	0	1	1	1	1	2	1
Marked	0	0	0	0	0	0	1	1
Tongue								
Arteritis/periarteritis								
Minimal	0	0	0	3	0	0	0	2
Slight	0	0	2	1	0	0	0	5
Moderate	0	0	0	1	0	0	0	1
Testes								
Arteritis/periarteritis								
Minimal	0	1	2	1	-	-	-	-
Slight	0	0	0	4	-	-	-	-
Moderate	0	0	0	5	-	-	-	-
Marked	0	0	1	1	-	-	-	-
Pancreas								
Arteritis/periarteritis								
Minimal	0	0	0	0	0	0	0	1
Slight	0	0	1	1	0	0	0	2
Moderate	0	0	0	1	0	0	0	0

Marked	0	0	0	0	0	0	1	2
Kidneys								
Chronic progressive nephropathy								
Minimal	14	17	20	8	8	10	7	13
Slight	3	4	8	17	1	1	5	10
Moderate	1	2	3	10	1	0	1	5
Marked	0	0	3	8	0	0	1	4
Severe	0	0	0	3	0	0	0	1
Spleen								
Arteritis/periarteritis (slight)	0	0	0	2	0	0	0	0
Thyroid								
C cell hyperplasia, focal								
Minimal	3	1	2	2	2	5	3	5
Slight	2	7	4	7	1	2	1	3
Moderate	0	0	3	1	1	1	2	4
Teeth								
Dentopathy								
Minimal	0	0	0	33	0	0	1	21
Slight	0	0	0	16	0	0	0	25

Toxicokinetics

Blood samples were collected from satellite animals on study day 1, week 26, and week 52 at 1, 2, 4, 8, and 24 hours post-dose. In addition, blood samples were collected on study week 105 from five males and five females from each group (main study animals) at 1 hour post-dose. Blood (0.3-0.4 mL) was collected from the lateral tail vein into tubes containing potassium EDTA as anticoagulant. A validated LC/MS/MS method was used for analysis of BIBF 1120, BIBF 1202 ZW, or BIBF 1202 GLUC in plasma. The LLOQs were: 1 ng/mL for BIBF 1120, 2 ng/mL for BIBF 1202 ZW, and 1 ng/mL for BIBF 1202 GLUC.

Tables 23, 24, and 25 below (from the study report) present the mean PK parameters for BIBF 1120, BIBF 1202 ZW, and BIBF 1202 GLUC; respectively. BIBF 1120 and BIBF 1202 ZW systemic exposure increased more than dose-proportional across doses the dose levels tested. BIBF 1202 GLUC systemic exposure increased in a dose-proportional manner across doses. The T_{max} was 1-4 hours post-dose for BIBF 1120 and 1-2 hours post-dose for the two metabolites. There was not a clear gender effect in PK parameters. There was some evidence of drug accumulation for BIBF 1120, BIBF 1202 ZW, and BIBF 1202 GLUC.

Table 23: Mean BIBF 1120 Pharmacokinetic Parameters in Wistar Rats – Study Weeks 1, 26, and 52.

Group	Dose [mg/kg]	week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	2.5	1	m	1	0.680	0.680
G2	2.5	1	f	NC	NC	NC
G2	2.5	26	m	2	1.33	2.00
G2	2.5	26	f	4	0.943	4.22
G2	2.5	52	m	2	1.36	2.04
G2	2.5	52	f	4	0.427	1.28
G3	5	1	m	2	0.706	1.06
G3	5	1	f	2	1.13	3.63
G3	5	26	m	2	5.64	29.7
G3	5	26	f	1	3.30	18.2
G3	5	52	m	2	7.16	37.7
G3	5	52	f	4	2.71	14.0
G4	10	1	m	2	4.74	12.1
G4	10	1	f	2	7.32	22.6
G4	10	26	m	2	8.39	55.7
G4	10	26	f	2	14.4	78.3
G4	10	52	m	4	8.36	78.0
G4	10	52	f	2	11.3	87.9

NC = not calculated
m = males; f = females

Table 24: Mean BIBF 1202 ZW Pharmacokinetic Parameters in Wistar Rats – Study Weeks 1, 26, and 52.

Group	Dose [mg/kg]	week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	2.5	1	m	1	1.52	1.52
G2	2.5	1	f	NC	NC	NC
G2	2.5	26	m	2	3.70	6.94
G2	2.5	26	f	1	4.70	14.9
G2	2.5	52	m	2	4.30	11.7
G2	2.5	52	f	1	4.28	19.3
G3	5	1	m	2	3.37	7.27
G3	5	1	f	2	7.18	16.7
G3	5	26	m	2	12.0	80.6
G3	5	26	f	1	15.3	74.0
G3	5	52	m	2	16.4	115
G3	5	52	f	1	13.0	96.5
G4	10	1	m	2	14.2	37.6
G4	10	1	f	2	22.6	73.9
G4	10	26	m	2	18.0	148
G4	10	26	f	2	35.3	220
G4	10	52	m	2	18.5	199
G4	10	52	f	2	51.2	287

NC = not calculated
m = males; f = females

Table 25: Mean BIBF 1202 GLUC Pharmacokinetic Parameters in Wistar Rats – Study Weeks 1, 26, and 52.

Group	Dose [mg/kg]	week	Sex	t(max) [h]	C(max) [ng/mL]	AUC(0-24h) [ng·h/mL]
G2	2.5	1	m	1	128	522
G2	2.5	1	f	2	62.8	318
G2	2.5	26	m	2	276	866
G2	2.5	26	f	1	314	1320
G2	2.5	52	m	2	217	818
G2	2.5	52	f	1	374	1480
G3	5	1	m	1	135	568
G3	5	1	f	1	261	1000
G3	5	26	m	2	298	1360
G3	5	26	f	1	571	2200
G3	5	52	m	2	572	2920
G3	5	52	f	1	762	3050
G4	10	1	m	2	338	1150
G4	10	1	f	2	383	1450
G4	10	26	m	2	1030	3430
G4	10	26	f	1	1250	3520
G4	10	52	m	1	1150	4650
G4	10	52	f	1	1340	6480

m = males; f = females

Dosing Solution Analysis

A stability test of dosing formulations for 2 days at ambient temperature followed by 15 days at 4ºC was conducted during the study. In addition, stability of the dosing formulations at concentrations of 2-12 mg/mL following 8 days of storage at room temperature was conducted for a previous study performed at the same laboratories. Homogeneity tests were conducted in samples (from top, middle, and bottom of the bottle) obtained from dosing formulations prepared during study weeks 1, 13, 26, 39, 52, 65, 78, 91, and 103. A validated (b) (4) method was used for the analysis.

All the results for stability and homogeneity of dosing formulations were considered acceptable (within 10% of nominal).

11 Integrated Summary and Safety Evaluation

Boehringer Ingelheim submitted a 505(b)(1) NDA on May 2nd, 2014 for Nintedanib oral capsules. Nintedanib (BIBF 1120) is a kinase inhibitor. Nintedanib is an inhibitor of tyrosine kinase receptors for PDGF, VEGF, and FGF, and is also an inhibitor of (b) (4) kinase and three members of the Src family of kinases. Nintedanib was developed by Boehringer Ingelheim for the treatment of IPF. The proposed dosing regimen is 150 mg orally twice daily for symptomatic treatment of IPF or 100 mg twice daily if any adverse reactions are observed at the higher dose.

Nintedanib was negative in a full battery of genetic toxicology studies (*in vitro* Ames and mouse lymphoma assays and *in vivo* micronucleus assay in rats).

Boehringer Ingelheim conducted two carcinogenicity bioassays (2-year studies in CD-1 mice and Han Wistar rats) to assess the carcinogenic potential of nintedanib. The study protocols and nintedanib doses used were found acceptable by the ECAC in a meeting held on September 14, 2010.

In the 2-year mouse bioassay (study number DDB0006), CD-1 mice (66/sex/group) received 0 (vehicle control), 5, 15, or 30 mg/kg/day nintedanib (BIBF 1120) orally once daily for 102 (males) or 104 (females) weeks. The doses were selected based on the maximum tolerated dose (MTD) identified in a 13-week oral toxicity study in CD-1 mice (*i.e.*, 100 mg/kg/day) due to findings of broken teeth.

No statistically significant tumor findings were observed in male or female mice. There was increased mortality in the HD male group starting approximately on study week 76. This group was terminated early on study week 102 based on recommendations provided by the Division via email (*i.e.*, to terminate a group when the number animals remaining reached 15). The male control, LD, and MD groups were terminated on study week 103. In females, mortality was higher at all BIBF 1120 doses compared to controls but did not follow a dose-response was not statistically significant. All the groups were maintained until scheduled necropsy. Treatment-related non-neoplastic findings were observed in the gallbladder (fibrosis and ulceration), skin (dermal inflammation, epidermal ulceration and hyperplasia, edema, and scabs), uterus (arteritis/periarteritis/vascular mural fibrinoid necrosis), and adipose tissue (inflammation and necrosis).

Results of the TK analysis in the mouse showed that C_{max} and AUC for BIBF 1120 increased in a greater than dose-proportional manner. There was not a clear gender difference in exposure or evidence of drug accumulation over time. The AUC_{0-24} at 30 mg/kg/day was 1,335 ng·hr/mL (males and females combined).

In the 2-year rat bioassay (study number DDB0007), HsdHan™;WIST rats (60/sex/group) received 0 (vehicle control), 2.5, 5, or 10 mg/kg/day nintedanib (BIBF 1120) orally once daily for 104 weeks. Doses were selected based on a MTD identified in a 13-week oral toxicity study in Han Wistar rats (*i.e.*, 20 mg/kg/day) due to findings of broken teeth.

Nintedanib was not carcinogenic in male or female Wistar rats. Mortality was not affected by treatment with nintedanib in rats. Also there were no changes in body weights or food consumption. Non-neoplastic histopathology findings were observed in the lungs (aggregation of alveolar macrophages, cholesterol cleft granuloma, granulomatous inflammation, and perivascular mononuclear cell inflammation), the liver (increased pigment in Kupffer cells), thyroid (focal C cell hyperplasia), kidney (increased incidence and severity of chronic progressive nephropathy) and teeth (dentopathy). In addition, arteritis/periarteritis was observed in the tongue, testes, pancreas, and spleen.

Results of the TK analysis in the rat showed that systemic exposure (C_{max} and AUC) of BIBF 1120 increased in a greater than dose-proportional manner across doses. There was not a clear gender difference in exposure. There was some evidence of drug accumulation over time. The AUC_{0-24} at 10 mg/kg/day was 82.95 ng·hr/mL (males and females combined).

The results from the two bioassays were discussed with the ECAC during a meeting held on July 15, 2014. The ECAC concluded that the two studies were acceptable, noting prior ECAC concurrence with the study protocols. In addition, the ECAC concluded that there were no drug-related neoplasms in mice or rats.

Exposure margins were estimated using systemic exposure (AUC) comparisons observed in mice and rats at the maximum dose of 30 mg/kg/day and 10 mg/kg/day, respectively; and in humans at the maximum proposed clinical dose of 150 mg twice daily (300 mg/day). Table 26 below presents the estimated exposure margins.

Table 26: Exposure Margins for the Proposed Clinical Dose of 300 mg/day Nintedanib.

Nonclinical Doses	Exposure margins*
Mouse carcinogenicity study High-Dose: 30 mg/kg/day $AUC_{0-24, ss}$: 1335 ng·hr/mL	4
Rat carcinogenicity study High-Dose: 10 mg/kg/day $AUC_{0-24, ss}$: 82.95 ng·hr/mL	0.25

* = $AUC_{0-24, ss}$ of 327 ng·hr/mL in humans at 300 mg/day

12 Appendix/Attachments

Appendix 1: ECAC meeting minutes dated September 16, 2010 (ECAC meeting held to discuss the two carcinogenicity protocols)

Appendix 2: ECAC meeting minutes dated July 16, 2014 (ECAC meeting held to discuss the carcinogenicity conclusions)

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

/s/

CAROL M GALVIS
08/22/2014

MARCIE L WOOD
08/22/2014

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

NDA/BLA Number: 205-832 **Applicant: GSK** **Stamp Date:** May 2, 2014

Drug Name: Nintedanib Esliate **NDA/BLA Type:** Original NDA

On **initial** overview of the NDA application for filing:

	Content Parameter	Yes	No	Comment
1	Is the pharmacology/toxicology section organized in accord with current regulations and guidelines for format and content in a manner to allow substantive review to begin?	x		None
2	Is the pharmacology/toxicology section indexed and paginated in a manner allowing substantive review to begin?	x		None
3	Is the pharmacology/toxicology section legible so that substantive review can begin?	x		None
4	Are all required (*) and requested IND studies (in accord with 505 b1 and b2 including referenced literature) completed and submitted (carcinogenicity, mutagenicity, teratogenicity, effects on fertility, juvenile studies, acute and repeat dose adult animal studies, animal ADME studies, safety pharmacology, etc)?	x		A pre-NDA meeting in IND 74,683 was held on October 31, 2013. The meeting minutes states that no further nonclinical studies are required to support the filing of an NDA. Also, carcinogenicity studies can be submitted as post NDA submission. The submission included the carcinogenicity study reports.
5	If the formulation to be marketed is different from the formulation used in the toxicology studies, have studies by the appropriate route been conducted with appropriate formulations? (For other than the oral route, some studies may be by routes different from the clinical route intentionally and by desire of the FDA).	x		Pivotal toxicity studies (PTS) and the clinical formulation differed, but there is no concern about the difference. The PTS were done in an aqueous solution (0.5% hydroxyethylcellulose) by oral gavage. The clinical formulation is a liquid capsule. The capsule contained no novel excipients.
6	Does the route of administration used in the animal studies appear to be the same as the intended human exposure route? If not, has the applicant submitted a rationale to justify the alternative route?	x		Both the nonclinical and clinical studies used the oral route of administration.
7	Has the applicant submitted a statement(s) that all of the pivotal pharm/tox studies have been performed in accordance with the GLP regulations (21 CFR 58) or an explanation for any significant deviations?	x		None
8	Has the applicant submitted all special studies or data requested by the Division during pre-submission discussions?	x		A complete battery of reproductive toxicity studies was submitted.

PHARMACOLOGY/TOXICOLOGY FILING CHECKLIST FOR NDA/BLA or Supplement

	Content Parameter	Yes	No	Comment
9	Are the proposed labeling sections relative to pharmacology/toxicology appropriate (including human dose multiples expressed in either mg/m^2 or comparative serum/plasma levels) and in accordance with 201.57?	x		The proposal labeling is in the PLR format.
10	Have any impurity – etc. issues been addressed? (New toxicity studies may not be needed.)	x		The safety evaluation will be done in consultation with the reviewing chemist.
11	Has the applicant addressed any abuse potential issues in the submission?			Not applicable
12	If this NDA/BLA is to support a Rx to OTC switch, have all relevant studies been submitted?			Not applicable

IS THE PHARMACOLOGY/TOXICOLOGY SECTION OF THE APPLICATION FILEABLE? __YES._____

If the NDA/BLA is not fileable from the pharmacology/toxicology 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.

Please include the following in the filing letter:

Use the recommended human daily dose of 300-mg nintedanib to assess exposures and conduct safety evaluations of drug impurities and degradants in nintedanib capsules .Your current estimates of exposures of patients to the impurities were based on a 250-mg nintedanib dose. Assessments made using this dose underestimate the exposure of patients to the impurities.

Luqi Pei, Ph.D. June 11, 2014

Reviewing Pharmacologist Date

Marcie Wood, Ph.D.

Supervisory Pharmacologist Date

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

/s/

LUQI PEI
06/11/2014

MARCIE L WOOD
06/11/2014